An Evaluation of the Ottawa Hospital Viral Hepatitis Telemedicine Program and Increasing Hepatitis C Virus Care Engagement of Indigenous Peoples Through Telemedicine

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Thesis submitted to the University of Ottawa in partial fulfillment of the requirements for the Master's of Science in Epidemiology

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ABSTRACT

Objective: Evaluate The Ottawa Hospital Viral Hepatitis Program (TOHVHP) telemedicine (TM) program for patient retention, treatment initiation and sustained virologic response (SVR) rates.

Methods: Retrospective analysis of TOHVHP cohort data for patients entering HCV care between 2012 and 2016. Logistic regression modeling was used to assess characteristics associated with patient retention, treatment initiation, and achieving SVR. TM outcomes were compared to the standard outpatient clinic and mixed delivery outcomes.

Results: Treatment initiation rates were comparable between TM and the outpatient clinic. TM delivered Direct Acting Antiviral treatments achieved high SVR outcomes across all patient populations. Patient retention was lower among TM patients.

Conclusion: TOHVHP TM program engaged patients facing barriers to traditional HCV care models. Efforts to improve TM retention are needed.

ABCKNOWLEDGEMENTS

I would like to extend my utmost gratitude and appreciation to my supervisor and mentor, Dr. Curtis Cooper, for sharing his tremendous amount of wisdom, unwavering support, and providing me with the motivation to push myself to become both a better graduate student and researcher throughout this MSc process. Regardless of your seemingly endless list of commitments between the clinic, your research, and family, you have always found time to help me work through any challenges that arose throughout my thesis, and for that I am forever grateful. Thank you for not only this incredible experience and the opportunity you have provided me, but for also going beyond your duties of a supervisor to provide me with guidance in both my personal life and with my future academic endeavors. I will cherish and apply the lessons learned under your supervision throughout my academic and professional career. I am also thankful for my co-supervisor Dr. Yoko Schreiber for sharing both her unfaltering passion for working with Indigenous populations and her tremendous amount of wisdom, which has in turn allowed me to find my place in research and instilled a passion within me that will follow me for the remainder of my career.

I am also appreciative of the members of my thesis committee, Dr. Lynne Leonard and Dr. Audrey Giles, for helping me navigate both the clinical aspect of my thesis but also for pushing me out of my comfort zone to develop the qualitative piece of my thesis. I am forever grateful for the wealth of knowledge you both brought to this thesis, the support your provided, and the skills you have provided me for my future endeavors in research. I would also like to acknowledge members of Dr. Cooper's clinical team including Chrissi Galanakis for sharing her Epidemiology experience and expertise, Jeremy Patern and David Mackie for their help

navigating the TOHVHP clinical database, and Holly Hatashita for her much appreciated company and laughter throughout the data analysis process.

Finally, I would like to thank my loving and supportive family and friends, my amazing fellow MSc. Epidemiology classmates, and my Epidemiology soul-mate, forever friend, and voice of reason, Jessica Yau, for being my rock during some of the toughest times that I have endured throughout this degree. These past two years of my life would not have been possible without the encouragement, support, patience, and comfort from all of you.

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CHAPTER 1: INTRODUCTION

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1.1.1 The Hepatitis C Virus

Hepatitis C virus (HCV), formerly known as 'non-A non-B' viral hepatitis was first identified in 1989 and was originally isolated among two particular sub-groups of patient populations, those who had received blood transfusions and those who had previously or currently engaged in injection drug use [1]. Hepatitis C virus is a phylogenetically diverse blood-borne pathogen. Globally, there have been seven different genotypes of the virus identified (1 through 7), whose prevalence vary dependent on both a patient's geographic location as well as having a history of injection drug use [2]. In North America and European countries, most people are infected with either genotype 1, accounting for nearly half of all infections globally, or genotype 2 or 3, which are often acquired through injection drug use [2,3]

Hepatitis C virus is a virus that targets the liver and can lead to liver cirrhosis, hepatocellular carcinoma, end stage liver disease, the need for liver transplantation, and/or HCV-related mortality [2,4–9] which can present as either an acute or chronic infection. An acute HCV infection occurs when the individual clears the infection spontaneously within six-months of exposure to the pathogen [1,8]. Unfortunately, approximately 70 – 85% of those infected with HCV will progress to develop a more severe form of the illness, known as chronic HCV [1,5,8]. A chronic HCV infection is a long-term illness that results in inflammation of the liver [10] and is diagnosed

when an individual is HCV-RNA positive more than six-months post initial exposure to the pathogen [1,8,9].

Due to the largely asymptomatic presentation of HCV infections [1] during the early stages of the disease, many people are unaware that they are infected with the virus until later in the disease progression, which can have serious implications for people living with chronic HCV. Of those that are chronically infected with HCV, approximately 16 – 20% [5,11] will develop persistent inflammation of the liver known as cirrhosis. Cirrhosis of the liver places the individual at a higher risk for developing hepatocellular carcinoma and having liver de-compensation. The development of cirrhosis of the liver however is found to be dependent on both patient and genetic factors including a patient's alcohol consumption, the presence of co-morbidities such as diabetes, a patient's age and sex, co-infection with either Hepatitis B virus (HBV) and/or Human Immunodeficiency Virus (HIV), and the infecting genotype's viral genetics [1,5,9].

1.1.2 Acquisition of Hepatitis C Virus

Hepatitis C virus is a challenging disease for the Canadian healthcare system to address as many individuals living with HCV often engage in multiple HCV-related risk behaviours. Hepatitis C virus is transmitted from person-to-person through contaminated blood and blood products [2,12]. Common routes of transmission include engaging in unsafe injection practices, (i.e., sharing of used needles and drug paraphernalia), high-risk sexual behaviours (including men who have sex with other men and unprotected sex with multiple heterosexual partners), unsanitary tattooing and piercing practices, and intranasal cocaine use [1,5,7,8,11,13,14]. Populations at higher risk for acquiring HCV include people who inject drugs, healthcare

workers due to and increased risk of experiencing needle stick injuries, individuals having received blood products prior to the implementation of blood screening protocols in 1992, individuals born between 1945 – 1964, and dialysis patients due to the increased potential exposure to contaminated dialysis machines and medical equipment [1,8,11,14].

In developed countries such as Canada and the United States, the main acquisition routes for HCV are through injection drug use and high-risk sexual behaviours, with injection drug use accounting for upwards of 60% of incident HCV cases in the United States [1,2,8,12,15]. In contrast, in developing countries such as Egypt, although injection drug use remains an important route for HCV acquisition, HCV acquisition is also centralized around poor infection control practices within healthcare infrastructures, such as clinics and hospitals. This includes the reuse of syringes for population wide inoculations, use of contaminated medical equipment, and a lack of blood screening protocols [12].

Although there are a variety of transmission routes that have been identified as risk behaviours for acquiring HCV, a variety of demographic and socioeconomic risk factors have also been identified to increase the likelihood of an individual contracting HCV. These factors include a history of incarceration, housing instability, poverty, inadequate access to healthcare and harm reduction services, presence of mental health disorders, insufficient social supports, co-infection with HIV, and poor physical and emotional well-being. All of the above may increase an individual's susceptibility to both acquiring HCV as well as their susceptibility for substance use[8,14,16].

1.1.3 Global Burden of Hepatitis C Virus

Chronic HCV infections are a growing global health concern due to its large contribution to liver-related morbidity and mortality [12,17]. Worldwide there are approximately 170 million individuals living with HCV [6,8,9,12,15] with an additional 4 to 5 million individuals contracting the virus annually [1,6]. In Canada, the Public Health Agency of Canada has reported that as of 2011, 0.96% of the Canadian population were anti-HCV antibody positive. This indicates that nearly 1% of all Canadians are either currently infected or have been exposed to HCV at some point in their lives [6]. Within Ontario specifically, there are currently 110,000 individuals living with chronic HCV. It is anticipated that this number may be underestimated given that many individuals are unaware of their positive HCV status [18].

Of the 170 million individuals living with chronic HCV infections, people who inject or have injected drugs and individuals living with HIV are disproportionately affected by HCV-related morbidity and mortality [5,19–21]. It is estimated that between 66-68% of people who inject drugs are living with HCV infections, accounting for almost 5.8 million people who currently are injecting drugs [4,5]. The high prevalence of HCV in this population, coupled with the increased risk of acquiring and transmitting HCV in early injecting years, highlights the need to quickly and effectively engage people who inject drugs with HCV care in order to reduce the overall global Hepatitis C virus burden and prevent ongoing transmission [20,21]. Individuals who are HIV positive are also disproportionately affected by HCV-related morbidity and mortality. Co-infection with HCV is common due to a shared transmission mechanism of high-risk sexual behaviours, particularly among men who have sex with men [11,12]. It is estimated that approximately 30% of people who are HIV positive worldwide are also living with HCV [12]. This high prevalence of co-infections are a concern for the global burden of HCV, as co-infection

among HIV positive persons has been found to be associated with increased rates of liver fibrosis that is associated with increased risk for developing hepatocellular carcinoma, end-stage liver disease, and HCV-related mortality [11,12,14]

It is known that chronic HCV can lead to liver fibrosis, hepatocellular carcinoma, end stage liver disease, and the need for liver transplantation. These outcomes are associated with increased costs to the Canadian healthcare system and decreased quality of life for patients [6,7,9,17]. These additional financial strains have already been observed in the United States where there have been documented obstacles to providing quality care to patients living with HCV due to the increasing numbers of individuals living with HCV, reduced accessibility to speciality care providers, lack of private insurance, and limited finances [22]. The Canadian healthcare system faces similar issues with providing quality treatment and care to individuals living with HCV due to the aging population of the country often associated with increased complexity of care, as well as increasing population numbers. In 2011 alone, 33% of the 482 liver transplants performed in Canada were due to HCV-related diseases [6] and it is estimated that annually 350,000 people die from HCV-related causes globally [1]. This high rate of HCV-related morbidity and mortality, along with increased costs associated with chronic HCV care, increased HCV diagnosis rates, and the increased demand for HCV morbidity related medical procedures, including transplantation or hepatocellular carcinoma treatment, highlights the critical need for a new approach in identifying, caring for, and treating individuals living with chronic HCV at early stages of the disease [18].

