Université de Montréal

Hepatitis C Cascade of Care in a specialized Clinic, Results and Success Rates

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Hepatitis C Cascade of Care in a Specialized Clinic, Results and Success Rates

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Résumé

Introduction : L'exposition au virus de l'hépatite C entraîne une infection virale du foie. La plupart des patients infectés sont asymptomatiques (85%). La phase aigüe de l'infection peut passer inaperçue mais le fardeau à long terme de l'infection est lourd, conduisant annuellement dans 1%-4% des cas à un cancer du foie ou nécessitante une greffe hépatique.

Au Canada, on diagnostique 11600 cas d'infections par le VHC par année. Avant l'ère des antiviraux à action directe (AAD) et avec les traitements d'interféron, le taux de guérison était à 50%. En outre, il y a eu beaucoup d'effets sur la santé mentale. C'est pour cela que s'ils n'avaient pas de support à la maison on leur refusait le traitement.

Les médicaments AAD ont révolutionné le traitement de l'infection par le virus de l'hépatite C (VHC). Leur taux de guérison de l'ordre de 95%, et moins d'effets secondaires en a fait le traitement de choix dans l'infection par le VHC. Afin de mieux gérer les patients infectés et d'identifier les obstacles à l'élimination de l'infection, nous avons créé et analysé la cascade de soins de l'hépatite C dans un centre extrahospitalier.

Méthodes: Nous avons analysé la cascade de soins en hépatite C pour une cohorte de patients suivis dans une clinique spécialisée en VIH/VHC avec au besoin suivi en toxicomanie et traitement à bas seuil (pas de refus de traitement a patients toxicomane). Tous les patients avec test d'anticorps anti-VHC positif de la clinique ont été inclus. Les patients coinfectés avec VIH ont été inclus. Les données démographiques, de laboratoire, de suivi médical et thérapeutiques ont été collectées à l'aide du dossier médical électronique. Les patients avec >=2 visites ont été considérés « pris en charge », la guérison a été mesurée par la réponse virologique soutenue (RVS) trois mois post-traitement. Nous avons calculé l'incidence cumulative de chaque étape de la cascade.

Résultats: Entre 2010 et 2018, 1135 patients avec test anti-VHC+ ont consulté à la clinique médicale urbaine du Quartier Latin (cmuQL). 75% étaient des hommes, leur âge médian était de 54 ans, 39% étaient des personnes qui utilisent des drogues par injection, 76% ont été traités

pour l'hépatite C. 1100 patients (97%) ont été pris en charge, 966 (85%) ont eu un test d'ARN, 825 (73%) ont reçu un traitement, 772 (68%) ont atteint la fin du traitement, et 703 (62%) ont eu une RVS. Au total, 46 patients (4%) sont décédés dont 21 sont décédés avant d'être traités. 69 patients (6%) ont eu une guérison spontanée et 90 patients ont été réinfectés au moins une fois.

Conclusions: Le traitement des patients infectés par le VHC dans une clinique multidisciplinaire avec prise en charge concomitante de la toxicomanie était un succès. Les défis majeurs de la cascade de soins en hépatite C étaient l'initiation du traitement et l'adhérence au suivi après la fin du traitement.

Mots-clés : Hépatite C, cascade de soins, traitement à bas seuil, DAA.

Abstract

Exposure to the hepatitis C virus leads to viral infection of the liver. Most infected patients are asymptomatic (85%). The acute phase of infection may go unnoticed, but the long-term burden of infection is heavy, leading to 1%-4% per year to liver cancer or requiring liver transplantation.

In Canada, 11,600 cases of HCV infection are diagnosed each year. Before the DAA era and at the time of treatment with interferon, the cure rate was around 50%. Also, there were a lot of effects on mental health. Therefore, if the patient didn't have sufficient family support, they were being refused for treatment.

DAAs have revolutionized the treatment of hepatitis C (HCV) infection. Their 95% cure rate and fewer side effects have made them the treatment of choice in HCV infection. To better manage infected patients and identify barriers to infection clearance, we designed and analyzed the hepatitis C care cascade in an out-of-hospital setting.

Methods: We analyzed the cascade of hepatitis C care for a cohort of patients followed in a clinic specializing in HIV/HCV with follow-up in substance abuse and low-threshold treatment (treatment offered even if the patient had drug dependence). All patients with positive anti-HCV antibody tests from the clinic were included. HIV positive patients were also entered in the research. Demographic, laboratory, medical follow-up, and therapeutic data were collected using the electronic medical record. Patients with >=2 visits were considered "in care", and cure was measured by sustained virologic response (SVR) three months post-treatment. We calculated the cumulative impact of each step of the cascade.

Results: Between 2010 and 2018, 1135 patients with an anti-HCV+ test consulted at the urban medical clinic in the Latin Quarter. 75% were men, their median age was 54 years, 39% were in the category of people who inject drugs (PWID), and 76% had already been treated. 1100 patients (97%) were taken care of, 966 (85%) had an RNA test, 825 (73%) received treatment and 772 (68%) reached the end of treatment and 703 (62 %) had an SVR. A total of 46 patients (4%) died,

of which 21 died before being treated. 69 patients (6%) recovered spontaneously, and 90 patients (8%) were reinfected at least once.

Conclusions: Treatment of HCV-infected patients in a multidisciplinary clinic with concurrent addiction management was successful. The major challenges of the hepatitis C cascade of care were treatment initiation and adherence to follow-up after the end of treatment.

Keywords: Hepatitis C, cascade of care, low threshold treatment, DAA.

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APRI: aminotransferase to platelet ratio index

CmuQL: Clinique de Medecine Urbaine du Quartier Latin

DAA: direct-acting antiviral

EoT: end of treatment

EMR: electronic medical record

FIB-4: fibrosis-4 index

FMG: Family Medicine Group

HCV: hepatitis C virus

HBV: hepatitis B virus

HCC: hepatocellular carcinoma

HIV: human immunodeficiency virus

IDU: Intravenous drug use

mDOT: modified directly observed therapy

NAT: nucleic acid testing/test

NS5B: non-structural protein 5B (of HCV)

NS3/NS4A: non-structural protein 3/non-structural protein 4A (of HCV)

OST: opioid substitution therapy

PWID: people who inject drug

STI: Sexually transmitted infection

SVR: sustained virological response

WHO: World Health Organization

To my husband, Javad and my children, Mawny and Niki

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Finally, I would like to express my gratitude to my husband Javad, and my children, Mawny and Niki. Without their tremendous understanding and encouragement in the past few years, it would be impossible for me to complete this degree.

Dedication

A special feeling of gratitude to my loving parents, Parvaneh and Hossein Babaki Fard, whose words of encouragement and push for tenacity ring in my ears. My sister Katy has never left my side and is very special to me.

Chapter 1 – INTRODUCTION

1.1 Introduction

HCV infection remains a problematic medical condition in terms of diagnosis and management. Due to asymptomatic cases, patients may remain unaware of their condition, and the clinical management is challenging as well.

HCV infection resulted in 290,000 deaths worldwide in 2019. The death in these patients is due to liver failure resulting from liver cirrhosis and HCC. In 2020, about 58 million people were affected by chronic HCV infection with about 1.5 million new cases of hepatitis C infection annually worldwide (1,2).

If left untreated, 85% of patients develop chronic hepatitis and about 20% develop cirrhosis after 20 years (3,4). HCV-associated cirrhosis results in a yearly incidence of HCC of 1% to 4%. There are psychological effects of hepatitis C infection such as depressive symptoms which affect the quality of life (5,6). Furthermore, HCV is the leading cause of liver transplants, which may impose huge effects on the costs of the health system in the countries (4).

At the end of 2011, an estimated 0.5% to 0.7% of the total Canadian population was living with chronic hepatitis C (7,8). About 44% of these patients with chronic hepatitis C infection were unaware of their status (7). Based on national data from 2017, the of hepatitis C incidence is declining steadily since 2008 (7).

The population at risk includes people who inject drugs (PWID), prisoners, men who have sex with the same sex, indigenous people and sex workers (9). PWID are estimated to make up 60%-85% of new cases of hepatitis C (10). Prisoners (24% antibody positive), men who have sex with men (5% antibody positive), and homeless people (5% antibody positive) represent the other important groups affected by Hepatitis C in Canada. (7).

The main routes of transmission of hepatitis C are through blood and blood products, and through sexual contact. Needle sharing associated with injection opioid use is an important route of contracting HCV infection in PWID (11).

Hepatitis C is a curable disease due to the revolutionary results of the novel antiviral therapies. The treatment and SVR with the use of DAA therapy reaches approximately 95% in different published research, compared to around 50% of SVR with the use of traditional interferon-based therapies (12–14).

Despite these recent achievements in the field of therapeutics, there are still obstacles to the treatment of hepatitis C. According to the WHO, among the 58 million cases of hepatitis C infection in 2019, only about 21% were aware of their disease (1).

Barriers to treatment remain present at different levels. They can be categorized at patient factors (knowledge and awareness, non-adherence, social and economic factors, injection drug use and the consequent deferral), healthcare provider factors (knowledge and awareness, specialist referral and availability and communication issues) and government and payer barriers.

At the patient's level, lack of one's adherence to care, and low level of awareness about the disease are important barriers of care (15,16). At the same level, economic and social pressure are also important factors. They include family obligations, low social support, and social rejection due to stigmatization and discrimination. The other factor is lack of healthcare access in at risk populations (17–19).

Some obstacles to care are related to the patients' living setting. Prisoners live in a complex environment with a high risk of transmission of HCV and other blood-borne viruses. Challenges include assessing trustworthy information (20), short sentences and high turnover rates in provincial prisons of Canada (21) and lack of integrated prison healthcare in some provinces of Canada (22).

Barriers of treatment at the level of healthcare providers include lack of experience and knowledge of the disease, in consequence not identifying the risk factors and not reporting regular screening in the high-risk group. The other factor is lack of specialist availability due to

presence of the specialists within academic medical centers and not in the local centers. Communication issues are another important factor which can lead to negative interaction with patients and hence lower the patient's adherence to treatment (15,23,24).

The solution for the cure of patients and advance toward the elimination of hepatitis C are multi-levelled. Governments can act on providing information for the public and health providers. Increasing funding, screening, surveillance programs, and collaboration with healthcare and educational partners are essential in increasing the diagnosis and care rate of hepatitis C (25,26).

Analysis of the cascade of care helps us evaluate the flaws of the system and to determine the steps between diagnosis and cure or sustained virological response that should be reinforced to eliminate hepatitis C. Thus, it guides to identify the type of interventions that can have the greatest impact on the outcomes (26).

Although there have been some studies in Canada, to our knowledge, there has not been any study on the cascade of care of Hepatitis C in Quebec. Due to the rich multicultural and multiethnic community in Quebec and especially in Montreal, the challenges of the cure of hepatitis C should have multiple implications.

In this study, we analysed the data of the patients followed at the Clinique de Médecine Urbaine du Quartier Latin (cmuQL). The patients were followed in our model of care consisting of a multidisciplinary team of a nurse, physician, pharmacist, and social worker. We aimed to evaluate the different steps and the treatment outcomes in the clientele. We describe the SVR rate at cmuQL, we show the SVR rate after the introduction of DAA-interferon free treatments for HCV, in a wide range of clienteles and the "difficult-to-treat" PWID clients as we offer them adequate support, such as OST.

Chapter 2- LITERATURE REVIEW

2.1 Introduction

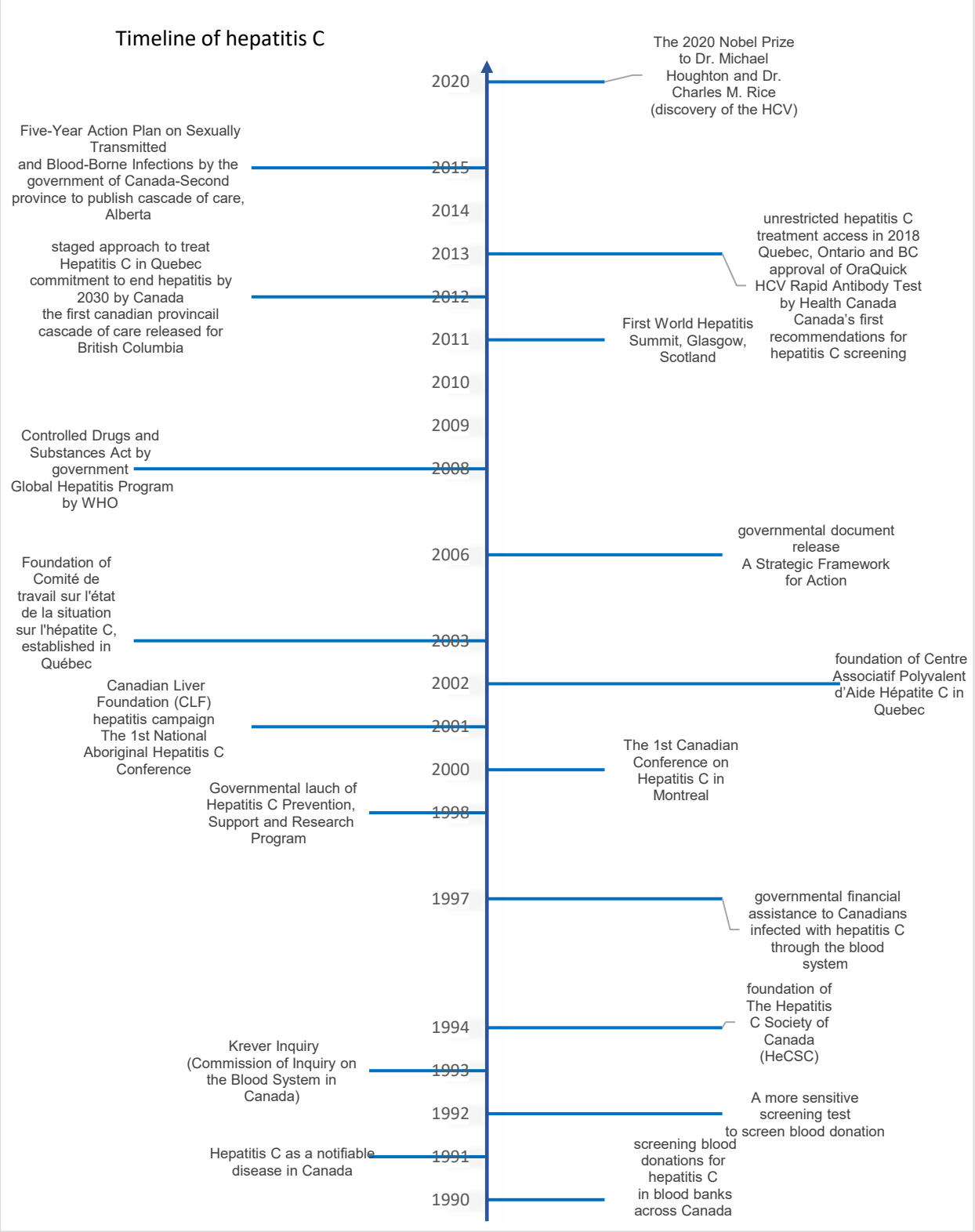
Hepatitis C was discovered in 1989. In 1990 and later in 1992, hepatitis C screening tests were developed. An estimated 90,000 to 160,000 Canadians contracted hepatitis C through blood or blood products between 1960 and 1992 (27). The routes of transmission are sexual transmission and transmission through blood (28).

