

HEPATITIS C VIRUS INFECTION / RE-INFECTION IN ILLICIT DRUG USERS

by

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

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

(Pharmacology and Therapeutics)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

November 2009

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ABSTRACT

Introduction: Over 300,000 Canadians have chronic Hepatitis C virus (HCV) infection, over half being current or former Injection drug users (IDUs). The possibility of re-infection is often cited as a reason for not initiating treatment in this group of patients, although recent observational data suggest that the rate of re-infection may be reduced following spontaneous or treatment-induced virologic clearance, such data are often retrospective and incomplete.

Methods: In a prospective study to evaluate the incidence of HCV viremia, we identified a cohort of IDUs at risk of new infection, who were receiving care at the Pender Community Health Centre on Vancouver's Downtown East Side. Potential subjects were identified as either: never been infected with HCV (non-infected arm), spontaneously cleared the virus (spontaneous arm), or achieved a sustained virologic response after treatment (SVR arm). A questionnaire to identify demographics, health status, risk behavior and drug use was administered at baseline and every 6 months, along with blood tests to identify their HCV status.

Results: 518 subjects were screened, 245 (47%) were excluded because of being viremic and 69 (13 %) met the criteria for inclusion in the study: 18 in the non-infected, 29 in the spontaneous and 22 in the SVR arm respectively. There were no significant differences among the 3 groups with respect to age, ethnicity, source of income, unstable housing, and being on opioid maintenance program. Over follow-up, 20% of the non-infected group became viremic, as compared to 0% of the other two groups ($p=0.04$). Injecting drugs in the past 30 days ($p=0.004$), sharing non-injection equipments ($p=0.015$), heroin, amphetamines, and combined drugs use was significantly higher in the non-infected compared to SVR arm ($p=0.02$, 0.04 and 0.02 respectively). There were no significant differences in drug use and risk behavior between non-infected and spontaneous arms.

Conclusion: We have demonstrated in a prospective cohort with systematic follow-up that HCV infection is more likely to occur in those who have never been previously

infected, and that this susceptibility to infection cannot be completely explained by an increase in risk behavior, at least as compared to individuals who have cleared their viremia spontaneously.

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LIST OF ABBREVIATIONS

HCV	Hepatitis C Virus
Kbp	Kilo-base pair
HIV	Human immunodeficiency virus
WHO	World Health Organization
IDU	Injection drug use
IDUs	Injection drug users
RNA	Ribonucleic acid
B.C.	British Columbia
IFN	Interferon
ALT	Alanine transaminase or alanine aminotransferase
SVR	Sustained virological response
RVR	Rapid virological response
TB	Tuberculosis
DOT	Directly observed therapy
US	United States
CD	Cluster of Differentiation
P value	Probability value
PCHC	Pender Community Health Centre
BCCDC	British Columbia Centre for Disease Control
IVDU	Intravenous Drug use
UK	United Kingdom
SRO	Single room occupancy
D4t	Stavudine

ACKNOWLEDGEMENTS

“وقل ربّي زدني علماً” ‘My Lord, increase me in knowledge.’ (Holy Quran, chapter 16, surat Ta ha, verse 114). Thanks to God for giving me the strength and ability to increase my knowledge and learn many things I didn’t know before starting my studies.

I would like to thank my supervisor Dr. Brian Conway for giving me the opportunity to pursue my studies. During my studies he has been very patient with me and provided me with the support I needed to learn things I have never known before. Watching him not caring about trivial issues, focusing on the important ones and always searching for common ground are things I will always try to imitate in my career.

I would like to thank my committee members; Dr. Stephan Schwarz and Dr. Mel Krajden for their support and valuable advice to enhance my knowledge and advance my research capabilities.

Many thanks to my family; my wife Mai, my kids Layan and Mahmoud, my mother, father, sisters and brother for their continuous support and encouragement.

I would like to thank my colleagues at the hepatitis C team, Pender Community health staff and patients for helping and participating in this study.

CHAPTER 1: INTRODUCTION

By the 1970s, scientists identified two viruses that can cause hepatitis (inflammation of the liver). These viruses were hepatitis A and B, but scientists couldn't identify the cause of another form of hepatitis that is usually associated with blood transfusion. This form of hepatitis was often identified as non-A, non-B hepatitis.[1] In 1989, scientists identified the causative agent of this form of hepatitis and were referred to as hepatitis C virus (HCV). [2]

1.1. Hepatitis C virus (HCV)

HCV is a spherical enveloped single stranded ribonucleic acid (RNA) virus that belongs to the Flaviviridae family, genus Hepacivirus.[3] The virus is almost 9.5 Kilo-base pair (kbp). The figure below shows the different regions of the HCV RNA genome.

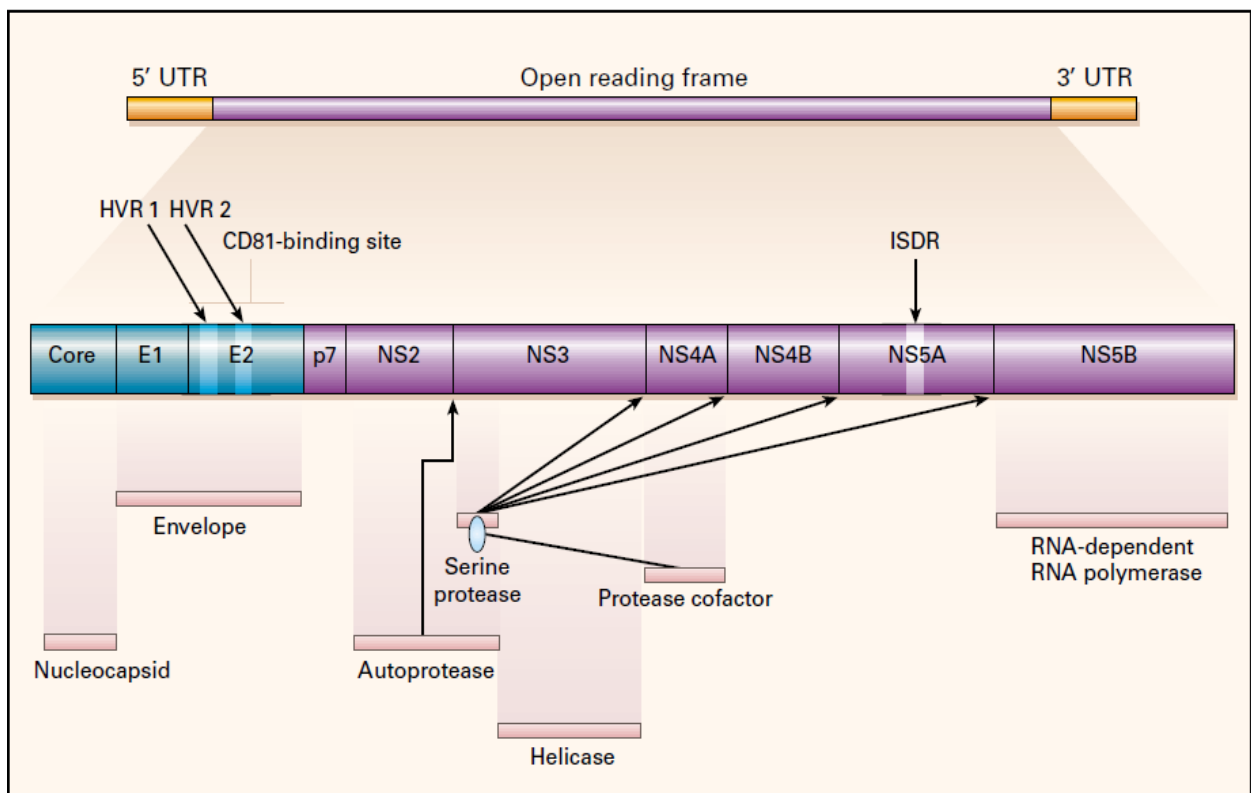


Figure 1: HCV genome.

Adapted from reference[4] with permission. UTRs: untranslated regions, NS: nonstructural region, E1 and E2: envelope proteins, HVR 1 and HVR 2: hypervariable

regions 1 and 2, CD81: Cluster of Differentiation 81, ISDR: interferon-sensitivity–determining region.

1.2. HCV transmission

HCV is transmitted mainly through contaminated blood or blood products. The transmissibility risk after a needle stick injury is estimated to be 3%, while the estimated risk for human immunodeficiency virus (HIV) is 0.3%. Depending on the viral load, the risk of getting HCV is 10 times higher than that of HIV after a needle stick injury.[4] The rate of vertical transmission from a mother to her child is estimated to range from 1.0% to 5.0% when the mother has positive HCV antibodies; the rate was higher and ranged from 3.1% to 6.9% when the mother has HCV RNA viremia.[5] HIV co-infection and intravenous drug use was reported among the factors that increased the rate of vertical transmission, on the other hand the method of delivery whether vaginal or caesarean and breast feeding seemed to have no effect on rate of mother to infant HCV transmission.[5]

Sexual transmission of HCV has been reported to be infrequent; the reason is not known yet. It may be because the virus is present in low levels in the semen or vaginal discharge or there are no target cells for the virus in the genital tract. The percentage of sexual transmission increases when the person is co-infected with HIV, in the case of anal sex, in the men having sex with men population, and in female sex workers.[4, 6] Nosocomial transmission through multiple syringe use, surgical diagnosis and treatment equipments reuse and needle stick injury are among the routes of transmission especially in the third world countries.[4]

Although HCV was detected in the saliva, casual contacts through kisses, hugs and sneezing have not been reported to transmit the disease.

Injection drug use is the main reason of HCV transmission in Canada and in the developed countries. In Canada, it accounts for more than 70% of new cases of HCV infection.[6] Sharing of the injection drug preparation paraphernalia was reported to result in transmission of the disease.

1.3. Disease progression

After being infected with HCV, the majority of patients don't develop any symptoms. Those who develop symptomatic infection often complain of jaundice, fatigue, malaise, nausea and vomiting.[7] It is approximate that 15-30% of infected individuals will clear the virus spontaneously, while the remaining 70-85% will develop chronic infection. From those who have chronic infection, nearly 20-30% will develop cirrhosis over a period of 20-30 years. 1-4% of cirrhotic individuals might end up having hepatocellular carcinoma. [8]

1.4. Epidemiology

Chronic hepatitis C infection is a worldwide disease, infecting more than 170 million individuals which represents almost (3%) of the world population.[9]

Table below shows hepatitis C prevalence by WHO region.

WHO region	Total Population (Millions)	Prevalence Rate (%)	Infected population (Millions)	No data available (No. of countries)
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
Eastern Mediterranean	466	4.6	21.3	5
Europe	858	1.03	8.9	19
South-East Asia	1500	2.15	32.3	3
Western pacific	1600	3.9	62.2	11
Total	5811	2.9	169.7	57

Table 1: Hepatitis C estimated prevalence rate and number infected by WHO region. Weekly epidemiological record, no. 49, 10 December 1999. WHO: World health organization.

From this table we can see that Africa has the highest prevalence of hepatitis C, on the other hand Europe has the lowest. The prevalence of hepatitis C not only differs from

continent to continent but also differs within the same continent, in Europe for example the prevalence in Germany is about 0.6% while in southern Italy it is 8.4-22.4%. [10, 11] In Egypt the prevalence ranges from 6-28% (mean 22%) and it is to be considered the highest prevalence worldwide. [4, 11]

In Canada, the prevalence of hepatitis C is estimated to be between 0.8-1.0% (240,000-300,000) and increasing over time. [12] The table below shows hepatitis C prevalence by exposure category.

Category	Population	HCV prevalence rate %	HCV prevalence	Proportion %
IDUs	91,000	55	49,900	20
Previous IDUs	181,400	49	89,400	36
IDUs total	272,500		139,300	56
Transfusion	2,748,200	1.2	32,900	13
Hemophilia		57	1200	0.5
Other	28,023,900	0.26	73,800	30
Total	31,046,600	0.80	247,200	100

Table 2: HCV prevalence by exposure category in Canada 2002. [12]
IDUs: (injection drug users)

The table above shows that more than half of the prevalent cases of HCV in Canada are among current or previous IDUs. Other studies showed that more than 70% of the prevalent cases of HCV infection in Canada are due to IDUs. In IDUs cohorts in B.C., the prevalence rate of HCV was 85% and the incidence rate was 26%. [13]

1.5. HCV genotypes

HCV replicates very rapidly in human body, it is estimated that infected individuals has 10^3 – 10^7 genomes per ml of serum. [14] HCV half life is estimated to be 3 hours and about 10^{12} viruses are created daily in an infected individual. [15] HCV replicates via RNA-dependent RNA polymerase that lacks proofreading resulting in having a lot of mutations and the virus will be present as quasispecies in the infected individuals.

The classification of genotypes depends on the sequence similarities. Table below explains a consensus classification of HCV genotypes:

Sequence similarities %	Description
< 72 % with any variant	New HCV type
75-86 % with other variant	New Subtype
>88 %	Shouldn't be assigned new type

Table 3: HCV genotype classification.[16]

HCV is classified into 6 major genotypes with several subtypes. Genotypes were given numbers 1 to 6 and subtypes were given letters a, b, c...etc. The genotype distribution worldwide is generally as shown in the map below.

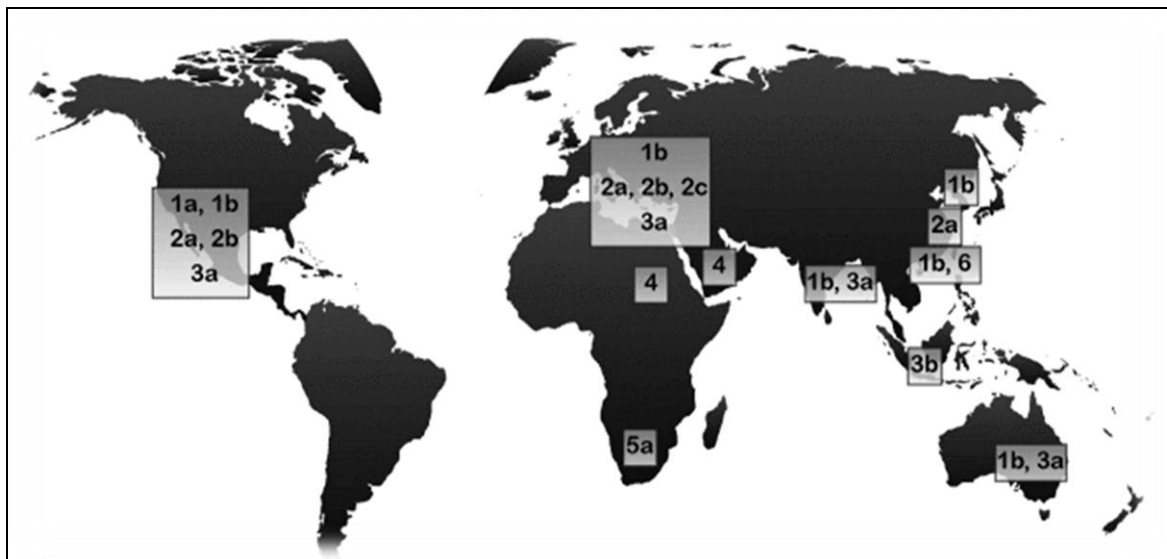


Figure 2: Hepatitis C virus genotype distribution.[17] Adapted with permission.

Genotype 1, 2, and 3 are distributed all over the world. Genotype 4 is highly prevalent in Egypt and some neighbouring countries; genotype 5 is mainly present in South Africa and genotype 6 primarily in some Asian countries. In Canada genotype 1 accounts for almost 67% of the prevalent cases, and genotypes 2 and 3 account for 31% of prevalent cases combined.[18] The genotype map in Canada differs from province to province, for example genotype 3a is the most prevalent in Winnipeg and accounts for 47%, compared to 37% for genotype 1a. HCV genotype also differs from one group of

patients to another, for example genotype 3a was more prevalent in IDUs (27%) than non IDUs (10%).[18]

Identifying which genotype the infected person carries is critical to determine the length of treatment and to predict the probability of a positive outcome from the treatment.

1.6. HCV treatment

1.6.1. Current HCV treatment

Chronic hepatitis C infection is a treatable disease. The treatment of HCV infection started with interferon (IFN) when HCV was identified as non-A, non-B hepatitis. IFN helped in normalizing alanine aminotransferase (ALT) levels.[19] After identifying HCV, it became possible to measure the success of treatment by the presence of sustained virological response (SVR) which is defined as the absence of HCV from the serum of the treated individuals 24 weeks after finishing treatment. SVR was around 5% when IFN monotherapy was used for 24 weeks and the SVR increased to around 20% when IFN was used for 48 weeks. When IFN was combined with ribavirin (oral antiviral drug), SVR rates approached 40% as the treatment duration was for 48 weeks. During this time IFN was given subcutaneously three times per week and ribavirin was given every day via the oral route. Another big leap in the success rate was achieved when polyethylene glycol moiety was attached to IFN in order to improve its pharmacokinetics and the SVR rates jumped to about 60%. Pegylated interferon (PEG-INF) injection given subcutaneously once a week combined with daily oral ribavirin is the standard treatment for HCV nowadays. There are two kinds of PEG-INF; the first one is PEG-INF alpha 2 b (PEG-Intron®; Schering-Plough, USA) and the second one is PEG-INF alpha-2a (PEGASYS®; Roche, Switzerland). The size of the polyethylene glycol moiety attached to each IFN molecule, the pharmacokinetics and the dosage are not the same but the efficacy and the success rate for both PEG-INF are comparable and they can be used interchangeably to treat HCV infected individuals. The figure below shows the improvement in SVR rate over the past years to its current state.[19]

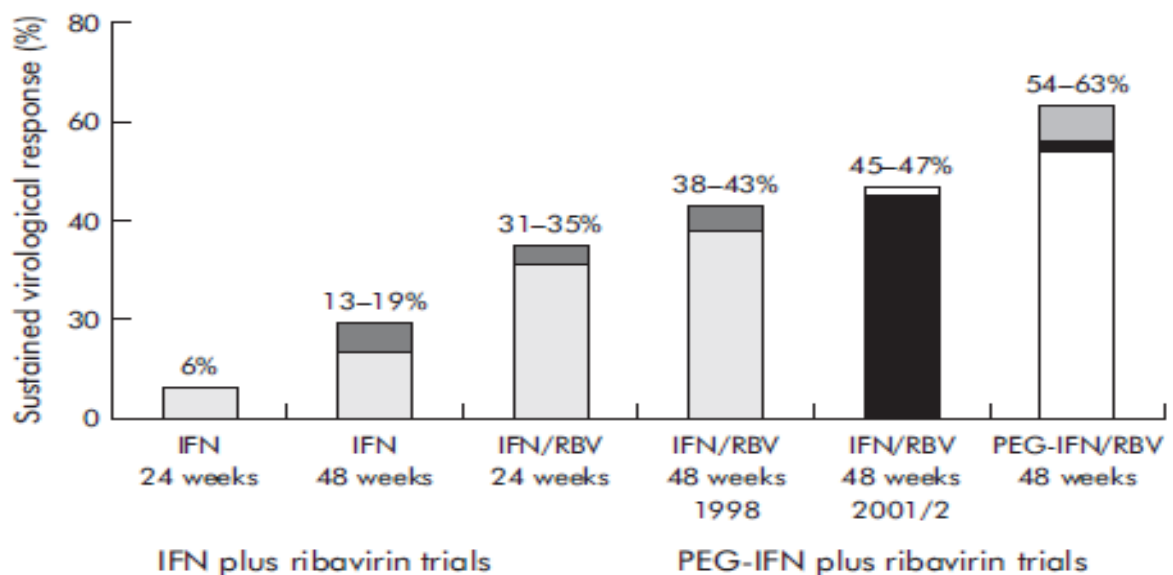


Figure 3: SVR rate improvement over years.[19] Adapted with permission.
IFN: Interferon, RBV: ribavirin, PEG: pegylated.

The duration of treatment for HCV depends mainly on the genotype of the virus, for genotypes 1, 4, 5 and 6 the recommended duration is 48 weeks, on the other hand for genotypes 2 and 3 the recommended duration is 24 weeks. The table below shows the current recommended dose and duration of HCV treatment.

HCV Genotype	Duration (weeks)	PEG-IFN (once/ week, sc)	Ribavirin (daily orally)
Genotype 1, 4-6	48	180 µg PEG-INF alpha-2a	1000 mg (< 75 kg) 1200 mg (≥ 75 kg)
		1.5 µg/kg PEG-INF alpha-2b	800 mg (< 65 kg) 1000 mg (65-85 kg) 1200 mg (>85 kg)
Genotype 2 & 3	24	180 µg PEG-INF alpha-2a	800 mg regardless to patient weight
		1.5 µg/kg PEG-INF alpha-2b	800 mg (< 65 kg) 1000 mg (65-85 kg) 1200 mg (>85 kg)

Table 4: Treatment recommendations for HCV.[19] Adapted with permission.
Peg-IFN: pegylated interferon. SC: subcutaneously.

The duration of HCV treatment is still investigated by different researchers. More than one study have shown the possibility of shortening the duration of treatment without compromising success rate, on the other hand other studies demonstrated that shorter duration of treatment was associated with higher relapse of HCV infection. In recent Canadian consensus guidelines it was agreed that, if the patient has no predictors of poor response which include (advanced fibrosis, high viral load, high body mass, African American ethnicity, and HIV co-infection) and the patient has rapid virological response (RVR) defined as no HCV RNA detected in serum (< 50 IU/ml) after 4 weeks of treatment, then it is possible to decrease the duration of treatment to 24 or 16 weeks for genotype 1 and genotypes 2/3 respectively. On the other hand for genotype 1, if RVR was not achieved and the patient has a $\geq 2 \log_{10}$ drop in HCV RNA serum level by week 12 and no HCV RNA by week 24 of treatment, this patient is considered as slow or delayed responder. Studies showed that slow responders may benefit from a longer 72 weeks of treatment instead of 48 weeks. There still no studies to show if genotypes 2/3 slow responders will benefit from a longer than 24 weeks of treatment.[12]

If the patient on treatment has genotype 1 and his HCV RNA level doesn't drop by $\geq 2 \log_{10}$ by week 12, then the treatment is considered unsuccessful and it should be stopped. For genotype 2/3 treatment should be continued for 24 weeks regardless of the week 12 HCV RNA result.