1.2. Historical Treatment Options for Hepatitis C Virus

The historical treatment standard for HCV, known as interferon, was first approved by the United States Food and Drug Administration (FDA) in 1991, allowing for the possibility to treat people living with HCV [23]. Although interferon treatments offered a cure for some patient populations affected by HCV, many patients were excluded from receiving this treatment. Patients were excluded from receiving interferon-based treatments if they previously did not respond to interferon, had autoimmune hepatitis, had other autoimmune disorders, had decompensated hepatic disease, were hypersensitive to pegylated interferon, or if they had major uncontrolled depressive disorder or a history of cardiac disease [24].

Interferon based treatments, often given in combination with ribavirin, consisted of a long, rigorous, and intensive treatment regimens that required patients to visit their HCV care provider on an average of 3x weekly for their interferon injections. The treatment duration was for a 24 to 48 week timeframe, creating issues of adherence over time [2,23]. Historically, these treatments were poorly received by patients due to the intensive nature of the treatment, the frequency of required interferon injections, and due to a large proportion of patients experiencing severe side affects such as psychiatric disorders including depression, as well as fatigue, irritability, interferon-induced bone marrow depression, haemolytic anemia, and nausea. This high prevalence of experienced adverse effects coupled with a difficult treatment plan led to high treatment discontinuation rates among patients [2,9,21,25]. Additionally, for those who were able to be treated and managed to finish their interferon therapies, the likelihood of being cured was very low, ranging from only 6 to 63%, and often resulting in poor patient outcomes [9,21,23,25]

In late 2013, the FDA approved the first form of Direct Acting Antivirals (DAAs) for use in treating individuals living with HCV [23,26]. With the introduction of DAA-based therapies,

previous barriers to treating patients with psychiatric illnesses such as depression, intolerance to interferon, as well as the institutional barriers brought on by the need for frequent in-clinic visits was overcome. Now treatments consist of an orally administered, easy to use prescription for a duration of 8 to 12-weeks, that requires minimal in-person clinic visits [2,21]. Clinical trials have demonstrated that DAA-based therapies are highly tolerable by various patient populations and are a highly effective treatment regimen [2,21].

Overall cure rates for DAA-based therapies range from 90 – 100% and have demonstrated great success among people who inject drugs. Research has demonstrated that among those who had recently engaged in injection drug use, defined as having injected drugs in the last 12-months, 91 to 98% of patients were able to achieve HCV cure with the use of DAAs[20]. Although cure rates have already drastically improved since the interferon era, the recent development of pangenotypic treatment regimens such as Sofosbuvir and Velpatasvir in 2016, as well as Glecaprevir and Pibrentasvir in 2017, will continue to improve treatment access and cure rates across all HCV genotypes and patient populations [5]

1.3. Barriers to Engaging in Hepatitis C Care

Many patients living with HCV face many barriers to engaging with HCV care. These include treatment-specific restriction barriers, diagnosis barriers, healthcare and institutional barriers, and patient and provider barriers. All of these make it difficult to access, initiate, and adhere to treatment [7,13]. Treatment restriction barriers vary dependent on the HCV treatment era in which a patient was engaged in HCV care. In the pre-DAA era, interferon-based treatments themselves were barriers for patients attempting to engage with HCV care. High rates of adverse effects, broad exclusion criteria, and the increased risk for experiencing depression when using

interferon-treatments led to many patients choosing to decline treatment for their HCV infection [15,26]. Additionally, treatment guideline restrictions on both the provider and institutional level created an environment of limited availability for the use of interferon-treatments among individuals with ongoing drug use due to the difficult nature and low tolerability of the treatment regimens [27]. Although the introduction of DAA-therapies have eliminated many barriers faced by patients in the interferon era, high treatment costs, limited insurance reimbursements, and treatment qualification restrictions remain as barriers to accessing HCV care [26]. One barrier to providing patients with effective DAA-therapies is the requirement of a patient undergoing a FibroScan ®, also known as transient elastography, which is a rapid, non-invasive technique used to evaluate the amount of liver fibrosis by measuring liver stiffness in kilopascal's (kPa) [28]. FibroScan ® scores range from 2.5 kPa to 75 kPa and are grouped into five (F0 – F4) levels [28]. Fibroscan scores represent the amount of scarring an individual has on their liver with F0 to F1 (2.5 kPa – 8kPa) consisting of minimal to no fibrosis, F2 (8kPa – 10kPa) consisting of moderate fibrosis, F3 (10kPa – 14kPa) consisting of severe fibrosis, and F4 (14 kPa or higher) representing cirrhosis of the liver[29]. The high costs associated with DAA-therapies has led many countries to ration DAA treatments to the most-ill patient populations thereby restricting access to HCV treatment regimens based on a patient's level of liver fibrosis, often requiring a minimum of a F2 Fibroscan score and moderate fibrosis of the liver [4,17,20,30].

Additionally, although access to superior DAA-treatments has created an opportunity for curing HCV among all those who are infected, a large proportion of individuals are still unaware of their HCV status and this continues to be a barrier for engaging individuals into HCV care [4,15,30,31]. The traditional HCV care cascade consists of six major steps: 1) HCV antibody test, 2) laboratory blood work for HCV RNA testing, 3) appointment with a physician to receive diagnosis of chronic HCV infection, 4) laboratory blood work to determine the infecting

genotype, fibrosis, and baseline HCV viral load, 5) treatment initiation, and 6) HCV cure (Figure 1).

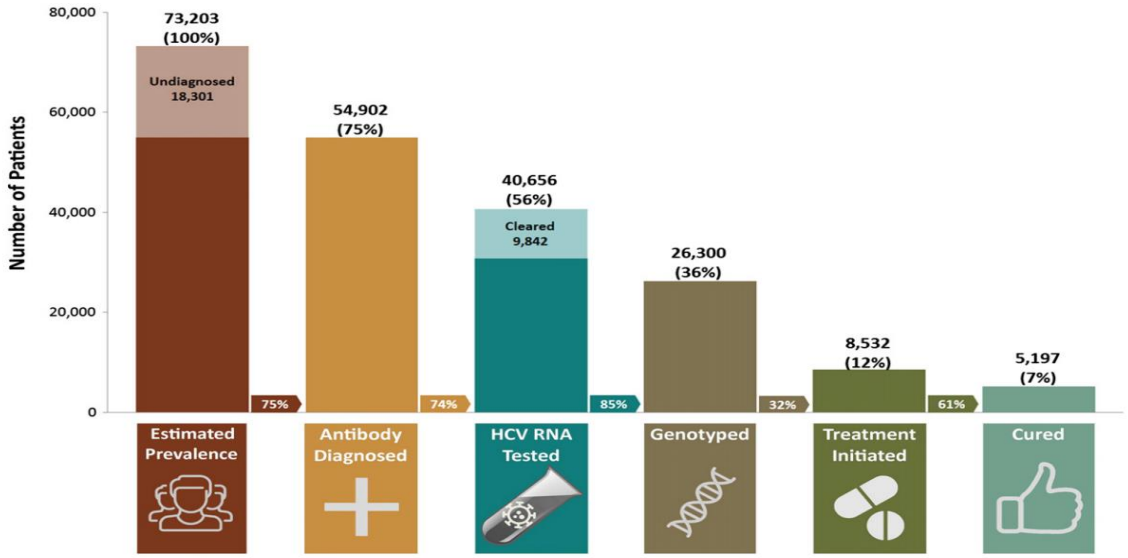

Figure 1. Canadian HCV Care Cascade [32]

The current two step diagnosis process, consisting of first a positive HCV antibody test followed by the need for a return visit for HCV RNA blood work, coupled with long wait times for laboratory test results, present as an ongoing barrier for engaging people in HCV care [15,30]. This barrier caused by the multi-step HCV cascade has been well documented in previous literature. Data from the Chronic Hepatitis Cohort Study found that of those who were HCV antibody positive, 38% did not return for their follow up appointment for HCV RNA blood work [33]. Similar inability to link patients to HCV care was noted in a Canadian cohort, the BC Hepatitis Testers Cohort, as it was found that of the individuals who were HCV antibody positive, 26% did not return for HCV RNA blood work [32]. This highlights the need to not only upscale current HCV screening protocols to capture the undiagnosed population, but also the need to simplify the current HCV care cascade being used in Canada [12,30,34]. The incorporation of novel and tested HCV point-of-care testing technologies, the use of non-invasive biomarkers for

assessing chronic HCV infections including ALT platelet-ratio tests, and the use of dried blood spots through reflex testing could eliminate these barriers faced in trying to engage individuals in HCV care that are imposed by the current multi-factorial HCV care cascade [30,34].

Inherent aspects of the healthcare system also present as barriers for patients attempting to engage in HCV care, particularly for vulnerable populations including people who inject drugs and people who are homeless [17]. In the past, limited knowledge among providers regarding how to effectively engage and treat people who inject drugs created institutional barriers to accessing HCV care [12]. In the interferon era specifically, current substance use, perceived issues with adherence due to the demanding nature of the treatment, and high prevalence of concurrent mental illnesses, caused people who injected drugs to be highly stigmatized by providers, often resulting in people who use drugs being deterred from initiating treatment [4,15,17,19]. In addition to the many misconceptions regarding the ability to treat people who inject drugs, established systematic barriers prevent many vulnerable populations from engaging in HCV care. Individuals living with HCV, especially those who inject drugs, are less likely to have private insurance and to engage regularly with traditional healthcare systems (i.e., hospitals and clinics), often leading to low HCV diagnosis rates, stressful financial barriers to cover treatment costs, and limited opportunities to discuss the potential for HCV care [4,15,17]. This highlights the need for multi-disciplinary approaches to be used in order to engage high-risk populations such as incorporating HCV testing and care into locations frequented by people who inject drugs including needle exchange programs, opioid substitution therapy programs, established harm reduction services, pharmacies, drug checking services, and among primary care providers in order to remove these barriers faced in engaging with traditionally delivered HCV care [20,27].