Hepatitis C infection is a global health burden. It is a major cause of cirrhosis and HCC. Despite the curative treatment available for hepatitis C, its complications continue to increase (29). Most cases of acute hepatitis C are undetected and only 15% of cases are symptomatic in the United States (29).

2.2 A brief timeline of hepatitis C in Canada and Quebec

Figure 1 is a brief timeline of the events that happened in Canada since the discovery of hepatitis C to the present (27).

Figure 1. – Timeline of hepatitis C events in Canada



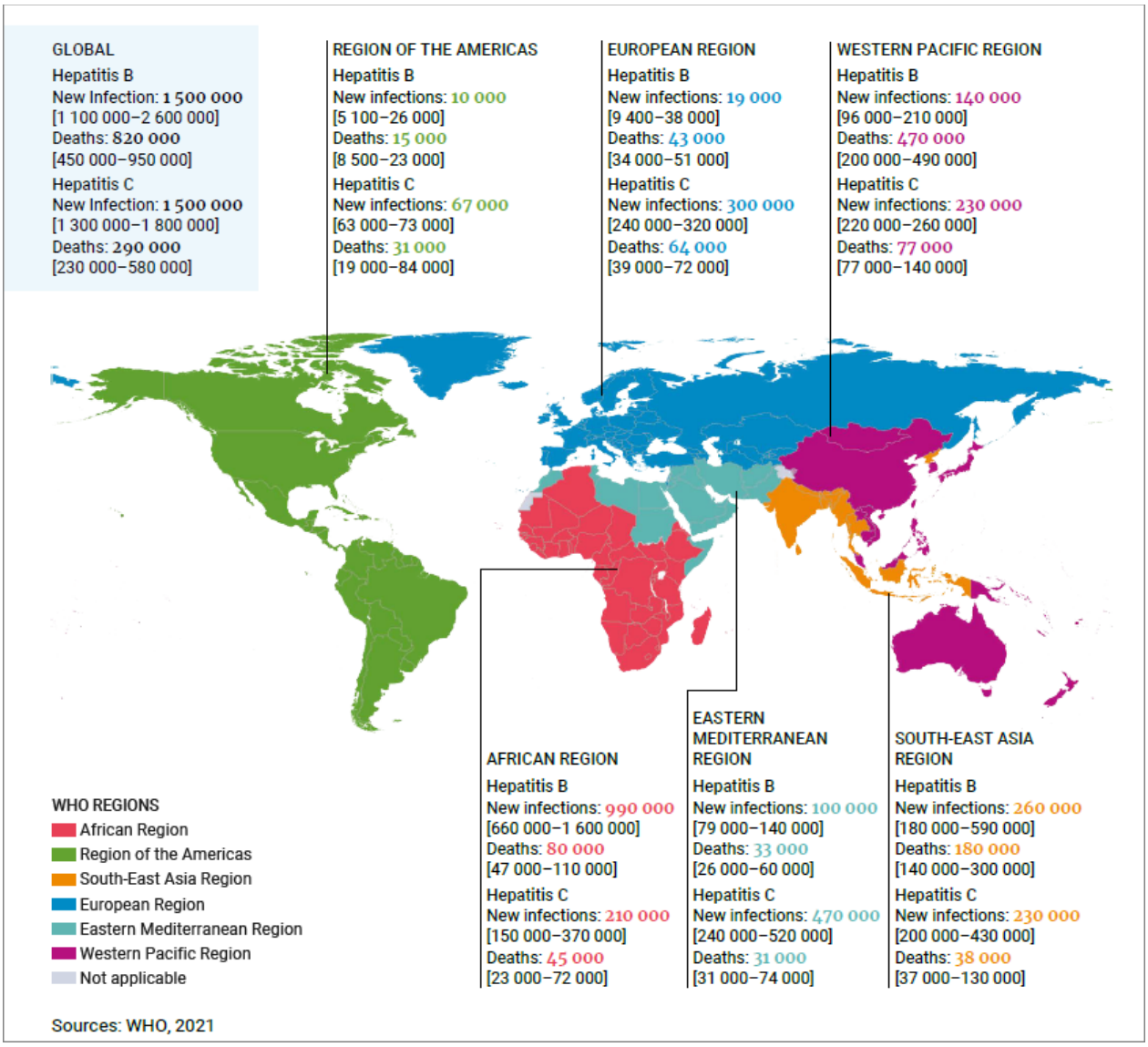
From: A brief history of hepatitis C, CATIE - Canada's source for HIV and hepatitis C information (27)

2.3 Epidemiology of HCV infection

2.3.1 Global epidemiology of HCV infection

Hepatitis C is considered a major public health threat worldwide. Based on the estimations of WHO, there are 58 million people with chronic hepatitis C worldwide and about 1.5 million new infections happen per year, figure 2 (30). According to an estimate by WHO in 2019, about 290,000 people died from hepatitis C, principally due to cirrhosis and hepatocellular carcinoma (1).

Figure 2. – Hepatitis B and C new infections and mortality by WHO region, 2019



From: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 (30)

During the pandemic and between May to September 2020, WHO has reported a widespread disruption of essential health services because of the pandemic. These include medications for hepatitis, needle and syringe distribution for PWID, and testing for viral hepatitis. However, the pandemic has given opportunities, such as accelerating policy implementation, leveraging health

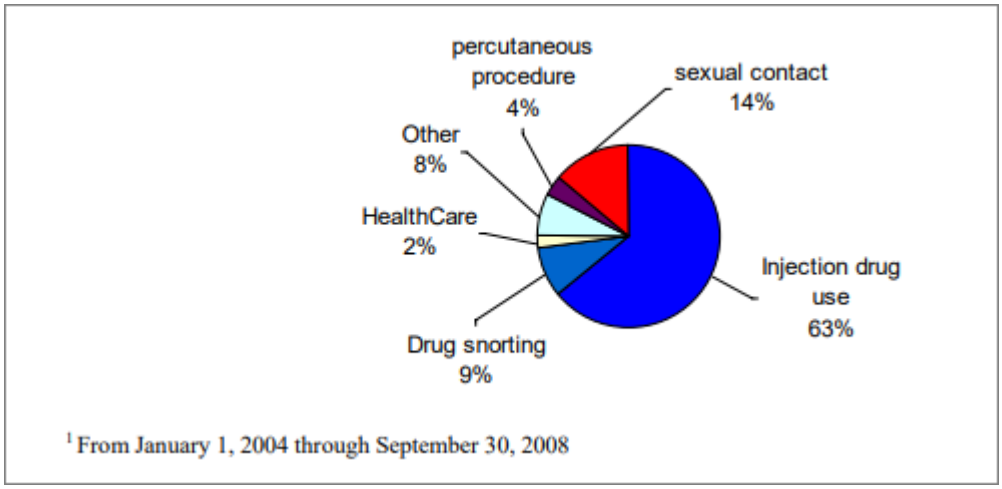
systems capacity, simplifying community-based delivery, expanding the use of self care interventions and increasing the use of digital health (30).

2.3.2 Epidemiology of HCV infection in Canada

Based on the different models, approximately 250,000 Canadians were infected with HCV in December 2007, with a prevalence rate of 0.5 to 0.7% (8,31). There are “twin epidemics” of HCV in Canada. One is in the young people who mainly inject drugs. The other is among people born between 1945 and 1975 who received contaminated blood or blood products. Based on national data from 2017, the rate of hepatitis C is declining steadily since 2008 (7).

Hepatitis C infection transmission in Canada is mostly through sharing equipment for street drugs, tattoos, or body piercing. These types of transmission can be stopped with awareness and sterilisation practices. Transmission through transfusion of blood or blood products no longer occurs because of screening of blood supply in Canada since 1990. Other ways of transmission are unprotected sex, using unsterilized medical equipment or sharing personal care items (toothbrushes, nail clippers and razors), and vertical transmission (figure 3) (7).

Figure 3. – Distribution of risk factors for newly acquired HCV infection among new cases with known risk factor information in Canada



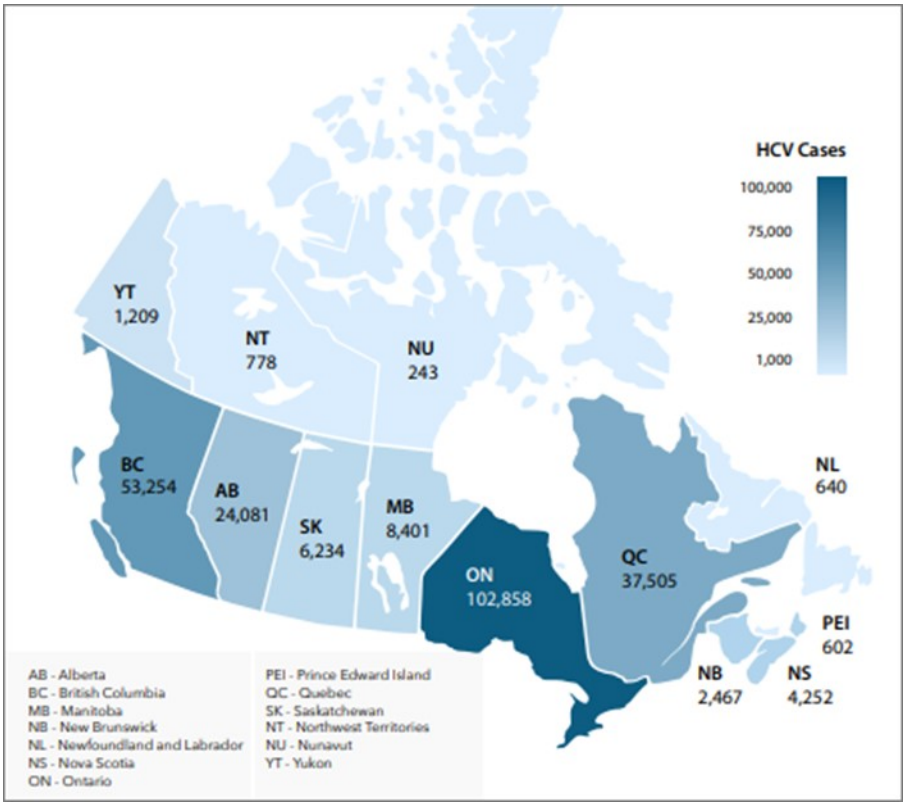
From: Enhanced Hepatitis Strain Surveillance System (EHSSS), 2004-2008 (32)

2.3.3 Epidemiology of HCV infection in Quebec

The prevalence of HCV infection in Quebec was about 37,500 in 2019 (figure 4). The number of declared new cases of hepatitis C in Quebec in 2019 is near 1000, This number has been relatively the same during the 5 previous years from that time (figures 5,6) (33). The incidence is more elevated in ages 50-64 and more elevated in men (figure 7).