HCV genotype not only important in deciding the duration of treatment, it also helps in predicting the success of treatment. The rate of SVR reported after treatment ranges from 42 to 52% and from 76 to 84% for genotype 1 and genotypes 2/3 respectively.[20] HCV treatment had advanced over years but still relatively considered long treatment with a wide variety of side effects. The table below shows main side effects associated with interferon and ribavirin treatment.

Frequency of side effects	Interferon alpha	Ribavirin
Very common ($> 30\%$)	Flu-like symptoms Headache Fatigue Fever Myalgia Thrombocytopenia	Hemolysis Nausea

Frequency of side effects	Interferon alpha	Ribavirin
Common (1 - 30%)	Anorexia Erythema at injection site Insomnia Alopecia Irritability Emotional lability Depression Diarrhea Leukocytopenia Taste perversion	Anemia Nasal congestion Pruritus
Rare (< 1%)	Paranoia or suicidal ideation Diabetes mellitus Retinopathy Hearing impairment Seizures Loss of libido Cardiotoxicity	Gout

Table 5: Side effects associated with interferon alpha and ribavirin treatment.[4]
Adapted with permission.

These side effects accompanied with long duration of treatment make patient adherence and compliance not easy and may necessitate decreasing the dose of either IFN or ribavirin or even stopping the treatment. It was estimated that 10-14% of patients discontinue HCV treatment due to side effects. Patient counseling about the importance of adherence and the occurrence rate of these side effects and how to handle them if they occur is very important in increasing the chance of success.[21]

1.6.2 Future HCV treatment categories

HCV standard treatment has limitations; one of which is the route of administration of IFN as a subcutaneous injection which is less convenient than oral administration, IFN needs to be kept in the refrigerator which may not be available for all patients, particularly for IDUs, the treatment has a variety of side effects and contraindications and a modest success rate especially for those individuals infected with genotype 1. So there is a need for new drugs that will be easier to administer, improve the treatment success rate and have fewer side effects.

There are different categories of drugs under evaluation that demonstrated improved HCV treatment:

- 1- **Protease Inhibitors (PIS):** PIS prevent viral replication by blocking the NS3/4A serine protease. Ciluprevir was the first PI developed that shown the efficacy of PIS against HCV but its development was discontinued due to cardiotoxicity. Two PIS which are under evaluation in clinical trials are Telaprevir and Boceprevir. Trials showed that both medications improved the success rate and are most effective when added to the standard treatment of PEG-INF and ribavirin and not as monotherapy. Resistance can develop against Telaprevir by HCV especially among those infected with genotype 1a. Main side effects reported with Telaprevir; were skin rash, nausea and anemia while gastrointestinal problems and anemia were reported with Boceprevir.[22]
- 2- **Polymerase Inhibitors:** polymerase inhibitors prevent viral replication by blocking HCV RNA dependent RNA polymerase NS5B enzyme. There are two kinds of polymerase inhibitors; nucleoside and non-nucleoside analogues. More than one molecule is under development but till recently only R-1626 (nucleoside analogue) has been into clinical trials. R-1626 which is a pro-drug showed modest results in improving success rates and it was associated with high grade of neutropenia, thus its' development was stopped.[22]
The future development of both PIS and polymerase inhibitors should deal with the possibility of resistance development by HCV. Their use at this time would be in addition to the standard PEG-IFN and ribavirin which may increase the possibility of adverse events and dosage complications but their usage with standard treatment may decrease the duration of treatment which may decrease the cost of therapy, improve adherence and outcomes.
- 3- **Albupheron:** which is an IFN- α - albumin protein; it has the same efficacy when combined with ribavirin as the current PEG-IFN. Its main advantage is that it can be administered biweekly instead of the once a week PEG-IFN. This molecule may add little advantage over the available treatments in terms of less side effects or better treatment success outcome.[23]
- 4- **Nitazoxanide:** is an oral thiazolide anti-infective agent that was developed by Romark Laboratories in the USA as an antiparasitic drug to treat *Cryptosporidium parvum* and *Giardia lamblia*. "Nitazoxanide mechanism of action

may be related to induction of protein kinase phosphorylation (PKR), which results in an increased intracellular concentration of phosphorylated eukaryotic initiation factor 2 α , a key mediator of host cell defenses against viral infection.”[24] This drug showed efficacy against HCV and was studied in combination with PEG-IFN without and with ribavirin in patients infected with genotype 4. The results were encouraging; as the patients who received triple therapy achieved a 79 % SVR rate and those treated with nitazoxanide and PEG-IFN achieved a 61 % SVR rate, and those who received standard treatment achieved a 50% SVR rate. The side effects were similar in all groups, only those received ribavirin had higher rate of anemia. Nitazoxanide would have a potential to be used in addition to the available standard treatment or instead of ribavirin if the results of this study are confirmed in other studies and with other genotypes.[24]

1.7. Who should be treated?

Hepatitis C virus testing and treatment had advanced rapidly in the past decade which enabled clinicians to successfully treat infected individuals. In order to get rid of the disease we should treat infected individuals and prevent the occurrence of new cases. When looking at table 2, we will find that more than half of the prevalent HCV infection in Canada is among current or previous IDUs, and almost all new cases of HCV infection that occur in Canada is due to IDU risk behaviors. It is also estimated that 20% of prevalent cases are among immigrants who came to Canada from countries where the disease is endemic (e.g. Egypt, Somalia, Pakistan, Italy and Greece), it is estimated that immigration contributes to almost one third of cases of HCV infection. [25]

Since immigrants and IDUs represent the most prevalent cases of HCV infection in Canada, then programs and efforts should be aimed toward identifying infected individuals, treating them and preventing them from spreading the disease to others.

Immigrants: In Canada, HCV infection is reportable in all provinces and territories and we have a surveillance system that identifies new cases but the accuracy of the collected information is still questionable since the disease is mostly asymptomatic in the majority of cases, it slowly progresses to become chronic infection and this will

make it difficult to identify new acute cases from those which happened a long time ago. [26] Also we don't have a surveillance system that identifies those who might have been infected prior to immigration to Canada. Developing such a surveillance system or even requiring a test of HCV before immigrating to Canada can be helpful in identifying these individuals. Targeted programs which educate about the disease, how to slow its progression and how to prevent its spread to other individuals plus treating those who need treatment would help in decreasing or even eradicating the disease among specific immigrant communities.

1.8. Injection drug users

The issues of identifying, treating and preventing HCV infection among IDUs are not easy and handling these issues requires a better understanding of addiction and the spread of addiction related diseases.

1.8.1. Epidemiology of HCV in IDUs

HCV infection is widely spread among the IDUs population in developed countries. In the United States HCV infection prevalence among IDUs ranges from 80-90% and incidence is about 10-20% per year.[27] In Canada, 55% and 49% of the prevalent cases of HCV infections are among current and previous IDUs respectively, in other estimates, injection drug use accounted for almost 70% of the prevalent cases in Canada.[13, 25] Within IDUs cohorts in Vancouver and Montreal, the prevalence was reported to be 85% and 70% and the annual incidence was 26% and 20% respectively.[13] In The Vancouver Injection Drug User Study (VIDUS) which is an open cohort study from 1996-1999 Patrick et al, founded that the prevalence of HCV among 1345 IDUs is 81.6% and the overall incidence density rate was around 29.1 per 100 person years and remained above 16 per 100 person years over the whole 3 years period of the study.[28]

From all these studies we may conclude that IDUs at least account for more than half of the prevalent HCV cases in Canada, and any strategy or initiative to prevent, treat or decrease the disease burden of chronic HCV infection must address the core or the reservoir of the disease, that is the IDUs.

1.8.2. Challenges of treating IDUs

At the beginning of HCV treatment, illicit drug use especially injection drug use was a reason to withhold treatment until the patient abstained from drug use for at least six months.[29] Since then, new guidelines in both the US and Canada acknowledged that treatment of HCV in IDUs should be evaluated on a case by case basis and injection drug use shouldn't be considered a reason to withhold treatment.[21, 30] Although injection drug use is no longer stated as a specific reason to withhold treatment in Canada, it is still challenging to treat IDUs. The following reasons might be stated to delay or withhold treatment:

- 1- **Poor adherence:** adherence to treatment is very important in order to achieve success. To treat or not to treat HCV should be decided by the patient with the approval of his physician, but before initiating treatment the doctor or a health professional should explain to the patient why this drug(s) has been prescribed, the action(s) of the drug, expected success rate, common side effects of the treatment and how to manage them when they occur. When such information is shared at the beginning this will increase the treatment adherence of the patient not only in the case of IDUs but also in the case of any treatment whether it is a 3 day antibiotic or 6 months chemotherapy or lifelong diabetes or HIV treatment.[31] Clinical studies showed that adherence of IDUs to treatment ranges from 30 to almost 100% which is comparable to that reported in subjects treated for hypertension, asthma and other similar chronic diseases.[27] Directly observed therapy (DOT) which was successful in improving compliance when treating tuberculosis and HIV might be applied in treating HCV infection. Other strategy that usually improves adherence is making the dosage simpler and easier to take. Since the pegylation of IFN; it became easier to be administered as once weekly injection is required instead of the earlier three times per week dosage.

Another issue to keep in mind when dealing with IDUs is that they are not all the same, some of them has a stable life and their addiction is relatively under control while others have a chaotic life. One should not lump them together and predict that all IDUs will not adhere to treatment. Assessments of adherence should be made on

a case by case basis and a plan to improve treatment adherence should be put into action in order to achieve higher treatment success.[31]

- 2- **Side effects:** The standard pegylated IFN and ribavirin HCV treatment has a wide range of side effects, some can be easily dealt with (e.g. headache and flu like symptoms) and others are more serious (e.g. anemia and leukocytopenia). Discussing these side effects with IDUs and having close follow- up to identify these side effects once they occur plus empowering patients with the tools and knowledge on how to prevent or decrease their severity will help in improving compliance and willingness to continue the treatment. For example, in our cohort of IDUs under treatment we provided them with acetaminophen and ibuprofen to help them deal with headaches and pain. And the antihistamine diphenhydramine to help in decreasing the flu like symptoms and itching. These simple measures helped in increasing compliance and adherence to treatment.
- 3- **Psychological problems:** Interferon based HCV therapy is contraindicated in patients having pre-existing severe psychiatric condition or a history of a severe psychiatric disorder. [32] Psychiatric assessment before initiating HCV treatment is needed for all patients regardless to the use of illicit drugs. The prevalence of psychiatric disorders is very common among illicit drug users; major depression and antisocial personality disorder were reported to be around 20% and 37% in opioid abusers respectively. [33] In contrast, other studies showed that depression was reported in 2-30% of people having chronic hepatitis C infection although they didn't report illicit drug use.[34] Since treatment with IFN may cause depression, anxiety and irritability, close follow-up with the patients is needed to ensure prompt recognition of these side effects. Treating patients with antidepressants or antipsychotics before or during treatment help in decreasing psychiatric side effects and stabilizing patients to a degree where treatment can be safely administered.
- 4- **Socioeconomic circumstances:** When treating HCV, the socioeconomic situation of the patient should be taken into consideration especially in the case of IDUs. Having stable housing and emotional and financial support can be a big factor in encouraging people to start and adhere to the treatment. Helping IDUs to find good housing and coordinate with addiction counselor will help improve their chances of

treatment success. The IFN part of the treatment needs to be refrigerated, so before treatment initiation the health care provider should make sure that they have a refrigerator in case they will self administer their medication and if they don't have a refrigerator an alternative should be discussed like keeping the medication in the clinic or pharmacy. Improving the socioeconomic circumstances and social supports of the IDUs will increase the intake and the adherence to the treatment. Health care providers should work with the patient and a comprehensive team instead of accepting that socioeconomic status alone is an obstacle to treatment.[35]

- 5- **Slow progression of the disease:** Chronic hepatitis C infection progresses slowly over 20 to 30 years before cirrhosis or end stage liver disease may develop. This slow progression may persuade some clinicians to see no urgency in treating HCV and encourage some to postpone the treatment. Postponing treatment might be the favorable option if the IDU feels he is not ready to start treatment or if the physician sees the patient's situation is not stable enough from an addiction perspective. In this case postponing treatment should involve a plan to treat patient's addictions and to eliminate the obstacles that might affect treatment success and then to initiate treatment at a later time.[31] In case the clinician would like to postpone treatment until new medications that might increase the success rate become available, this plan should be communicated with the patient and a follow-up should be agreed upon in order to start treatment when the new medications are marketed. Also related to slow progression and when it is suitable to treat HCV, the issue of drug use related death might be asked. In a study involving more than 3,000 opioid drug users Joe et al showed that the percentage of death among drug users is 3 to 14 times higher than that of the general US population.[36] When deaths were analyzed according to age the highest difference was in the < 21 years old which was 14 times as high as the general population. Death rates were 10 and 4 times higher in 21-30 years old and those > 30 years old respectively.[36] The causes of death among these groups were mainly violence and drug use related which accounted for 72% of the deaths combined. Drug related in specific were reported in 44% as the cause of death, and when looked at deaths according to age; 63%, 50% and 29% were reported in the < 21, 21-30 and > 30 years old age group

respectively.[36] So one may conclude that if the HCV infected IDUs are more likely to die - especially the young ones - not because of HCV but because of drug use so it is appropriate to postpone the HCV treatment and treat their addictions first.

Treating drug addiction is very important and may positively affect adherence of patient to HCV treatment but shouldn't be a prerequisite to qualify to HCV treatment. So clinicians may initiate addiction treatment and HCV treatment simultaneously or plan when to treat HCV after initiating the addiction treatment. Again the issue is that not all young IDUs are same, some may seek treatment for HCV while they are drug free and shouldn't be denied treatment. During treatment they should be educated about safe injection practices which may decrease the possibility of drug related deaths in case they relapsed to drug use.

Treating HCV infected young IDUs might be useful in decreasing the spread of the disease if the treatment was successful, because they will be no longer infectious to other non-infected individuals if they achieve SVR. So having programs specifically targeting this group of IDUs may help decrease HCV transmission.

- 6- **Effect of substance use on treatment:** the effect of alcohol and other illicit drugs on HCV progression and treatment success might be cited as a reason to withhold treatment. Alcohol use in HCV infected individuals results in faster progression of end stage liver disease (liver cirrhosis and hepatocellular carcinoma).[37, 38] "In alcoholic individuals the prevalence of HCV ranges from 14-36%; even though the reason for this high prevalence was not clear, intravenous drug use was considered the primary risk factor for HCV among alcoholics." [38] Alcohol use especially in excessive amounts (> 50 gm/day) is thought to decrease the efficacy of IFN, impair host general immunity and increase the levels of HCV in the blood which will compromise the treatment efficacy.[35, 37, 38] Cessation of alcohol use before and during HCV treatment should be encouraged regardless if the patients are IDUs or non IDUs in order to maximize the benefit from treatment. However alcohol use shouldn't be a major factor in denying treatment and patients shouldn't be asked for long duration of abstinence (e.g. > 6 months) before initiating treatment especially if they are occasional or mild drinkers. [37]

Cigarette smoking is very common among HCV infected individuals, approximately 63% in a Canadian cohort while smoking among general Canadian public is about 24%.[35] Cigarette smoking negatively affects the quality of life and since it can be modified with different interventions and medication, patients undergoing HCV treatment should be counseled about smoking cessation.

7- **Risk of re-infection:** The possibility of re-infection after treatment is usually considered by health care providers as a valid reason to withhold HCV treatment from IDUs. If we add the high cost of the medication and the challenges of providing HCV treatment for IDUs, the argument that if we treat HCV in IDUs and they achieve SVR they might get involved in a risk behavior for acquisition and get re-infected; then no health benefit will occur and we will be just wasting money and effort. Evaluating the risk of re-infection is a key element of my thesis and it will be discussed from multiple perspectives.

1.9. HCV re-infection

1.9.1. Re-infection and the lack of protective immunity

- Chimpanzees were used to study HCV infection since they can be chronically infected with HCV. With a rapid and spontaneous HCV clearance of up to 60%, chimpanzees are considered a good model for studying acute infection, the frequency of viral clearance and re-infection mechanisms and rates. [39].
- Farci et al. studied re-infection possibility and lack of protective immunity against HCV in chimpanzees. In this study 5 chimpanzees were challenged with HCV and all of them developed viremia which was transient in 4 but persistent in one. All 5 chimpanzees tested positive for HCV antibodies and 4 of them tested negative for HCV RNA after less than 18 weeks. All five were re-challenged with HCV, one with the same homologous inoculum and 4 with heterogonous inocula and all redeveloped viremia. The one that developed persistent viremia from the first challenge was inoculated with different strain in the second challenge. Three of the chimpanzees cleared the virus again within a shorter period of 3 to 10 weeks and one developed persistent viremia. Two of those who tested negative for HCV RNA where challenged for the third time and

one of them developed transient viremia for 1 week and the other developed persistent viremia, these two were re-challenged for the fourth time and the one who was HCV RNA negative developed persistent viremia.[40] This study demonstrated that re-infection in chimpanzees is possible with either the same or heterologous strain of HCV and being infected once doesn't protect against future HCV infection regardless if the virus was cleared or persisted. These findings should be kept in mind when considering HCV vaccine development.[40]

- In another study, Lai et al. demonstrated that 3 thalassaemic children who received blood transfusion from HCV infected donors developed viremia and elevated ALT levels that lasted for 12 months then ALT levels went back to normal and no HCV RNA was detected in their serum. Subsequent transfusion associated with HCV infection took place at least 17 months later and all of the 3 children developed persistent viremia. When trying to differentiate whether the second infection was a new infection or just a relapse from the first one, two of the three children were infected with a different HCV strain which suggest that it was a new infection, but the third child was infected with the same strain and the investigators couldn't rule out the possibility of a relapse from the primary infection. This study demonstrates that HCV re-infection may happen in humans and there is no clear protective immunity against new infection.[41]

- In a case report, Proust et al. confirmed the findings of previous studies after reporting re-infection case. An occasional intravenous drug user female was infected with HCV genotype 1a in December 1995 after reporting sharing a needle with another female and developed transient viremia with elevated ALT levels. The patient cleared HCV RNA almost 3 months after infection and her ALT levels became normal. Two years later and after sharing needles with another female, different from the previous one, the patient tested positive for HCV RNA with above normal ALT levels and she was infected with HCV genotype 3a. This report showed that spontaneous clearance of one HCV genotype doesn't protect against infection with another genotype. The presence of different HCV genotypes and the virus ability to mutate rapidly makes it difficult to develop protective immunity and as a result it will be difficult to develop a vaccine.[42]

1.9.2. Re-infection and the presence of protective immunity

1.9.2.1 Chimpanzees studies

- Bassett et al. evaluated the presence of protective immunity against HCV re-infection in chimpanzees that had cleared the virus previously. When they challenged a chimpanzee with non-homologous genotype 1.5 years after it cleared previous HCV infection they found that the chimpanzee had a sterilizing immunity and it cleared the virus without developing viremia but the virus was detected in a liver biopsy. When this study was repeated with another chimpanzee that cleared the virus 6 years before re-challenge, this chimpanzee developed viremia but cleared the HCV from both the liver and serum after 4 weeks of re-challenge which was shorter than the 15 weeks that took the chimpanzee to clear the virus 6 years prior. This observation suggested that the protective immunity was higher when the viral clearance was more recent and even after 6 years a shorter time was needed to clear non-homologous HCV. In another chimpanzee that cleared the HCV 16 years before, the investigators re-challenged it with a homologous genotype and found that the chimpanzee was able to clear the virus after 6 weeks from the blood and the liver compared to >12 weeks that were needed to clear the virus 16 years before. This study suggested that chimpanzees developed a protective immunity after previous clearance of the HCV and this immunity is long lasting. This immunity extends to different subtypes and T-cell plays an important role in developing protective immunity. These findings suggest that vaccine development may be feasible. [39]
- Studies by Shoukry et al. and Nascimbeni et al. supported the previous study results by demonstrating the presence of protective immunity among chimpanzees when re-challenged with HCV. Nascimbeni et al. showed that HCV clearance is mainly mediated through CD4⁺ and CD8⁺ memory T-cell response and that HCV antibodies have a minimal role in clearing HCV. Shoukry et al. study showed that HCV clearance after re-challenge is mainly mediated through CD8⁺ memory T-cells.[43, 44]
- In another study, Lanford et al. took 4 chimpanzees that had cleared HCV genotype 1 and re-challenged them with HCV genotype 1, genotype 4, a mixture of genotypes 2 and 3, and a mixture of genotypes 1, 2, 3 and 4 respectively. The chimpanzee that was re-challenged with the same genotype showed a sterilizing immunity, no HCV RNA was

detected in the blood or liver. By contrast, it took this chimpanzee 8 and 16 weeks to clear the virus from the blood and liver respectively in the primary infection 1 year before. When the second chimpanzee was re-challenged with a mixture of genotype 2b and 3a, a low level of viremia was detected and no HCV RNA was detected by week 8 and the genotype detected was 3a only, by contrast this chimpanzee cleared the primary genotype 1a infection 2.5 years before in 11 weeks. The chimpanzee who was inoculated with genotype 4a also managed to clear the virus within 8 weeks while 2.5 years ago it needed 22 weeks to clear the primary infection with genotype 1a. The fourth chimpanzee cleared genotype 1a within 14 weeks 4 years earlier and was re-challenged in this study with a mixture of 4 HCV genotypes 1a, 2b, 3a, and 4a. This chimpanzee also managed to clear this mixture in 3 weeks. The HCV genotypes detected were genotype 4 and 1 only and in 3:1 level ratio. The low level of genotype 1 can be explained by the presence of protective immunity against this genotype from the primary infection. This chimpanzee was challenged with the most complex inoculum and after the longest period of time but still managed to clear the virus. This study demonstrated that clearing certain HCV genotype will provide protective immunity not only to the same genotype but will extend to other genotypes. This cross genotype protective immunity increases the chances of success in developing an effective vaccine.[45]

1.9.2.2 Human studies

- Mehta et al. studied the presence of protective immunity against HCV in humans. They compared the rate of HCV re-infection among IDUs who cleared the virus spontaneously with the rate of HCV infection in IDUs whom had never been infected before. The investigators identified 98 IDUs whom had been infected with HCV and cleared the virus spontaneously without treatment; they tested positive for HCV antibodies but negative for HCV RNA. They also identified 164 IDUs who had never been infected with HCV before; they tested negative for both HCV antibodies and HCV RNA. Both groups were followed for 4 consecutive 6 months period. The incidence of HCV re-infection among those who previously cleared the virus was 12% (12/98); on the other hand the rate of infection in the IDUs who have never been infected before was 21% (35/164). While the rate of infection was almost twice the rate of re-infection

but still it was not statistically significant ($p=0.07$). When the investigators compared the rate of re-infection/infection in HIV negative individuals, the rate was 33% (3/9) and 84 % (27/32) in those who were previously and never infected before respectively.