Finally, factors intrinsic to patients' lives can also create additional barriers to engaging in HCV care. Many individuals living with HCV experience difficult socio-economic

barriers to accessing care due to stigma, poverty, food insecurity, social and material deprivation, financial instability, and geographic isolation (i.e., rural, Indigenous reserve) [4,7,13,15,17], making it difficult to engage with HCV care. Limited education among high-risk populations is also a barrier for engaging in HCV care as many of these individuals have limited knowledge of the natural history of HCV and HCV transmission. This lack of knowledge, coupled with past negative experiences with the healthcare system and the lack of awareness of newly available, easier to tolerate DAA treatments, serve as deterrents for engaging in HCV care [4,17,19,27,31]. This knowledge gap was observed in a Vancouver based Hepatitis Cohort, as 58% of the 584 participants stated that what they had heard about the side effects of HCV treatment negatively impacted their wiliness to initiate therapy. Additionally, more than 50% of participants were under the impression that current HCV treatment still consisted of weekly interferon injections, demonstrating the power of misconceptions shared by peer networks among this population [19,27]. This highlights the need to continue with HCV education outreach among high-risk populations within familiar locations, including needle exchanges and drug treatment programs to make patients aware of not only risk factors for acquiring HCV, but also to reduce the feelings of fear they may have regarding HCV treatment and make people aware of new, easy-to-tolerate treatment options [27].

1.4. Overview of Telemedicine

Telemedicine, a term coined in the 1970s, is the use of technology such as computers, video-conferencing, mobile phones, and the internet, to provide long distance healthcare to distant, remote or isolated populations [35–38]. The aim of telemedicine is to: 1) provide clinical support to primary care physicians, 2) overcome geographic barriers to accessing healthcare

services for patients, 3) incorporate the use of information communication technologies into patient care, and 4) improve overall patient health outcomes [36]. The World Health Organization [36] broadly defines telemedicine as the following:

> Delivery of health care services where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interest of advancing the health of individuals and their communities (p. 9)

Due to the increased demand for improved access to health care services, increased prevalence of chronic illnesses, aging populations, and increased demand for speciality care among geographically segregated patient populations, telemedicine, also known as telehealth services, is one of the largest and fastest growing health care delivery models [39,40]. Telemedicine services are offered in two forms: 1) store and forward and 2) real-time consultation using audio and visual technologies [40,41]. Store and forward telemedicine is the transfer of pre-recorded or previously completed diagnostic test results and images to either a local practitioner or specialty care provider for later assessment. Alternatively, real-time consultations are interactive appointments between local practitioners and their patients with a geographically distant speciality care provider that allows for immediate consultation and simultaneous communications [40].

Within Canada, the use of real-time telemedicine consultation is particularly important and advantageous due to Canada's vast geographic area that creates many remote and isolated populations. In Canada, as of 2015, telemedicine was being used in 89 medical fields including

cardiology, family medicine, geriatrics, dermatology, psychiatry, and infectious diseases [42]. Since the development of the Canadian Telehealth Report, the use of telemedicine in Canada has increased rapidly from 282, 529 sessions in 2012 to 411, 778 sessions in 2014. This demonstrates that there was an increased uptake and utilization of telemedicine of more than 45% in two years, highlighting the growing potential of telemedicine to improve health equity across Canadian populations [42].

1.4.1 Demand for Telemedicine in Ontario and The Ottawa Hospital Viral Hepatitis and Telemedicine Program

Ontario, much like the rest of Canada, has experienced a rapid expansion of telemedicine services in clinical care, seeing a 40% increase in telemedicine sessions through the Ontario Telehealth Networks [42]. As of 2015, nearly 394,000 people participated in the Ontario Telehealth Networks, encompassing 1,688 communities and 59 First Nations communities [42]. This increased demand for telemedicine services is echoed in Ottawa, particularly in the context of managing infectious diseases, such as HCV.

In Ottawa, the Ottawa Hospital Viral Hepatitis Program (TOHVHP) has implemented a multidisciplinary HCV care system that serves Eastern Ontario, Western Quebec, and Nunavut to address the increased demand for HCV care [18]. In the spring of 2013, TOHVHP established a telemedicine program as part of the Ontario Telemedicine Network (OTN). This program was created in response to the increased demand for HCV care, the need for increased accessibility of HCV care in rural and isolated populations, to reduce the financial strain occurred by both patients and care-givers, reduce costs associated with travel to the Ottawa Hospital-General campus, and in attempts to decrease both the wait times for HCV consultation/treatment and the

number of individuals lost to follow up [18]. To date, over 500 patients from Eastern Ontario have been provided healthcare via telemedicine for their initial consultation and subsequent treatment/follow up [18].

1.5. Telemedicine As A Means To Improve Access to Hepatitis C Care

Telemedicine has been used in the management and care of many diseases including infectious diseases. With its founding principles rooted in portability and accessibility through the use of information communication technologies, telemedicine has the potential to improve health care delivery for many marginalized populations in underserviced remote and isolated populations. It can increase access to specialty care provided in urban-central tertiary care centres and allows for real time, patient-centered, consultation, diagnosis, and disease management [35,38,41–44].

Previous studies that have evaluated the use of telemedicine in treating individuals living with HIV found that individuals using telemedicine were more likely to adhere to the prescribed treatment regimen [35]. A prison cohort study supported these findings as prisoners who were HIV positive and used telemedicine were found to have higher CD4+ recovery levels because of the increased adherence to their prescribed treatment regimen [22].

Telemedicine has also been demonstrated to be successful in the treatment of HCV. Project Extension of Community Healthcare Outcomes (ECHO) is a telemedicine program that operates in New Mexico in attempts to improve care for individuals living with HCV by creating a link between primary care providers in underserviced areas and HCV specialists [45,46]. Results from the ECHO programs demonstrated that individuals treated at ECHO sites had a sustained viral response (SVR) of 58% compared to the 57% rate observed among individuals who were

treated at the HCV speciality clinic. Likewise, a cohort study of 6,431 patients living with HCV from Veteran Affairs in the United States (VA-ECHO) found that individuals utilizing the VA-ECHO telemedicine program were more likely to initiate treatment for their HCV [47]. These results show that HCV treatment utilizing telemedicine supports can achieve similar outcomes to those obtained in traditional clinic settings [48].

In addition to the initial successes outlined by the ECHO telemedicine programs (i.e., adherence to treatment, equivalent or better disease/treatment outcomes), establishing continuing medical education for physicians in rural clinics is also an important outcome of telemedicine [22]. Individuals in rural and isolated areas will often seek treatment at local primary care clinics to avoid the financial burden of transportation costs and/or to engage with a familiar healthcare provider with mutual cultural values and customs [48]. Recognizing this, it is crucial that primary care physicians are educated by speciality physicians on how to diagnose, treat, and monitor patients living with HCV [48]. Continuing medical education is an important outcome of telemedicine as it provides primary care physicians with current HCV management protocols and ensures patients are receiving appropriate treatment for their HCV diagnosis. This also increases the likelihood that individuals living with HCV are identified earlier to reduce the risk of the patient developing HCV-related end-stage liver diseases, and thereby, reducing both HCV-specific morbidity and mortality [6,48]. Therefore, telemedicine has the capacity to bridge the knowledge gap in underserviced communities and among local primary care providers, and improve HCV diagnosis and care within a patient-centered model [49]

1.6. Benefits and Limitations of Using Telemedicine

As previously described, the use of telemedicine, particularly in underserviced and remote populations in Canada that have limited access to speciality care, is an important healthcare delivery tool to reduce the risk of patients developing complex complications that have the potential to cause life-long HCV-morbidity if left untreated [6,13,50]. The use of telemedicine in these populations highlight the potential benefit of telemedicine programs for addressing health inequity issues within Canada which prevent many patients from accessing, initiating, and adhering to HCV treatment. Previous research has highlighted the potential benefit of using telemedicine for the management of chronic and infectious diseases such as HCV. In Project ECHO, the use of telemedicine to address complex, chronic diseases among underserviced and low socio-economic, minority populations resulted in reduced racial and ethnic disparities experienced by patients when accessing HCV treatment by providing speciality care services within their community [49]. This demonstrates how telemedicine can be used to provide patient-centred care by bringing much needed speciality care to patients in their local community [40,43].

The benefits to patients and providers from using telemedicine include reducing transportation costs, reducing time spent away from home for individuals receiving HCV treatment, decreasing waiting times for specialty care, improved patient follow up, and encouraging more individuals to engage in treatment for their positive HCV infection by making speciality care more accessible. Telemedicine therefore has the potential to reduce the financial burden on the government and healthcare infrastructures [18,35,37,41]. Telemedicine also allows for an improved patient experience as the patient is engaged with a consistent speciality care provider which can improve both the patient's perceived quality of care as well as allow for

comprehensive and continuity of care [37,40,41]. Additionally, telemedicine within Indigenous populations in Canada has the ability to build community capacity by improving HCV-access via primary care physicians and acting as an early intervention strategy for individuals in the community who are unaware of their HCV positive status [51]

Although there are many advantages to using telemedicine, consideration must be given to potential factors that may influence the successful integration of the program into communities which may include the local governing body of existing telemedicine services and the patient's ability to access telemedicine technologies within their community [42]. Access to telemedicine technologies remains as a barrier to program implementation as access and knowledge of such technologies may be limited due to a patient's age, geographic location, and level of education. These barriers can be overcome by allowing for increased patient outreach education on available telemedicine technological devices and by establishing device borrowing programs during a patient's disease management [43].