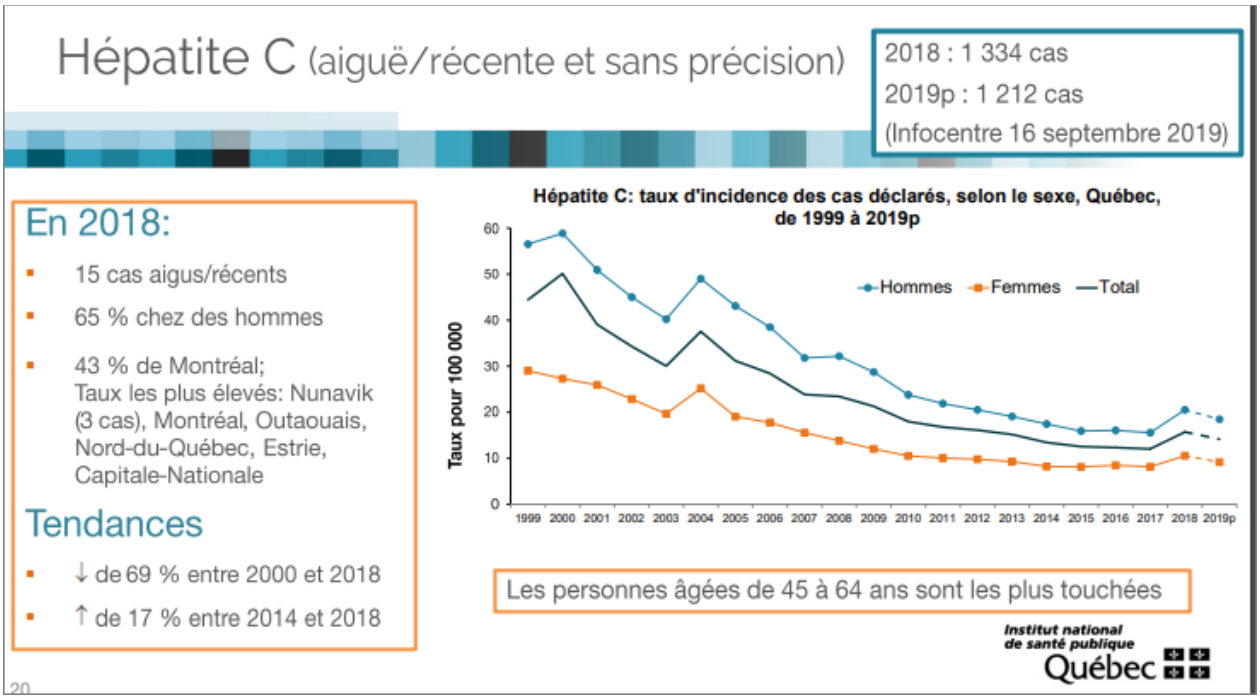
The year 2020 has been special because of the COVID-19 pandemics. Analysis of the data from January to September of 2020 shows that there is a reduction of declared cases compared to 2019. There are three hypotheses to these results. Limited access to tests, the shedding of certain monitoring activities and the populational measures of prevention of COVID-19 (33).

Figure 4. – Provincial and territorial hepatitis C (HCV) estimates of total cases



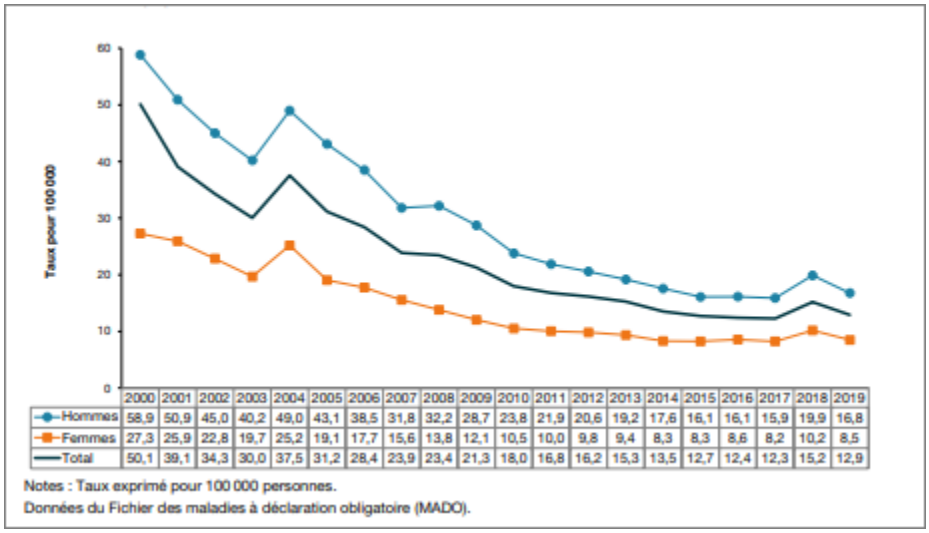
From: Report on Hepatitis B and C Surveillance in Canada: 2019 , government of Canada (10)

Figure 5. – Portrait of acute Hepatitis C in Quebec



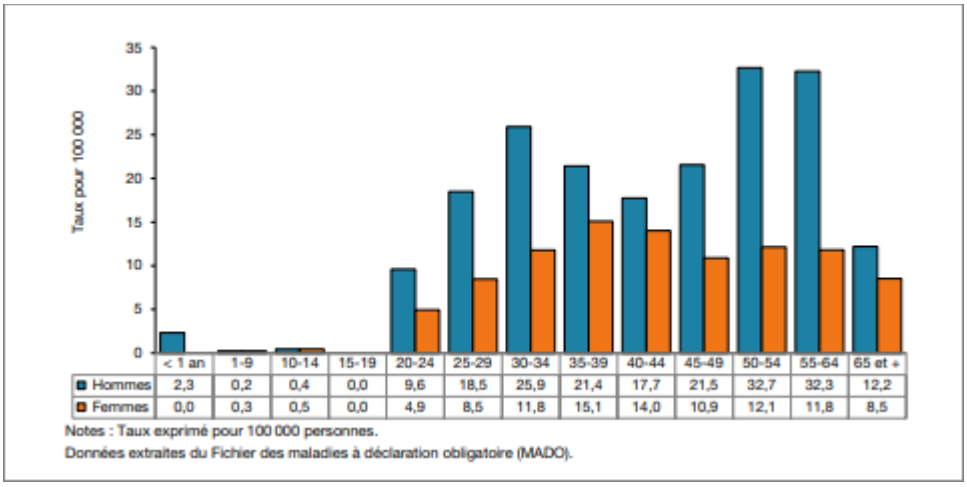
From: INSPQ (33)

Figure 6. – Incidence of declared cases of hepatitis C, based on age, in Quebec, from 2000 to 2019



From: INSPQ (33)

Figure 7. – Incidence rate of hepatitis C, based on sex and age, Quebec, 2019



	< 1 an	1-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-64	65 et +
Hommes	2,3	0,2	0,4	0,0	9,6	18,5	25,9	21,4	17,7	21,5	32,7	32,3	12,2
Femmes	0,0	0,3	0,5	0,0	4,9	8,5	11,8	15,1	14,0	10,9	12,1	11,8	8,5

Notes : Taux exprimé pour 100 000 personnes.
Données extraites du Fichier des maladies à déclaration obligatoire (MADO).

From: INSPQ (33)

2.3.4 Risk factors

There are different populations at risk of infection with HCV. In the process of cure of hepatitis C, some social health determinants can change the outcomes. On the other hand, some co-infections can influence the treatment of the patients.

specific populations at risk

There are five groups of people at risk. These groups include PWID, prisoners, men who have sex with men, indigenous people, and sex workers. Important issues are the high incidence and high prevalence of hepatitis C among these groups, the possibility of stigmatization and discrimination, and problems with healthcare access (34).

coinfection (HIV/HCV)

Coinfection of hepatitis C with HIV infection has adverse effects on the outcomes. In these patients, the progression to cirrhosis and hepatitis C are accelerated. This is especially more prominent in HIV positive patients with advanced immunodeficiency (CD4 count lower than 200 cells per mm3) (34).

Demographic characteristics

Some factors can positively affect the rate of SVR after treatment, these include lower body mass index, HCV genotype non-3, absence of cirrhosis, female sex, and higher platelet counts.

PWID

In a systemic review, data from 77 countries in the world were collected. Based on the findings, the prevalence of the anti-HCV in PWID was between 60-80%. China, the USA, and Russia had the highest positive rates. The reported HBsAg positive rate in the same population was 5-10% (35).

Recent studies suggest that the introduction of the DAA in the treatment of hepatitis C makes the treatment possible for every patient, including the PWID. The same SVR rates are reported with the direct-acting antiviral treatment in patients with drug use, with or without OST compared to patients without a history of drug use (36).

2.4 Clinical manifestations

More than two-thirds of the patients are asymptomatic (29,37). In these cases, people living with HCV infection are unaware of their condition and they do not receive care and necessary treatment. This will not only lead to HCV-related complications such as cirrhosis and liver cancer but also can lead to the spreading of the infection to other people (38,39).

If symptomatic, the symptoms include fatigue, low-grade fever and chills, loss of appetite, pruritis, muscle aches, mood disturbances, joint pain, dyspepsia, and confusion. (29,37). These symptoms typically develop 2 to 26 weeks (mean 7 to 8 weeks) after exposure to HCV. The symptoms usually last 2 to 12 weeks. (29,37).

2.5 Natural history

About 2-14 days after exposure, the HCV appears in the blood, followed by an increase of alanine transaminase (ALT) level in serum and the gradual appearance of anti-HCV antibody at the day 30-60 (39).

In around 25% of patients, the acute HCV infection will be followed by spontaneous clearance. The remaining 75% will progress to chronic HCV and its consequences, the most important are

chronic liver failure and cirrhosis, and HCC. The progression to cirrhosis is reported from 16% to 56%, 20 years or more after the infection (37,39–41). There are some predictive factors determining the spontaneous clearance such as female sex, favourable IL28B genotype and HCV genotype 1 (39,42).

In some patients there is HCV recurrence, either from late relapse after SVR or reinfection. Reinfection, is a particular concern in PWID (43,44) and shows that the immunity to HCV after treatment or spontaneous resolution is not adequately protective (45).

2.6 Laboratory findings

The HCV RNA level has three phases: a pre-ramp-up phase, a ramp-up phase when there is a rapid increase in HCV RNA level and a plateau phase (46,47).

In acute HCV infection, the aminotransferases are elevated, often greater than 10 to 20 times the upper limit of normal and are widely variable within short time intervals. In chronic infection, the aminotransferases are elevated but relatively stable (29).

In symptomatic patients, the aminotransferases start to increase shortly before the onset of symptoms and before the detection of anti-HCV antibodies. The normal level of serum aminotransferase levels after acute infection does not mean the clearance of infection. The total bilirubin levels may also increase (29).

There are about six different genotypes of HCV, genotype 1 is the most prevalent in the world and in Canada (48,49). The rate of fibrosis and SVR are affected by the genotype of HCV (50).

2.7 Diagnosis

In the first step, an HCV antibody test will be done. Detection of anti HCV antibodies is done by enzyme-linked immunosorbent assay (ELISA), which becomes positive between two to six months after exposure (29). It is not possible to distinguish the current HCV infection alone, based on this test. In the second step, we need a follow-up test to verify if the infection is active, with the test HCV RNA (29).

After detection of HCV RNA by polymerase chain reaction (PCR), the patient is considered positive for HCV infection. In some conditions, acute HCV infection is suspected: in patients with clinical manifestations or patients with high-risk behaviour like recent drug use or healthcare workers with needle stick injury (29). There is a window period, which means it may take 5 to 10 weeks after exposure to the HCV before HCV antibodies become detectable in the blood. In this case, a repeated anti-HCV test may be needed (51).

The strategy for diagnosis after HCV exposure, for example needle stick injury, are HCV antibody and alanine aminotransferase testing (to assess if the patient is already infected with HCV) (29). In case the patient develops clinical signs and symptoms of acute hepatitis, the tests for diagnosis are HCV RNA detection by PCR, and HCV antibody testing (29).

Even after treatment and SVR, there is a risk of reinfection of HCV (43). There are some criteria to apply for the reinfection. The diagnosis of HCV reinfection is done when a patient has a positive HCV PCR test after they have either spontaneous clearance or a SVR (52).

To evaluate the liver in hepatitis C infected patients, there are invasive and non-invasive methods. Hepatic biopsy remains the gold standard. It is used to estimate the activity of the disease and the stage of liver fibrosis. It is also used to assess response to treatment, detection of lesions and prediction of prognosis. It has the complications of an invasive method, and the costs are high (53). Blood based markers (APRI of Fib-4) as well as transient elastography have increasingly replaced the liver biopsy. Transient elastography is a reliable non-invasive tool to evaluate the presence and staging of liver fibrosis. It also helps to monitor the response to treatment (54).

2.8 Management

According to WHO guidelines for the care and treatment of Hepatitis C, an eight-step model of service delivery is considered in the treatment of hepatitis C:

-national planning for the elimination of the disease,

-standard and simplified algorithms to deliver care to the patients,

-assimilation of care with other services,

-planification to maintain adherence to different steps of the cascade of care,

-decentralizing,

-support from the community to reduce discrimination or stigmatization,

-maintain medication and supplies,

-and, implement a monitoring system(34).

2.8.1 Counselling

Counselling is performed after the patients' diagnosis and is primarily on the subjects such as treatment plans, discussing risk exposures and evaluating risky activities with patients. Injection drug use is the most common cause of acute HCV infection in North America and Europe. The patient is encouraged to avoid sharing needles or other drug use equipment and to avoid high-risk sexual practices (15,29,55).

Patients are counselled to avoid further liver injuries (use of alcohol or high dose acetaminophen) (29). If a patient goes through spontaneous viral clearance or SVR, the risks of reinfection should be reminded (29).