And when adjusting to potential confounders (age, sex, and ethnicity) it was 12 times less likely to develop HCV viremia if previously infected and cleared the virus than if haven't been infected before.

From this study it was shown that the incidence of HCV infection in IDUs is high (21% in non-infected and 12% in those who previously cleared the virus). Those who cleared HCV spontaneously developed a kind of protective immunity and are less likely to develop persistent infection than those who have never been infected before. This kind of acquired immunity helped not only in preventing re-infection but also decreased the severity of viremia that occurred after developing persistent infection. Also this immunity is not universal as demonstrated by the 12% re-infection rate and as noted in this study that one subject who cleared the virus when he was HIV negative but developed persistent HCV infection after becoming HIV positive. HIV infection may play a role in decreasing the protective immunity and increasing the possibility of re-infection in some subjects. [46]

There are some limitations of this study:

- 1) It was a retrospective study where the reliability and the accuracy of the data collected was not consistent and the analysis was post hoc.
- 2) There was no systematic collection of risk behavior information. There was no data about sharing of injection or drug use paraphernalia.
- 3) There were significant differences in age, drug use and HIV status among the studied groups, those who cleared the virus spontaneously were older, and higher percentage of them were infected with HIV which might increase the chance of persistent infection on the other hand they injected and shared less drugs which decreases the chance of infection.

This study suggested that there is a kind of protective immunity in humans comparable to that found in chimpanzees. These findings should encourage the research towards finding a protective vaccine that might put an end to the HCV endemic especially in the IDUs population where treatment is more challenging. [46, 47]

- In another study, Grebely et al. compared the rates of re-infection / infection between IDUs who cleared the virus spontaneously to those who have not been infected before. After identifying IDUs from a cohort study where demographics, HIV and HCV testing, illicit drug use and health care utilization information were collected, the investigators linked this data with the data available in two provincial laboratories in order to identify the HCV antibody and RNA and HIV status for these individuals. They identified 152 and 926 subjects who cleared the virus spontaneously or never been infected before respectively. Those uninfected and those who cleared the virus were followed for a median of 2.8 and 5.2 years respectively. The rate of infection was 18.6% (172/926) or 8.1 case per 100 person years in the uninfected group, by contrast the rate of re-infection was 9.2% (14/152) or 1.8 cases per 100 person years in those who have cleared the virus before. The group who cleared the virus spontaneously was older, were more likely to be of aboriginal ethnicity, were more likely to be HIV positive and more likely to have injected drugs; these differences were statistically significant. When the investigators compared the rate of re-infection among the cleared group in regard to HIV they found that 6.8% (8/117) or 1.4 cases / 100 person-years and 17.1% (6/35) or 2.8 cases / 100 person-years became re-infected in HIV negative and HIV positive individuals respectively.

After adjusting to age, sex, drug use and other confounders, it was concluded from this study that; IDUs who clear the virus spontaneously are 4 times less likely to become re-infected and develop viremia when compared to those who have never been infected before. This study supported the results found by the Mehta et al. group and they suggested that this phenomenon might be due to the development of protective immunity. [48]

Some of the limitations of this study include:

- 1) It is a retrospective linkage study that was originally intended to evaluate health care utilization among those who live in Vancouver downtown eastside and not to evaluate HCV re-infection / infection.
- 2) There was no specific information regarding drug use. For example no information about injection and injection equipments sharing which would be beneficial in evaluating risk behaviors and may help in explaining whether the

low re-infection incidence was due to protective immunity or lower rates of risk behaviors.

- 3) The individuals' data was linked to laboratory data collected from 1992 to 2005, during this period more than one testing method for HCV antibodies and RNA were used. These tests have different specificity and sensitivity which may have affected the rate of infection / re-infection results in both groups.
- 4) There was no systematic testing for HCV antibodies or HCV RNA which may indicate that information about infection / re-infection might have been missed in the individuals recruited in each group.
- 5) In this study the investigators compared HCV infection in regard to HIV status in the cleared group only, it might be beneficial to compare the rate of re-infection / infection between the two studied groups in regard to HIV status as was done in Mehta et al study. This might help in shedding more light about the effect of having intact immunity to prevent new HCV infection.

Both previous studies showed lower re-infection rates after clearing HCV spontaneously and suggested that if this phenomenon would be replicated in those who clear the virus via treatment it would be more encouraging to clinicians to treat more IDUs with less concern about the possibility of re-infection.[46, 48]

- In an Australian study, Micallef et al. [49] presented a contradictory results to those presented in the previous two studies. In a retrospective study the investigators evaluated the incidence of HCV infection / re-infection among a cohort of IDUs using stored serum samples. They assembled a cohort of 423 IDUs who tested negative for HCV antibodies and 18 IDUs whom were HCV antibody positive but HCV RNA negative.

Among the antibody negative IDUs, 27% (114/423) or 17/100 person-years were infected and became antibody positive. On the other hand 72% (13/18) or 42/100 person-years were re-infected after spontaneously clearing the virus. As a result, the incidence of re-infection was higher than the incidence of infection.

When the investigators tried to differentiate re-infection from relapse by comparing the genotypes, they found that 9 of the 13 probably can be considered re-infection, decreasing the incidence of re-infection to 31/100 person-years. After adjusting for risk

factors like sharing of injection and injection equipments, imprisonment and drug use the investigators concluded that the incidence of infection among negative individuals was similar to the incidence of re-infection among those who cleared the virus before (incidence rate ratio 1.11, P value=0.8).

By showing higher or even similar rate of HCV re-infection after spontaneous clearance to the rate of HCV infection, this study contradicts the previous studies and shows there is no protective immunity against re-infection after clearance especially if the person is exposed to heterologous HCV genotype. [49]

Limitations of this study:

- 1- This was a retrospective study with small number of subjects who cleared the virus spontaneously.
- 2- The investigators evaluated the incidence of infection / re-infection depending on serum samples stored at – 20 °C which might have affected the level of HCV RNA with time and become below the detection limit resulting in lower detection of rate of re-infection.
- 3- There was a significant heterogeneity between the studied groups since there was no systematic assessment of HCV RNA and antibodies and there was no systemic evaluation of risk behaviors over the study period.

1.9.3. Re-infection possibility after treatment:

Few studies evaluated the risk of HCV re-infection in IDUs after treatment and that might be due to the fact that treatment uptake by IDUs is still very low.

- Backmund et al. followed 18 IDUs for a mean of more than 33 months. These patients were tested for HCV RNA nearly every year and if tested positive, HCV was genotyped. 15 patients (83%) remained HCV RNA negative, 1 patient died and 2 (11%) became HCV RNA positive. One of the two re-infected individuals was originally treated for genotype 1b and 4 months after achieving SVR tested positive for the same genotype. The other person was treated for genotype 3a and became re-infected with genotype 1a after a needle stick injury while working as a nurse. In the first individual relapse from the first infection couldn't be ruled out, since HCV re-emerged only 4 months after achieving SVR and the patient tested positive for the same genotype. Late relapse was

reported in previous studies, 8% late relapse was reported after > 2 year of treatment. [50] But since this subject has relapsed to drug use during that period, the new occurrence of HCV might have been due to re-infection. The other person denied illicit drug use after achieving SVR and claimed re-infection had happened in relation to a work related risk. The investigators calculated the rate of re-infection due to injection drug use after treatment as 0–4.1 cases per 100 person-years, even though 50% (9) of the treated IDUs relapsed to drug use after treatment. None of those who relapsed to drug use reported sharing needles that have been used by other person. The IDUs in this study were informed about the possibility of re-infection and were taught how to practice safe injection techniques in case they relapsed to drug use. The low re-infection rate reported in this study stresses the point that, when treating HCV infection in IDUs it is still very important to teach them about methods of prevention of re-infection and the importance of not sharing injections with others.[51]

From the limitations of this study:

- 1- The study was small and retrospective that involved only 18 patients.
 - 2- There was no consistent follow-up for these patients; it was mentioned that blood tests were done at approximately 1 year intervals and during this period re-infections could be missed especially if the cured underwent spontaneous clearance.
 - 3- There was no systematic evaluation of ongoing risk behavior (e.g. administering a questionnaire by fixed intervals).
 - 4- Two treatment regimens were used (IFN α -2a monotherapy for 48 weeks through 1998 or IFN α -2a and ribavirin for 24–48 weeks, according to HCV genotype starting in 1998). It would have been useful if the investigators showed whether the use of any regimen might have an effect on the re-occurrence of HCV infection.
- In another study, Dalgard et al. studied the risk of re-infection in a Norwegian IDUs cohort. The investigators followed a group of 116 subjects 69 of them were IDUs whom were treated with either IFN monotherapy or combination of IFN and ribavirin. 45 subjects achieved SVR, 27 (39%) of 69 IDUs as compared to 18 (38%) of 47 non-IDUs ($p = 0.93$). The investigators followed those who achieved SVR for a mean of > 5years

and found that HCV re-occurred in one of the IDUs and didn't re-occur in any of the non-IDUs ($p=0.41$). The IDUs cohort of the 27 subjects was classified according to drug use as, 18 former IDUs and 9 as casual drug users. The subject who was re-infected had genotype 1a before treatment and 1b after 18 months of finishing, the patient reported using illicit drugs and sharing needle with another subject who was positive to HCV antibodies. The incidence of re-infection among the 27 IDUs was 0.8 cases / 100 person-years and among the 9 who reported casual engagement in drug use as 2.5 cases / 100 person-years.[52, 53]

From the limitations of this study:

- 1- This was a small retrospective study; sample size was 27 IDUs and 18 controls.
- 2- Although there was long follow-up and there was a questionnaire administered upon follow-up, it was unclear if follow-up was systematic or not.
- 3- There was heterogeneity in the treatment given to patients (different dosages of IFN with or without ribavirin), and heterogeneity in the number of treatments given before achieving SVR (some subjects in the cohort were treated once; others twice and some were treated for a third time).

From the previously discussed human and animal studies, it may be concluded that the question of protective immunity after spontaneous clearance or after treatment is not yet answered. Also the previous studies showed that there is a possibility of re-infection but couldn't conclude whether the re-infection rates are large enough to withhold treatment from IDUs till they discontinue drug use behaviors. These studies didn't show clearly if the re-infection possibility is minimal and shouldn't be taken as an excuse to withhold treatment from IDUs.

We propose that a prospective study that might help clarify the risk of re-infection in IDUs after spontaneous clearance or treatment based SVR and compare it with the rate of infection among IDUs whom have never been infected before.

This study will be discussed in the next chapters

CHAPTER 2: STUDY DESIGN AND METHODS

2.1. Study hypothesis

On the basis of our team's previous study as well as the findings of the previous studies discussed earlier we hypothesized that.

First Hypothesis: Injection drug users (IDUs) with spontaneous or treatment-induced clearance of viremia will exhibit lower rates of HCV re-occurrence despite ongoing risk behaviors for HCV acquisition when compared to IDUs whom have never been infected before.

Second Hypothesis: IDUs with spontaneous clearance of HCV viremia will exhibit a lower rate of HCV re-occurrence compared to those with treatment-induced clearance of viremia.

2.2. Study objectives

Objective 1: To compare the rate and characteristics of HCV viremia occurrence in IDUs that have never been infected with HCV before with the re-occurrence of HCV viremia in IDUs who cleared the HCV spontaneously or via treatment.

Objective 2: To compare the rate and characteristics of HCV re-occurrence in IDUs who cleared the virus spontaneously with those IDUs who had cleared the virus through treatment.

Before discussing the research design and methods there are some definitions to establish:

2.3 Study definitions

HCV infection: Individuals will be considered to have HCV infection if they have documented negative HCV antibody test at the time of recruitment followed by positive HCV antibody test and two positive -3 months apart- HCV RNA tests.

Spontaneous HCV clearance: Subjects who have two HCV RNA negative tests – at least 3 months apart - following a positive antibody test will be considered as spontaneously cleared HCV.

Treatment-induced HCV clearance: Subjects who achieved sustained virologic response (the absence of detectable HCV RNA in the blood 24 weeks after the end of therapy).

HCV re-occurrence: Documented two positive HCV RNA tests - at least one month apart - following spontaneous or treatment-induced HCV clearance.

2.4. Study summary

We sought to assemble a prospective longitudinal cohort of HCV antibody positive IDUs in whom the tests for viremia (HCV RNA) are negative, either as a result of spontaneous clearance or sustained virologic response (SVR). The rate of HCV re-occurrence in these individuals will be compared to the incidence of HCV infection in a group of HCV antibody negative IDUs followed over the same period of time, taking ongoing risk behaviors for HCV acquisition into account.

In the process of screening for participation, we set out to identify a number of patients who are not infected with HCV, patients who have spontaneously cleared HCV viremia and patients who received treatment for HCV and experienced an SVR. These will constitute the inception cohorts for a study of HCV infection / re-occurrence.

Baseline demographic data will be collected, along with information on HIV status and treatment, medical care utilization, history and current addiction treatment and previous and current recreational drug use. Patients will be re-evaluated for an assessment of ongoing risk behavior for HCV acquisition, and for HCV antibody and HCV RNA viremia every 6 months after the baseline date.

The figure below explains the study arms, blood tests and questionnaires that would be administered at follow-up.

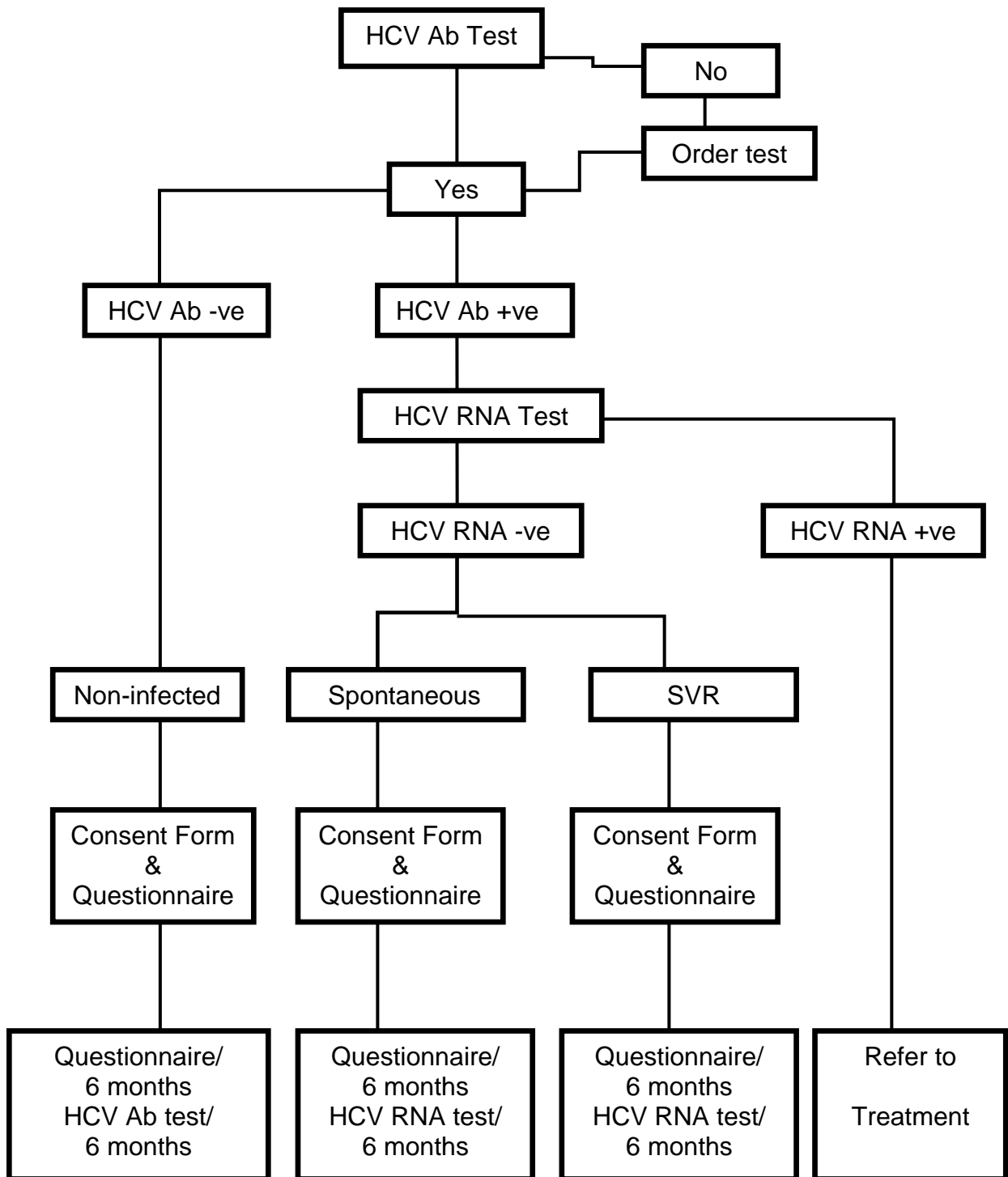


Figure 4: Study summary.

Ab: Antibody. SVR: Sustained virological response. HCV: Hepatitis C virus. RNA: Ribonucleic acid.

2.5. Recruitment strategies and study participants

2.5.1. Recruitment

Subjects were recruited for this study from Pender Community Health Centre (PCHC) located in Vancouver downtown eastside. PCHC is part of Vancouver coastal health and it provides services for the residents of the downtown eastside, these services include primary care, addiction treatment by offering methadone maintenance prescriptions and through addiction counselors. The centre also offers onsite infectious disease specialty care, it has needle exchange program and offers home visits and nursing support. The vast majority of individuals seeking care in PCHC are either current illicit drug users or those with previous history of illicit drug use, making it very suitable to recruit for this study.

Individuals with HCV clearance either spontaneous or treatment-induced and individuals never infected with HCV will be identified from an ongoing study of HCV infection at PCHC with the help of their primary care physician or nurse when they come for their regular health care visit at Pender Community Health Centre.

Ethical approval has been obtained to use the information in this study to screen patients for other studies of HCV infection. The consent approved by the research ethics board allows for the collection of information from the subjects medical records on their medical history and HCV testing. Subjects are also required to fill out a questionnaire (HCV Drug Use Questionnaire) containing questions on demographics, housing, health and welfare, HIV status and treatment, previous and current addiction treatment and previous and current use of illicit drugs. Based on this information, subjects will be identified for participation in this study in order to evaluate HCV occurrence and re-occurrence.

Subjects fulfilling the inclusion criteria and interested in the study will be approached by a research assistant and invited to participate in this study.

Once the patient consents to take part in this study:

- Detailed locator information at baseline and active updates at subsequent visits will be used for follow-up purposes.

- An attention physician card will be placed in each chart when blood tests are needed according to standard of practice.
- An appointment card will be given at the end of each visit to remind patient of the next visit date.
- Immediate follow-up on missed visits will be performed.
- Bi-annual re-evaluation of contact and recruitment rates with ongoing re-evaluation of potential community partnerships and expansion of recruitment strategies will be scheduled.

2.5.2. Inclusion and exclusion criteria

Patients will be enrolled when they have met all inclusion criteria and no exclusion criteria.

- Inclusion Criteria

1. Age \geq 19 years.
2. History of Injection Drug Use.
3. Illicit drug use in the past year (injection/non injection of heroin, crystal meth, or cocaine, drug use cannot just be marijuana use).
4. Ability to provide informed consent.

- Exclusion criteria

1. Detectable qualitative PCR for HCV RNA.
2. Life expectancy < 2 years.

2.6. Study procedures

2.6.1. Screening phase

Subjects fulfilling the inclusion criteria of the study will be identified and offered participation in the study. If interested in the study, they will be asked to provide written, informed consent. This consent will allow the investigator to collect information from the subjects' medical records on their medical history and HCV work up. During the screening phase there might be some blood tests needed in order to identify the subject HCV antibody, RNA and genotype status and HIV status. The procedure to get these tests was to call British Columbia Centre for Disease Control (BCCDC) first to check if

any of these tests is available in their database. If the tests were not done before, a request by the primary care doctor will be prepared in order to identify their status according to their risk behavior and standard of care.

Information on illicit drug use will be determined from the urine drug screening tests especially for those who are on methadone maintenance program and from the physicians, nurses and counselors notes. If the notes don't state clearly the subject drug use, the study coordinator will confirm if the subject meets all the inclusion and none of the exclusion criteria.

2.6.2. Baseline visit

- Behavioral and Clinical Assessment: At baseline, a structured face-to-face interview and medical record review will occur. Using the HCV questionnaire, information will be collected on sociodemographics, health and welfare, addiction treatment, prior anti-HCV antibody and HCV RNA testing, prior HIV testing and treatment, HCV risk behaviors and illicit drug use.

- Laboratory Investigations: According to the standard of care, baseline investigations will include anti-HCV antibody, qualitative HCV RNA and serology for HIV. Subjects enrolled into the longitudinal cohort will be followed every 6 months. Blood samples will be withdrawn at PCHC or at any other laboratory according to subject preference.

- Virologic Testing: According to the standard of care, virology testing will be performed at the provincial laboratory of BCCDC. HCV antibody testing will be performed by the AxSYM HCV v 3.0 (Abbott Diagnostics) and confirmed by Ortho Ecl (Ortho Diagnostics). Qualitative HCV RNA testing is performed by using COBAS®AmpliPrep/COBAS®AMPLICOR® HCV Test, version 2.0 (Roche Diagnostic Systems) with limit of detection of 50 IU/ml while Quantitative HCV RNA testing will be measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test (Roche Diagnostic Systems) with limit of detection of 15 IU/ml.

2.6.3. Follow-up visits

HCV infection / re-infection will be evaluated at months 6, 12, 18, 24, 30 and 36 (more frequently if indicated).

On each visit:

Subjects who cleared HCV spontaneously or via treatment will be evaluated for:

- HCV risk behaviors and drug and alcohol use (subjects will be requested to fill out the short version of the HCV Drug Use Questionnaire).
- HCV RNA (qualitative blood test will be done).