Some research has found telemedicine to be under utilized and having low satisfaction rates due to technological issues and concerns with respect to maintaining patient confidentiality [52]. Legal confidentiality concerns are a key issue with telemedicine, especially regarding the use of videoconferencing technologies to communicate confidential patient information [43,53]. A review by the Infectious Disease Society of America found that encryption videoconferencing software could be used if there was a connection speed of at least 384 kbps, equivalent to high-speed Internet [53]. Similar internet speed was also found to be required for real-time telemedicine interactions between the provider and patient [53]. Although Internet speed may not be an issue in more central or rural areas, it is a limitation for the implementation of telemedicine in some remote and isolated communities, particularly Indigenous Canadian populations. This is because a large proportion of remote and isolated communities are underserviced (i.e., having a low

speed of 1.5 Mbs per household) or are still without access to broadband (not connected or no residential access) [42,54,55].

The inability to have physical interactions, surrounding the quality of physical examinations with patients, has also been identified as a barrier to telemedicine utilization. As telemedicine technologies continue to develop, this becomes less of a concern with increased availability of peripheral technologies to allow for improved physical examinations [43]. Finally, telemedicine utilization hinges on the perceived quality of the clinical interaction by the patient [43]. The inability to have physical, face-to-face interactions between the provider and the patient could negatively impact a patient's perception of their appointment experience. Without the ability to easily recognize verbal or non-verbal cues, the potential difficulty of language barriers, and the inability to engage on an equal level may impact a patient's experience [36,43].

Within Indigenous communities there are additional limitations regarding the use of telemedicine. A review of TeleMental Health in Canada's Indigenous population of Northern Ontario found that individuals, although satisfied with the service, raised concerns regarding the lack of trust in an unknown provider as well as the lack of acknowledgement of Indigenous cultural values that emphasizes face-to-face interactions occurring in their own language, and the lack of acknowledgement by the providing physician on the importance of socio-economic factors (i.e., lack of clean water, no power, no internet, and inadequate housing) by the inability to see the client and the patient's current medical illness [36,55]. These concerns highlight the need for telemedicine to respect and acknowledge cultural and local needs of the Indigenous communities. The implementation of HCV Telemedicine must ensure community specific Indigenous cultural practices and traditions are integrated into the telemedicine program [50,56]. When all of these factors are achieved, telemedicine may then have the potential to be successful within Indigenous Canadian populations.

CHAPTER 2: RESEARCH RATIONALE AND THESIS OBJECTIVES

2.1. Rationale for this study

Although telemedicine has been shown to be an effective care delivery method to manage other infectious diseases, the use of telemedicine via the Ontario Telemedicine Network (OTN) requires evaluation to determine its effectiveness. The TOHVHP telemedicine program remains under-evaluated and further analysis will allow insight into the effectiveness of the TOHVHP telemedicine program in terms of patient engagement (i.e., treatment initiation) and patient retention. Comparing patients receiving HCV care via telemedicine to patients receiving HCV care at the Ottawa Hospital-General Campus Outpatient Clinic setting (i.e., in person) will contribute to the evaluation of the effectiveness of the telemedicine program. Additionally, only ten percent (11 of 106) of the TOHVHP telemedicine database are individuals who self-identified as Indigenous, compared to the indicating that there may be an issue with the current telemedicine program in engaging Indigenous individuals living with HCV in Ottawa.

2.2. Research Questions

1. *Is the TOHVHP telemedicine program achieving similar rates of patient retention compared to traditional outpatient delivered HCV care at the Ottawa Hospital – General Campus?*
2. *Are HCV treatment initiation rates comparable between TOHVHP telemedicine patient and TOHVHP outpatients?*

3. *Are TOHVHP telemedicine patients achieving similar HCV cure rates compared to those observed in patients receiving traditional outpatient delivered HCV care?*
4. *Are Indigenous TOHVHP patients achieving comparable clinical outcomes compared to non-Indigenous TOHVHP patients, for both telemedicine and outpatient delivered HCV care?*

Analysis of TOHVHP cohort data, individual clinic patient charts, and linkage with existing Statistics Canada data, with emphasis on the Indigenous participants, will allow for the evaluation of additional risk factors such as socio-economic status (SES) and mental health as they may influence the growing number of identified chronic HCV cases.

2.3. Thesis Objectives

The key objectives of component one of this thesis include the evaluation of the TOHVHP telemedicine program for a variety of clinical outcomes. These clinical outcomes include:

1) Evaluate patient retention in HCV care at the TOHVHP through secondary analysis of TOHVHP cohort data.
    i. Identify the average time lapsed between entry into HCV care at the TOHVHP and treatment initiation.
    ii. Identify the proportion of patients lost to follow up.
    iii. Identify average length of patient retention from entry into HCV care and HCV cure, or dismissal from TOHVP.

iv. Identify factors (i.e., clinical, socioeconomic, demographic, mental health) associated with successful patient retention (i.e., successfully completing treatment and returning for SVR confirmation blood work).

v. Compare objectives i, ii, iii, and iv between telemedicine, mixed delivery, and outpatient clinic patients.

2) Evaluate the proportion of patients initiating HCV treatment in the TOHVHP through secondary analysis of TOHVHP cohort data.

   i. Identify the proportion of patients initiating treatment, by treatment type.

   ii. Identify factors (i.e., clinical, socioeconomic, demographic, mental health) associated with treatment initiation.

   iii. Compare objectives i and ii between telemedicine, mixed delivery, and outpatient clinic patients.

3) Evaluate the proportion of patients achieving HCV cure, defined as a patient having a sustained virologic response (SVR), meaning an undetectable amount of HCV virus in their system 12-weeks after treatment completion, in the TOHVHP through secondary analysis of TOHVHP data.

   i. Identify the proportion of patients achieving HCV cure

   ii. Identify factors (i.e., clinical, socioeconomic, demographic, mental health) associated with achieving HCV cure.

   iii. Compare objectives i and ii between telemedicine, mixed delivery, and outpatient clinic patients.

4) Evaluate and compare clinical outcomes 1- 3 above among Indigenous patients in the TOHVHP.

For all the above listed objectives, clinical outcomes of TOHVHP telemedicine patients will be compared to those of patients managed in person at the TOHVHP outpatient clinic at the Ottawa Hospital-General Campus. The effects of mental health and socio-economic factors will be considered in the evaluation of all outcomes, specifically in the context of Indigenous populations.

CHAPTER 3: METHODOLOGY

3.1. Thesis Hypotheses

It is hypothesized that the TOHVHP Telemedicine program will have similar patient retention in care, proportion of patients initiating treatment, and rates of achieved HCV cure compared to the TOHVHP Outpatient Clinic.

3.2. Study Design

This thesis consists of a secondary analysis of retrospective telemedicine and outpatient cohort data for patients living with chronic hepatitis c virus collected from the TOHVHP Data Base Project.

3.3. Patient Recruitment

Patient recruitment occurred prior to this thesis analysis. Study personnel and physicians recruited patients at TOHVHP during regular scheduled HCV care appointments. Once identified, patients were explained that the TOHVHP Data Base Project was a program being established to improve care for patients living with viral hepatitis and to facilitate future research related to viral hepatitis. Patients were informed that if enrolled, clinic personnel would collect information regarding their hepatitis illness, previous treatments, concurrent medical conditions, ethnicity, and engagement in known risk factors for acquiring viral hepatitis, and perform both physical examinations and laboratory blood work. Clinic personnel explained to patients that

their participation in the study was voluntary and that no identifying information would be entered into the TOHVHP Data Base Project including name, initials, date of birth or hospital chart number, and instead each participant would be assigned a unique, non-identifying study number. A copy of the patient recruitment form for the TOHVHP Data Base Project is included in **Appendix A**.

3.4. Definition of Thesis Patient Population

Patients within the TOHVHP Data Base Project were individuals who were diagnosed with chronic HCV. An individual was defined as having chronic HCV if confirmatory RNA blood work using PCR found presence of HCV viral RNA. Diagnosing chronic HCV requires the use of PCR to confirm the presence of HCV RNA within the individual's system [57]. For this thesis, data was restricted to patients 18 years of age or older. When entering the TOHVHP Data Base Project, participants consented to share their demographic information (age, sex, country of origin, race, immigration status, residence), socio-economic assessment (education level, employment status, housing status), baseline clinical assessment (viral load, genotype, co infection with HIV or HBV, fibrosis assessment), liver functioning assessments (ALT, fibrosis score by transient elastography (kPa)), body mass index, treatment regimen, mental health assessment (bipolar disorder, depression, mania, paranoia, personality disorder, PTSD, schizophrenia), risk factors for HCV acquisitions, HCV treatment center (Ottawa Hospital VH Program, telemedicine, other sites), HCV treatment initiation, experienced serious adverse effects or treatment failures (patient interruption, infection, substance use, lost to follow up, viral relapse) and sustained viral response.

Two separate data files, one containing clinic patients and the other containing telemedicine patients, were individually reviewed. Data files were reviewed by confirming patient data against electronic medical records using the Ottawa Hospital OACIS program as well as using a physical patient chart review when required on various clinic variables to ensure data accuracy for the thesis. Patients who were not registered within the TOHVHP in either the clinic data file (n = 660) or telemedicine data file (n = 3) were removed from the data set. Within the telemedicine data file individuals who were HCV RNA negative (i.e., spontaneously cleared the infection on their own) (n = 12), those mono-infected with HBV (n = 9), and those who failed to attend any of their scheduled appointments (n = 4), were also removed. Patients from both data files with multiple treatments were restricted to the latest available treatment.