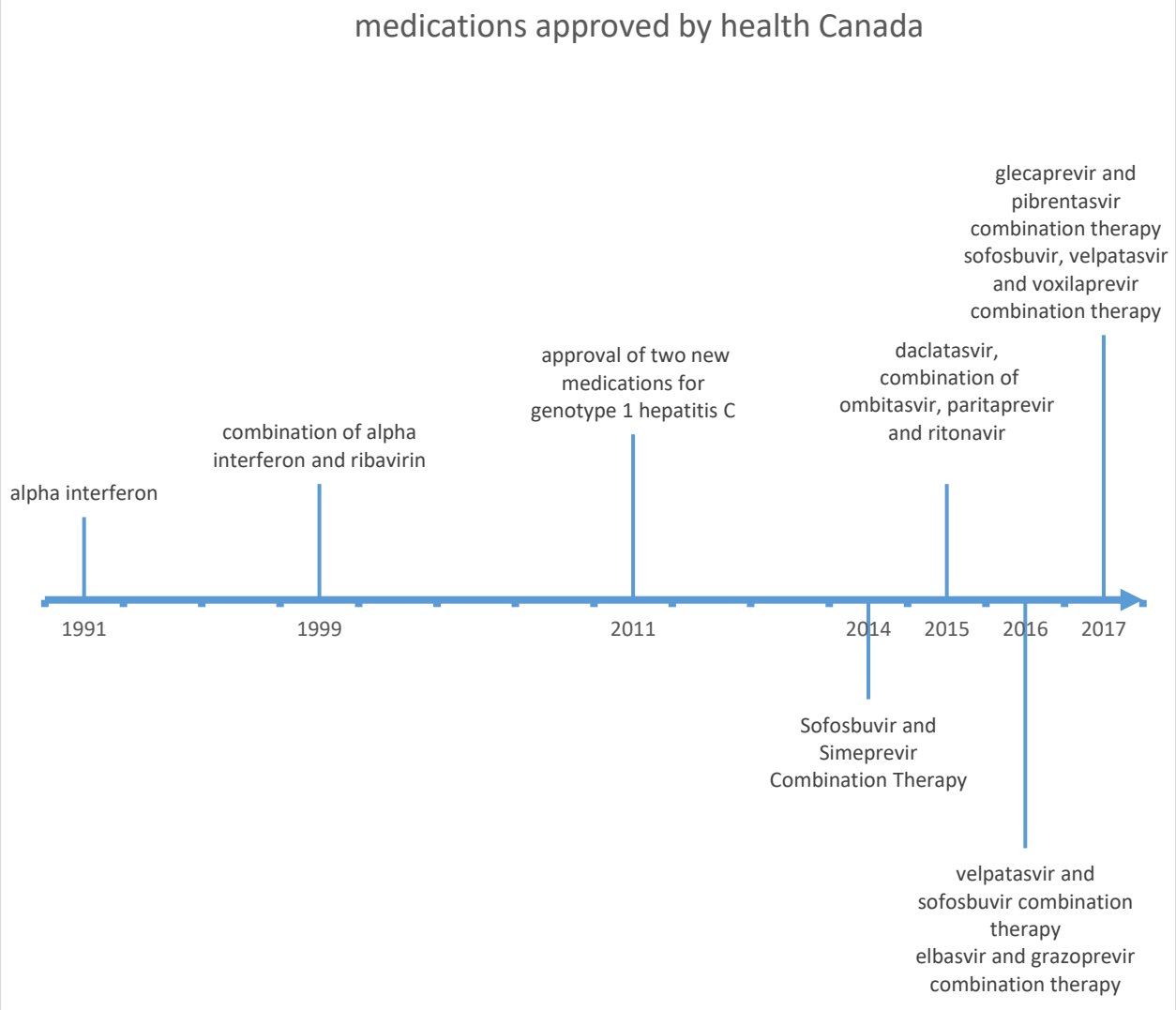
2.8.2 Antiviral therapy

The treatment of hepatitis C is divided into before, and after the DAA era, due to the great impact of the new DAA medications on the cure and management of the disease. The first treatment agent for hepatitis C was alpha interferon, which is an immunomodulatory agent. The SVR after the interferon monotherapy was estimated to be 15%, this rate reached 50% after adding Ribavirin to the treatment regimen. The problem with the use of interferons was the long-term treatment duration, parenteral injections, and the multiple side effects. The new DAA medications used in hepatitis C treatment have a SVR of near 100% and fewer side effects (56,57).

Timeline of hepatitis C medications in Canada

The use of a combination of alpha interferon and Ribavirin for the treatment of hepatitis C was approved in Canada in 1999. About ten years later, in 2011, the new medications named direct-acting antivirals were approved for genotype 1 HCV (figure 8) (27).

Figure 8. – Timeline of hepatitis C medications in Canada



From: Catie, Canada's source for HIV and hepatitis C information (27)

Major strains (genotypes) of HCV

Hepatitis C virus is a single-stranded RNA virus that requires RNA polymerase to reproduce. The error rate of this polymerase is very high, as the result, the viral genome is heterogeneous (58). There are six major strains (genotypes) of HCV. There is a genotype distribution of the virus by region. Genotypes are detected by the blood test. The most common genotype of HCV in Canada is genotype 1 (51).

Treatments, goals, effects, accessibility, and risks

The approach of joint American Association for the Study of Liver Diseases (AASLD) and the infectious Diseases Society of America (IDSA) guidelines recommend immediate treatment after documenting viremia in patients with acute HCV infection (59). The goal of treatment of hepatitis C infection is to eliminate the virus and decrease mortality and morbidity due to liver-related health problems (59).

There is a list of DAA medications available (table 1). The selected regimen is based on the patient specifications and the genotype of the HCV, severity of disease, access to the specific medications and their insurance coverage. The definition of SVR (virologic cure) is defined as not detecting the HCV RNA for twelve weeks after completion of treatment (59).

Tableau 1. – Classification of DAAs

NS3/4A (protease) inhibitors	**NS5A inhibitors**	**NS5B polymerase inhibitor (nucleotide analogue)**	**NS5B polymerase inhibitor (non-nucleoside analogue)**
Glecaprevir	Daclatasvir	Sofosbuvir	Dasabuvir
Voxilaprevir	Velpatasvir		
Grazoprevir	Ledipasvir		
Paritaprevir	Ombitasvir		
Simeprevir	Pibrentasvir		
	Elbasvir		

From: WHO guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (34)

There are some risks and considerations in the prescription of DAA medications. Because the treatment needs two and up to five DAA medications, the possibility of drug-drug interaction should be taken into consideration, especially in patients with comorbidity (60). Knowledge about pharmacokinetics and metabolism of the mediations are essential in the treatment of patients and the comorbidities should be taken into consideration (for example dose adjustments, therapeutic drug monitoring or alternative safe medications) (50, chapter 7).

Another stake in the treatment of HCV-infected patients is drug resistance. The HCV mutations affect the binding of DAA to target proteins and result in resistance or virological relapses. Substitutions influencing the replication fitness of some mutations is another reason for treatment failure (50, chapter 8).

At the beginning of the arrival of DAAs, their access was restricted, only patients with a high degree of liver damage (stage F3 of fibrosis or even at the stage of F4 and cirrhosis), were eligible for treatment. Subsequently, the availability of medications improved, and the access criteria became widened. In 2018, Quebec has removed the fibrosis level criterion to further reach Canada's commitment to the World Health Organization's Global Hepatitis C elimination efforts (61). Currently, there is a list of medications available in Canada, for the treatment of hepatitis C (table 2) (62).

Tableau 2. – Common hepatitis C medications available in Canada for adults

Brand name (generic name)	Genotypes	Dosage schedule	Weeks of treatment
Epclusa (velpatasvir + sofosbuvir) with or without ribavirin	All	One tablet once daily	12
Maviret (glecaprevir + pibrentasvir)	All	Three tablets once daily	8, 12 or 16
Treatments for specific genotypes			
Harvoni (ledipasvir + sofosbuvir)	1a, 1b, 4, 5, 6	One tablet once daily	8 or 12
Zepatier (elbasvir + grazoprevir) with or without ribavirin*	1a, 1b, 4	One tablet once daily	8, 12 or 16
Treatment after a previous course of direct-acting antiviral treatment			
Vosevi (sofosbuvir + velpatasvir + voxilaprevir)	All	One tablet once daily	12
ribavirin as a possible treatment addition			
Ibavyr (ribavirin)		twice daily	in accordance with the medication in combination

2.8.3 Cure and Spontaneous viral clearance:

The goal of treatment in chronic hepatitis C is the cure or the complete elimination of the virus. The time of the test should be 12 to 24 weeks after the completion of treatment. The cure has a positive impact on mortality from HCV due to liver-related and all-cause mortality (13,63).

In patients with hepatitis C infection, there are two natural possibilities: spontaneous viral clearance or chronic infection. To be sure of spontaneous viral clearance, at least two negative HCV RNA tests 12 weeks apart and at least 6 months after the estimated date of exposure should be detected. Spontaneous viral clearance is estimated from 14 to 50 percent. The likelihood of spontaneous viral clearance is elevated in symptomatic patients, younger patients, female patients, and patients infected by genotype 1 virus. This clearance mostly happens within 12 weeks of infection (29).

2.9 CASCADE OF CARE IN HEPATITIS C

2.9.1. definition

Cascade of care is a tool to monitor the progress of HCV-infected patients and identify gaps in services and access to care. For any hepatitis C treatment program to have a major impact, patients must be diagnosed, connected to care, started, completed treatment, and finally cured (table 3). With the cascade of care, one can therefore monitor patient progress, assess the effectiveness of hepatitis C care and treatment programs, and identify gaps in each step of the cascade.

Safreed-Harmon et al. proposed using a consensus HCV cascade of care with clearly defined stages as a global instrument. They suggested that it may help communicate and facilitate clear and consistent reporting and monitoring to achieve the WHO 2030 target of elimination of hepatitis C (64).

Tableau 3. – Steps of cascade of care for hepatitis C

STEP 1: Patients with Anti HCV+ results
STEP 2: HCV+ patients who are engaged in care
STEP3: HCV+ pateints who had an RNA+ test at least once
STEP 4: HCV+ pateints who have undergone a liver evaluation
STEP 5: HCV+ patients who start treatment
STEP 6: HCV+ patients who have completed treatment
STEP 7: HCV+ patients who are cured (SVR)

2.9.2 WHO program of elimination of Hepatitis C by 2030

Viral hepatitis has become the 7th leading cause of death worldwide and HCV is the cause of 90% of deaths with viral hepatitis. Discovery of new DAAs has raised the hope for elimination of HCV. These new drugs are effective in more than 95% of cases to eliminate HCV and patients remain in SVR on follow-ups (65).

In 2016, the WHO Global Health Sector Strategy (GHSS) on viral hepatitis provided the initial roadmap for the elimination of viral hepatitis as a public health problem by 2030: a 90% reduction in incidence and a 65% reduction in mortality by 2030, compared with a 2015 baseline (66). The WHO target of HCV elimination by 2030 requires that 90% of HCV patients need to be diagnosed, and 80% of these individuals need to be treated in conjunction with means to reduce the incidence of HCV in high-risk groups, such as PWID, dialysis patients, and recipients of unsafe blood transfusion. These strategies are set for prevention of new infections are of equal importance to screening, diagnosing, and treating the existing HCV pool (67). Canada, along with 193 other countries, is committed to reaching the WHO 2030 goal of hepatitis C elimination (27).

To determine the achievability WHO launched an analysis that suggests if five prevention and treatment service coverage targets are reached, HCV could be eliminated as a public health threat (68).

The elimination of HCV is feasible using combining prevention and treatment. Prevention of HCV consists of blood, injection, and surgical safety, and providing sterile needle and syringe for PWID. The new generation of highly effective DAA can cure HCV in a short course of usually 12 weeks with few side effects. Treatment of HCV will reduce the prevalence of the disease and reduces the risk of new infections. The approaches based on population test and treat are highly cost effective.

The WHO requires every country to look at its existing health care system and to develop a cascade of care to ensure capacity building, performance amplification at each step, and surveillance mechanisms to ensure case capture and treatment.

Although treatment is the pivot of cascade of care in WHO guideline, cost is important as many patients are from low-socioeconomic class. Several studies have shown the use of DAAs to be cost-effective because they effectively curtail the progression of HCV and reduce risk for cirrhosis, decompensation, and HCC, thus making them cost saving in public health terms in the long run (69).

Several studies have shown the use of DAAs to be cost-effective because they effectively curtail the progression of HCV and reduce risk for cirrhosis, decompensation, and HCC, thus making them cost saving in public health terms in the long run. However, despite cost-effectiveness, the uptake of HCV treatment is lower than expected because of lack of access to care. Several countries, including Argentina, Brazil, Egypt, Georgia, Indonesia, Morocco, Nigeria, Pakistan, Thailand, and Ukraine, are getting medications for HCV elimination thanks to the WHO and partners' aid for treatment access and favorable licensing agreements. In southern countries with national health insurance systems, HCV treatment has been incorporated in insurance strategies (70).

Adopting the dual approach of depleting the reservoir of HCV and decreasing the incidence of new infection would help curtail the disease and decrease liver-related mortality attributable to HCV.

2.9.3 Barriers of care for hepatitis C infection

patient level

There are different barriers to the cascade of care for hepatitis C at the patient level. These include lack of information (about the transmission routes, treatment, and care), lack of adherence to care and other problems of health (15).

Worldwide about 65-75% of patients with HCV infection do not know their status of hepatitis. In Canada, the estimated number of people unaware of their infection is 44% (71). This is one of the most important barriers to care. Also, there is confusion about the test result and its interpretation, among the patients (72). The distinction between being anti-HCV positive and having an RNA HCV positive test is not necessarily clear for patients.

About 25-35% of the people with positive antibody tests do not come for the follow-up HCV RNA test. This percentage is even higher among the high risk population (46-73%) (73,74). Models have shown that concurrent screening and treatment would be beneficial for some high-risk groups in Canada (75).