Previously uninfected subjects will be evaluated for:

- HCV risk behaviors and drug and alcohol use (subjects will be requested to fill out the short version of the HCV Drug Use Questionnaire).
- HCV antibody.
- HCV RNA (qualitative blood test will be done).

2.7. Sample size

The study will test the rate of infection/re-infections in injection drug users (IDUs). The study has 3 arms and will test:

- 1- Rate of infection in previously uninfected IDUs.
- 2- Rate of re-infection in IDUs who spontaneously cleared the infection.
- 3- Rate of re-infection in IDUs who cleared infection via treatment.

Previous literature showed the following:

A) Rate of infection in previously uninfected IDUs. (Median follow-up in brackets)

- Grebely study: 18.6 cases per 100 person years (2.8 years)
- Mehta study: 21% (2.35 years)
- Micallef study: 17 cases per 100 person years (1.0 year)
- Other studies: 15-40%

B) Rate of re-infection in IDUs who spontaneously cleared the infection. (Median follow-up in brackets)

- Grebely study: 9.2% per 100 person years (5.2 years)
- Mehta study: 12% (2.14 years)
- Michalief study: 31% per 100 person years (1.2 years)

C) Rate of re-infection in IDUs who cleared infection via treatment.

- Backmund Study: 0-4.1 cases/100 person years. (Mean follow-up 2.82 years)
- Dalgard study: 0.8-2.5 cases/100 person years. (Median follow-up 5 years)

Depending on the results observed in the above mentioned studies, we are hypothesizing to be able to detect:

- (I)- Rate of infection in previously uninfected IDU to be around 25%
- (II)- Rate of re-infection in IDUs who spontaneously cleared the infection of around 10 % (excluding Micallef study since not consistent with other studies and low patient number)
- (III)- Rate of re-infection in IDUs who cleared infection via treatment of around 4 %.

Using alpha of 0.05 and 0.80 power, two sided test.

- When comparing (I) with (II) we need sample size of 100 patients / arm.
- When comparing (I) with (III) we need sample size of 43 patient / arm.

We are targeting to recruit 100 patient in both uninfected and spontaneous arms and 50 subjects in the SVR arm to be able to be to detect the difference in infection / re-infection.

When calculating the sample size I used the sample size calculator available at the UBC statistics website and the link is: <http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html>

2.8. Study endpoint

The table below summarizes the endpoint for each of the study three arms, and what changes we will be looking for in each individual recruited in each study arm.

	SVR Arm		Spontaneous Arm		Non-infected Arm	
Baseline	Ab +ve	RNA –ve	Ab +ve	RNA –ve	Ab –ve	RNA –ve
Blood Test & Questionnaire / 6 months						
Endpoint	RNA +ve		RNA +ve		Ab +ve	RNA +ve

Table 6: Endpoint for each study arm.

SVR: Sustained virological response. AB: Antibody. RNA: Ribonucleic acid.

2.9. Analysis

Descriptive analysis will be done to the data collected in order to give an idea about the subjects' different characteristics and risks that might affect the rate of HCV infection/re-infection. ChiSquare and Fisher's exact tests will be applied as appropriate.

We will apply Multiple logistic regression analysis model to compare the rate of re-infection in the treated and spontaneous clearance groups, with the rate of infection in those who were never infected before and adjust for known confounders of re-infection including sex, ethnicity, age, and risk behavior markers.

2.10. Study timeline

June - July 2007: obtaining ethical approval for consent form and protocol. Ethical approval was obtained from UBC Clinical Research Ethics Board (CREB) on September 06, 2007 and the study CREB number is: H06-03294

August 2007 – August 2010: Subjects screening, enrollment and follow-up.

February 2011: End of study.

April 2011: study analysis and publishing

CHAPTER 3: RESULTS

3.1. Screening results

I presented a summary of the study I am conducting and explained the inclusion / exclusion criteria to the physicians, nurses and counselors at PCHC and asked them to help in identifying subjects that fit the criteria so I can approach them and ask them to participate in this study (Copy of the study summary is available at the Appendix A). I prepared a subject recruiting page summary which was approved by the ethics and placed it in the waiting room at PCHC for the clients to read and be able reach me in case they have questions or interested in participation in the study (Copy of the recruiting letter is available at the appendix B).

3.1.1. All subjects screening results

During the period of December 2007 till February 2009 I screened 518 subjects' files at PCHC and collected demographic data, HCV antibody, HCV RNA status and genotype, HIV status and treatment, methadone maintenance treatment and illicit drug use. The results are shown in the table below.

Characteristics	N (%)
Patients Screened	518 (100)
Gender: Male Female Transgender	365 (70) 150 (29) 3 (1)
Mean Age (SD)	47 (10.12)
HCV Ab +ve	346 (67)
HCV RNA +ve	245 (47)
Genotyped	220 (42)
Not genotyped	25 (5)
HIV infected	72 (14)
HIV – HCV Co-infected	55 (11)

Characteristics	N (%)
Drug use	382 (74)
Methadone Maintenance Treatment	259 (50)

Table 7: Patients screened characteristics.

HCV Ab: Hepatitis C virus antibody. RNA: Ribonucleic acid. HIV: Human immunodeficiency virus. SD: Standard deviation.

Regarding drug use, it ranged from marijuana or crack smoking to intravenous drug use of heroin or cocaine and may involve multidrug use.

The 74 % drug use reflects their use at the time of screening, and within 1 year from the time they were screened. Although I updated the data on February 2009 this percentage may have been higher or lower at anytime over the screening period; since a lot of our clients abstain from drug use while they are involved in drug addiction treatment for a certain period and then they might relapse back to drug use. If a client didn't use any drugs at the time of screening or within the last year he/she was considered non drug user even though he might used drugs before.

The uptake of methadone maintenance treatment as a method of drug addiction treatment by our client was around 50% and this percentage might be higher or lower over the screening period since some clients do manage to decrease their dependence to a point that they might be weaned off methadone. On the other hand some of our clients are still using illicit drugs even though they have been on methadone maintenance program for long period of time and for them it is considered as element of harm reduction method. Some of our clients are taking methadone maintenance treatment prescription from their family physician or from other clinics and they are coming to PCHC for their HCV treatment or to receive addiction counseling support. Regarding the age of the subjects screened, the median age was 47 years which is the same as the mean. The age of our clients ranged from 22 to 88 years and almost 77% (399/518) of our client were ≥ 40 years of old. Only 5% (26/518) were below 30 years of old which may give an indication that our clinic mostly deals with experienced drug users.

HIV-HCV co-infected represent individuals who were positive for HIV and positive for both HCV antibody and RNA.

The following graph shows age distribution for all the 518 subjects divided by 10 years intervals.

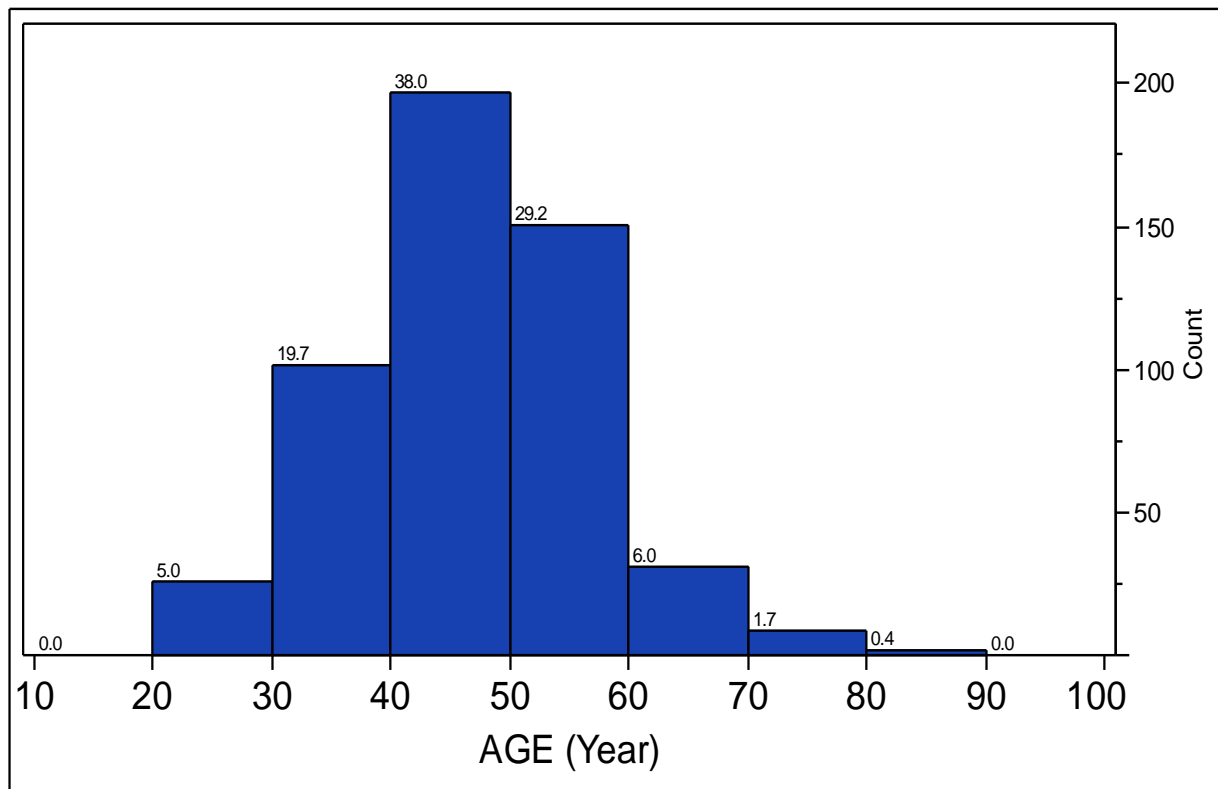


Figure 5: Age distribution of screened subjects.

3.1.2. HCV infected screening results

The table above showed that the prevalence of HCV infection among the screened subjects was almost 67% (346/518).

More detailed information from the perspective of HCV infection, the number of individuals been infected (antibody positive), spontaneous clearance prevalence, and how many individuals developed chronic hepatitis C infection and have HCV viremia (HCV RNA positive), and HIV status information plus other characteristics will be discussed in this part (see table below).

Characteristic	N (%)
HCV Ab +ve	346 (100)
Gender: Male	245 (71)
Female	99 (29)
Transgender	2(1)

Characteristic	N (%)
Mean Age (SD)	47 (9.53)
Sustained Virologic Response (SVR)	26 (8)
HCV Spontaneous Clearance	75 (22)
HCV RNA +ve	245 (71)
Genotyped	220 (64)
Not Genotyped	25 (7)
HIV infected	69 (20)
HIV – HCV Co-infected	55 (16)
Drug use	289 (83)
Methadone Treatment	216 (62)

Table 8: Characteristics of subjects infected with HCV.

HCV Ab: Hepatitis C virus antibody. RNA: Ribonucleic acid. HIV: Human immunodeficiency virus. SD: Standard deviation.

The comments regarding drug use in the previous table still applies here.

Subjects who had SVR where tested positive for HCV antibody but were negative for RNA and there were documentation that they received treatment for HCV either in our clinic or in other clinic.

Spontaneous clearance subjects are those who were tested positive for HCV antibody but negative for RNA and were not treated for HCV.

7% (25/346) subjects were not genotyped; either because they were lost to follow-up or the results of the test was not yet available.

Regarding the age median for this group of subjects it was 47 year and the range was 22-88 years, which was the same median reported for all the patients screened.

The percentage of age distribution is almost the same as described in the previous table.

3.1.3. HCV infected genotypes distribution

Regarding the prevalence of HCV genotypes among our cohort, only genotype 1, 2 and 3 with different subtypes were reported. The graph below shows HCV genotypes distribution in our cohort.

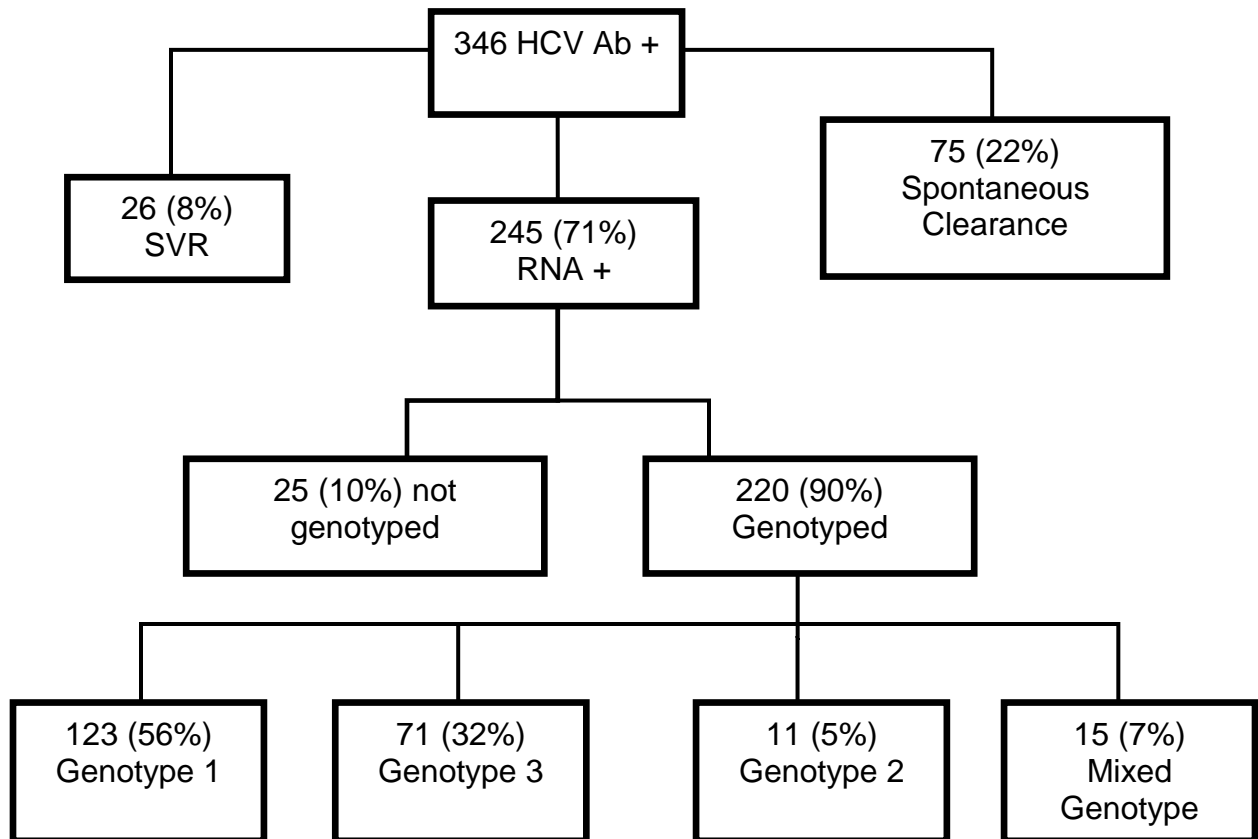


Figure 6: HCV genotypes distribution among HCV infected subjects.

HCV Ab: Hepatitis C virus antibody. RNA: Ribonucleic acid.

Regarding SVR and spontaneous clearance, the comments after the previous table applies here too.

Subjects are considered to have mixed genotype if he/she had more than one genotype or more than one subtype.

3.1.4. HIV infected screening results

HIV and HCV infection are common among IDUs. In our cohort 20 % of HCV infected individuals were infected with HIV. The table below will describe the same characteristics described above but in regard to HIV infected IDUs.

Characteristic	HIV N= 72 (%)
HCV Ab +ve	69 (96)
HIV mono infected (HCV Ab –ve)	3 (4)
Gender: Male Female	47 (65) 25 (35)
Mean Age (SD)	45 (8.11)
HCV Sustained Virologic Response (SVR)	3 (4)
HCV Spontaneous Clearance	11 (15)
HIV – HCV Co-infected (HCV RNA +ve)	55 (76)
HCV Genotyped	51 (71)
Not Genotyped	4 (5)
Drug use	60 (83)
Methadone Treatment	52 (72)

Table 9: Characteristics of subjects infected with HIV.

HCV Ab: Hepatitis C virus antibody. RNA: Ribonucleic acid. HIV: Human immunodeficiency virus. SD: Standard deviation.

The source of HIV infection in those who were HCV negative was not clear. Drug use couldn't be confirmed at least with one subject but sexual transmission couldn't be excluded.

3.1.5. HCV genotype distribution in HIV infected individuals

The distribution of HCV genotypes in those co-infected with HIV is described in the graph below.

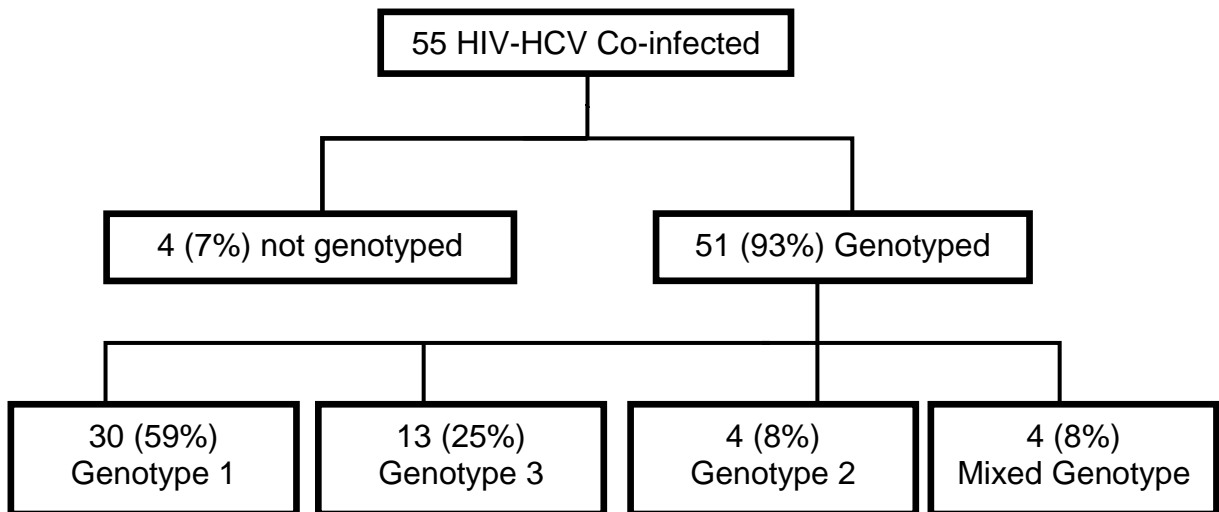


Figure 7: HCV genotypes distribution among HIV-HCV co-infected subjects.

The statements mentioned before regarding methadone, drug use and why there were 4 individuals not genotyped still applied to the above HIV cohort.

3.2. Recruitment results

From the screened individuals, 69 subjects were recruited. The graph below summarizes the recruitment process results.

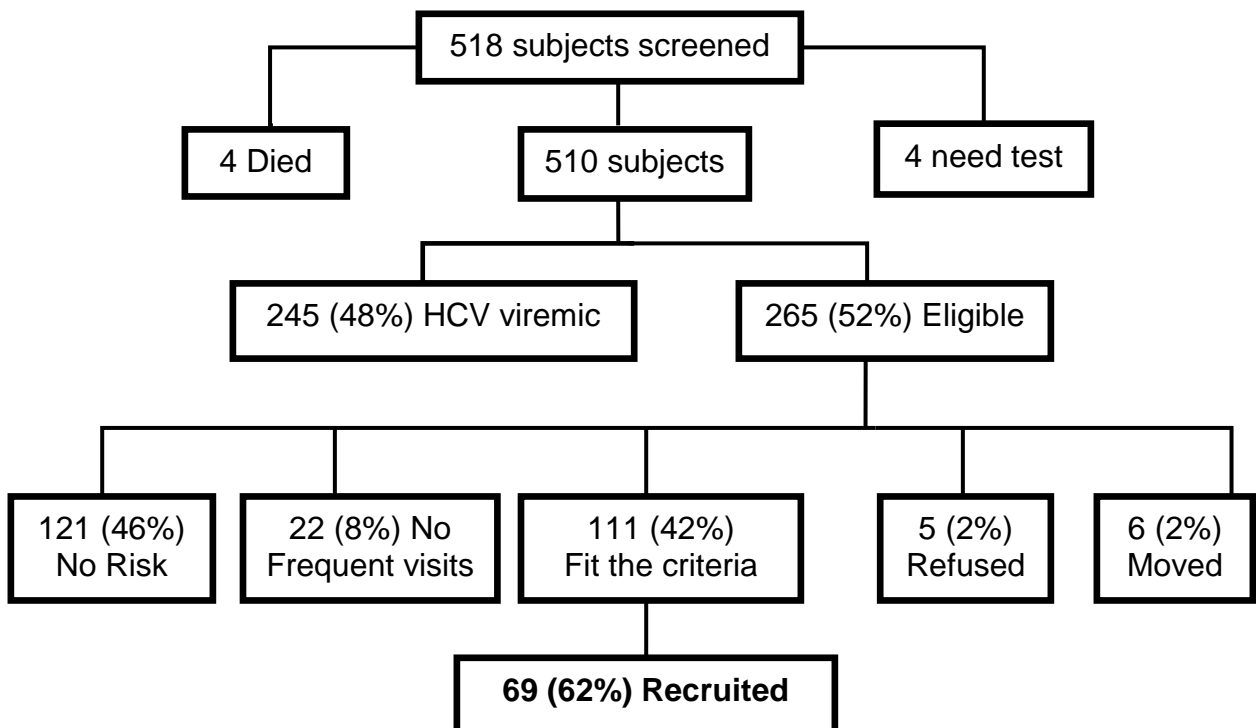


Figure 8: Recruitment results.

Of the subjects who needed tests, 3 were HCV antibody positive but there were no RNA tests so we couldn't determine whether they will be eligible to this study. The 4th subject was treated for 21 weeks and he didn't have the 24 weeks post treatment RNA test in order to conclude whether he achieved SVR or had viral relapse after treatment.

Subjects were concluded to be at no risk and excluded, if they hadn't used any drugs within the last year, if they never injected drugs before and if they only used marijuana within the last year.

Subjects were considered to be no frequent visits and excluded, if they didn't come back for any kind of primary care or counseling for almost 1 year since the date they were screened and there were no indication or documentation in their file that they have moved to other clinic for their primary care.