3.5. Definitions and Determination of HCV Care Delivery Method

HCV delivery care method was determined using data from physical patient charts and electronic medical records in TOHVHP Data Base Project. TOHVHP patients were identified as having received HCV care by one of three HCV care delivery methods: telemedicine, outpatient clinic, or mixed delivery. Telemedicine patients were those that received all of their HCV care via clinic visits conducted using the Ontario Telemedicine Health Network visual and audio and visual equipment at geographically separated medical clinics. Clinic patients were those that received all of their HCV care exclusively in the outpatient clinic at the Ottawa Hospital – General Campus. Patients who were allocated to the mixed delivery method were patients who had both outpatient clinic and telemedicine visits on their hospital record.

Once patients who were not registered within the TOHVHP were removed, 1,904 patient files remained for the two original clinic (n = 1663) and telemedicine (n = 241) data files. After a

review of electronic and physical patient charts, four individuals were re-assigned as having received their HCV care via the Ottawa Hospital – General Campus outpatient clinic and not telemedicine, as originally classified. Once data was restricted to the latest HCV treatment regimen and to those who engaged with the TOHVHP for HCV care between January 1, 2012 and December 31, 2016 and excluded those with acute HCV, those mono-infected with HBV, and those who did not attend any scheduled appointments, 1,454 unique patient files remained for analysis. Of this, 1267 were outpatient clinic patients, 81 were mixed delivery patients, and 106 were telemedicine patients (Figure 2).

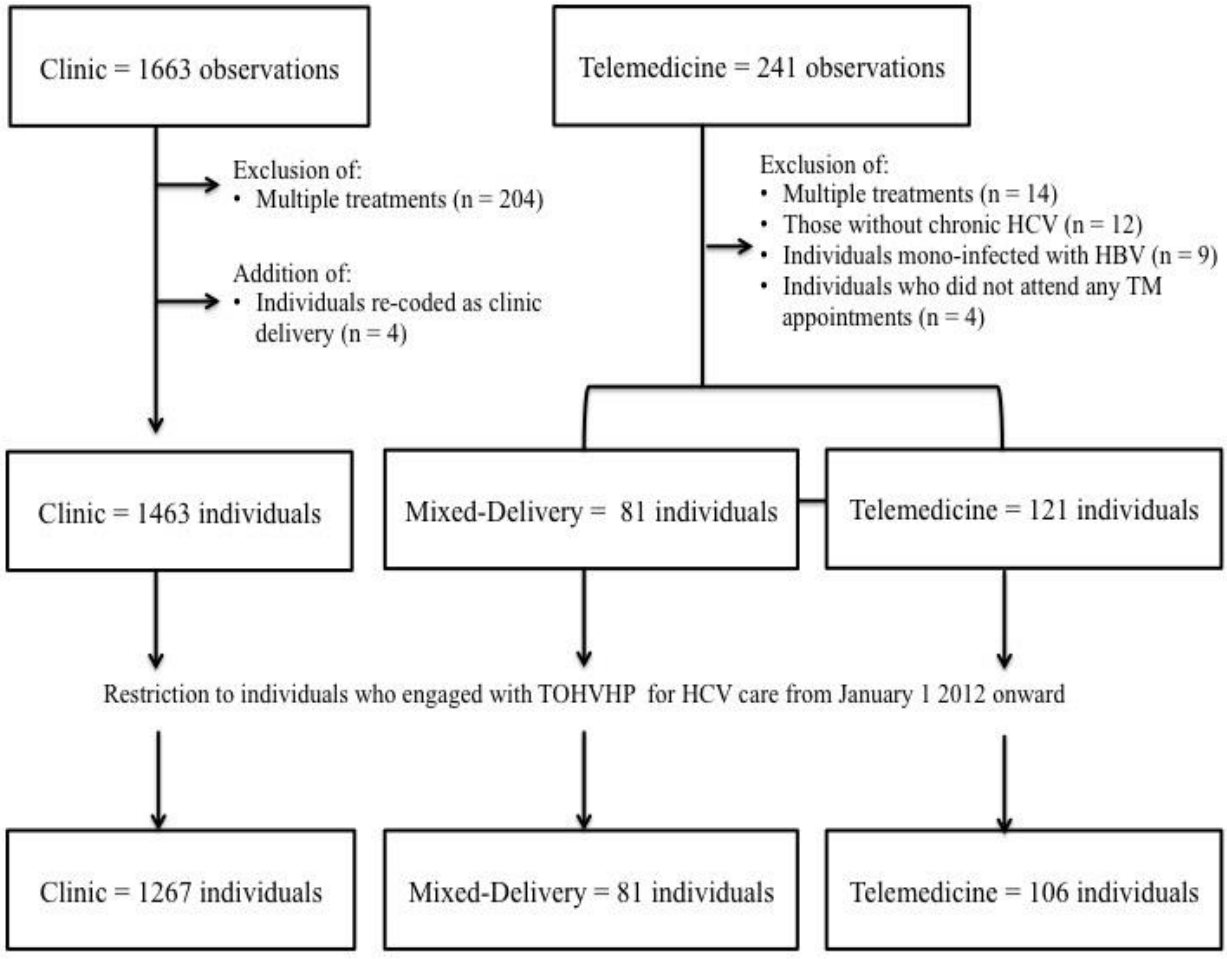

Figure 2. Flow diagram of patient populations by HCV care delivery method.

3.6. Included Clinical and Patient Demographic Variables

Clinical outcomes included fibrosis score by transient elastography (kPa) (known as a Fibroscan score), treatment initiation and completion dates, type of HCV antiviral treatment received, and sustained virologic response (SVR) status. SVR status was determined based on the most recent treatment on file for individuals who received multiple courses of HCV antiviral therapies. Risk factors for acquiring HCV included having a history of injection drug use, history of engaging in high-risk sex (defined as men who have sex men (MSM) and unprotected heterosexual sex), having received blood products (defined as those receiving blood products or having blood transfusions), history of intranasal cocaine use, having had tattoos or piercings, and/ or having been previously incarcerated.

Demographic and socioeconomic information including race, education level, housing suitability, sex, and having a history of mental illness were analyzed. Risk factors, demographic, socioeconomic, and mental health information were self-reported by a patient at entry into TOHVHP. Laboratory results including pre-treatment fibrosis scores by transient elastography, HCV genotype, HIV and/or HBV co-infection, HCV viral load (IU/mL), and ALT (IU/L) were collected when a patient entered care within TOHVHP.

3.7. Use of Statistics Canada Census Data for Principal Component Analysis

Additional data was sought out to provide information for the principal component analysis required to create indices of material and social deprivation within the TOHVHP patient population using the 2016 Statistics Canada Census Data. Geographic information was obtained using the 2016 Statistics Canada Postal Code Conversion File, to provide linkage between the

six-character Canada Post postal codes of TOHVHP patients and population-level census information available from the identified Statistics Canada geographic areas (Statistics Canada, 2017). Access to both the 2016 Statistics Canada Census Data and the 2016 Statistics Canada Postal Code Conversion File was facilitated through a signed agreement with the University of Ottawa Geographic, Statistical and Government Information Centre. The signed copy of this agreement can be found in **Appendix B**.

Geographic level census information for the TOHVHP patient population was determined through linkage of extracted TOHVHP patient postal codes with available 2016 Statistics Canada postal codes which represented geographic areas used in the 2016 Statistics Canada Census Data (Statistics Canada, 2017). Postal codes for TOHVHP patients were collected during patient intake and were updated if there was a change of address throughout the course of a patients HCV care. Geographic information was obtained on the level of dissemination-areas, to represent the smallest geographic unit, containing approximately 400 – 700 individuals to whom census information was collected from in Canada.

Population-level, Statistics Canada Census Data was used to capture variables to measure the proportion of individuals living alone, housing suitability (suitable or not suitable), proportion of individuals without a high school diploma, proportion of individuals divorced, separated, or widowed, proportion of single parent families, employment-to-population ratio, and mean-income after taxes were obtained from the linked 2016 Statistics Canada Census Data. Formulas for the calculation used to create the proportions can be found in **Appendix C.**

Geographic area classification was also extracted from the 2016 Statistics Canada Census Data. Geographic area of residence for patients was originally classified into four possible designations: 1) rural, 2) small urban center, 3) medium urban center, or 4) urban center. For this

thesis both small and medium urban centers were grouped and classified as intermediate, as both experienced influence from larger, urban city centers.

3.8. Statistics Canada Census Variable Definitions

Adjusted after-tax-income. Measured at the statistical unit of private households, referring to the amount of income after tax deductions. Variable is adjusted for economies of scale, equivalent to the square root of the number of people in the statistical unit in order to best represent that individuals living together may share resources.

Rural Area. Rural areas were defined by Statistics Canada as the area that remained after the delineation of population centers, using the current population data. It included small towns, villages with less than 1,000 people, rural areas of census metropolitan areas that may contain estate lots, agricultural lands, undeveloped, and non-developed lands, and remote and wilderness areas.

Proportion of People Living Alone. Calculated as the number of one-person households/total number of private households in the dissemination area. A one-person household was defined as a type of non-census family household, with only one person occupying the private household. A private household was defined as a person or group of persons occupying the same household capturing only private households.

Proportion of Lone-Parent Families. Calculated as the number of lone parent families/total number of census families. Lone parents were defined as a mother or father with no married spouse or common-law parent present, living in a dwelling with one or more children. Census family was defined as a married couple and their children, if any, of either spouse, a couple living common law and the children of any or either partners, or a lone parent of any martial

status with at least one child living in the same household and included couples of opposite and same sex, and children by birth, marriage, common-law union, or adoption.