Nonadherence to physician recommendations due to asymptomatic infection and the worries in one of the patient's levels barriers. Zuckerman et al evaluated the cascade of care in 187 patients referred to Clinic for HCV infection at Vanderbilt University Medical Center. They concluded that non-linkage to care after the referral was a significant barrier to the cascade of care completion (76). They also found a gender disparity, with women three times less likely to complete the evaluation. On the contrary, they found minimal loss of patients between the evaluation and medication prescription. An estimated 95% of their patients who initiated DAA therapy achieved the full prescribed course (76).

In a study by Sirpal et al., patient level obstacles in the cascade of care were lack of health knowledge, transportation, and financial problems to present in the appointments (77).

Wade et al. Analyzed the cascade of care of hepatitis C in 462 PWID, using a linked viral hepatitis service in a tertiary hospital with a primary care clinic. They suggest that providing community-based HCV services to PWID results in high rates of hepatitis C treatment uptake and cure (78). In

their study among 200 HCV-infected patients, Sherbuk et al. showed that substance use was not identified to be a barrier to care due to providing care in a specialized clinic with experienced staff. Instead, the participants reported stigma, a factor influencing the follow up in the clinic (79).

In research by O'Brien et al, they concluded that there are serious misconceptions between the PWID, one of the most disturbing is that "some people are immune to virus". The other important misinformation about PWID is that they think they can't infect the others (72). Fraenkel et al. emphasized the conceptualization of illness in HCV-infected patients. They refer to how patients think about their illness in different areas such as the cause, the length of the disease, its control, and the consequences of their illness (67).

Financial problems and lack of healthcare insurance are barriers to care of hepatitis C infection. In a study in Texas, USA, up to 46% of Medicaid, and 10% of patients with private insurance were being rejected for the treatment of hepatitis C (80). In their research in 2015-2016, Bolatova et al. found that the higher-income households in Canada are more likely to hold private drug insurance coverage and more likely access to medications (81)

The other social factors include lack of support, social stigmatization, social isolation and other health problems like the presence of depression . In a review held by Treloar et al., the central role of stigma in patient's decision-making and engagement in HCV care was highlighted. They addressed the role of trust in an effective relationship between the client, the caregiver and the health system (83). Evon et al analyzed 126 patients at two specialty HCV clinics. They found that depressive symptoms were independently considered among barriers to care for hepatitis C (84).

Healthcare provider level

The barriers of the cascade of care of hepatitis C at the level of the healthcare providers are different. Among them, limited knowledge about the treatments and the efficacy of the medications and lack of experience, non-available healthcare providers, and communication barriers are the important points (15,24,79). Also, the concept of healthcare about eligibility criteria influences the different treatment uptakes between different clinics (85).

In a study by Aesch in Toronto, one of the themes identified as the treatment barriers was physicians' lack of up-to-date treatment knowledge. They suggested the treatment facilitators such as access to specialist consultation, pharmacist support and primary care HCV treatment guidelines (86).

In the study held by Clark et al., they found that in the care of patients with hepatitis C, more than 60% of the family physicians assess risk factors but rarely in a systematic way. Also, the family physicians may underestimate the antiviral therapy efficacy which can affect their decision (87).

The patient-provider relationship is an important part of health outcomes. In a study held by Rogal et al., they concluded that patients with HCV who perceived communication problems with their clinician were less likely eligible for treatment. They suggested that the poor quality of communication and relationship between patient and healthcare negatively affects treatment adherence and may lead to patient perception of stigma. They recommended more assessments in future due to the teachable nature of the communicational skills (88). In the study of Sherbuk et al. of 200 patients with hepatitis C, patient-provider relationship problems were identified as a barrier to the care of hepatitis C (79).

Government level

The most important barriers at the government level are the lack of financial resources, variations in the delivery of healthcare services, and incomplete national prevention programs (15,26). It is estimated that the cost of treatment for a patient with hepatitis C ranges from $60,000 to $180,000, depending on the type of medication and duration of treatment (89).

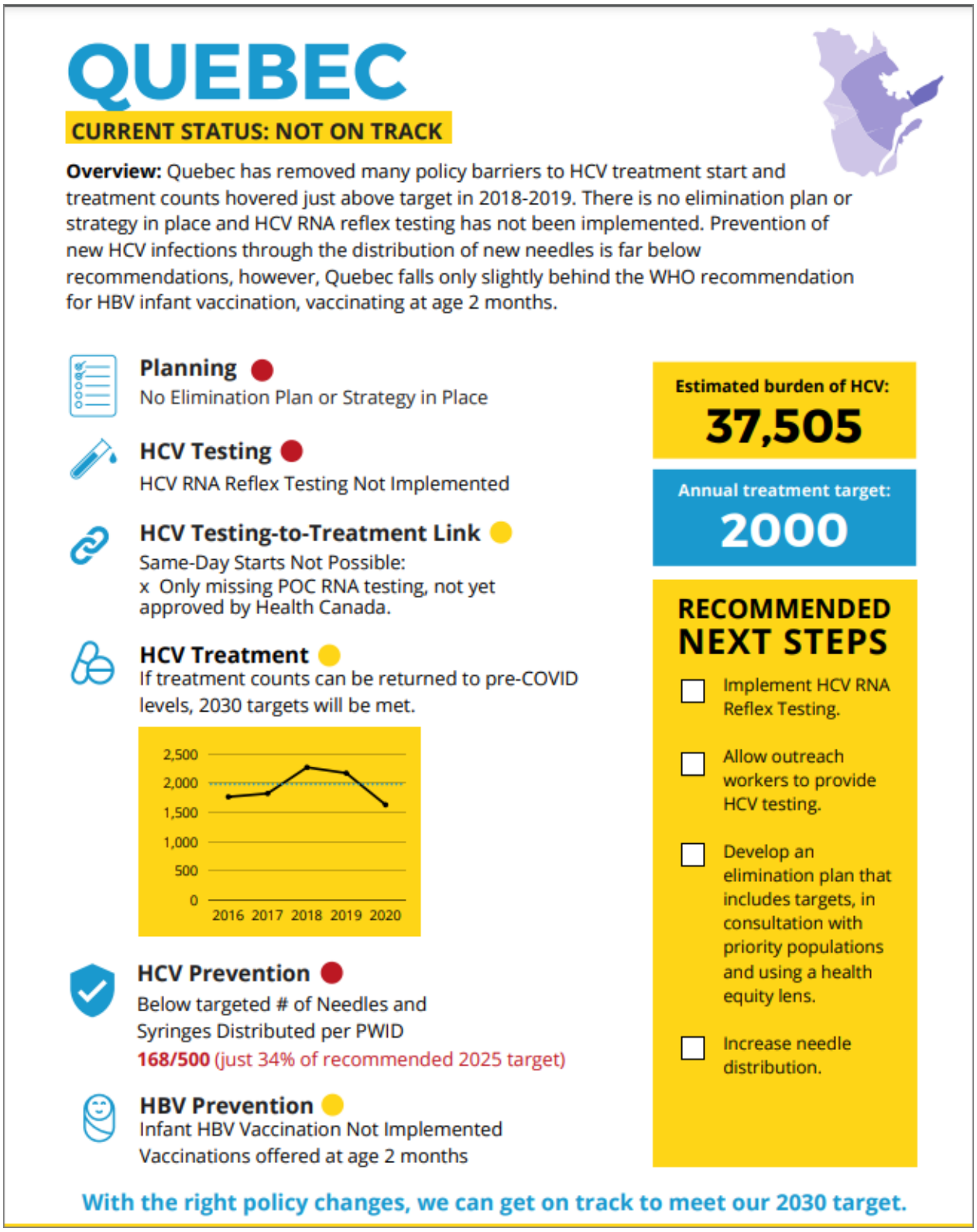
In Canada, until recently, there have been restrictions on reimbursement of DAA medications for hepatitis C treatment. In a study by Marchal et al. in 2018, they found variable criteria for reimbursement of DAA to treat hepatitis C in different provinces of Canada. At the time of the study, in 2018, they found that 85%–92% of provinces had limited criteria for reimbursement to patients with fibrosis stage F2 or more. They reported no alcohol or drug restriction. In Quebec, they found restrictions on HCV treatment reimbursement in HIV coinfected patients (90).

In 2016, Canada was one of the 194 countries that committed to eliminating the disease by 2030 (91). In 2018, Quebec has removed the fibrosis level criterion of reimbursement for DAA medications, to further reach Canada's commitment to the World Health Organization's Global Hepatitis C elimination efforts (61).

In concordance with hepatitis C elimination by 2030, there are federal benefits applicable to different vulnerable groups such as First Nations and Inuit clients. There is a list of medications which are covered. This list is updated monthly. For example, Sublocade (for treatment of opioid use), entered the list of covered medications in April 2022 (92,93). Also, there are programs to help people access and complete their treatment for hepatitis C, offered by the pharmaceutical companies. These programs offer phone support for patients on treatment. They can inform the patients about federal and provincial programs of treatment access and help patients search for any public funding or private medical insurance (94).

Despite all the efforts taken by the federal and provincial governments, there are still areas that do not conform to the goal of eliminating hepatitis C by 2030. According to the CanHepC report published in 2021, Quebec is not on the track to the elimination of hepatitis C toward the elimination of HCV in 2030, in terms of planning, HCV testing, and HCV testing to treatment link (Figure 9) (95).

Figure 9. – Territorial policies in Quebec towards the elimination of hepatitis C until 2030



From: CanHepC 2021 report

2.9.4 Cascade of care of hepatitis C in other provinces

The first province of Canada that released the cascade of care of hepatitis C was British Columbia in 2016 (30). In their study published in 2016, Junjua et al. concluded that the major gap in the cascade of care of hepatitis C in British Columbia was low treatment initiation. They found that people with comorbidities progress in the cascade of testing, but few received treatment. They also reported gaps between HCV RNA testing and genotyping after HCV diagnosis (87).

Young et al. derived a cohort study of PWID in Vancouver, British Columbia, among 1571 participants with chronic HCV between 2005 and 2015. Among this cohort of PWID, only 10% had started treatment and less than half of the patients who started treatment, completed treatment for HCV (96).

Pearce et al. analyzed the HCV cascade of care among people diagnosed with HCV in British Columbia, in 2019. They demonstrated that women are engaged in the HCV cascade of care equally compared to men. They found that women with concurrent social and health conditions are less involved in the cascade of care for hepatitis C. They emphasized the importance of the approaches focused on the needs of younger women, women who inject drugs and those with mental health diagnoses (97).

O'Neil et al. published their research on the cascade of care in Alberta for all Albertan hepatitis C patients between 2009-2014. They found that only 3.4% of patients were cured of hepatitis C within two years of diagnosis at that time (98).

Chapter 3 – RESEARCH OBJECTIVES

The aim of this study was to describe the cascade of care for patients infected by HCV in a clinical setting and to investigate the potential gap in our model of care.

The secondary objectives of our study were:

To analyse if there is disparity among drug users in the HCV cascade of care.

To analyse the impact of HIV-HCV coinfection in the HCV cascade of care.

Chapter 4 – METHODS

4.1 Study Design:

This was an observational retrospective cohort study of patients consulting for hepatitis C in a community clinic in Montreal. It was a single-site quantitative study with exhaustive sampling meaning that all HCV-infected patients who consulted at the Clinique de Medecine Urbaine du Quartier Latin (cmuQL) between January 2010 and October 2018 were included.

We restricted our study to this time because EMR only existed since May 2010, which allowed us to have access to patients' information. Otherwise, the charts were stocked in a secure storing space and access to data was very hard.

After having a positive HCV antibody result (step 1) and engaging in care (step 2), step 3 was to ensure if HCV-infected patients have had an RNA test. An RNA negative result indicates that a patient either recovered spontaneously or received treatment and was cured. If the patient had never been treated for hepatitis C, these results meant that the patient had been necessarily in contact and infected with HCV and had recovered spontaneously. An RNA+ result indicates that the patient is infectious and needs treatment. Next, in step 4 we also looked at who received a liver assessment, such as transient elastography (Fibroscan) or equivalent. This step was important and regulated the access to treatment at the beginning of the availability of DAA.

Step 5 was for patients who started the treatment, completed the treatment (STEP 6) and reached the SVR (STEP 7) so the patient must come back for an RNA test at the clinic 3 months post-treatment, to assess the SVR and to be considered cured of HCV.

Before the arrival of DAAs on the market, the medical follow-up of patients for whom treatment was initiated was much closer and interferon injections were done at the clinic. To determine the adherence to treatment, we used a modified directly observed therapy (mDOT) model of treatment. The patients consulted the clinic at a regular basis (every other week) and they self reported their medication taking.

4.2 CmuQL clinic model (Site)

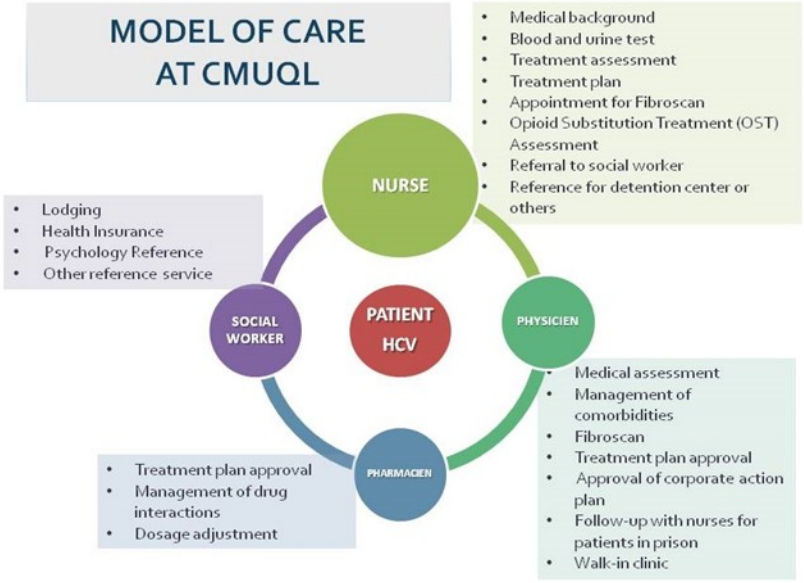
The cmuQL is a health center anchored in downtown Montreal and located near places of concentration of PWID. The clinic has developed expertise in sexual health care and prevention as well as HIV and hepatitis C and care of patients affected by problems related to drug use.