Subjects were considered refused and excluded, since I had asked them personally to participate and they clearly stated that they are not interested in participating in such study.

Subjects were considered moved and excluded, if it clearly indicated in their file that they have moved to other province or moved from the area and are getting their primary care at other clinic.

The remaining 42 subjects who fit the criteria should be approached or offered participating in the study. Some of them although fit the criteria but they don't come to the clinic regularly which makes it difficult to recruit and retain them. Others need to update their HCV antibody or HCV RNA tests in order to confirm their status and to which study group they fit in.

3.2.1. Characteristics of all the recruited subjects

Demographics and risk behavior characteristics for all the recruited subjects at baseline and after follow-up are shown below.

Characteristic	All Groups Baseline N= 69 (%)	All Groups (Follow-up) N= 48 (%)
Mean Age (SD)	44 (8.6)	45 (8.7)
Gender:- Male - Female	52 (75) 17 (25)	35 (73) 13 (27)

Characteristic	All Groups Baseline N= 69 (%)	All Groups (Follow-up) N= 48 (%)
Ethnicity - White - Aboriginal	48 (69) 16 (23)	31 (65) 12 (25)
Unstable Housing	44 (54)	28 (58)
Source of Income: - Paid Work - Social Assistance or Disability	11 (16) 64 (93)	7 (15) 44 (92)
Arrested in the past 12 months	18 (26)	0 (0)*
Detained in the past 12 months	16 (23)	1 (2)*
Have health care provider	67 (97)	47 (98)
Frequency of visits to health care provider: - 1-3 Visits / month - ≥ 1 Visit weekly - < 1 Visit / month	42 (61) 16 (23) 11 (16)	37 (77) 8 (17) 3 (6)
Self Reported Health Status: - Excellent / V.good - Good - Fair / Poor	19 (28) 28 (41) 22 (32)	17 (35) 17 (35) 14 (29)
Physical Problems	44 (64)	NA
Mental Problems	30 (44)	NA
HIV Co-infected	9 (13)	6 (13)
Opiate Maintenance Treatment	48 (70)	35 (73)
Taking Opiate carries	7 (10)	5 (10)
Ever Injected Drugs	68 (99)	NA
Injected Drugs in last 30 days	30 (43)	17 (35)
Ever Shared Needle	44 (64)	1 (2)**
Ever shared injection Equipment	46 (67)	2 (4)**
Ever shared non injection Equipment	55 (80)	12 (25)**

Table 10: Characteristics of all recruited subjects.

*: The question was limited to the past 30 days when asked at follow-up time. **: The question refers to ever before in your lifetime at baseline, but limited to the past 30

day's period when asked at the follow-up visit. NA: not applicable. Some questions were asked at baseline only.

- Regarding source of income the total count is higher than the recruited individuals, because some of the subjected reported more than one source of income.
- Injection equipment like the water, cooker, filter, spoon, cotton or any other equipment that usually used in the process of preparing or taking the illicit drug for injection use.
- Non injection equipment like the pipe, straw or any equipment that usually used to prepare or take non injectable illicit drugs. Usually it is used for smoking or via nasal route.

3.2.2 Recruited subjects per study arm results

3.2.2.1 Baseline results

The distribution of the recruited subjected per study arm at baseline is shown in the table below:

Arm	SVR N (%)	Spontaneous N (%)	Non infected N (%)	Total
Subjects Recruited	22 (32)	29 (42)	18 (26)	69

Table 11: Subjects recruited by study arm at baseline.

SVR: Sustained virological response. Percentage between brackets represents number of individuals recruited in each arm to the total number of recruited individuals.

The characteristics for subjects recruited per study arm at baseline are shown in the table below.

Characteristic (Baseline)	SVR N=22 (%)	Spontaneous N=29 (%)	Non- infected N=18 (%)	P
Mean Age (SD)	46.7(6.8)	42.0(9.7)	43.0(8.2)	0.14
Gender: - Male - Female	19 (86) 3 (14)	19 (65) 10 (34)	14 (78) 4 (22)	0.22
* Ethnicity: - White - Aboriginal	18 (90) 2 (10)	18 (62) 11 (38)	12 (80) 3 (20)	0.07
Unstable Housing	10 (45)	21 (72)	13 (72)	0.09

Characteristic (Baseline)	SVR N=22 (%)	Spontaneous N=29 (%)	Non- infected N=18 (%)	P
Paid work	4 (18)	3 (10)	4 (22)	0.52^
Arrested in last 12 months	5 (22)	10 (34)	3 (17)	0.36
Detained in last 12 months	5 (31)	8 (28)	3 (17)	0.68
Have health care provider	21 (95)	29 (100)	17 (94)	0.47
Physical Problems	17 (77)	18 (62)	9 (53)**	0.27
Mental Problems	9 (41)	12 (43)**	9 (50)	0.83
HIV infected	3 (14)	6 (21)	0 (0)	0.12
Opiate Maintenance Treatment	13 (59)	24 (83)	11 (61)	0.13
Ever Injected Drugs	21 (95)	29 (100)	18 (100)	0.34
Injected Drugs in last 30 days	4 (18)	17 (61)**	9 (50)	0.009
Ever Shared Needle	16 (76)**	22 (76)	6 (33)	0.005
Ever shared injection Equipment	16 (76)**	22 (76)	8 (44)	0.05
Ever shared non injection Equipment	15 (68)	25 (86)	15 (83)	0.26^

Table 12: Baseline characteristics per study arm.

P value: ChiSquare test applied. * Ethnicity: total count became 64 after removing other ethnicities. ** 1 Subject was excluded since he either reported I don't know or the question was not applicable to his situation. ^ 20% of cells have expected count less than 5. SD: Standard deviation. HIV: Human immunodeficiency virus.

- In the ethnicity analysis, both First nation and Metis were combined under aboriginal.
- Unstable housing was considered for anyone who didn't live in permanent location, which could be single room occupancy hotel, shelter, detoxification centre or homeless.

3.2.2.2 Follow-up results

The second visit was scheduled after 6 months; the table below shows how many patients were followed in each study arm and how many were lost to follow-up.

Arm	SVR N=22 (%)	Spontaneous N= 29 (%)	Non infected N=18 (%)	Total N= 69
Follow-up	17 (77)	21 (72)	10 (56)	48 (70)
Lost to follow-up	0	2 (7)	4 (22)	6 (9)

Table 13: Follow-up and lost to follow-up per study arm.

Percentage in brackets represents the number of subjects was followed / lost to follow-up from each arm to the total number recruited in each arm.

The reasons why 6 patients were lost to follow-up are:

4 individuals started receiving their primary at other clinic and their medical files were transferred. The other 2 individuals stopped coming to our clinic but there was no request for their files to be transferred to other clinic and might show up in later date.

The remaining individuals whom we don't have follow-up data are either not yet due to follow-up or failed to show up in their regular visits to do the follow-up.

The characteristics for subjects recruited per study arm at follow-up are shown in the table below.

Characteristic (Follow-up)	SVR N=17 (%)	Spontaneous N=21 (%)	Non-infected N=10 (%)	P
Mean Age (SD)	47.7(7.0)	42.6(10.1)	43.4(7.5)	0.14
Gender: Male	15 (88)	12 (57)	8(80)	0.09
* Ethnicity: - White - Aboriginal	13 (87) 2 (13)	13 (62) 8 (38)	5 (71) 2 (29)	0.26^
Unstable Housing	8 (47)	13 (62)	7 (70)	0.46
Arrested in past 30 days	0 (0)	0 (0)	0 (0)	0.0
Detained in past 30 days	0 (0)	1 (5)	0 (0)	0.52^
Have health care provider	16 (94)	21 (100)	10 (100)	0.39
HIV infected	3 (18)	3 (14)	0 (0)	0.39
Opiate Maintenance Treatment	10 (59)	18 (85)	7 (70)	0.17
Injected Drugs in last 30 days	1 (6)	10 (48)	6 (60)	0.005

Characteristic (Follow-up)	SVR N=17 (%)	Spontaneous N=21 (%)	Non-infected N=10 (%)	P
Shared Needle in past 30 days	0 (0)	1 (5)	0 (0)	0.52^
Shared injection Equipment in past 30 days	0 (0)	1 (5)	1 (10)	0.45^
Shared non injection Equipment in past 30 days	1 (6)	6 (29)	5 (50)	0.03^
Infected / Re-infected	0 (0)	0 (0)	2 (20)	0.02^

Table 14: Characteristics of subjects at follow-up.

* Ethnicity: total count became 43 after removing other ethnicities. ** 1 Subject was excluded since he either reported I don't know or the question was not applicable to his situation. ^ 20% of cells have expected count less than 5. P value: ChiSquare test applied.

3.3. Illicit drug use results

- Illicit drug use at baseline per study arm is summarized in the table below.

Drugs Use in Past 30 days (Baseline)	SVR N=22 (%)	Spontaneous N=29 (%)	Non-infected N=18 (%)	P
Alcohol use	6 (29)**	11 (38)	6 (33)	0.79
Tobacco	18 (82)	25 (86)	16 (94)**	0.53
Cannabis	9 (41)	10 (34)	8 (44)	0.78
Cocaine	3 (14)	14 (48)	4 (22)	0.02
Crack	10 (45)	21 (72)	10 (56)	0.14
Amphetamines	0 (0)	7 (24)	3 (17)	0.05^
Heroin	2 (9)	14 (48)	8 (44)	0.009
Opioids	2 (9)	3 (10)	2 (11)	0.98^
Benzodiazepines	2 (9)	5 (17)	3 (17)	0.68^
Combined Drugs	5 (23)	14 (48)	13 (72)	0.007
Unsafe Sex	1 (5)	4 (14)	1 (6)	0.44^

Table 15: Drug use by study arm at baseline.

** 1 Subject was excluded since he either reported I don't know or the question was not applicable to his situation. ^ 20% of cells have expected count less than 5. P value: ChiSquare test applied.

- Combined drugs mean that the subjects used more than one illicit drug simultaneously.

- Illicit drug use at follow-up per study arm is summarized in the table below.

Drugs Use in Past 30 days (Follow-up)	SVR N=17 (%)	Spontaneous N=21 (%)	Non-infected N=10 (%)	P
Alcohol use	4 (24)	6 (29)	3 (30)	0.92^
Tobacco	15 (88)	17 (81)	9 (90)	0.74^
Cannabis	6 (35)	7 (33)	4 (40)	0.94
Cocaine	1 (6)	4 (19)	2 (20)	0.45^
Crack	5 (29)	11 (52)	6 (60)	0.22
Amphetamines	0 (0)	4 (19)	3 (30)	0.08^
Heroin	2 (12)	7 (33)	6 (60)	0.03
Opioids	0 (0)	2 (10)	2 (20)	0.19^
Benzodiazepines	1 (6)	5 (24)	1 (10)	0.27^
Combined Drugs	2 (12)	9 (45)**	6 (60)	0.02
Unsafe Sex	0 (0)	4 (19)	1 (10)	0.16^

Table 16: Drug use by study arm at follow-up.

** 1 Subject was excluded since he either reported I don't know or the question was not applicable to his situation. ^ 20% of cells have expected count less than 5. P value: ChiSquare test applied.

3.4. Drug use and risk behavior by arm pairs results

Drug use and risk behavior evaluation between each arm pair will provide more information about which risk behavior or drug use was statistically significant and may have been associated with HCV infection and re-infection. And since infection / re-

infection happened upon follow-up so the analysis was done only at the follow-up time and not at baseline.

The results of this analysis are shown in the tables below.

3.4.1. Non-infected versus SVR arm

Characteristic (Follow-up)	Non-infected N=10 (%)	SVR N=17 (%)	Odds Ratio	Lower 95%	Upper 95%	P
Injected Drugs in last 30 days	6 (60)	1 (6)	0.042	0.004	0.45	0.004
Shared Needle in past 30 days	0 (0)	0 (0)	NA	NA	NA	NA
Shared injection Equipment in past 30 days	1 (10)	0 (0)	NA	NA	NA	0.37
Shared non injection Equipment in past 30 days	5 (50)	1 (6)	0.063	0.006	0.67	0.015
Alcohol use	3 (30)	4 (24)	0.72	0.12	4.16	1.00
Tobacco	9 (90)	15 (88)	0.83	0.07	10.55	1.00
Cannabis	4 (40)	6 (35)	0.82	0.16	4.09	1.00
Cocaine	2 (20)	1 (6)	0.25	0.02	3.19	0.54
Crack	6 (60)	5 (29)	0.28	0.05	1.43	0.22
Amphetamines	3 (30)	0 (0)	NA	NA	NA	0.04
Heroin	6 (60)	2 (12)	0.089	0.01	0.62	0.02
Opioids	2 (20)	0 (0)	NA	NA	NA	0.13
Benzodiazepines	1 (10)	1 (6)	0.56	0.03	10.11	1.00
Combined Drugs	6 (60)	2 (12)	0.089	0.01	0.62	0.02
Unsafe Sex	1 (10)	0 (0)	NA	NA	NA	0.37
Infected / Re-infected	2 (20)	0 (0)	NA	NA	NA	0.13

Table 17: Non-infected versus SVR arm drug use and risk behavior comparison
- NA: not applicable. P value: Fisher's exact test.

3.4.2. Non-infected versus spontaneous arm

Characteristic (Follow-up)	Non- infected N=10 (%)	Spontaneous N=21 (%)	Odds Ratio	Lower 95%	Upper 95%	P
Injected Drugs in last 30 days	6 (60)	10 (48)	0.61	0.13	2.79	0.70
Shared Needle in past 30 days	0 (0)	1 (5)	NA	NA	NA	NA
Shared injection Equipment in past 30 days	1 (10)	1 (5)	0.45	0.03	8.03	1.00
Shared non injection Equipment in past 30 days	5 (50)	6 (29)	0.40	0.08	1.90	0.42
Alcohol use	3 (30)	6 (29)	0.93	0.18	4.86	1.00
Tobacco	9 (90)	17 (81)	0.47	0.05	4.88	1.00
Cannabis	4 (40)	7 (33)	0.75	0.16	3.56	1.00
Cocaine	2 (20)	4 (19)	0.94	0.14	6.25	1.00
Crack	6 (60)	11 (52)	0.73	0.16	3.38	1.00
Amphetamines	3 (30)	4 (19)	0.55	0.10	3.12	0.65
Heroin	6 (60)	7 (33)	0.33	0.07	1.58	0.25
Opioids	2 (20)	2 (10)	0.42	0.05	3.53	0.58
Benzodiazepines	1 (10)	5 (24)	2.81	0.28	27.97	0.63
Combined Drugs	6 (60)	9 (45)**	0.55	0.12	2.55	0.70
Unsafe Sex	1 (10)	4 (19)	2.11	0.20	21.89	1.00
Infected / Re- infected	2 (20)	0 (0)	NA	NA	NA	0.097

Table 18: Non-infected versus spontaneous arm drug use and risk behavior comparison.

** 1 Subject was excluded since he either reported I don't know or the question was not applicable to his situation. NA: not applicable. P value: Fisher's exact test.

3.4.3. SVR versus spontaneous arm

Characteristic (Follow-up)	Spontaneous N=21 (%)	SVR N=17 (%)	Odds Ratio	Lower 95%	Upper 95%	P
Injected Drugs in last 30 days	10 (48)	1 (6)	0.07	0.008	0.62	0.01
Shared Needle in past 30 days	1 (5)	0 (0)	NA	NA	NA	1.00
Shared injection Equipment in past 30 days	1 (5)	0 (0)	NA	NA	NA	1.00
Shared non injection Equipment in past 30 days	6 (29)	1 (6)	0.16	0.02	1.45	0.10
Alcohol use	6 (29)	4 (24)	0.77	0.18	3.33	1.00
Tobacco	17 (81)	15 (88)	1.76	0.28	11.04	0.67
Cannabis	7 (33)	6 (35)	1.09	0.28	4.19	1.00
Cocaine	4 (19)	1 (6)	0.27	0.03	2.64	0.36
Crack	11 (52)	5 (29)	0.38	0.10	1.46	0.20
Amphetamines	4 (19)	0 (0)	NA	NA	NA	0.11
Heroin	7 (33)	2 (12)	0.27	0.05	1.51	0.15
Opioids	2 (10)	0 (0)	NA	NA	NA	0.49
Benzodiazepines	5 (24)	1 (6)	0.20	0.02	1.91	0.20
Combined Drugs	9 (45)**	2 (12)	0.16	0.03	0.91	0.04
Unsafe Sex	4 (19)	0 (0)	NA	NA	NA	0.11
Infected / Re-infected	0 (0)	0.0	NA	NA	NA	NA

Table 19: Non-infected versus spontaneous arm drug use and risk behavior comparison.

** 1 Subject was excluded since he either reported I don't know or the question was not applicable to his situation. NA: not applicable. P value: Fisher's exact test. There was no infection / re-infection among subjects of both arms, but the analysis was done to determine if there were any significant differences in drug use and risk behavior among these two arms.

3.4.4. Non-infected versus SVR and spontaneous arms combined

Characteristic (Follow-up)	Non-infected N=10 (%)	SVR & Spontaneous N=38 (%)	Odds Ratio	Lower 95%	Upper 95%	P
Injected Drugs in last 30 days	6 (60)	11 (29)	0.27	0.064	1.15	0.13
Shared Needle in past 30 days	0 (0)	1 (3)	NA	NA	NA	1.00
Shared injection Equipment in past 30 days	1 (10)	1 (3)	0.24	0.014	4.27	0.38
Shared non injection Equipment in past 30 days	5 (50)	7 (18)	0.23	0.051	1.00	0.09
Alcohol use	3 (30)	10 (26)	0.83	0.18	3.86	1.00
Tobacco	9 (90)	32 (84)	0.59	0.063	5.58	1.00
Cannabis	4 (40)	13 (34)	0.78	0.19	3.26	0.73
Cocaine	2 (20)	5 (13)	0.61	0.099	3.71	0.63
Crack	6 (60)	16 (42)	0.48	0.12	2.01	0.48
Amphetamines	3 (30)	4 (11)	0.27	0.05	1.51	0.15
Heroin	6 (60)	9 (24)	0.21	0.05	0.90	0.05
Opioids	2 (20)	2 (5)	0.22	0.03	1.82	0.19
Benzodiazepines	1 (10)	6 (16)	1.69	0.18	15.89	1.00
Combined Drugs	6 (60)	11 (30)**	0.28	0.07	1.20	0.14
Unsafe Sex	1 (10)	4 (11)	1.06	0.10	10.68	1.00
Infected / Re-infected	2 (20)	0 (0)	NA	NA	NA	0.04

Table 20: Non-infected versus SVR and spontaneous arm combined drug use and risk behavior comparison.

** 1 Subject was excluded since he either reported I don't know or the question was not applicable to his situation. NA: not applicable. P value: Fisher's exact test.

- Comparison between non-infected arm and the other arms combined was done to detect differences among those who have cleared HCV either spontaneously or via

treatment on one side and those who have never been infected before on the other side and verify what differences will stand as significant.

3.5. Comparison of drug use and risk behavior among SVR subjects

Another kind of analysis I became interested in while conducting this study is, whether HCV treatment will have an effect in changing drug use and engagement in risk behavior for acquisition in IDUs. And does this change in behavior vary over time.

In order to examine this I divided the SVR arm into two groups, the first one will be from subjects who were recruited within 6 months after the SVR date and the other group will be from subjects who were recruited after more than 6 months after the SVR date. The analysis was done both at baseline and follow-up time. The table below summarizes the drug use and risk behavior comparison among SVR subjects at baseline.

Characteristic (Baseline)	SVR N= 8 (%)	SVR 6 months N=14 (%)	Odds Ratio	Lower 95%	Upper 95%	P
Injected Drugs in last 30 days	2 (25)	2 (14)	0.5	0.056	4.47	0.60
Alcohol use	4 (50)	2 (15)**	0.18	0.023	1.41	0.15
Tobacco	5 (63)	13 (93)	7.80	0.65	93.81	0.12
Cannabis	1 (13)	8 (57)	9.33	0.89	97.6	0.07
Cocaine	1 (13)	2 (14)	1.17	0.089	15.32	1.00
Crack	2 (25)	8 (57)	4.00	0.59	27.25	0.20
Amphetamines	0 (0)	0 (0)	NA	NA	NA	0 (0)
Heroin	2 (25)	0 (0)	NA	NA	NA	0.12
Opioids	0 (0)	2 (14)	NA	NA	NA	0.52
Benzodiazepines	1 (13)	1 (7)	0.54	0.030	9.99	1.00
Combined Drugs	1 (13)	4 (29)	2.8	0.26	30.70	0.61
Unsafe Sex	0 (0)	1 (7)	NA	NA	NA	1.00

Table 21: Baseline SVR versus SVR 6 months drug use and risk behavior comparison.

** 1 Subject was excluded since he either reported I don't know or the question was not applicable to his situation. NA: not applicable. P value: Fisher's exact test. SVR 6 months: subjects who were recruited nearly within 6 months from the SVR date.

The table below summarizes the drug use and risk behavior comparison among SVR subjects at follow-up.

Characteristic (Follow-up)	SVR N= 7 (%)	SVR 6 months N=10 (%)	Odds Ratio	Lower 95%	Upper 95%	P
Injected Drugs in last 30 days	1 (14)	0 (0)	NA	NA	NA	0.41
Shared Needle in past 30 days	0 (0)	0 (0)	NA	NA	NA	0 (0)
Shared injection Equipment in past 30 days	0 (0)	0 (0)	NA	NA	NA	0 (0)
Shared non injection Equipment in past 30 days	1 (14)	0 (0)	NA	NA	NA	0.41
Alcohol use	2 (29)	2 (20)	0.63	0.65	5.97	1.00
Tobacco	6 (86)	9 (90)	1.5	0.078	28.89	1.00
Cannabis	1 (14)	5 (50)	6	0.52	69.75	0.30
Cocaine	0 (0)	1 (14)	NA	NA	NA	1.00
Crack	2 (29)	3 (30)	1.07	0.13	8.98	1.00
Amphetamines	0 (0)	0 (0)	NA	NA	NA	0 (0)
Heroin	2 (29)	0 (0)	NA	NA	NA	0.15
Opioids	0 (0)	0 (0)	NA	NA	NA	0 (0)
Benzodiazepines	1 (10)	0 (0)	NA	NA	NA	0.41
Combined Drugs	0 (0)	2 (20)	NA	NA	NA	0.49
Unsafe Sex	0 (0)	0 (0)	NA	NA	NA	0 (0)

Table 22: Follow-up SVR versus SVR 6 months drug use and risk behavior comparison. NA: not applicable. P value: Fisher's exact test. SVR 6 months: subjects whom were recruited nearly within 6 months from the date they achieved SVR.