Proportion of People who are Widowed, Separated, or Divorced. Calculated as the number of people who are widowed, separated, or divorced/total number of people with marital status information within the dissemination area. A person who was separated was a person who was married but no longer lived with their spouse but had not obtained a divorce. A person who was divorced was a person who had obtained a legal divorce and who had not remarried. A person who was widowed was a person whose spouse had died and who had not remarried. Total number of people with marital status information included both same-sex and opposite sex couples.

Proportion of Individuals Without a High School Diploma. Calculated as the number of people without a certificate, diploma, or degree/total number of people with information regarding highest level of education that person has successfully completed in the dissemination area.

Employment-to-Population Ratio. Calculated as the proportion of the population, aged 15 years and older, currently employed in the labor force. The labor force was defined as persons who contributed to or were able to contribute to the production of goods and services within Canada. A person was considered employed if during the reference period (2015 – 2016) they: a) did any work at all at a job/business, that was paid work in the context of a employee-employer relationship or self-employment, or unpaid family work or b) had a job but were not able to work due to an illness, disability, personal or family responsibilities, or labor dispute. It excluded anyone who could not work because they were laid off, between jobs, or did not have a current job.

Housing Suitability. Defined as a private household that has suitable accommodations according to the National Occupancy Standards. This means that there are enough bedrooms for the size of

the family and the family's composition, while taking into account the age, sex, and relationships among household members.

3.9. Building the Principal Component Analysis Model to Calculate Social and Material Deprivation Indices

Six socio-economic indicators were selected based on available literature for their known association with material and social deprivation. These indicators were: 1) the proportion of individuals widowed, separated, or divorced, 2) proportion of individuals living alone, 3) proportion of lone-parent families, 4) proportion of individuals without a high school diploma, 5) employment-to-population ratio, and 6) average household income. All variables were derived from the 2016 Statistics Canada Population Census and included individuals aged 15 years or older, and all except the proportion of lone-parent families were adjusted for population age and sex structure. The indicator of mean household income was additionally adjusted for the economies scale, as previously described.

3.9.1 Assessing Assumptions for Using a Principal Component Analysis

There are five main assumptions behind using a principal component analysis that had to be considered prior to building the social and material deprivation indices. These assumptions were: 1) that variables were measured at the continuous level, 2) there is a linear relationship between all variables, 3) that there was an adequate sample size, 4) that there was adequate correlation between the variables to allow for reduction, and 5) that there are no significant

outliers. These five assumptions were investigated using various statistical tests and through exploratory analysis.

The first assumption was satisfied as all indicators obtained from the 2016 Statistics Canada Census Data were transformed into continuous proportions using the formulas found in Appendix C. The second assumption of linear relationships for all variables measuring social deprivation (proportion of individuals living alone, proportion of single parent families, and proportion of individuals who have been divorced, widowed or separated) and material deprivation (proportion of individuals without a high school diploma, employed-to-population ratio, and mean income) were assessed using scatterplots. Upon investigation, the variables of not having been married, not having a high school diploma, and employed-to-population ratio demonstrated a curvilinear relationship due to a skewed distribution. These variables were log-transformed to satisfy the assumption of linearity. Once transformed, variables representing both social and material deprivation demonstrated reasonable linear relationships and even distribution of residuals.

The third assumption of having an adequate sample size was assessed using Kaiser's measure of sampling adequacy (MSA) statistic. All individual MSA values were determined to be acceptable for the variables of proportion of lone parent families (MSA = 0.78), proportion of individuals living alone (MSA = 0.62), proportion of people widowed, divorced, or separated (MSA = 0.69), proportion of individuals without a high school diploma (MSA = 0.80), employment-to-population ratio (MSA = 0.81), and mean annual income after taxes (MSA = 0.80). The overall MSA value of the material and social deprivation indices was 0.75, indicating that the model had a sufficient sample size and did not require the addition of more variables.

The fourth assumption of having adequate correlation between the variables to allow for reduction was assessed using Bartlett's test of sphericity. Analysis demonstrated that based on

the 1384 observations used, the Bartlett's test p-value ($p < 0.0001$), rejected the null hypothesis, where the null hypothesis indicated there were no common factors. This demonstrated that the variables measuring persons without a high school diploma, employment-to-population ratio, persons living alone, single-parent families, persons separated, divorced, or widowed, persons living in the low-income bracket, mean household income, were appropriate to be used in a principal component analysis.

The fifth assumption that there were no significant outliers was assessed using QQ plots and histograms. Fifteen outliers, defined as observations more than 3 standard deviations from the mean, were identified for the variable of mean income. A sensitivity analysis was performed by removing these variables and comparing the variable coefficients. The identified outliers were not removed of the variables as it only represented 1% of the dataset. As all assumptions were adequately satisfied, it was decided to move forward with using a primary component analysis to combine the six indicators of material and social deprivation.

3.9.2 Assessing Scree Plots to Create Loading Factors within the Primary Component Analysis

Visual inspection of the resulting scree plot for the primary component analysis demonstrated a large drop after factor one, with the decline leveling out from factor three onward, suggesting that only two loading factors were needed to account for enough of the variance in the model.

3.9.3 Assessing Eigenvalues to Create Loading Factors within the Primary Component Analysis

The resulting primary component analysis found that only two variables had an eigenvalue greater than one, further supporting that two factors were needed for the principal component analysis.

3.9.4 Building of Material and Social Deprivation Indices Using the Verified Primary Component Analysis

Overall, visual inspection of scree plots and assessment of eigenvalues supported the use of the resulting deprivation model with two loading factors that formed the primary component analysis to represent material and social deprivation indices within the thesis analysis. The six indicators, the proportion of individuals widowed, separated, or divorced, proportion of individuals living alone, proportion of lone-parent families, proportion of individuals without a high school diploma, employment-to-population ratio, and average household income, were combined using the above verified primary component analysis to create two components of material and social deprivation. The primary component analysis extracted two main components, which were assigned as social (proportion of lone-parent families, proportion of individuals living alone, proportion of proportion go individuals widowed, separated, or divorced) and material (proportion of individuals without a high school diploma, employment-to-population ratio, average household income) deprivation indices. Using this, a value was created that represented the greatest level of deprivation for TOHVHP patients. Quintiles (20% increments) were calculated for each deprivation indices, with the lowest quintile representing the greatest level of deprivation.

3.10. Preparation of TOHVHP Data Base Project Data for Retrospective Analysis

For this thesis, the existing variables used from the TOHVHP Data Base Project were: race, sex, HCV genotype, HIV status, HBV status, FibroScan score by transient elastography (kPa), baseline HCV viral load, baseline ALT, history of anxiety disorder, schizophrenia, post traumatic stress disorder, depression, personality disorder, bipolar disorder, history of injection drug use, history of intranasal cocaine use, having tattoos, having piercings, history of incarceration and a new variable that was created called high-risk sex that captured individuals that engaged in high risk heterosexual sex and men who have sex with men. Definitions of these variables can be found in **Appendix D**.

In order for the TOHVHP Data Base Project Data to be used in retrospective analyses to answer the three thesis objectives previously discussed, multiple assessments had to be conducted to ensure validity of the data.

3.10.1 Handling Missing Data

Each variable within the dataset was assessed to determine the total number of observations missing for each variable. Variables with more than 20% of observations missing were considered unreliable and were removed from the dataset. Total proportion missing observations for each variable can be found in **Appendix E**.

The following variables were identified as having a have a high proportion of missing observations:

1. Self-reported highest level of education (89.6%)
2. Self-reported housing stability (74.8%)

3. Fibro scan score by transient elastography based on treatment round (61.4%)

Further exploratory analysis was performed to better understand the high proportion of missing data for these three variables in TOHVHP Data Base Project Dataset. Further discussion regarding the self-reported variables of highest level of education and housing stability from the TOHVHP Data Base Project found that both of these data had unsatisfactory data quality. Consultation with TOHVHP Clinician, Dr. Curtis Cooper, revealed that the highest level of education was not being consistently captured during the patient's intake process. Additionally, it was noted that intake personnel would have only captured housing status (i.e., unstable or stable) if the patient revealed that their current housing status would present as a challenge to initiating HCV treatment and engaging in HCV care. There was also a large proportion of missing data for FibroScan as the FDA only approved the use of FibroScan technology in 2013. Additionally, TOHVHP did not acquire a FibroScan machine until 2013 and it was further not used in remote assessments for telemedicine patients until 2014 at the earliest therefore, accounting for the lack of available FibroScan data for many patients.

To overcome these issues of missing data, three approaches were taken:

1. We used 2016 Statistics Canada population level data to capture the proportion of people without a high school degree as a proxy for a patient's education level.
2. We used 2016 Statistics Canada population level data to capture the proportion of individuals with suitable and not suitable housing situations.
3. We restricted analysis for DAA treatments, the focus of this thesis, to treatments initiated between January 1, 2014 and December 31, 2016, to account for large proportion of

missing fibro scan data due to TOHVHP not having fibro scan available for remote visits until 2014.

Once these approaches were taken, the proportion of missing data for three variables identified were:

1. No high school (2.4%)
2. Suitable housing (2.4%)
3. Not suitable housing (2.4%)
4. Fibro scan score by transient elastography for DAA patients (38.2%)

The new variables of the proportion of individuals without a high school diploma, the proportion of individuals with suitable housing, and the proportion of individuals without suitable housing was determined to have an acceptable level of missing data. Although there was still a large degree of missing FibroScan for DAA patients, the decision was made to move forward with this being a limitation and indicator of future improvement for the clinic and telemedicine programs.