The medical team is made up of 11 doctors who care for hepatitis C patients, 10 of whom are methadone/suboxone prescribers, 2 hepatologists and a nurse specializing in hepatitis. CmuQL is constituted as a FMG and recognized by the Government of Quebec. FMGs provide free care to anyone with access to Quebec public medical insurance.

Clinical care for hepatitis C patients is comprehensive by a multidisciplinary team consisting of a nurse who plays a central role in the care, the doctor, the pharmacist and the social worker, everyone has their mission. Figure 10 shows the interdependence of care services related to hepatitis C, and this holistic approach makes it possible to consider each patient as a whole.

There is an advantage to provide care to hepatitis patients in a specialized clinic in HIV/HCV rather than in a specialized clinic exclusively in HCV. The low CD4 count has been especially common following interferon-based treatments for hepatitis C. At the cmuQL, the treating physicians are familiar with treatment of HIV infected patients and how to approach the low CD4 in these patients. They know the dynamic of the immune system and can manage the continuation of treatment even in the low CD4 levels.

Figure 10. – Model of care at CMUQL



4.3 Study Participants, inclusion and exclusion criteria:

All patients aged 18+ with positive HCV antibody attending health services in cmuQL between 2010-2018 were included in this study. Patients without EMR were excluded from the study because of the impossibility to access the paper charts (table 4). In the next section, we explain how we attempted to trace all the patients infected with hepatitis C at the Clinic.

Patients could have been infected by HCV more than once, for patients with HCV re-infection or multiple treatments we considered only their last situation. For this data, we gathered information from each patient's EMR, individually, to get the exact information.

At cmuQL we have full expertise to take care of PWID. If patients want, we accompany them and take care of their addiction as well. We were able to prescribe them methadone or suboxone according to their needs and follow them for their addiction as well. Our model of care being a low threshold, in no case did drug or alcohol abuse prevent us from treating them for hepatitis C.

Tableau 4. – Inclusion and exclusion criteria:

Inclusion criteria
• Anti HCV+ test • Consulting at CMUQL between mai 2010 and october 2018 • Aged 18+
Exclusion criteria
• patients without EMR

4.4 Sampling and source of data:

The sampling was exhaustive, and all patients infected with hepatitis C consulting at cmuQL, between 2010 and 2018, were included in this study. Data were extracted from several data sources including:

1. The EMR

From there we extracted the patients' personal history and risk factor information, their medical history and comorbidities, their lab results, their anti HCV + status, their transient elastography tests and liver evaluation, their information related to medical consultations and finally their prescription of drugs related to hepatitis C. The interpretation of the stage of the fibrosis was done by the treating physician, based on the findings of the transient elastography or fibrosis-4 index (FIB-4) or by the pathologist reporting the biopsy and the result was accessible through the EMR.

The transient elastography is a recent assessment tool. At the clinic, we had a fibroscan machine on site in 2017, which greatly facilitated our patients' access to this type of evaluation of the liver.

Before, patients had to go to hospitals or radiological centers to perform the test. And before the arrival of transient elastography, we used biopsies to find out the degree of damage to their liver. At that time, many patients refused the biopsy because it was considered too invasive. Although the Quebec guidelines permit to access treatment also with simple fibrosis biomarkers such as aminotransferase to platelet ratio index (APRI) and FIB-4. All information related to liver assessment was extracted from the EMR. We relied either on the result of the biopsy/scan reported in the medical notes or on the complete result of the test or the biopsy itself.

The lab results were also available in the electronic record, and when the tests were not done at the Clinic and were not listed in the lab results, we relied on what the doctor reported in his notes.

2. The clinic's administrative database

- At the level of code 7 of RAMQ billing, which makes it possible to identify among the patients cared for at the clinic (therefore GMF patients) those who were infected with HIV or hepatitis C.

- At the level of the types of medical appointments, we included all patients with an indication of an appointment for hepatitis follow-up, suspected hepatitis, or a transient elastography test.

- At the level of administrative or medical tasks, any code that may refer to the care/needs of patients infected with hepatitis (code Res07 and CRDS).

3. The clinic's HIV database

At CMUQL we have an electronic database and conduct research on our cohort of HIV-infected patients. So, in the clinic's HIV database, we searched for patients who were co-infected with HIV and hepatitis C.

We then merged all these data to identify among this pre-selection, which of our patients were really infected with the hepatitis C virus.

4.5 Data Analysis:

All the analysis has been done on SPSS for Macintosh Version 20.0.0.

For the descriptive analysis, we used frequency tables, number, and proportion for categorical variables and median, range and IQR for continuous variables.

For bivariate analysis, we used ANOVA for continuous variables and Chi-2 for categorical variables, with an alpha=0.05 for signification. The reason we used ANOVA was because our sample size was big enough, permitted us to use parametric tests and gave us more possibilities, like comparing a continuous dependent variable to two categorical variables at the same time.

Data have been truncated (right truncated) at the end of the study observation period (October 2018). We did not have access to the data after October 2018. So to produce the cascade of care, all patients were included in the analyses and those who were still on treatment at the end of the observation period were considered as patients who has not ended treatment (EoT = No), and those who reach the end of treatment but did not yet achieve the 3 months post-treatment or have not been yet tested for viral load, have been considered as not cured (SVR = No).

The proportions were calculated for each of the stages of the cascade, first in relation to the previous column and then in relation to the entire population of the sample. In the cascades, the proportions are those relative to the entire sample.

The objective of this work was not to analyze the determinants of each step of the cascade, but we nevertheless carried out some univariate logistic regression analysis to see the importance of controversial factors to reach the endpoint and maintain a sustainable virological response.

Chapter 5 – RESULTS

5.1 The patients

In our retrospective study of all the cmuQL patients, 1277 had positive serology and antibodies against the hepatitis C virus (anti-HCV+ test). Due to lack of access to physical patient records, we excluded 142 patients and retained the remaining 1135 who were followed between 2010 and 2018 and had an EMR at the clinic and for whom data was available. By using different means to identify cases, we are quite confident that we have identified all the patients infected with hepatitis C in the clinic. The characteristics of patients are demonstrated in Table 5. Patient age and sex, IDU, state of substitution therapy, co morbidities (HIV, axis 1 related problems, depression, renal failure, diabetes, chronic pain, chronic obstructive pulmonary disease, heart disease, cancer, attention deficit hyperactivity disorder and neurological problems) were identified.

In the sample of HCV patients, 53% were FMG patients, who are registered at the clinic as regular patients and the clinic has the responsibility to take care of their health. The non FMG patients come to the clinic for their particular needs, like HCV treatment, and for regular needs, they see their proper family doctor.

We did not have access to the information related to the liver fibrosis stage. However, based on previously published documents on old data from the same cohort, patients were quite advanced in their liver disease (99). In 2015, based on the baseline METAVIR score of the 396 patients in the cohort, 30% of the patients were cirrhotic (table 6). The information of body mass index and ethnicity were not available (99).

Tableau 5. – Patients Characteristics

Patients features	N= 1135	%
Sex		
Male	852	75%
Female	283	25%
Age (med, Range, IQR) years	54 (R 22-92; IQR 47-60)	
Patient's status		
Active*	1087	96%
Death	47	4%
GMF patients	602	53%
Has been treated for HCV	867	76%
IDU	439	39%
Under substitution therapy **	178	16%
Comorbidities		
HIV	564	50%
Axe-1 related problems	173	15%
Depression	65	6%
Renal failure	39	3%
Diabetes	28	3%
Chronic pain	24	2%
COPD (Chronic Obstructive Pulmonary Disease)	20	2%
Heart problem	15	1%
Cancer	16	1%
ADHD (attention deficit hyperactivity disorder)	9	1%
CNS problem	5	0%

* Active = who came to the clinic at least once in the last 3 years

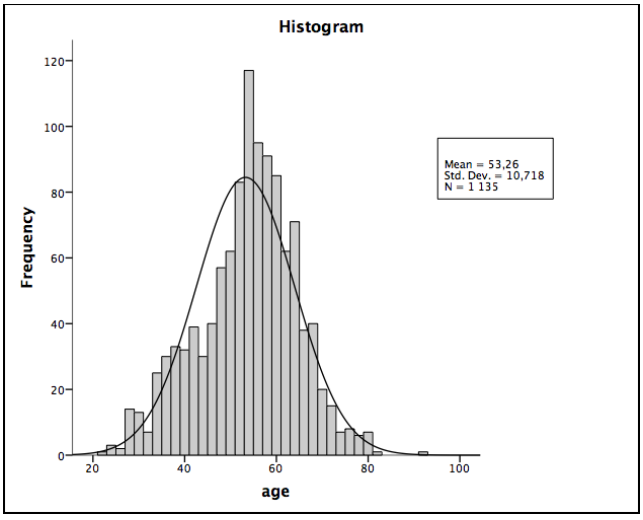
** Either Suboxone or Methadone

Tableau 6. – Baseline METAVIR score

Baseline METAVIR score			
METAVIR score	Naïve	Treated	Total
	N (%)	N (%)	N (%)
F0-F1	94 (66)	69 (27)	163 (41)
F2	14 (10)	39 (15)	53 (13)
F3	17 (12)	45 (18)	62 (16)
F4	17 (12)	101 (40)	118 (30)
Total	142 (100)	254 (100)	396 (100)

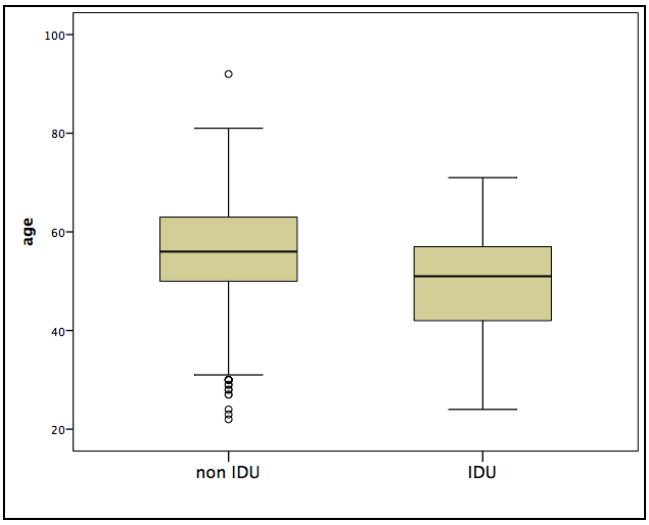
From: http://www.corevih-bretagne.fr/ckfinder/userfiles/files/Congr%C3%A8s/IAS_2015_Vancouver/IAS2015_Poster_Trottier.pdf

Figure 11. – age distribution of our sample



Two-thirds of the patients were male, and the average age of our sample was 53 years (median 54 years). The age of our patients ranged from 22 to 92 years (figure 11). However, the age distribution was not uniform according to certain factors, including injection drug use. PWID were significantly younger than those who did not use drugs (50 vs 56-year-old, $p < 0.001$) (figure 12).

Figure 12. – Age distribution of patients by drug use



HCV-HIV co-infection and IDU:

A significant proportion (50%) of patients were co-infected with Hepatitis C and HIV. Of all HIV-HCV co-infected patients, 63% were PWID (table 7). However, it should be noted that the sexual transmission of hepatitis C is also increasingly seen in men who have sex with other men.

Tableau 7. – HCV-HIV co-infections in PWID vs non-PWID patients.

	Non-PWID	PWID	Total
Mono Infected by HCV	489 (86%)	82 (14%)	**571 (100%)**
Co-infected HIV-HCV	207 (37%)	357 (63%)	**564 (100%)**
Total	**696 (61%)**	**439 (39%)**	**1135 (100%)**

History of treatment in our patients

The number of treatments in our patients is depicted in table 8. Of all HCV-infected patients at the clinic, 268 (24%) never received treatment, including 69 who had a spontaneous recovery. Most of the remainder, 820 (72%) received treatment and 4% received more than one treatment for hepatitis C (table 8).

Tableau 8. – HCV treatment and issue

Number of anti HCV treatments received	Treatment issues				Total
	Treatment needed	Actually in treatment	Spontaneous clearance	Treated and cured	
None/ Naïve to treatment	199	0	69	0	268
One	38	85	6	691	820
Two	6	5	0	29	40
Third	1	0	0	5	6
Six	0	0	0	1	1
Total	244	90	75	726	1135

So, we have experienced 924 treatments for 867 patients. For the details of the treatment and cure of our patients please refer to Table 9 «history of treatment».

Tableau 9. – History of treatment.