3.6. Infected individuals results

The two infected individuals HCV antibody and RNA blood tests history confirms that; HCV infection occurred after recruitment and both individuals are newly infected.

Table below summarizes their HCV antibody and RNA test results history.

Patient 1	Patient 2
June 2008: Last HCV Ab (-) test	November 2008: Last HCV Ab (-) test
August 2008: First HCV Ab (+) test	February 2009: First HCV Ab (+) test
September 2008: HCV RNA (+) Genotype 1	March 2009: HCV RNA (+) Genotype 1b
February 2009: Confirmed HCV RNA (+)	NA

Table 23: Infected subjected HCV blood tests history.

The characteristics and drug use behavior for both infected individuals are shown in the table below.

Characteristic	Patient 1		Patient 2	
	Baseline	Follow-up	Baseline	Follow-up
Age (at baseline)	32		57	
Gender	Female		Male	
Ethnicity	Aboriginal		Black	
Housing	Permanent	Permanent	Temporary	Temporary
Source of Income	Social Assistance	Social Assistance	Social Assistance	Social Assistance
Arrested in the past 12 months	No	No*	Yes	No*
Detained in the past 12 months	No	No*	Yes	No*
Have health care provider	Yes	Yes	Yes	Yes
Frequency of visits to health care provider	1-3/month	1/month*	6-12/year	1/month*
Self Reported Health Status	V.good	V.good	Good	Good
Physical Problems	No	NA	Yes	NA
Mental Problems	No	NA	No	NA

Characteristic	Patient 1		Patient 2	
	Baseline	Follow-up	Baseline	Follow-up
HIV infected	(-)	(-)	(-)	(-)
Opiate Maintenance Treatment	Yes	Yes	No	Yes
Taking Opiate carries	No	No	NA	No
Ever Injected Drugs**	Yes	NA	Yes	NA
Ever Shared Needle**	No	NA	No	NA
Ever shared injection Equipment**	Yes	NA	No	NA
Ever shared non injection Equipment**	Yes	NA	Yes	NA
Injected Drugs in last 30 days	Yes	Yes	Yes	Yes
Shared Needle in past 30 days***	NA	No	NA	No
Shared injection Equipment in past 30 days***	NA	No	NA	No
Shared non injection Equipment in past 30 days***	NA	Yes	NA	Yes
Alcohol use	No	No	No	No
Tobacco	Yes	Yes	Yes	Yes
Cannabis	Yes	Yes	Yes	Yes
Cocaine (route)	No	No	Yes (smoke)	No
Crack (route)	No	Yes (smoke)	Yes (smoke)	Yes (smoke)
Amphetamines (route)	Yes (nasal)	No	Yes (inject)	Yes (inject)
Heroin (route)	Yes (inject)	Yes (inject)	Yes (inject)	Yes (inject & smoke)
Opioids	No	No	No	No
Benzodiazepines	No	No	Yes	No
Combined Drugs	Yes	Yes	Yes	Yes
Unsafe Sex	No	No	No	No

Table 24: Characteristics of infected individuals.

* The question was limited to the past 30 day's period when asked at the follow-up visit.

** The question was asked only at baseline and meant ever in your lifetime. *** The question was asked only at follow-up visit. Route: route of illicit drug administration is specified when more than one possible route. NA: not applicable.

CHAPTER 4: DISCUSSION

Chronic hepatitis C infection is a worldwide disease affecting more than 170 million people. [54] The means of transmission depend largely on risk exposure which differs from one country to another; in developing countries people may have become infected from tainted blood or blood products, multiple uses of same syringe / needle in hospitals or clinics or through intravenous use of illicit drugs. At the present time in our part of the world, HCV infection is mainly transmitted through sharing of injections or injection equipments among IDUs. In Canada it is estimated that more than half of the prevalent case of chronic hepatitis C is among current or previous IDUs.[25] Most of the new cases of HCV infection will occur among IDUs, as the risk of injection drug use accounts for more than 75% of the new cases.[55]. In British Columbia there were almost 2900 new HCV infection reported in 2007 which is less than the previous year. The incidence rate of infection was 66 per 100,000 population which remains as twice as the national rate.[56]

Any attempt to control HCV in our province or even in Canada must involve a strategy that deals with prevention and control of the epidemic among our population of IDUs.

4.1. All screened individuals cohort

During the period from December 2007 to February 2009 518 individuals were screened who receive their primary medical care and counseling services at PCHC. The prevalence of HCV infection from those screened was as high as 67% (346/518) and the percentage of drug use within the past year among this sample was 74% (382/518).

The 67% HCV antibody positive in this sample is an indicator to the rate in the whole clinic population and it is in line with the prevalence reported by two previous community based studies by Patrick et al and Grebely et al which reported the prevalence to be 81.6% and 54% respectively.[28, 48]

The prevalence of HIV among screened individuals was 14% (72/518) which is close to the 21% reported in the Patrick et al. study.[28] The prevalence of HCV was almost 5 times that of HIV which might be due to the fact that the transmissibility of HCV is higher

than that of HIV. Also it might be as a result of the awareness and knowledge of HIV among our population is higher than that of HCV, so the IDUs tend to be more cautious about sharing injection or injection equipments when their colleague(s) is HIV infected than when he/she is HCV infected. The incidence of new HIV cases reported by BCCDC in 2007 was almost 400 cases and the rate was 9.1 cases per 100,000 populations which is higher than the previous year and a little higher than the Canadian rate of 7.5 cases per 100,000 populations. The incidences of new HCV cases in our province is 7 times higher than the HIV incidence and double that of the national; which indicates that we are doing better job in combating HIV than with HCV and means more effort should be done in our province to decrease the prevalence of HCV and prevent the occurrence of new cases. And since the core of the HCV endemic is among IDUs, then more resources should be allocated to educate them about HCV infection, chronic hepatitis C disease and about the safest ways of injecting drugs. On the other hand treating drug addiction and HCV infection will have a big impact in decreasing the prevalence and preventing new infections in those who keep sharing injections and injection equipments.

Our sample showed that 11% (55/518) of screened individuals were HIV-HCV co-infected and since HIV co-infection accelerates the progression of cirrhosis[4]; more effort should be aimed at treating HCV in this group in order to decrease the progression of the disease. Keeping in mind that SVR rates reported in this group were reasonable and treatment of HCV can be given to those receiving HIV treatment with minimal need for medication changes except in those who receives d4t (Stavudine) or Zidovudine which are contraindicated to be given with ribavirin.[25]

The mean age of our cohort was 47 years with only 5% under 30 years old and more than three quarters ≥ 40 years old, which represents experienced drug users where the prevalence of HCV is expected to be high. The incidence of new infection will be less than that if our cohort was of younger individuals. In a study involved young IDUs in Vancouver, half of new infections occurred within 2 years of initiating drug use and young IDUs were more likely to share injections or injection equipments than older IDUs. [57]

The low number of young individuals might be due to the fact that the lifestyle of young individuals is more chaotic and may not stay at the same clinic or be less consistent in follow-up with their primary care physician or counselor. Also our clinic was closed to new patients for almost a year which may have decreased the possibility of getting new young individuals. Young individuals should be specifically targeted in prevention programs; by increasing awareness about HCV and safe injection practices in order to decrease the incidence of new infection and eventually decrease the prevalence of HCV in B.C.

4.2. HCV infected cohort

When looking to our cohort of HCV antibody positive individuals and compare the prevalence of HIV, drug use and methadone treatment to that of the general cohort; we will find that the prevalence is always higher in the HCV positive cohort.

In the HCV antibody positive cohort 20% (69/346) were HIV positive which has been reported in other studies.[28]

4.2.1. Spontaneous clearance

Spontaneous clearance of HCV is often described to be in the range of 15-30 in the general population, and in our cohort of IDUs 22% (75/346) cleared the virus spontaneously. These numbers shows that IDUs are no difference from the general population in clearing the virus and those who provide addiction counseling and primary health care to IDUs should build on this information. While giving advice about addiction treatment they should advise this group specifically about safe injection drug use in order to prevent them from acquiring HCV viremia themselves or giving it to other IDUs. This will decrease the burden of HCV infection which will return benefits not only to this group of IDUs but also to the whole society by decreasing the costs of future HCV treatment or any of its complications.

4.2.2. Current drug and methadone treatment use

- Drug use among those who were HCV antibody positive was 83% (289/346) and the remaining 17% are mostly those who have history of drug use.

- Methadone maintenance program use was 62% (216/346) which on one hand can be considered a positive achievement in engaging that many IDUs in drug addiction treatment program - although some of them are on methadone as a way of harm reduction - but on the other hand those IDUs on methadone may represent a missed opportunity for health care givers. Those on methadone are already engaged with at least two health care professionals, a primary care physician and a pharmacist and some of them are HCV RNA negative but most of them are HCV infected. There should be more attention directed toward this group in order to reduce transmission by encouraging safe injection techniques and this would prevent acquiring HCV, HIV and other kind of infections if they are HCV RNA negative. If they are HCV RNA positive they should be educated about HCV treatment and encouraged to receive treatment which can be synchronized with their methadone treatment. In case they were not interested in treatment they should at least be taught and encouraged to practice safe methods of injecting drugs in order to help in preventing the spread of the virus to other IDUs.

4.2.3. HCV genotypes

When looking at the HCV genotypes distribution among this cohort, it was found that 90% (220/245) were genotyped leaving only 10% (25/245) that needs to be genotyped. Although the benefit of genotyping might be questioned on the basis that it is enough to know that they are infected with HCV and they should be genotyped when they decide to get treatment. Knowing the genotype of the individual will be very helpful in giving advice about the treatment length and success rate and identifying the genotype may encourage both the patient and the physician to take an informed decision about treatment and help develop a plan that will maximize the possibility of treatment success. In our cohort of IDUs 37% (82/220) of the individuals are infected with genotype 2 or 3 combined. These individuals will only need 24 weeks of HCV treatment and the success rate of can be above 80%, compared to genotype 1 infected individuals who will need 48 weeks and almost half of the individuals won't respond successfully to the treatment. These numbers are comparable to those reported by Chaudhary et al who reported that the prevalence of HCV genotypes 2 and 3 among IDUs to be around 35% combined. [18] If we manage to engage those infected with

genotype 2 and 3 in treatment and with 80% success rate, we will be able to reduce chronic HCV infections burden by almost 30% among IDUs and we will prevent or at least decrease the spread of the disease by making them aviremic and not contagious.

4.3. HIV infected cohort

When looking at the HIV infected subjects as a cohort in our sample, it will be noticed that 96% (69/72) are HCV antibody positive which is almost 5 times higher than the 20% (69/346) of HIV infected individuals in HCV positive subjects. Almost all HIV infected individuals have been or currently infected with HCV. The prevalence of HCV among HIV infected IDUs in our cohort is comparable to what has been reported in previous studies to range from 52% to 93%.[58-60] The high prevalence of HCV among HIV infected IDU suggests that; screening for HCV should be routinely performed for those infected with HIV.

The spontaneous clearance of HCV among HIV infected was 15% (11/69) which is within the range seen among mono-infected individuals. I couldn't exactly identify whether the clearance of the virus happened before or after being infected with HIV. Previous studies should that clearance of HCV is less likely to occur among HIV infected individuals and I couldn't confirm these results in this cohort.

HCV RNA positive was 76% (55/72) among HIV infected individuals; which is alarming because HIV co-infection is known to fasten the progression of liver cirrhosis and it has been reported that end stage liver disease is becoming the leading cause of death among HIV infected individuals. In one study it caused up to 50% of the deaths among HIV infected individuals.[4, 61] Treating HCV in those co-infected with HIV has been approved to be effective but the success rate is thought to be inferior to that reported in those who are HIV negative.[62] Both Canadian and American consensus guidelines recommended treatment for HCV in HIV infected individuals to be 48 weeks regardless to the genotype and in other study recommendation was made to extend treatment to 72 weeks in genotype 1 individuals who have high HCV viral load or who do not achieve rapid virological response (RVR) defined as no HCV RNA detected after 4 weeks of treatment. [25, 62, 63]

In our cohort, it is to be noted that 4% (3/72) achieved SVR after treatment. That said; there are more than three quarters need to be treated. Although more than > 80% of our cohort are using drugs but > 70% are on methadone treatment, which will make it easier for health care provider to approach and engage them in HCV treatment especially those who are genotypes 2 and 3 which represent one third of the cohort and who can achieve a high SVR rate.

4.4. Recruitment

The recruitment process took place at PCHC over more than one year period, during this time a total of 518 individuals were screened. From the screened subjects, only 111 fit the inclusion criteria and 69 individuals were recruited and distributed as 22, 29 and 18 over the study arms of SVR, spontaneous and non-infected respectively.

Eligible individuals who did not have HCV viremia represented almost half of the screened individuals but more than half of them didn't fit the inclusion criteria and mostly because they didn't have a known risk for acquiring HCV.

The main reason for excluding those who were HCV antibody negative from being recruited in the non-infected arm is that; they didn't have a history of intravenous drug use (IVDU). Which on one hand makes sense, if they have been using drugs intravenously most probably they will not be HCV negative. Especially in such a sample like ours that is made of older and experienced drug users, on the other hand it makes it more difficult to find and recruit subjects in the non-infected arm and if we decide to relax the inclusion criteria and remove the IVDU history; this will generate a cohort of subjects less likely to acquire the infection and might bias the study results in regards of infection / re-infection possibility. For most of these individuals the drug of choice was smoking crack cocaine. Keeping this in mind; there was a study done on crack smokers and concluded that there is a risk of acquiring HCV via pipe sharing especially if there is mouth sores and ulcerations. But the risk might not be large enough to include those who smokes crack cocaine in our study that aims to evaluate re-infection.[64]

The main reason for excluding those who spontaneously cleared the virus although they had a history of IVDU from the spontaneous arm is that they didn't use any illicit drugs within the past year which put them at no risk of HCV re-infection. Some of them

managed to stop illicit drug use after successful addiction treatment program and others have their health deteriorated to the extent they cannot tolerate any further illicit drug use.

The SVR subjects were the most easier to recruit in a sense that most of them were thankful to the doctors and nurses involved in their treatment and welcomed participating in this study but some of them didn't use any drugs before starting treatment and didn't use while on treatment which makes their abstinence from drugs for more than 1 year and made them ineligible for recruitment. Some of those who were not recently treated for HCV but still coming to the clinic for their primary or counseling care relapsed to drug use and were recruited for this study.

There were a group of screened subjects that fit the inclusion criteria but were excluded on the basis that they didn't come regularly to the clinic to be able to recruit and make follow-up and were referred to in the recruitment graph (Figure 8) as no frequent visits. After being screened, their next visit was almost after 1 year or they have never come back for any further primary or counseling visits after their first visit and no indication was made on their file that they moved to other clinic.

This is one of the obstacles that makes it difficult to recruit and retain IDUs. Many have chaotic lifestyles making it difficult to attend follow-up appointments even though they are on methadone maintenance program. Others, who reach a certain extent of stability or manage to abstain from drug use, tend to leave the downtown eastside area to a place where there is no obvious drug use but do not inform the clinic that they are moving.

4.4.1. Recruited subjects demographics

Out of the 69 recruited subjects, a follow-up questionnaire was done with 70% (48/69) of the subjects and 9% (6/69) were lost to follow-up. Blood tests were also done on these individuals. By looking at the demographic results for these individuals at baseline and after follow-up we will find that:

- Our sample is constituted of mainly older individuals with mean age above 40 years.

- Three quarters of the subjects were males; the two main ethnicities were white and aboriginals. Although aboriginals only constitutes almost 5% of our province population [65] but they represent higher percentage among illicit drug users.
- More than half of the subjects in our sample lived in unstable housing such as single room occupancy (SRO) hotels, shelter, detoxification or being homeless. More than 90% had their source of income as either disability or social assistance. These two factors combined contribute to having less stable life and may keep the IDUs in the downtown eastside since it has the structure of SROs and that's where the drugs are more prevalent. Staying in the downtown eastside may decrease their chances of drug addiction treatment success. Providing stable housing and income to IDUs will help in improving the intake of addiction and HCV treatment. And those who become stable should be encouraged to leave the eastside area and start living away from drugs.
- More than 70% of our subjects were on methadone maintenance program which made them less chaotic and helped in recruiting and retaining them in the study. This population of IDUs should be targeted first for future studies and for treatment engagement.
- Regarding drug use, less people injected drugs upon follow-up than at baseline. Only one person shared injection, two persons shared injection equipment but 12 or one quarter of the persons shared non injection equipments. It is encouraging to find that less people are sharing needles or injection equipment which may indicate that the message of prevention is working among these IDUs and we should reach more IDUs with this message if we want to decrease the burden of HCV infection and other blood borne diseases. Although the possibility of HCV transmission via sharing non injection equipment is less significant than with injection or injection equipment but there still a possibility; and having 25% of our cohort sharing non injection equipment indicates that more needs to be done to educate IDUs about not sharing any of the illicit drugs equipments in order to minimize the possibility of disease transmission.

4.5. All study arms

- When comparing the three study arms, it will be found that all arms are comparable in age, gender, ethnicity, mental and physical problems, source of income and other demographics.
- SVR arm individuals had the highest percentage of stable housing, which may support the argument that providing stable housing to IDUs will increase the intake of HCV treatment. Still 45% (10/22) of SVR subjects had unstable housing which may indicate that although housing stability is important in order to increasing the chances of treatment success, treatment can be successfully administered to IDUs who are living in SRO or detoxification centre if enough support was provided.
- Drug injection in the past 30 days was significantly the lowest among the SVR subjects at both baseline and follow-up. Their behavioral change might have been affected by HCV treatment since almost half of them were recruited within 6 months after finishing treatment and achieving SVR.
- Regarding needle and injection equipment sharing over life time, the non infected group was significantly the lowest at baseline and this is probably the main reason why they were not infected with not only HCV but also HIV. Upon follow-up neither SVR nor non infected subjects reported needle sharing in the last 30 days, and none of the SVR subjects reported sharing injection equipment at follow-up but one subjects reported sharing injection equipment in the non infected group which still reminds us that further effort should be provided to keep reminding IDUs about the importance of not sharing the injection equipment with other subjects.
- Sharing non injection equipment was reported in all study arms which necessitate that additional education and preventive program needs to be applied in order to prevent sharing of these equipments among IDUs and thus decrease the possibility of HCV transmission.
- Both spontaneous and non infected subjects' behavior of injecting drugs in the past 30 days was comparable and significantly higher than that of the SVR subjects at both baseline and after follow-up, but HCV infection only occurred among the non infected individuals and not among spontaneous clearance subjects. This difference in infection rate can't be explained by risk behavior and might be due to the presence of protective

immunity at the spontaneous arm side. Our finding here echoes the findings from other studies which reported that protective immunity might help decrease the rate of re-infection in those who cleared the virus spontaneously. [48]

4.5.1 Illicit drugs used at baseline and follow-up in all study arms

- Generally speaking; the subjects under the SVR arm consumed the lowest amount of illicit drugs. This pattern adds another support to the argument that HCV treatment may positively change IDUs behavior and decrease their engagement in risky behavior for re-infection.
- All three arms were comparable in their use of alcohol, cannabis, crack, opioids, and benzodiazepines at both baseline and follow-up. Most of these drugs were used orally or by smoking which still poses a risk of HCV transmission but the risk is inferior to that of injectable drugs.
- Cocaine (powder), amphetamines and heroin use at baseline was significantly higher among spontaneous arm subjects compared to SVR arm but comparable to that of the non- infected arm. These drugs were mainly used via injection.
- Upon follow-up, cocaine use was comparable among non-infected and spontaneous subjects and higher than the SVR subjects but the difference was not statistically significant. Amphetamine use was significantly higher in the non-infected arm compared with the SVR but comparable to that of spontaneous. Heroin use was significantly high in non-infected group compared to the SVR group but not significantly higher than the spontaneous arm. Spontaneous arm usage of heroin was higher than the SVR arm but not statistically significant.
- Drug use especially those used via injection among both spontaneous and non-infected groups was comparable but still no one was infected among the spontaneous group and 2 were infected among the non-infected group which might be due to factors other than risk behavior.

4.6. Drug use and risk behavior between arm pairs

Further evaluation of risk behavior and drug use among arm pairs was done, in order to identify which risk behavior or drug use will be significant and may explain the infection / re-infection incidences.

4.6.1. Non-infected versus SVR arm

The non-infected arm subjects' engagement in risk behavior was generally higher than that of the SVR subjects. Injecting drugs in last 30 days and sharing non injection equipment was significantly higher ($p=0.004$ and 0.015 respectively). Use of amphetamines, heroin and combined drugs was significantly higher in the non-infected arm ($p=0.04$, 0.02 and 0.02 respectively). HCV infection occurrence in the non-infected group and not in the SVR group might be explained by their engagement in risk behavior that increased their chances of acquiring the virus. Other reasons like development of a kind of immunity to the virus after treatment by the SVR group can't be ruled out since this group was still engaged in risk behavior but didn't get infected. Most of the subjects in the SVR arm have been involved in a peer support group and had access to drug addiction counselors during HCV treatment. This kind of involvement might have been the factor behind decreasing their drug use and engagement in risk behavior for HCV acquisition.

4.6.2. Non-infected versus spontaneous arm

When comparing these two arms head to head there was no significant difference in risk behavior or drug use; even though HCV infection occurred in the non-infected group and no re-infection occurred in the spontaneous arm. The reason for this can't be explained by risk behavior only and the difference in infection might be due an acquired immunity by the spontaneous arm which prevented the development of new infections although being at risk for acquisition comparable to that in the non-infected arm.

4.6.3. SVR versus spontaneous arm

Generally, spontaneous arm subjects were engaged in higher drug use and risk behavior than the SVR arm. Injecting in last 30 days and combined drug were significantly higher in the spontaneous arm compared to the SVR arm. Despite the difference in risk behavior no re-infection occurred in either arm which also adds to the argument that re-infection can't only be explained by risk behavior and the subject immunity plays a role in determining whether he or she will become re-infected again. Those who managed to clear the virus once before without any kind of treatment might have the fittest immunity to clear it again in spite of the high risk for acquisition.