3.10.2 Identification of Faulty Observations or Outliers

Continuous variables were assessed for outliers (i.e., more than two standard deviations from the mean) and invalid values (i.e., year of treatment initiation or treatment completion dates of January 1, 1900). Categorical variables were also assessed using two-by-two frequency tables to assess for potential collinearity. The following issues were noted:

1. Time until treatment initiation (calculated as treatment start – date of first visit to TOHVHP) values less than 0 days

2. High collinearity between different mental illnesses (i.e., depressive disorder and anxiety disorder)
3. Treatment initiation or completion dates of January 1, 1900
4. Values more than two standard deviations away from the mean for baseline ALT
5. Values more than two standard deviations away from the mean for Fibroscan (kPa) scores

These issues were addressed in the following ways:

1. For time until treatment initiation, it was discovered that patients with values less than 0 days, had initiated HCV treatment in other clinics than TOHVHP. To address this and to allow for accurate reflection from time until treatment initiation within TOHVHP patients, an additional variable was created entitled *Treatment Initiation Clinic*. This variable was categorical and consisted of a two-category outcome: 1) TOHVHP, for patients with time until initiation values equal to or greater than 0 days and whom had initiated treatment in TOHVHP, and 2) Other, for patients with time until initiation values less than 0 days and whom had initiated treatment elsewhere. For the patient retention model to address objective one of this thesis, data analysis was restricted to patients who initiated treatment within TOHVHP.
2. Due to high collinearity and prevalence of TOHVHP patients having experienced more than one mental illness in their lifetime, a composite variable was created entitled *Mental Illness*. This variable was categorical and consisted of a two-category outcome: 1) Yes, for patients having ever reported a history of any mental illness and 2) No, for patients who had not reported ever having a history of any mental illness.

3. Electronic and physical patient chart review was performed for patients with treatment initiation or completion dates of January 1, 1900. Those whose treatment initiation or completion dates were not recorded in patient records were kept as January 1, 1900 and were excluded from the patient retention model.
4. Outliers identified for both ALT values and Fibroscan (kPa) values were verified using electronic and physical patient chart review. All values were validated and the decision was made to keep these patients in the model in order to allow the models to be most representative of the patient population accessing HCV care at TOHVHP.

3.11. Objective 1: Patient Retention

3.11.1 Lost to Follow- Up

A patient was defined as being lost to follow up if the patient: 1) failed to return for SVR blood work at a minimum of 3-months post treatment completion, 2) was lost from HCV care during their treatment regimen, or 3) had pending SVR blood work at time of analysis. Lost to follow up rates were presented as proportions using both per-protocol and intent-to-treat SVR definitions and were compared between telemedicine, outpatient clinic, and mixed delivery patients using Chi-Square analysis.

3.11.2 Time Until Treatment Initiation

Time until treatment was defined as the period of time from a patient's first encounter with TOHVHP to the date a patient started their first recorded treatment regimen for HCV. Time until treatment initiation calculations excluded individuals who initiated their treatment regimen

outside of TOHVHP. Time until treatment initiation was compared between HCV care delivery groups and assessed using a Kruskall-Wallis analysis and presented as median days and range until treatment initiation and standard deviation.

3.11.3 Follow-Up Time

Follow up time was compared using a variety of models: 1) by care delivery method, 2) for interferon, treatment naive patients, 3) for interferon, treatment experienced patients, 4) for Direct Acting Antiviral, treatment naïve patients, and 5) for Direct Acting Antiviral, treatment experienced patients. Follow up time for each model was assessed using a Kruskall-Wallis analysis and presented as median days and range in days.

3.11.4 Creating Multivariable Logistic Regression Model To Assess Patient Characteristics Associated With Retention in HCV Care

To assess the relationship between patient retention and patient demographic characteristics, a logistic regression model was used. The primary variable of interest was HCV care delivery method. Potential known influential covariates included age, sex, identifying as Indigenous, HCV genotype, co-infection with HIV and/or HBV, history of injection drug use, history of intranasal cocaine use, previous tattoos, previous piercings, history of receiving blood products, history of incarceration, history of mental illness, housing suitability, geographic area of residence, proportion of individuals who did not graduate high school, and indicators of greatest level of material and social deprivation.

The logistic regression model was built using a three step process including: 1) exploratory analysis based on knowledge obtained from previous literature review, 2) stepwise, manual, backwards selection for building of a multivariable model, and 3) assessing potential confounding and effect modification between the predictor of interest and covariates.

Exploratory analysis was conducted to assess for associations between the primary predictor of interest of HCV care delivery, identified covariates, and the outcome of patient retention in HCV care, as well as to assess for potential collinearity, influential outliers, and proportions of missing data. As both the primary predictor of interest, HCV care delivery, and all covariates were categorical, associations with the outcome of patient retention in HCV care were assessed using Chi-Square analyses. Collinearity between predictors of patient retention was assessed using two-by-two frequency tables and no issues of collinearity were identified. Outliers were identified for the variables of baseline ALT and Fibroscan scores, however as previously described, were verified using electronic and physical patient chart review. All observations flagged as outliers were discovered to be valid and therefore were not excluded from analysis. Missing data for treatment initiation or completion dates (i.e., treatment initiation or completion dates of January 1, 1900) were addressed by including only those patients with known treatment initiation and completion dates.

Multiple, simple logistic regression models were used to assess patient characteristics associated with the outcome of patient retention in HCV care. When initially building the multivariable logistic regression model, all variables with p-values < 0.2 were included in the initial multinomial logistic regression model. Once all variables were included, various nested multivariable regression models were made by using stepwise, manual, backwards selection principals with a stay criterion of $p < 0.2$. This approach was used until the final model contained only clinically significant covariates or covariates significantly associated with the outcome of

patient retention in HCV care. Although the covariates of age and sex were not significantly associated (i.e., p-value exceeded 0.5) with the outcome of interest, previous research has demonstrated that both are important covariates that may impact a patient's likelihood of being retained in HCV care, and therefore were deemed as clinically significant and were included in the model.

Potential confounding between the primary predictor of interest, HCV care delivery and all covariates on the outcome of patient retention in HCV care was assessed using two variable logistic regression models. As the change in the beta coefficient for the variable of HCV care delivery method did not exceed 20% in any of the two variable logistic regression models, it was determined that the relationship between HCV care delivery method and patient retention in HCV care was not confounded by any of the selected covariates. Effect modification was assessed by incorporating interaction terms between all covariates and the primary predictor of HCV care delivery in the multinomial logistic regression model. As none of the interaction p-values exceeded 0.05, this indicated that no effect modification was occurring between HCV care delivery method and the selected covariates.

3.11.5 Assessing the Fit of The Multivariable Logistic Regression Model

Model fit of the multivariable logistic regression model assessing patient characteristics associated with patient retention in HCV care was assessed using five strategies: 1) assessment for goodness-of-fit (i.e., Hosmer-Lemeshow test), 2) assessment for model discrimination (i.e. C-statistic), 3) visual inspection of observations using influence plots, 4) visual inspection of observations with high leverage, and 5) visual inspection of the Q-Q plots of residuals.

Model fit statistics demonstrated that the final model, containing HCV care delivery method, proportion of individuals experiencing the greatest quintile of social deprivation, sex, and age had acceptable discrimination (0.738) and acceptable goodness-of-fit ($p = 0.306$). Comparisons between the full and two, nested multivariable logistic regression models was assessed using a likelihood ratio statistic. Results of the likelihood ratio test supported that the selected nested model was a better fit than the other two larger models ($p = 0.92$). Model fit statistics for the multiple logistic regression model selection can be found in **Appendix F.**

Visual inspection of influence plots demonstrated normal distribution of residuals. No observations within the model were found to have high leverage, where high leverage was defined as having an h-statistic > 0.2. The QQ plot of the residuals demonstrated a slight deviation from normality. Upon further investigation, it was noted that 149 of the 899 individuals had residuals that did not fit the model well. However, these data points only represented 16.6% of the overall sample, and it was decided to accept the model and to understand the limitations, meaning that the model may not be able to best determine likelihood of patient retention for ~ 17% of the TOHVHP patient population. Based on this, the final logistic regression model was selected to represent variables associated with patient retention in HCV care.

3.12. Objective 2: Retrospective Analysis of Treatment Initiation Among Patients using TOHVHP Data Base Project Data

To meet the second objective of this thesis, patient-level data collected from the TOHVHP Data Base Project was analyzed. From the larger data set, a sub data set containing information on a patient's last HCV treatment regimen on file was created, consisting of 1,454 patients.

3.12.1 Proportion of Patients Initiating HCV Treatment By Care delivery Method

TOHVHP Data was assessed for the proportion of patients initiating HCV treatment by HCV care delivery method. Proportions, by treatment allocation (i.e., exclusively interferon, interferon-Direct Acting Antivirals combination therapies, and exclusively Direct Acting Antivirals) and HCV care delivery method (i.e., telemedicine, mixed delivery, and outpatient clinic) were presented as frequencies.

3.12.2 Creating a Multinomial Logistic Regression Model To Assess Patient and Clinical Characteristics Associated with Initiating HCV Treatment

Due to vast differences regarding time of treatment regimen availability and broad exclusion criteria surrounding the use of interferon-based treatments for individuals with pre-existing mental health disorders, particularly depressive disorder, a multinomial logistic regression analysis was used to analyze variables associated with the initiation of HCV treatment within the TOHVHP. The model included a 3-category outcome, defined by the type of treatment initiated: 1) no treatment initiation, 2) initiation of interferon-treatment regimens (including interferon-Direct Acting Antiviral combination treatments), or 3) initiation of interferon-free, Direct Acting Antiviral treatment regimens. The variable of interest was HCV care delivery method, and potential covariates including age, sex, genotype, race, co infection with HIV or HBV, baseline ALT, pre-treatment Fibroscan score, history of injection drug use, history of intranasal cocaine use, previous tattoos, previous piercings, history of receiving blood products, history of incarceration, history of mental illness, housing suitability, geographic area

of residence, proportion of individuals who did not graduate high school and proportion of individuals experiencing the greatest level of material and social deprivation.