Number of treatments

Number of treatments received	N	local code	n	
None, naïve patient	268	C200	198	Never treated => candidate for treatment
		Cs	68	Spontaneous recovery
		CsCs	1	Spontaneous recovery, reinfection, spontaneous recovery again
		CsCsC200	1	Spontaneous recovery, reinfection, spontaneous recovery again, reinfection => candidate for treatment
single treatment	820	C*	691	treated and cured
		C*200	28	Treated and cured, then relapse => candidate for retreatment
		C*C200	9	Treated and cured, then reinfected => candidate for retreatment
		C*Cs	6	Treated and cured, then reinfected and spontaneous recovery
		C*CsC200	1	Treated and cured, then re-infected, spontaneous recovery, then re-infected => candidate for re-treatment
		C300	48	Treatment started (in progress)
		C400	32	Treatment finished for less than 3 months
		C500	5	Treatment completed for >3 months and awaiting SVR evaluation
Two treatments	40	C**	21	Treated x2 and cured
		C**200	3	Treaty x2 and relapse => candidate for retreatment
		C**C200	1	Treated x2 and cured, then reinfected => candidate for retreatment
		C*300	2	Treated and relapse, during the 2nd treatment
		C*400	1	Treated and relapse, 2nd treatment finished less than 3 months ago
		C*500	1	Treated and relapsed, 2nd treatment finished >3 months ago and awaiting SVR evaluation
		C*C*	8	Treated and cured, then re-infected, treated and cured again
		C*C*C200	2	Treated and cured, then reinfected, treated and cured again, then 2nd reinfection => candidate for retreatment
		C*C400	1	Treated and cured, then reinfected, 2nd treatment finished less than 3 months ago
Three treatments	6	C***	5	Treated x3 and cured
		C***200	1	Treated x3 and relapse => candidate for retreatment
Six treatments	1	C******	1	Treated x6 and healed
		Total	**1135**	

legend

C = infection with hepatitis C

* =treated and cured

s =spontaneous recovery

200 = treatment candidate

300 = ongoing treatment

400 =treatment ended since <3 months

500 = treatment ended since >3 months, awaiting evaluation of SVR

As presented in table 9, some people don't respond to treatment and don't reach a cure or seem to be cured but then have relapse and HCV rises again. Some patients recover completely but become infected again with the HCV, sometimes with a different genotype from the first infection and sometimes with the same virus, depending on their exposure.

Relapse rate, re-infection and re-treatment:

In this study, we included 1135 patients. Among them, 867 patients were treated, while 198 patients were never treated, and 68 patients spontaneously recovered. Two patients were reinfected after spontaneous recoveries. In total, 820 patients had a single treatment, 40 patients had two, 6 had three treatments and 1 patient had been treated six times. Of the 820 patients who had a single treatment, 84% (691 patients) were treated and cured. In 6% (48 patients), a single treatment was in progress and in 4% (32 patients), patients' treatment had been finished less than 3 months, so we could not evaluate yet if they were cured or not, while in 5 patients (<1%), treatment completed for more than 3 months and still awaiting SVR evaluation. Interestingly, of 40 patients who were treated twice, 52% (21 patients) were finally cured (Table 9).

The relapse rate was 28 patients out of 820 with a single treatment and eventually, patients were candidates for re-treatment. Regarding the relapse rate, in patients who had been treated twice, 18% (7 patients out of 40) had relapsed again. In patients who received three treatments, 1 patient (16%) relapsed (Table 9).

We decided to take the last state of the patient for the purposes of the cascade analysis, their status is presented in table 10:

Tableau 10. – HCV Patients' Status

Patients' status	N	%
Treatment needed	244	22%
On treatment	90	8%
Spontaneous clearance	75	7%
Sustained Virological Response (SVR)	726	64%

Of the entire sample, we had 7% spontaneous clearances. In fact, some of these patients spontaneously cleared their viruses on more than one occasion: 7 patients had a spontaneous recovery after treatment (including one who subsequently became reinfected), 3 patients

became infected and recovered spontaneously twice (including one who subsequently reinfected with a third infection).

In table 11 we compared the status of patients according to their intravenous drug use characteristics. A greater proportion of PWID reached SVR (68.6% vs 61.1% for non-PWID; p=0.006). Curiously PWID had more spontaneous clearance (8.9% vs 5.2%; p=0.011), a smaller proportion of PWID seems to need treatment (18.9% vs 23.1% of non-IDU; p=0.053) and finally, we have less PWID on treatment now (3.6% vs 10.6% of non IDU; p<0.001).

Tableau 11. – HCV Patients' Status by their drug use status as a risk factor for HCV

Patients' status	Non-PWID	PWID	Total
	n=696 (100 %)	n=439 (100%)	n=1135 (100 %)
Treatment needed	161 (23 %)	83 (19 %)	244 (22 %)
On treatment	74 (11 %)	16 (4 %)	90 (8 %)
Spontaneous clearance *	36 (5 %)	39 (9 %)	75 (7 %)
SVR	425 (61 %)	301 (69 %)	726 (64 %)

* 2 of the patients who had a spontaneous clearance of their viruses, had been reinfected and then categorise as patients who needed treatment

5.2 The cascade

Of these 1135 HCV-infected patients, 1100 (97%) were linked to care and were treated (Table 12). This means that they came to the clinic, among other evaluations they were screened for HCV and came back at least once to have a follow-up and their anti-HCV serology was positive. Among them, 966 (88% or 85% 0f the whole sample) had an RNA test and 825 (85% or 73% of the whole sample) received treatment before the end of the study.

Of all the patients treated, 776 (94%) completed their treatment, which represents 68% of our entire sample for the calculations of the cascade.

Fifty patients had not yet finished their course of treatment, 34 had finished their treatment less than 3 months, and 6 were awaiting their post-3month evaluation for SVR. These patients have

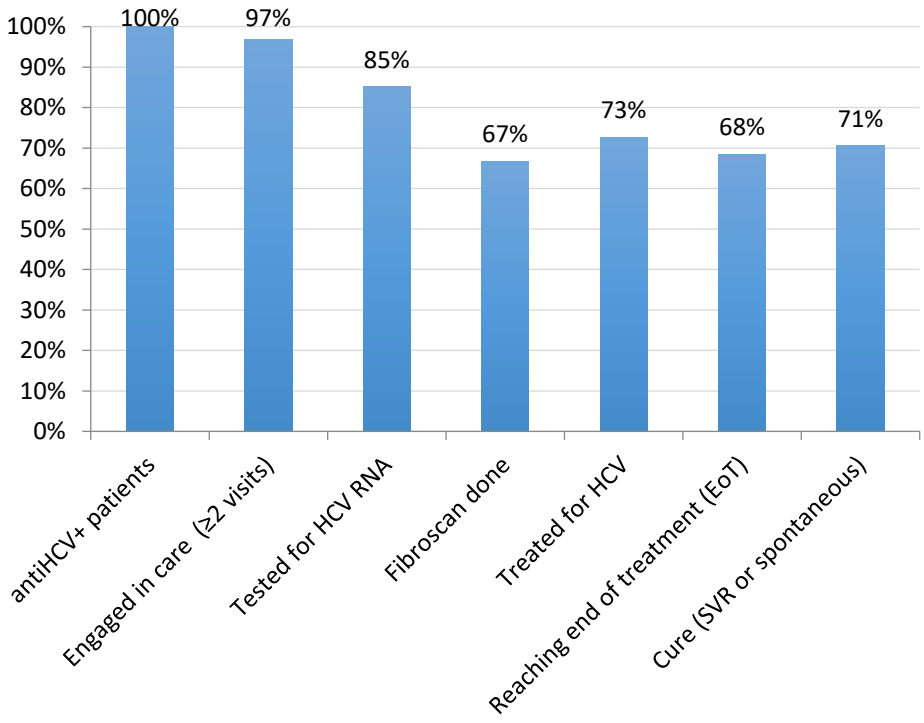
been considered “on treatment”. Finally, among the patients treated, 726 patients (88% or 64% of the whole sample) of patients were cured (SVR) after antiviral treatment.

Tableau 12. – CMUQL’s HCV cascade of care

	Cascade for HCV+ patients	
	N=1135	
HCV+ patients	1135	100%
Engaged in care (≥2 visits)	1100	97%
Tested for HCV RNA	966	85%
Transient elastography done	758	67%
Treated for HCV	825	73%
Reaching EoT	776	68%
Cure (SVR or spontaneous)	801	71%

As is shown in figure 13, from 100% of HCV+ patients, 97% of patients were visited more than twice, 85% of them had an RNA test, 73% received treatment, 70% achieved SVR and a little bit higher than 68% patients reached the end of EOT, because we considered the patients with spontaneous clearance as well. If we did not count the spontaneous clearance, 64% reached SVR after treatment.

Figure 13. – Cascade of care in our study.



HCV cascade of care for HIV-HCV co-infected patients:

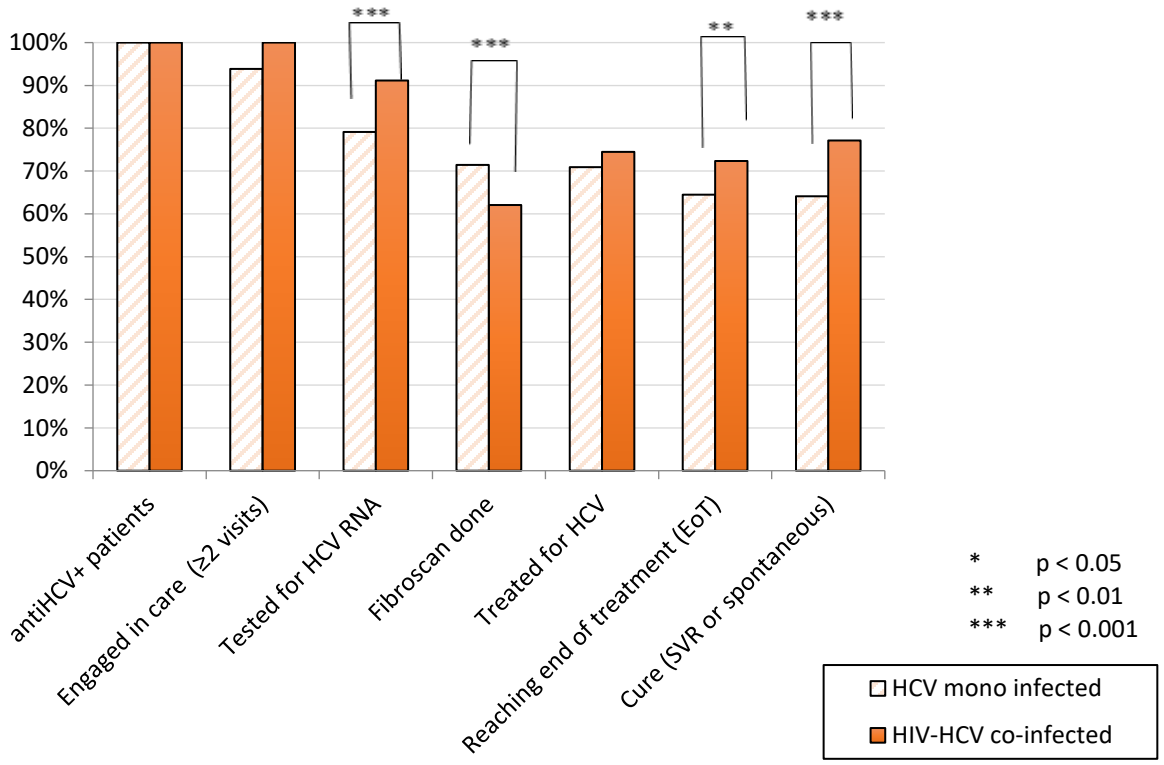
The number of HIV-HCV co-infected patients in our study was 564. All of them had more than 2 visits and 514 (91%) were tested for RNA for HCV. 350 (62%) of them had at least one transient elastography and 420 (62%) underwent treatment while 408 (72%) reached EOT. However, in total 438 (77%) reached SVR or cured spontaneously (Table 13). Among the co-infected patients, 56 (10%) died and 34 (6%) spontaneously cured the virus. Finally, 102 (18%) still needed treatment at the end of the observation period.

Tableau 13. – Cascade of care in HIV-HCV co-infected patients

	Cascade for HIV-HCV infected patients	
	N	
anti HCV+ patients	564	100%
Engaged in care (≥2 visits)	564	100%
Tested for HCV RNA	514	91%
Transient elastography done	350	62%
Treated for HCV	420	74%
Reaching end of treatment (EoT)	408	72%
Cure (SVR or spontaneous)	435	77%

In the following Figure, we showed the comparison between the cascade of care in HCV mono-infected with HIV-HCV co-infected patients (figure 14).

Figure 14. – Comparison of the HCV cascade of care among mono infected and HCV-HIV co-infected patients.



Compared to the mono-infected patients, HIV-HCV co-infected patients had been more frequently tested for HCV RNA (91% vs 79%, p<0.001), had a superior rate of reaching the end of the treatment course (72% vs 64%, p=0.003) and a superior rate of cure (71% vs 64%, p<0.001). However, they were less frequently tested with transient elastography (62% vs 71%, p<0.001).

An interesting point in this comparison is the fact that access to treatment was not different for patients with or without HIV (74% vs 71%, p=0,102).

Effect of addiction, methadone, and HIV on spontaneous clearance of HCV

Spontaneous clearance of HCV occurred in 7% of our patients. Unexpectedly we observed that spontaneous clearance was more prevalent in HIV-HCV co-infected patients, IDU and those on opioid substitution therapy (Table 14).

Tableau 14. – Particularity of spontaneous clearance of HCV

Patients' characteristics	Spontaneous clearance of HCV		
	N=77	%	p-value
HIV-HCV co-infection	48	9%	0.014
HCV mono-infection	29	5%	
Men	59	7%	0.432
Women	18	6%	
IDU	40	9%	0.010
Non-IDU	37	5%	
Methadone program	25	14%	< 0.001
No methadone program	52	5%	
Diabetes	2	7%	0.578
No diabetes	75	7%	

To interpret adequately this disparity, we proceed to univariate and multivariate regression analysis (Table 15).