4.6.4. Non-infected versus SVR and spontaneous arms combined

The non-infected group was compared with the spontaneous and SVR group combined in regard to risk behavior and drug use. HCV infection in non-infected group was significantly higher than re-infection in the SVR/spontaneous group ($p=0.04$). Risk behavior and drug use was generally higher in the non-infected group but only heroin use was statistically significant ($p=0.05$). In this comparison; by combining the spontaneous group to SVR, the risk behavior increased and became comparable to that of the non-infected group but since there was no re-infection in both spontaneous and SVR group we may conclude again that risk behavior is not the only factor in HCV infection or re-infection and acquired immunity might have a role in preventing re-infection in SVR and spontaneous arms and the lack of such immunity in the non-infected group resulted in acquiring HCV infection.

4.7. SVR group comparison

It was noticed that SVR group subjects were the least engaged in risk behavior and drug use compared to other two groups. It was discussed earlier that HCV treatment might be the reason behind decreased risk behavior and drug use. When comparing the risk behavior and drug use for those who were recruited within 6 months after SVR date to those who achieved SVR earlier; it was found that:

- The early SVR injected drug in last 30 days and used heroin at a higher rate both at baseline and follow-up. On the other hand cannabis and combined drugs was higher in those who were recruited within 6 months at both baseline and follow-up. The use of other drug was relatively comparable and in both groups.
- No risk behavior or drug use was significantly higher in either group, which may indicate that HCV treatment has a positive long lasting effect in decreasing risk behavior or drug use which reduces the possibility of re-infection.

This finding if replicated in other studies should encourage more clinicians to treat HCV in IDUs with confidence that the possibility of re-infection is very low.

4.8. Infection / re-infection

The two infected individuals' blood tests history confirms that both were newly infected with hepatitis C virus. The two infected individuals' gender, ethnicity, housing, being arrested and detained were different but their source of income, having a health care provider, not having HIV were similar. They belonged to different age group and both can be considered experienced drug users.

Their drug use was similar in a way that; both never shared a needle in their life and probably this is the reason why they were HCV antibody negative at baseline. Patient 1 used to share injection equipment but not patient 2 and both were sharing non injection equipment. When they were asked about how they think they got the virus, patient 1 didn't know exactly but she used to share injection equipment and that might be the route of infection. The second patient was almost certain that he got infected by sharing the spoon (where he prepares the drug before injection) with his girlfriend who has chronic HCV infection.

Both infection cases were caused by not sharing the needle, and this may indicate that additional education by health care providers should aim toward reminding the IDUs that not only they must not share needles and syringes but also they must not share injection equipments or even share non injection equipment in order to protect themselves from acquiring HCV infection and other infections.

4.9. Future projects

4.9.1 Mixed HCV genotypes Infection prevalence in IDUs

Previous studies in chimpanzees and in humans demonstrated the possibility of HCV re-infection and in one chimpanzee study when investigators challenged two animals with mixed HCV genotypes, in one animal one genotype was expressed in blood and in the other two genotypes were expressed in the blood. [45] In IDUs who engage in risk behaviors for acquisition of HCV the possibility of mixed genotype might be higher than that in the general population whom got infected from one source and don't get exposed to new source of infection or different genotypes.

The prevalence of mixed genotypes among those who were HCV antibody positive in our cohort of IDUs was 7% (15/220) as shown in figure (6).

The prevalence of mixed HCV genotypes was reported to range from 1% in Italy [66], 2.5% in non epidemic to 18.3% in were 'Suidama', a folk medicine used to relieve muscle stiffness by cutting the skin and sucking blood using non-sterilized devices, may possibly be a cause of the epidemic in Japan [67].

1.6% mixed genotypes were reported among hemophilic patients in the United Kingdom (UK) [68], 13% mixed genotype was reported among patients on haemodialysis in the US [69] and 4.8% in Pakistan with more than half of the cases occurring among thalassaemic patients who received multiple transfusions.[70]

These previous studies demonstrated the possibility of mixed genotype infections and the possibility increases among those at higher risk of multiple exposures to the virus like hemophilic, thalassaemic and IVDUs.

In our sample the percentage was 7% and the percentage might be higher; since in our province once the subject genotype was determined the provincial lab won't redo the genotype again in the future. This may result in missing mixed infections especially in a population like ours where multiple exposures to HCV are common.

Our data should be replicated in a longitudinal study where HCV genotype for a group of IDUs is tested blindly and compared with the reported results to determine whether genotype changes over time and whether the prevalence of mixed genotype will be higher or lower than what is reported in our cohort.

Another goal of mixed genotype study is to identify whether HCV change genotypes once under pressure of treatment and whether new genotype / subtype will occur while on treatment which can be studied by re-genotyping those receiving treatment at different points of the treatment duration.

Identifying mixed or changing HCV genotype is crucial not only in deciding the duration of treatment at the time being, but also when future oral treatment come about as different resistance patterns to these new treatments emerge by different genotypes / subtypes.

4.9.2 Short HCV treatment efficacy among IDUs

New Canadian consensus guidelines suggested that; duration of chronic HCV genotype 1 treatment may be reduced to 24 weeks instead of 48 if the patient had RVR and there were no poor response predictors like HIV co-infection, black ethnicity, high viral load, advanced fibrosis and high body mass index. For genotypes 2 and 3 the duration of treatment may be shortened to 12 or 16 weeks instead of 24 if the patient had RVR.

[25]

Some studies that evaluated shorter duration of HCV treatment excluded IDUs or those who used illicit drugs from their study population. [71-74]. In a retrospective-prospective model the duration of HCV treatment of IDUs who were treated in our clinic was studied and compared SVR rates among those who received standard treatment to those who received shorter duration than the standard. The results were comparable for both genotype 1 and genotype 2/3.

In the future it would be beneficial to evaluate the efficacy of shorter duration in IDUs especially in those who achieve RVR and identify the predictors of SVR in this group of patients. Shorter duration may encourage the intake of treatment by IDUs and may encourage the health care providers to become more aggressive in offering treatment to this group of patients without the worry about complete adherence to treatment duration. Shorter duration was associated with fewer side effects and less drop outs which will also improve adherence to treatment. Financially it will save taxpayers the costs of treatment and caring for these patients plus the savings we will get by preventing the development of end stage liver disease and decreasing the spread of HCV to new individuals.

CHAPTER 5: SUMMARY AND CONCLUSION

There are more than 300,000 Canadians have chronic HCV infection, more than half of them are either current or previous IDUs. Any plan or attempt to terminate or reduce the burden of this disease must include a plan to treat IDUs living with chronic HCV and prevent the occurrence of new cases. The justification of denying HCV treatment for IDUs by health care providers can be due to different reasons. One of the reasons which are very frequently mentioned either explicitly or implicitly is the expected high rate of re-infection in this population after treatment as a result of their continuous engagement in risk behaviors for acquisition.

Previous studies demonstrated that HCV treatment success rates in IDUs are comparable to that shown in non IDUs.

In this study we defined three distinct populations at risk of infection / re-infection which is a unique approach in quantifying this risk in a definitive manner in a group of patients that have not previously been studied in this way in a prospective fashion.

Our study of HCV re-infection is of key significance. Not only will it help establish whether this concern should influence treatment decisions, but it will help identify patients who appear resistant to HCV infection / re-infection.

This study also helped in telling about the risk behaviors that may lead to HCV infection and helped in formulating suggestions and ideas about how to minimize these risk behaviors that lead to HCV infection / re-infection. These ideas should be communicated to IDUs who are not yet infected to prevent or at least minimize the possibility of getting infected with HCV also we should communicate these ideas with those IDUs who are engaged or will be engaged in HCV treatment in order to prevent or at least minimize the possibility of re-infection.

We have now demonstrated in a prospective cohort with systematic follow-up that viremic HCV infection in IDUs is more likely to occur in those who have never been infected before in comparison to those who have cleared the virus either spontaneously or through treatment. This higher susceptibility to infection cannot be completely explained by higher engagement in risk behavior, at least as compared to individuals who have cleared their viremia spontaneously.

To some extent, the lower rate of re-infection following SVR can be due to lower engagement in risk behavior for acquisition which maybe the result of their engagement in the health care system during the treatment process. The lower rate of re-infection after SVR as a result of some host-related protective factors can't be ruled out since the subjects in this group did engage in risk behavior for acquisition during the follow-up period.

Both re-infection incidences occurred as a result of not direct sharing of the needle or the syringe used in illicit drug use. Which may suggest that we somewhat succeeded in convincing these IDUs of not sharing these tools to prevent acquiring serious diseases but more education is needed to clarify the risks associated with sharing injection equipments and sharing non injection equipment.

In our inner city we have a program for needle exchange and maybe we need to expand this program to include injection equipments too and study the benefits of such expansion in reducing HCV and HIV in our IDUs population.

The results of our study should encourage more clinicians to engage IDUs in HCV treatment without the fear of high risk of re-infection after treatment. Health care providers should start discussing the best ways of engaging IDUs in treatment and put policies and procedures that would maximize the adherence to treatment which will result in increasing the success rate of achieving SVR.

Governments should adapt policies that promote treating more IDUs and remove the obstacles that face clinicians in gaining treatment coverage such as the proof of inflammation or fibrosis needed to gain treatment coverage in our province of British Columbia.

5.1. Study limitation

Our study has the following limitations:

- 1- Relatively small sample size: This affects the strength of analysis, results and conclusions derived from this study. One needs to keep in mind that recruiting and retaining subjects from this population is a challenging process and more difficult that when dealing with more stable and sober subjects.

- 2- 6 months follow-up intervals period: Having 6 month's interval period between baseline and each follow-up might resulted in missing re-infection that may have occurred among subjects in the spontaneous arm since the time needed to clear new infection is approximately 14 weeks. That said; if new re-infection was cleared before detecting them this will support the argument that clearing the virus spontaneously protects against viremic new infection.
- 3- Data collected from questionnaire: There are questions that would make the data collected more informative. From these questions:
 - a- How you think you got infected with HCV for spontaneous, SVR and those who become infected. This data would help in evaluating what our cohort of IDUs believes the source of their infection and we can get recommendation that would help prevent them and other IDUs from getting infected.
 - b- The question about injecting, sharing injection and non injecting equipment at follow-up should be expanded to the last 6 months instead of the last 30 days. Since couple of subjects I interviewed used drug after baseline but not in the last 30 days and by asking about the last 6 months it would be more comprehensive.

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APPENDICES

Appendix A: Publications

Poster presentation

Efficacy of shorter duration HCV treatment in injection drug users (IDUs)

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from Ninth International Congress on Drug Therapy in HIV Infection
Glasgow, UK. 9–13 November 2008

Published: 10 November 2008

Journal of the International AIDS Society 2008, 11(Suppl 1):P278 doi:10.1186/1758-2652-11-S1-P278

THE CANADIAN JOURNAL OF
**INFECTIOUS DISEASES &
MEDICAL MICROBIOLOGY**
JOURNAL CANADIEN DES MALADIES INFECTIEUSES
ET DE LA MICROBIOLOGIE MEDICALE

P150

EFFICACY OF SHORTER DURATION (SD) OF HEPATITIS C VIRUS (HCV) TREATMENT IN ILLICIT DRUG USERS (IDUS)

A Barrieshee, L Gallagher, E Knight, M Storms, F Duncan,
S deVlaming, B Conway
Vancouver, BC

P185

MIXED GENOTYPE HEPATITIS C VIRUS (HCV) INFECTIONS AMONG HIV AND HCV CO-INFECTED ILLICIT DRUG USERS (IDUS)

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Appendix B: Re-infection summary

Re-infection Study Summary

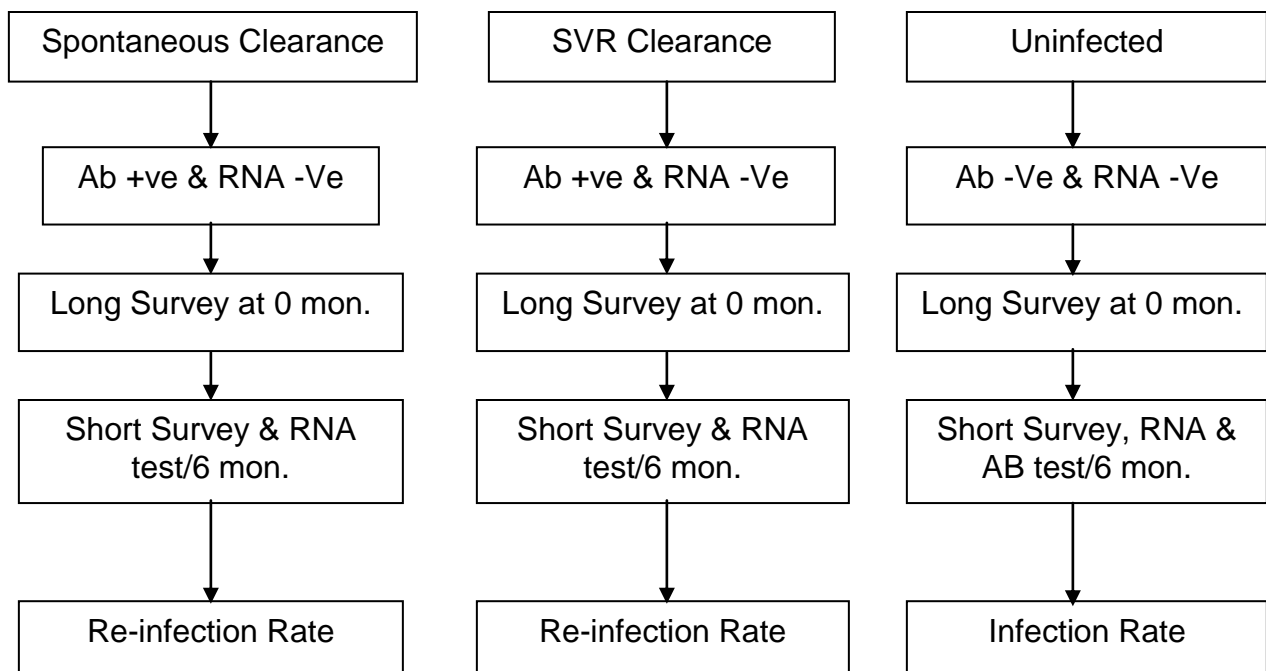
Objectives:

- 1- To compare the rate and characteristics of HCV viremia occurrence in HCV uninfected IDUs with the re-occurrence of HCV viremia in individuals with spontaneous or treatment-induced clearance.
- 2- To compare the rate and characteristics of HCV re-occurrence in IDUs with spontaneous and treatment-induced clearance of HCV viremia.

Inclusion Criteria:

Inclusion Criteria	Exclusion Criteria
Age \geq 19 years.	Detectable qualitative PCR for HCV RNA.
History of Injection Drug Use.	Life expectancy $<$ 2 years.
Illicit drug use in the past year (injection/non injection of heroin, crystal meth, or cocaine, drug use cannot just be marijuana use).	
Ability to provide informed consent.	

Study Arms:



Appendix C: Re-infection recruitment summary

Re-infection Study for Hepatitis C Infection

You may be eligible to participate in a research study to find out the possibility of Hep C **re-infection** in different groups of people

To be eligible you must fit the following criteria:

- ☐ Be currently using or have used illicit drugs in the past year.
- ☐ Have a history of injection drug use.

And you must fall into one the following 3 categories: (1) you were treated for hepatitis C and cleared the virus, (2) you cleared the virus naturally on your own, or (3) you have never been infected with the hepatitis C virus.

Participation will involve giving a blood sample and completing a questionnaire every six months for a 3-year period. Each time you complete a questionnaire you will be reimbursed for your time.

In order to participate and determine if you are eligible for the study you will need to meet with the research staff to review and sign the consent form. All information will be kept confidential.

You can call and speak further with the research staff or leave a message at: 604-642-5802. Or complete the section below and staff will contact you.

☐ Yes I am interested in participating in the **re-infection** study at Pender Clinic and can be contacted at the numbers below for an appointment.

Name: _____

Contact #: _____

Alternate #: _____

Appendix D: Baseline questionnaire



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Patient Number

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Location

Time :

Interviewer

Instructions:

If questions are 'skipped' by the interviewer, please manually note (this can be done during or after the interview) e.g., by drawing a line through the question item, or putting a large 'S' next to it.

Please use a black pen and mark your answers with an X inside the box.

If corrections are made, draw a line through the error (initial and date), then clearly mark the correct answer.



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Patient Number

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☐ Baseline

I. Socio-demographics

1. What is your sex?

(Please mark one box with a checkmark; and only ask about gender if necessary to clarify)

01 ☐ Male

02 ☐ Female

03 ☐ Transgendered

88 ☐ Don't know/unsure/don't remember

99 ☐ Refused

2. What is your age? Years

88 ☐ Don't know/unsure/don't remember

99 ☐ Refused

3. What is your ethnic group?

(Scan the list below and mark one box with a checkmark)

01 ☐ Black (not Hispanic origin)

02 ☐ White (not Hispanic origin)

03 ☐ Hispanic

04 ☐ Middle Eastern origins

05 ☐ Asian, South Asian or Pacific Islander

06 ☐ First Nations or American Indian

07 ☐ Inuit

08 ☐ Metis

09 ☐ Other origins, please specify:

10 ☐ Mixed origins, please specify:

88 ☐ Don't know/unsure/don't remember

99 ☐ Refused

4. Please describe your current or predominant housing situation in the last 30 days?

01 ☐ Permanent (e.g. house or apartment)

02 ☐ Temporary (e.g. boarding house, shelter, detox centre, group home, hotel [SRO], hospital)

03 ☐ Homeless (e.g. living on the streets/no fixed address)

88 ☐ Don't know/unsure/don't remember

99 ☐ Refused



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5. In the past 30 days, what were your different sources of income?
(read all options to respondent and mark all that apply)

- 01 ☐ Paid work (legal)
02 ☐ Social assistance/welfare/unemployment benefits
03 ☐ Disability or health benefits
04 ☐ Illegal activity (e.g. stealing, sex work, drug dealing, other)
05 ☐ Binning/Panhandling /Soliciting etc.
06 ☐ Gifts/Loans
07 ☐ Other, please Specify:
08 ☐ None
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

6. If paid legal work, on how many days out of the last 30 did you work?

days

7. In the past 12 months, have you been arrested?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 9*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

8. If you have been arrested, how many times have you been arrested in the past 12 months?

times

9. In the past 12 months, have you been in any form of detention (e.g. prison, jail, detention centre)

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 11*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

10. If you have been in any form of detention, on how many days have you been in detention in the past 12 months?

times



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II. Health and Health Care

11. Do you have a regular health care provider (i.e. a specific clinic, hospital, or doctor where you go when you have health problems and where people know you and keep information about you on file)?

- 01 ☐ Yes
02 ☐ No
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

12. In the past 12 months, how often have you attended this regular care provider?

- 01 ☐ Never (first visit)
02 ☐ Once
03 ☐ 2-5 times a year
04 ☐ 6-12 times a year
05 ☐ 1-3 times a month
06 ☐ 1 or multiple times a week
07 ☐ Daily
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

13. In general, how would you say your health is?

(Read out the question and the possible ratings). CHECK ONE ONLY:

- 01 ☐ Excellent
02 ☐ Very Good
03 ☐ Good
04 ☐ Fair
05 ☐ Poor
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

14. Do you currently have any physical health problems?

- 01 ☐ Yes
02 ☐ No → PROCEED TO QUESTION 16
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused



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15. a. Thinking about the physical health problem(s) you have, could you list them (to a maximum of 3, starting with the most serious one)?

(Please write down responses in column I)

b. How long have you had this/these problem(s)?

(Please write down responses and time units [months] in column II)

c. Are you receiving or have you received medical attention for this/these problem(s)? (Please mark one box with a checkmark in column III)

d. Are you receiving or have you received prescribed medication(s) for this/these problem(s)? If so, which medication(s)? (Please mark one of the boxes in column IV and then fill in the name of the medication if applicable)

I	II	III	IV
Physical Health Problem	For how long (# of months)	Receiving/Rec'd medical attention	Receiving/Rec'd prescribed medication(s) and which one(s)
	88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes Type(s): <input type="text"/> 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused
	88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes Type(s): <input type="text"/> 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused
	88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes Type(s): <input type="text"/> 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused

16. Do you have any mental health problems?

- 01 ☐ Yes
02 ☐ No → PROCEED TO SECTION III (CIDI)
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

88= Don't know/unsure/don't remember



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Patient Number

Date of Visit / /

Patient Initials

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17. a. Thinking about the mental health problem(s) you have, could you list them (to a maximum of 3, starting with the most serious)? (Please write down responses in column I)
- b. How long have you had this/these problem(s)? (Please write down responses and time units [months] in column II.)
- c. Are you receiving or have you received medical attention for this/these problem(s)? (Please mark one box with a checkmark in column III)
- d. Are you receiving or have you received prescribed medication(s) for this/these problem(s)? If so, which medication(s)? (Please mark one of the boxes in column IV and then fill in the name of the medication if applicable)

I	II	III	IV
Mental Health Problem	For how long (# of months)	Receiving/Rec'd medical attention	Receiving/Rec'd prescribed medication(s) and which one(s)
	88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes Type(s): <input type="text"/> 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused
	88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes Type(s): <input type="text"/> 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused
	88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Yes Type(s): <input type="text"/> 02 <input type="checkbox"/> No 88 <input type="checkbox"/> Don't know 99 <input type="checkbox"/> Refused

88= Don't know/unsure/don't remember



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Patient Number

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Date of Visit

Day	Month	Year						
<table border="1"><tr><td></td><td></td></tr></table>			<table border="1"><tr><td></td><td></td></tr></table>			<table border="1"><tr><td></td><td></td></tr></table>		

Patient Initials

--	--	--

☐ Screening

☐ Baseline

III. ADMINISTER CIDI QUESTIONNAIRE HERE TO ALL
PARTICIPANTS



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Patient Initials

☐ Screening
☐ Baseline

IV. Infectious Diseases

HCV

18. Have you ever been tested for Hepatitis C Virus (HCV)?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 28*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

19. When were you last tested for HCV? (month and year if possible)

Month Year
 /

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

20. What method was used for the test?

- 01 ☐ Blood test
02 ☐ Saliva test
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

21. What was the result of the test?

- 01 ☐ Positive
02 ☐ Negative → *PROCEED TO QUESTION 28*
88 ☐ Don't know/unsure/don't remember → *PROCEED TO QUESTION 28*
99 ☐ Refused → *PROCEED TO QUESTION 28*

22. What is your HCV genotype?

- 01 ☐ Genotype 1
02 ☐ Genotype 2
03 ☐ Genotype 3
04 ☐ Other
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused



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23. Have you ever sought treatment for HCV (e.g. Interferon-based therapy such as Pegatron, Pegasys, or Rebetron)?

- 01 ☐ Yes → *PROCEED TO QUESTION 25*
02 ☐ No
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

24. Why have you not sought treatment for HCV?

Reason:

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

25. Have you ever been offered HCV treatment?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 28*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

26. Have you ever received HCV treatment?

- 01 ☐ Yes → *PROCEED TO QUESTION 28*
02 ☐ No
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

27. If you were offered HCV treatment, why were you not treated?
(Answered "yes" for question 25, but "no" for question 26)

Reason:

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused



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☐ Baseline

HIV

28. Have you ever been tested for HIV?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 37*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

29. When were you last tested for HIV? (month and year if possible)

Month / Year

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

30. What method was used for the test?

- 01 ☐ Blood test
02 ☐ Saliva test
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

31. What was the result of the test?

- 01 ☐ Positive
02 ☐ Negative → *PROCEED TO QUESTION 37*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

32. Have you ever received HIV treatment?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 37*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused



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☐ Baseline

33. When did your HIV treatment begin? (month and year if possible)

Month / Year

88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

34. When was your most recent treatment visit? (month and year if possible)

Month / Year

88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

35. Are you currently receiving HIV treatment?

01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 37*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

36. Where are you currently receiving HIV treatment?

01 ☐ Hospital
02 ☐ Community physician or General physician
03 ☐ Drug treatment or methadone clinic
04 ☐ Other, please specify:

88 ☐ Don't know/unsure/don't remember
99 ☐ Refused



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Patient Number	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Date of Visit	Day <input type="text"/> <input type="text"/>	/	Month <input type="text"/> <input type="text"/>	/	Year <input type="text"/> <input type="text"/>
Patient Initials	<input type="text"/> <input type="text"/> <input type="text"/>		99=Screening 00=Baseline		Week #	<input type="text"/> <input type="text"/>	

V. HCV Treatment Motivation

Questions 37 to 39: Ask only of participants who reported that they are HCV POSITIVE (i.e., answered 'positive' to question 21) AND HAVE NOT previously received HCV treatment (i.e. answered 'no' to question 26); all others proceed to Question 40.

37. Do you think that HCV infection can be effectively treated or cured?

- 01 ☐ Yes
02 ☐ No
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

38. Given that you are HCV positive, how interested would you be in receiving treatment for HCV (e.g. Interferon-based therapy)?

- 01 ☐ Definitely not willing
02 ☐ Somewhat not willing
03 ☐ Neither willing nor unwilling
04 ☐ Somewhat willing
05 ☐ Definitely willing
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused



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Week #

39. As you may know, treatment for Hepatitis C exists and involves taking interferon drugs and other prescription medication for 6 to 12 months, depending on the type of virus you have. I am now going to present you with 5 different statements. For each statement, considered on its own, please indicate how interested you would be to receive HCV treatment given that:

a) The HCV treatment only works for about ½ the people who receive it.

- 01 ☐ Definitely not willing
02 ☐ Somewhat not willing
03 ☐ Neither willing nor unwilling
04 ☐ Somewhat willing
05 ☐ Definitely willing
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

b) The majority of people receiving HCV treatment experience side effects such as flu-like symptoms, nausea, fatigue and depression.

- 01 ☐ Definitely not willing
02 ☐ Somewhat not willing
03 ☐ Neither willing nor unwilling
04 ☐ Somewhat willing
05 ☐ Definitely willing
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

c) HCV treatment requires you to visit a doctor or clinic at least once a week for the duration of treatment (6-12 months).

- 01 ☐ Definitely not willing
02 ☐ Somewhat not willing
03 ☐ Neither willing nor unwilling
04 ☐ Somewhat willing
05 ☐ Definitely willing
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

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Patient Initials	<input type="text"/> <input type="text"/> <input type="text"/>		99=Screening		Week #	<input type="text"/> <input type="text"/>	
			00=Baseline				

d) You need to also participate in addiction treatment (e.g. methadone maintenance treatment) with or before the hepatitis treatment

- 01 ☐ Definitely not willing
- 02 ☐ Somewhat not willing
- 03 ☐ Neither willing nor unwilling
- 04 ☐ Somewhat willing
- 05 ☐ Definitely willing
- 88 ☐ Don't know/unsure/don't remember
- 99 ☐ Refused

e) Before HCV treatment, you need to undergo a liver biopsy (a minor surgical procedure, often done under local anesthetic, in which a small amount of liver tissue is removed and examined under a microscope).

- 01 ☐ Definitely not willing
- 02 ☐ Somewhat not willing
- 03 ☐ Neither willing nor unwilling
- 04 ☐ Somewhat willing
- 05 ☐ Definitely willing
- 88 ☐ Don't know/unsure/don't remember
- 99 ☐ Refused

f) Your chance of developing liver cirrhosis or liver cancer in the next 10-20 years is about 10-25%.

- 01 ☐ Definitely not willing
- 02 ☐ Somewhat not willing
- 03 ☐ Neither willing nor unwilling
- 04 ☐ Somewhat willing
- 05 ☐ Definitely willing
- 88 ☐ Don't know/unsure/don't remember
- 99 ☐ Refused

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00=Baseline

Week #

VI. Addiction Treatment

40. Have you received any kind of drug addiction treatment in the past 12 months?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 43*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

If yes, what kind of drug treatment have you received in the past 12 months?
(Please scan the list and check the applicable treatment options in column I)

a. From the list of checked treatment options, ask: How many days in the past year have you been in each of these kinds of drug treatment (Please write answers in column II)

I	II
01 <input type="checkbox"/> Detox (non-medical or medical)	<input type="text"/> <input type="text"/> times/year 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
02 <input type="checkbox"/> In-patient treatment (short or long-term)	<input type="text"/> <input type="text"/> times/year 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
03 <input type="checkbox"/> Recovery house	<input type="text"/> <input type="text"/> times/year 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
04 <input type="checkbox"/> Outpatient/Ambulatory treatment	<input type="text"/> <input type="text"/> times/year 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
05 <input type="checkbox"/> Opiate maintenance (clinic, GP or prison)	<input type="text"/> <input type="text"/> times/year 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
06 <input type="checkbox"/> Other, please specify <input type="text"/>	<input type="text"/> <input type="text"/> times/year 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused



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Patient Number

Patient Initials

Date of Visit

Day	Month	Year
<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

 /

<input type="text"/> <input type="text"/>

 /

<input type="text"/> <input type="text"/>

99=Screening
00=Baseline
Week #

<input type="text"/> <input type="text"/>

46. What is the setting where the treatment is provided?

- 01 ☐ Hospital-based
- 02 ☐ GP Practice or community health clinic
- 03 ☐ Drug treatment or methadone clinic
- 04 ☐ Prison
- 05 ☐ Needle exchange (low-threshold)
- 06 ☐ Other
- 88 ☐ Don't know/unsure/don't remember
- 99 ☐ Refused

47. What is the daily dosage you are receiving? (Mark the dosage and units)

<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

 mg/per day

- 88 ☐ Don't know/unsure/don't remember
- 99 ☐ Refused

48. Do you currently receive take-homes
(e.g. methadone to take home with you or "carries")?

- 01 ☐ Yes
- 02 ☐ No
- 88 ☐ Don't know/unsure/don't remember
- 99 ☐ Refused

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00=Baseline

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VII. Drug Use/Sex-Related Risk Behaviours

49. Have you ever injected drugs?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 60*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

50. When did you inject drugs for the first time? (month and year if possible)

Month / Year

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

51. Have you injected any drugs in the last 30 days?

- 01 ☐ Yes → *PROCEED TO QUESTION 53*
02 ☐ No
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

52. If no, when was the last time you injected drugs? (month and year if possible)

Month / Year

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

53. On average, when you injected most recently, how many times did you inject drugs per day?

- 01 ☐ Once
02 ☐ Twice
03 ☐ 3 Times
04 ☐ 4 Times
05 ☐ 5 Times
06 ☐ 10 or more
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

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00=Baseline

Week #

54. Have you ever shared a needle or syringe (i.e. used a needle/syringe that had been used by someone else before)?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 57*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

55. When was the first time you shared a needle or syringe (i.e. used a needle/syringe that had been used by someone else before)?
(month and year if possible)

Month / Year

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

56. How many times overall would you say you have shared needles or syringes (i.e. used a needle/syringe that had been used by someone else before)?

times

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

57. Have you ever shared other injection drug use equipment (i.e. used other IDU equipment that had been used by someone else before) (e.g. cooker, filter, water, etc.)?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 60*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

58. When was the first time you shared other injection drug use equipment (i.e. used other IDU equipment that had been used by someone else before)?
(month and year if possible)

Month / Year

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

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00=Baseline

Week #

59. How many times overall would you say you shared other injection drug use equipment (i.e. used other IDU equipment that had been used by someone else before)?

times

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

60. Have you ever shared any non-injection drug use equipment (i.e. used other non-injection equipment that had been used by someone else before) (e.g. crack or meth pipe, coke straw, etc.)?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 63*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

61. When was the first time you shared non-injection drug use equipment (i.e. used other non-injection equipment that had been used by someone else before) (e.g. crack or meth pipe, coke straw, etc.)? (month and year if possible)

Month / Year

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

62. How many times overall would you say you shared any non-injection drug use equipment (i.e. used other non-injection equipment that had been used by someone else before) (e.g. crack or meth pipe, coke straw, etc.)?

times

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

Evaluation of a Multi-Disciplinary Approach for the
Treatment of Hepatitis C in Injection Drug Users
Drug Use Survey

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Patient Number

Patient Initials

Date of Visit Day / Month / Year

99=Screening
00=Baseline

Week #

63. a. In the past 30 days, have you used any of the following drugs?
(Check the drug in column I)
- b. On how many days in the last 30 did you use each of these drugs?
(enter number in column II)
- c. For each of these drugs, what was your primary mode of use?
(e.g. injection, snorting, inhalation)

I	II	III
Drug Type	Number of Days Used (in the last 30 days)	Primary Mode of Use
01 <input type="checkbox"/> Alcohol	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
02 <input type="checkbox"/> Tobacco	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
03 <input type="checkbox"/> Cannabis (Marijuana, Hashish)	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
04 <input type="checkbox"/> Cocaine	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused

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05 <input type="checkbox"/> Crack	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused
06 <input type="checkbox"/> Methamphetamine, Amphetamines, Hallucinogens (including Ecstasy, Speed, LSD, Angel Dust, Crystal Meth)	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused
07 <input type="checkbox"/> Heroin	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused
08 <input type="checkbox"/> Methadone (not prescribed to you)	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused
09 <input type="checkbox"/> Prescription Opioids (including Oxycodone, Hydromorphone, Codeine, Morphine, Hydrocodone, etc.) that were not prescribed to you	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused

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Week #

10 <input type="checkbox"/> Inhalants (glue, solvents, aerosols, etc.)	88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
11 <input type="checkbox"/> Benzodiazepines or Sedatives (Valium, Librium, etc.)	88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
12 <input type="checkbox"/> Other (Please Specify: _____)	88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused

64. If cannabis (marijuana or hashish) use is reported in the last 30 days: On average, in the last 30 days, how many times (i.e. use episodes) did you use cannabis per day?

- 01 ☐ Once
02 ☐ Twice
03 ☐ 3 times
04 ☐ 4 times
05 ☐ 5-9 times
06 ☐ 10 or more times
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

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Patient Number

Patient Initials

Date of Visit Day / Month / Year

99=Screening
00=Baseline

Week #

65. Have you combined any drugs in the past 30 days (*Combining drugs means using more than one drug simultaneously or using one drug immediately after another*)?

- 01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 67*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

66. What were your 3 main or most frequent used drugs/drug combinations in the past 30 days?

1	<input type="text"/>
2	<input type="text"/>
3	<input type="text"/>

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

67. Have you had unsafe sex (i.e. sex with someone whose STD – or infectious disease – free status you can not be certain, or without adequate protection e.g. intercourse or oral sex without a condom) in the last 30 days?

- 01 ☐ Yes
02 ☐ No (*END OF INTERVIEW*)
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

68. If yes, how many times have you had unsafe sex in the last 30 days?

times

- 88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

END OF INTERVIEW

Evaluation of a Multi-Disciplinary Approach for the
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Patient Number

Patient Initials

Date of Visit / /

Day Month Year

99=Screening Week #

00=Baseline

69. Question for Interviewer: How valid overall do you believe the information given by the respondent was?

- 01 ☐ Credible
02 ☐ Uncertain/Mixed
03 ☐ Not Credible

Interviewer Notes (please elaborate on question 69 if answer was "Not credible" or "Uncertain/Mixed"):

Appendix E: Follow-up questionnaire



**Evaluation of a Multi-Disciplinary Approach for the
Treatment of Hepatitis C in Injection Drug Users
Drug Use Survey - Treatment**
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Patient Number	<input type="text"/>	Date of Visit	<input type="text"/>	/	<input type="text"/>	/	<input type="text"/>
	<input type="text"/>		<input type="text"/>		<input type="text"/>		<input type="text"/>
Patient Initials	<input type="text"/>					Week #	<input type="text"/>
	<input type="text"/>						<input type="text"/>
Location	<input type="text"/>						
Time	<input type="text"/>	:	<input type="text"/>				
	<input type="text"/>		<input type="text"/>				
Interviewer	<input type="text"/>						

☐ Early Discontinuation

Instructions:

If questions are 'skipped' by the interviewer, please manually note (this can be done during or after the interview) e.g., by drawing a line through the question item, or putting a large 'S' next to it.

Please use a black pen and mark your answers with an X inside the box.

If corrections are made, draw a line through the error (initial and date), than clearly mark the correct answer.



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Drug Use Survey - Treatment

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Patient Number

Patient Initials

Date of Visit Day / Month / Year

Week #

☐ Early Discontinuation

II. Health, Health Care and Addiction Treatment

8. Do you have a regular health care provider (i.e. a specific clinic, hospital, or doctor where you go when you have health problems and where people know you and keep information about you on file)?

- 01 ☐ Yes
02 ☐ No
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

9. In the past 30 days, how often have you attended this regular care provider?

- 01 ☐ Never (first visit)
02 ☐ Once
03 ☐ 2-3 times a month
04 ☐ 1 or multiple times a week
05 ☐ Daily
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

10. In general, would you say your health is? (Read out the question and the possible ratings). CHECK ONE ONLY:

- 01 ☐ Excellent
02 ☐ Very Good
03 ☐ Good
04 ☐ Fair
05 ☐ Poor
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

11. Have you received any kind of drug addiction treatment in the past 30 days?

- 01 ☐ Yes
02 ☐ No → PROCEED TO QUESTION 12
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

If yes, what kind of drug treatment have you received in the past 30 days?
(Please scan the list and check the applicable treatment options in column I)

- a. From the list of checked treatment options, ask: How many days in the past 30 days have you ever been in each of these kinds of drug treatment (Please write answers in column II)

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Patient Number

Date of Visit / /

Patient Initials

Week #

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I	II
01 <input type="checkbox"/> Detox (non-medical or medical)	<input type="text"/> <input type="text"/> days / 30 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
02 <input type="checkbox"/> In-patient treatment (short or long-term)	<input type="text"/> <input type="text"/> days / 30 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
03 <input type="checkbox"/> Recovery house	<input type="text"/> <input type="text"/> days / 30 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
04 <input type="checkbox"/> Outpatient/Ambulatory treatment	<input type="text"/> <input type="text"/> days / 30 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
05 <input type="checkbox"/> Opiate maintenance (clinic, GP or prison)	<input type="text"/> <input type="text"/> days / 30 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
06 <input type="checkbox"/> Other, please Specify: <input type="text"/>	<input type="text"/> <input type="text"/> days / 30 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused

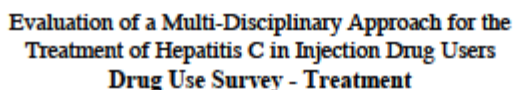
12. Are you currently enrolled in an opiate (e.g. methadone or buprenorphine) maintenance treatment program?

01 ☐ Yes

02 ☐ No → *PROCEED TO QUESTION 18*

88 ☐ Don't know/unsure/don't remember

99 ☐ Refused



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Patient Number					
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Date of Visit

Day	
Month	
Year	

 /

Day	
Month	
Year	

 /

Day	
Month	
Year	

Patient Initials			
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Week #		
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☐ Early Discontinuation

III. Drug Use/Sex-Related Risk Behaviours

18. Have you injected any drugs in the last 30 days?
01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 25*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused
19. When did you last inject drugs?
(month and year if possible)

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 /

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88 ☐ Don't know/unsure/don't remember
99 ☐ Refused
20. On average, when you injected most recently, how many times did you inject drugs per day?
01 ☐ Once
02 ☐ Twice
03 ☐ 3 Times
04 ☐ 4 Times
05 ☐ 5 Times
06 ☐ 10 or more
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused
21. Have you shared any needles or syringes in the last 30 days (i.e. used a needle/syringe that had been used by someone else before)?
01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 23*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused



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☐ Early Discontinuation

22. If yes, how many times would you say you have shared a needle or syringe in the last 30 days (i.e. used a needle/syringe that had been used by someone else before)?

times

88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

23. Have you shared other injection drug use equipment in the last 30 days (i.e. used other IDU equipment that had been used by someone else before) (e.g. cooker, filter, water, etc.)?

01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 25*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

24. If yes, how many times would you say you shared other injection drug use equipment in the last 30 days (i.e. used other IDU equipment that had been used by someone else before) (e.g. cooker, filter, water, etc.)?

times

88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

25. Have you shared any non-injection drug use equipment in the last 30 days (i.e. used other non-injection equipment that had been used by someone else before) (e.g. crack or meth pipe, coke straw, etc.)?

01 ☐ Yes
02 ☐ No → *PROCEED TO QUESTION 27*
88 ☐ Don't know/unsure/don't remember
99 ☐ Refused

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Patient Initials

Date of Visit / /

Day Month Year

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26. If yes, how many times would you say you shared any non-injection drug use equipment in the last 30 days (i.e. used other non-injection equipment that had been used by someone else before) (e.g. crack or meth pipe, coke straw, etc.)?

times

88 ☐ Don't know/unsure/don't remember

99 ☐ Refused

27. a. In the past 30 days, have you used any of the following drugs? (Check the drug in column I)

b. On how many days would in the last 30 would you say you used each of these drugs (enter number in column II)

c. For each of these drugs, what was your primary mode of use? (e.g. injection, snorting, inhalation)

I	II	III
Drug Type	Number of Days Used (in the last 30 days)	Primary Mode of Use
01 <input type="checkbox"/> Alcohol	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused
02 <input type="checkbox"/> Tobacco	<input type="text"/> <input type="text"/> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused



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Patient Number						
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Date of Visit

Day	
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Month		
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 /

Year	
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Patient Initials			
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Week #

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☐ Early Discontinuation

03 <input type="checkbox"/> Cannabis (Marijuana, Hashish)	<div> <div></div> <div></div> </div> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused
04 <input type="checkbox"/> Cocaine	<div> <div></div> <div></div> </div> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused
05 <input type="checkbox"/> Crack	<div> <div></div> <div></div> </div> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused
06 <input type="checkbox"/> Methamphetamine, Amphetamines, Hallucinogens (including Ecstasy, Speed, LSD, Angel Dust)	<div> <div></div> <div></div> </div> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused
07 <input type="checkbox"/> Heroin	<div> <div></div> <div></div> </div> days 88 <input type="checkbox"/> Don't know/unsure/don't remember 99 <input type="checkbox"/> Refused	01 <input type="checkbox"/> Injected 02 <input type="checkbox"/> Nasal 03 <input type="checkbox"/> Oral 04 <input type="checkbox"/> Smoked 88 <input type="checkbox"/> Don't know/ unsure/don't remember 99 <input type="checkbox"/> Refused

Appendix F: Study ethics approval

*The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room
210, 828 West 10th Avenue, Vancouver,
BC V5Z 1L8*

ETHICS CERTIFICATE OF FULL BOARD APPROVAL

PRINCIPAL INVESTIGATOR: Brian Conway	INSTITUTION / DEPARTMENT: UBC/Medicine, Faculty of/Anesthesiology, Pharmacology & Therapeutics	UBC CREB NUMBER: H06-03294
INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:		
Institution		Site
Vancouver Coastal Health (VCHRI/VCHA)		Vancouver Community
Other locations where the research will be conducted: N/A		
CO-INVESTIGATOR(S): Stanley De Vlaming Fiona Duncan		
SPONSORING AGENCIES: Canadian Institutes of Health Research (CIHR) - "Evaluation of a multi-disciplinary approach for the treatment of hepatitis C virus in injection drug users"		
PROJECT TITLE: Study To Assess HCV Clearance and Re-infection in the Treatment of HCV in injection drug users (START-HCV)		
THE CURRENT UBC CREB APPROVAL FOR THIS STUDY EXPIRES: August 14, 2008		
The full UBC Clinical Research Ethics Board has reviewed the above described research project, including associated documentation noted below, and finds the research project acceptable on ethical grounds for research involving human subjects and hereby grants approval.		
REB FULL BOARD MEETING REVIEW DATE: August 14, 2007		
DOCUMENTS INCLUDED IN THIS APPROVAL:		DATE DOCUMENTS APPROVED:
Document Name	Version	Date
Protocol: HI-Lo HCV re-infection Substudy	N/A	June 6, 2007
Consent Forms: HI-Lo re-infection Substudy ICF - track changes	II	August 24,
		September 5, 2007

	2007
Questionnaire, Questionnaire Cover Letter, Tests:	
HI-Lo Drug Use Survey Screening	N/A June 4, 2007
HI-Lo Drug Use Survey - monthly visits	N/A June 4, 2007
CERTIFICATION: In respect of clinical trials: <i>1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.</i> <i>2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.</i> <i>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.</i>	
The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.	
<i>Approval of the Clinical Research Ethics Board by one of:</i>	
Dr. Gail Bellward, Chair	