Tableau 15. – Univariate analysis for determinants of spontaneous clearance of HCV (n=77)

Determinants of Spontaneous clearance of HCV (N=77)	Univariate analysis		
	OR	(95% CI)	p-value
Men	1.095	0.635 - 1.891	0.744
HIV-HCV co-infection	1.739	1.080 - 2.800	0.023
IDU	1.786	1.123 - 2.840	0.014
On opioid substitution therapy	2.844	1.713 - 4.721	< 0.001
Diabetitis	1.058	0.247 - 4.545	0.939

In the simple model, co-infection, drug use and being in the opioid-substitution program were statistically significant and we detect a direct relation between each of these determinants with spontaneous clearance of HCV.

To proceed with the adjusted model, we analyse the correlation matrix as the first step. Table 16 shows the correlation matrix between the variables of interest.

Tableau 16. – Correlation matrix for the determinants of spontaneous clearance of HCV

Correlation Matrix							
		Constant	HIV-HCV (1)	SEX (1)	IDU (1)	methadone (1)	DB (1)
Step 1	Constant	1,000	-,266	-,720	-,152	-,077	-,041
	HIV-HCV (1)	-,266	1,000	-,128	-,413	,050	-,068
	SEX (1)	-,720	-,128	1,000	,019	,077	-,004
	IDU (1)	-,152	-,413	,019	1,000	-,617	,032
	methadone (1)	-,077	,050	,077	-,617	1,000	-,007
	DB(1)	-,041	-,068	-,004	,032	-,007	1,000
Step 2	Constant	1,000	-,269	-,721	-,151	-,077	
	HIV-HCV (1)	-,269	1,000	-,129	-,411	,050	
	SEX (1)	-,721	-,129	1,000	,019	,077	
	IDU (1)	-,151	-,411	,019	1,000	-,617	
	methadone (1)	-,077	,050	,077	-,617	1,000	
Step 3	Constant	1,000	-,369	-,726		-,223	
	HIV-HCV (1)	-,369	1,000	-,133		-,278	
	SEX (1)	-,726	-,133	1,000		,113	
	methadone (1)	-,223	-,278	,113		1,000	
Step 4	Constant	1,000	-,683			-,206	
	HIV-HCV (1)	-,683	1,000			-,266	
	methadone (1)	-,206	-,266			1,000	
Step 5	Constant	1,000				-,551	
	methadone (1)	-,551				1,000	

Obviously, the IDU variable was highly correlated with the co-infection variable (r= -0.413) and with methadone (r= -0.617), therefore, to prevent multicollinearity we decided to omit the IDU variable in the adjusted model.

In multivariate analysis or adjusted model, the only variable that comes out as significant was being under substitution for the opioid program (OR=2.844, p<0.001).

The Cascade of care in female and male patients was not different as expected by the results of the regression analysis. Regarding the second step of the cascade, in fact, male patients seem more engaged in care (98% vs 95% P=0.033). However, in other parts of the cascade such as RNA tested (85% vs 85%, p=0.468), transient elastography (67% vs 67%, p=0.531), treated (72% vs 73%, p=0.379), EOT (68% vs 70%, p=0.219), and cure (70% vs 71%, p=0.511) as expected, there was no significant difference them.

Treatment failures following therapies including Interferon, compared to DAA-based therapies

The results of treatment in the cohort of our patients, with detailed findings in the HIV co-infected patients are shown in the tables 17 and 18.

They are put here just for information, as the data is not completed after 2015.

Tableau 17. – Evolution of the treatment in our cohort

	Type of treatment			Total
	INF without DAA	INF_ DAA	INF free DAA	
1990	1	0	0	1
1994	1	0	0	1
1995	2	0	0	2
1997	3	0	0	3
1998	3	0	0	3
1999	4	0	0	4
2000	13	0	0	13
2001	6	0	0	6
2002	8	0	0	8
2003	19	0	0	19
2004	10	0	0	10
2005	26	0	0	26
2006	21	0	0	21
2007	29	0	0	29
2008	59	0	0	59
2009	59	4	0	63
2010	61	6	0	67
2011	39	8	0	47
2012	21	47	3	71
2013	29	23	11	63
2014	5	26	77	108
2015	0	4	115	119
2016	0	0	2	2
missing	8	0	0	8
Total	427	118	208	753

Tableau 18. – Treatment efficacy disaggregated by HIV co-infection

HIV-HCV co infection	hepC Treatment	Treatment outcome									
		Cured (SVR)		relapser		Treatment failure		LTFU		Total	
		N	%	N	%	N	%	N	%	N	%
mono infected HCV	INF without DAA	186	55%	60	18%	93	27%	2	1%	341	100%
	INF_DAA	68	67%	16	16%	16	16%	2	2%	102	100%
	INF free DAA	99	92%	3	3%	2	2%	4	4%	108	100%
	Total	**353**	**64%**	**79**	**14%**	**111**	**20%**	**8**	**2%**	**551**	**100%**
HIV - HCV co infected	INF without DAA	47	55%	12	14%	24	28%	2	2%	85	100%
	INF_DAA	8	62%	1	8%	4	31%	0	0%	13	100%
	INF free DAA	17	81%	1	5%	2	10%	1	5%	21	100%
	Total	**72**	**61%**	**14**	**12%**	**30**	**25%**	**3**	**3%**	**119**	**100%**
Total	INF without DAA	233	55%	72	17%	117	28%	4	1%	426	100%
	INF_DAA	76	66%	17	15%	20	17%	2	2%	115	100%
	INF free DAA	116	90%	4	3%	4	3%	5	4%	129	100%
	Total	**425**	**63%**	**93**	**14%**	**141**	**21%**	**11**	**2%**	**670**	**100%**

Chapter 6 – DISCUSSION

6.1 Discussion:

This study gave us the opportunity to create a cascade of care of HCV infected patients in a particular clinical setting. The setting was particular because cmuQL is a specialised clinic for STI in general and hepatitis with a whole team taking care of patients who use drugs, either with or without substitution treatment for opioids.

There is a need for a reminder here, that people can be reinfected by hepatitis C and for the purpose of this study we used only the last infection of our patients.

In the interpretation of the results, it is important to consider the particularity of the first 2 columns of the cascade in our study. We are dressing the cascade inside a clinic, which means the patients did already the first step of approaching the healthcare system, came to seek help at the clinic and have been tested for HCV based on their risk factors and behaviour or based on their health needs. Then they have been identified as antiHCV+ patients. That's why our linkage to care seems so high (97%) compared to studies based on outreach (%). Moreover, we did not need to refer them elsewhere to be treated for HCV, the cases were managed by the family doctor backed by the specialist in-site and a whole team of nursing and social workers to take care of their HCV infection. Normally a high proportion of patients lost in the cascade are lost at this step, with the holistic approach at cmuQL we fill the gap between screening and linkage to care.

Using various ways to identify patients (admin/clinic/lab/prescription databases) helped us to ensure a complete case finding procedure. Our aim was to be sure that no one had been left behind. Among the 1277 people identified as antiHCV+, we were able to include 1135 (89%) in our study because they were included in the electronic chart at the clinic. The 142 patients excluded were because we did not have any information about the issue of their disease nor their treatment.

Globally, we can see that the SVR rate is high. This is because the clinic specializes in HCV. 53% of our HCV patients were FMG patients, meaning that they were at their primary source of care, but

this means also that 47% were not regular patients of the clinic and they came there particularly for their Hepatitis C or their HIV-HCV co-infection. Sometimes patients came only to receive HCV treatment at cmuQL and then went back to their family doctor for regular follow-up once treatment is finished. Some other patients also came just to have a transient elastography done at our clinic because in 2017 we got a fibroscan machine. We used this tool for our patients but also for those coming from outside the clinic upon a reference letter.

Engagement in care seems particularly high (97%). We have to interpret this high rate with caution because of the definition we used for engagement in care (at least 2 visits since 2010). There are no predefined criteria for being engaged in care, so we chose this one, but if we had chosen other criteria (ex. At least 3 visits at the clinic) the results would be different.

Going to the third step of the cascade, we lost some patients. Of the 1100 patients only 966 had active virus (HCV RNA+), 75 of them spontaneously cleared their viruses meaning that of the 1025 remaining patients, 94% had a test and were positive. In reality, we lost 6% of our patients at this step. However, for the calculation of the cascade, since all the calculations are based on the initial total number of HCV infected patients, we are at 85% of the whole sample.

Sixty-nine patients had a spontaneous recovery and more precisely, we had 77 occurrences of spontaneous clearance of HCV, which represent 7% of our cases. This is far less than the 25% reported in the literature. We can probably explain this difference by the particularity of our population. Our patients were high risk with multiple comorbidities and were not necessarily in a good health and solid immune system. We had patients with spontaneous clearance who had been reinfected and either the infection cleared spontaneously again or needed treatment to cure.

Interestingly, spontaneous clearance seems to be more frequent among the patients in substitution treatment (14% vs 7%, $p<0.001$) and among those co-infected with HIV (11% vs 7%, $p=0.013$). This difference is probably because those patients were more frequently tested.

The next step of the cascade is the initiation of treatment. At this step we had a gap of 12% again. For some of the patients who did not initiate treatment the reason was that they did not

want to, or they were not ready to be treated at that moment The reason for some others was because they did not come back to the clinic and were lost.

But once the treatment was initiated, the rate of completion and cure was very high. There was less than 5% difference between starting and ending treatment and between ending treatment and reaching SVR. So once the patient started treatment, almost 90% of patients continued until the end. This is due to the clinic's model of care, a holistic management of hepatitis C patients that creates a bond of trust and a very tight follow-up with often vulnerable and marginalized patients, and with substance abuse.

Some of the patients with drug addiction are under methadone and OST for their addiction. These patients come to the clinic for their substitution treatment every week. So, we do not lose them, their HCV treatment could even be considered as a mDOT. We have a specialized nurse who takes care of their drug addiction and a nurse that cares for their treatment of hepatitis C. We have a social worker that takes care of their homing and their healthcare card. They are very difficult patients. If we can keep them to start the treatment, we can keep them to the end of treatment.

The disparity among mono-infected and co-infected patients did not exist in our clinic because all the physicians treating the patients for HCV were also specialized in treating HIV. So, they did not have the fear of interference of HCV drugs with HIV drugs, because they could adjust them upon needs, nor the fear of harm to the immune system of HIV coinfected patients.

In the transient elastography column, we see the numbers are low. This is a question of access to transient elastography. To assess the liver of patients traditionally patients had ultrasound or biopsy. Very few patients consent to have a biopsy because of the invasive nature of the procedure. But with the new technology of transient elastography, liver evaluation became accessible and easy. However, referring patients to other centres to have the evaluation done was a potential risk of losing them. So, the clinic managed to have a fibroscan machine on-site in 2017 and since then, we started to do the transient elastography for all our patients. All those who had treatment before 2017 were less staged for their liver, but after 2017, about 100% had transient elastography results. At that time the liver evaluation was mandatory to have access to

the new drugs. The DAA were available to use based on the fibrosis stage. For example, in the years 2015-2016 patients with F0-F1 were not prioritised for treatment.

To maintain the beneficial health outcomes following HCV treatment we have to keep the education done on liver health and safe injection practices. Being in contact with needle and syringe exchange programs could further help identify patients who need to facilitate access to health care and also raise safe practices among IDUs.

6.2 Limitations of the study

There are some limitations in this cascade of care to consider: first, it is a retrospective study, so we have no control over missing data and information bias. We can only do better to avoid selection bias. However, because data were extracted from medical charts, we can be easily confident that data were reliable and assigned at the time of the event which considerably reduces the memory bias.

At the end of the observation period of our study, 90 patients were still on treatment, or they finished treatment but did not reach the 3 months post-treatment required to evaluate if they got a SVR or not, we considered all those patients as if they did not reach the end of treatment point outcome or did not achieve an SVR. This means that our results underestimated the reality and are very conservative. There is also a risk of underestimating the SVR rate because, for patients who are re-infected several times, we only considered their last status in the cascade.

And when no trace is found to indicate that the patient received treatment in their electronic medical record, it is considered that this patient did not manage to complete the cascade of care, but it is possible that the patient had treatment elsewhere.

Another limitation of our study is that there are no data of the ethnocultural characteristics of the participants.

Chapter 7- Conclusion

In conclusion, our analysis shows that the management of HCV-infected patients in this kind of specialized clinic with a substitution program and holistic care could be successful.

With the development of interferon-free DAA, which are well tolerated and offer a very high rate of cure, we now have an opportunity to eliminate hepatitis C. To accomplish this goal, we need a serious DAA scale-up. With these new treatments, even hard-to-treat patients like HIV-HCV coinfected or IDU patients can easily get cured.

As a public health threat, hepatitis can now be eliminated by micro-elimination on particular populations or even by macro-elimination with a nationwide program. To accomplish this, we also need to have a provincial cascade for hepatitis C which will clearly help identify gaps and help to correct them, to reach this elimination goal.

Engagement in care is one of the classic gaps encountered in the cascade of care, particularly in people who inject drugs and other hard-to-reach populations. The holistic model of care of cmuQL and availability of complementary services like nursing care, social worker services, pharmacy, and substitution therapy, solidifies the engagement of this particular population to care. We have shown that IDUs who have been treated with substitution therapy engage very well in care and successfully complete their treatment for HCV.

The two major challenges in the cascade of care were the initiation of treatment in patients and adherence to follow-up after the end of treatment. They should therefore be considered in future practice to further improve care services for hepatitis C patients.

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