The multinomial logistic regression model was built using a three step process including: 1) exploratory analysis based on knowledge obtained from previous literature review, 2) stepwise, manual, backwards selection for building a multivariable model and 3) assessing potential confounding and effect modification between predictor of interest and covariates.

Exploratory analysis was conducted to assess for associations between the primary predictor of interest of HCV care delivery method, above identified covariates, and the outcome of initiating either interferon-based or Direct Acting Antiviral HCV treatment regimens, as well as to assess for potential collinearity, influential outliers, and proportions of missing data. Associations between the predictor of interest, HCV care delivery method, and categorical covariates with the outcome of treatment initiation were assessed using Chi-Square analyses. Associations between continuous covariates were assessed using ANOVA analyses. Collinearity between continuous covariates was assessed using Pearson's Correlation coefficients whereas collinearity between categorical covariates was assessed using two-by-two frequency tables. No issues of collinearity were identified. Outliers were identified for the variables of baseline ALT and Fibroscan scores, however as previously described, were verified using electronic and physical patient chart review. All observations flagged as outliers were discovered to be valid and therefore were not excluded from analysis. Proportion of missing data for covariates did not exceed 20%, and therefore all covariates were retained in the model.

Multiple, simple logistic regression models were used to assess patient characteristics associated with the outcome of initiating HCV treatment. When initially building the multivariable logistic regression model, all variables with p-values < 0.2 were included in the initial multinomial logistic regression model. Once all variables were included, various nested

multivariable regression models were made by using stepwise, manual, backwards selection principals with a stay criterion of $p < 0.2$. This approach was used until the final model contained only clinically important covariates or covariates significantly associated with the outcome of initiating an HCV treatment regimen. Although the covariates of age and sex were not statistically significant (i.e., p-values exceeded 0.5) with the outcome of interest, previous research has demonstrated that both are covariates that may impact a patient's likelihood of initiating HCV treatment, and therefore were deemed as clinically significant and were included in the model.

Potential confounding between the primary predictor of interest, HCV care delivery method and all covariates on the outcome of initiating HCV treatment was assessed using two variable logistic regression models. As the change in the beta coefficient for the variable of HCV care delivery method did not exceed 20% in any of the two variable logistic regression models, it was determined that the relationship between HCV care delivery method and initiating HCV treatment was not confounded by any of the selected covariates. Effect modification was assessed by incorporating interaction terms between all covariates and the primary predictor of HCV care delivery in the multinomial logistic regression model. As none of the interaction p-values exceeded 0.05, this indicated that no effect modification was occurring between HCV care delivery method and the selected covariates.

3.12.3 Assessing the Fit of The Multinomial Logistic Regression Model

Due to the limitations of model verification in using multinomial logistic regression, two separate paired logistic regression models were analyzed to assess for issues with the data and support the decision to use a multinomial logistic regression model. The two models analyzed

were: 1) no treatment vs. interferon-based treatment and 2) no treatment vs. DAA-based treatment.

Model fit of the two separate multivariable logistic regression models, one for initiating interferon based treatments and the other for initiating Direct Acting Antiviral treatments, were assessed for patient and clinic characteristics associated with initiating HCV treatment using five strategies: 1) assessment for goodness-of-fit (i.e., Hosmer-Lemeshow test), 2) assessment for model discrimination (i.e. C-statistic), 3) visual inspection of observations using influence plots, 4) visual inspection of observations with high leverage, and 5) visual inspection of the Q-Q plots of residuals.

For patients initiating interferon-based treatments, model fit statistics demonstrated that the final model, containing HCV care delivery method, sex, age, presence of ever having a liver biopsy, pretreatment Fibroscan score, and baseline ALT had excellent discrimination (0.826) and acceptable goodness-of-fit ($p = 0.663$). Comparison between the full and nested multivariable logistic regression models was additionally assessed using a likelihood ratio statistic. Results of the likelihood ratio test supported that the selected nested model was a better fit than the other larger models ($p = 0.09$).

For patients initiating Direct Acting Antiviral treatments, model fit statistics demonstrated that the final model, containing HCV care delivery method, sex, age, presence of ever having a liver biopsy, pretreatment Fibroscan score, HCV genotype, history of engaging in high-risk sex, and history of mental illness had excellent discrimination (0.857) and acceptable goodness-of-fit ($p = 0.202$). Comparison between the full and nested multivariable logistic regression models was additionally assessed using a likelihood ratio statistic. Results of the likelihood ratio test failed to support that the selected nested model was a better fit than the other larger models ($p = 0.000$), this was largely due to the strong association between pretreatment

Fibroscan scores and initiating a Direct Acting Antiviral treatment, therefore since the model having acceptable discrimination and goodness of fit, the decision was made to use the model. Model fit statistics for the multiple logistic regression models can be found in **Appendix G**.

Visual inspection of both of the models influence plots demonstrated that some residuals had abnormal distribution. Fifteen observations within the model were found to have high leverage, where high leverage was defined as having an h-statistic > 0.2. A sensitivity analysis was performed and removing the observations did result in significant changes in beta coefficients. Further investigation of these fifteen individuals found no common factor and did not provide further explanation for their high leverage, other than a majority of the patients had high baseline ALT and pretreatment Fibroscan scores. Upon consultation with my supervisor, Dr. Cooper, the decision was made to keep the observations in the model, to allow for the most representative model of the patients presenting to TOHVHP for HCV care.

The plotted QQ of the residuals demonstrated a slight deviation from normality. Upon further investigation, it was noted that 217 of the 1454 individuals had residuals that did not fit the model well. Upon further investigation, it was noted that 46% (99 of 217) of these individuals did not have pretreatment fibrosis score by transient elastography on file, which was highly associated with initiating HCV treatment, which may have accounted for the skewed normality. However, these data points only represented 14.9% of the overall sample, and it was decided to accept the model and to understand the limitation, meaning that the model may not be able to best determine likelihood of treatment initiation for ~ 15% of the TOHVHP patient population. Based this, the final multiple logistic regression model was selected to represent variables associated with initiating a HCV treatment regimen.

3.13 Objective 3: Retrospective Analysis of Achieved SVR Proportions Among Patients Using TOHVHP Data Base Project Data

3.13.1 Proportion of Patients Achieving SVR by Care delivery Method Using Per-protocol Analysis

A per-protocol SVR analysis was used to calculate the proportion of individuals achieving SVR, by HCV care delivery method. Per-protocol SVR included only those individuals who successfully completed their treatment regimen and had a minimum of 3 months post-treatment blood work confirming SVR. Analysis included 855 individuals. Due to treatment allocation being a clinically significant effect modifier on achieving SVR, treatment allocation was controlled for using Cochran-Mantel-Haenszel statistic.

3.13.2 Proportion of Patients Achieving SVR by Care delivery Method Using Intention To Treat Analysis

An intent-to-treat SVR analysis was used to calculate the proportion of individuals achieving SVR, by HCV care delivery method. Intent-to-treat SVR analysis included all individuals who initiated a treatment regimen within TOHVHP, and also included those who discontinued treatment, were lost from HCV care during treatment, and who did not return for 3 months post treatment blood work. Analysis included 914 individuals. Due to treatment allocation being a clinical significant effect modifier on achieving SVR, treatment allocation was controlled for using Cochran-Mantel-Haenszel statistic.

3.13.3 Creating a Multivariable Logistic Regression Model To Assess Patient and Clinical Characteristics Associated with Achieving SVR (Per-protocol and Intention To Treat Models)

Two separate multivariable logistic regression models were prepared: 1) using a per-protocol SVR analysis and 2) using an intent-to-treat SVR analysis, to determine variables associated with achieving SVR at the TOHVHP. Both models used a patient's SVR status according to the patient's last HCV treatment regimen on file. To assess the relationship between achieving SVR and patient and clinic characteristics, a logistic regression model was used. The primary variable of interest was HCV care delivery method. Potential known influential covariates included HIV co-infection, HBV co-infection, HCV genotype, treatment baseline fibro score by transient elastography, presence of ever having a liver biopsy, HCV risk factors, treatment allocation, previous treatment exposure, history of mental illness, identifying as Indigenous, geographic area of residence, proportion of individuals without a high school diploma, housing suitability, and proportion of individuals experiencing the greatest quintiles of material and social deprivation and the outcome of achieving a sustained virologic response.

Both of the multinomial logistic regression model were built using a three step process including: 1) exploratory analysis based on knowledge obtained from previous literature review, 2) stepwise, manual, backwards selection for building a multivariable model and 3) assessing potential confounding and effect modification between the predictor of interest and covariates.

Exploratory analysis was conducted to assess for associations between the primary predictor of interest of HCV care delivery method, identified covariates, and the outcome of achieving SVR, as well as to assess for potential collinearity, influential outliers, and proportions of missing data. Associations between HCV care delivery method, and categorical covariates with the outcome of achieving SVR care were assessed using Chi-Square analyses. T-Tests were

performed to assess the potential association between continuous variables of baseline ALT, treatment baseline fibrosis score by transient elastography, age, and baseline viral load and the outcome of achieving SVR. Collinearity between continuous covariates was assessed using Pearson's Correlation coefficients whereas collinearity between categorical covariates was assessed using two-by-two frequency tables. No issues of collinearity were identified. Outliers were identified for the variables of baseline ALT and Fibroscan scores, however as previously described, were verified using electronic and physical patient chart review. All observations flagged as outliers were discovered to be valid and therefore were not excluded from analysis. Proportion of missing data for covariates did not exceed 20%, and therefore all covariates were retained in the model.

Multiple, simple logistic regression models were used to assess patient and clinical characteristics associated with achieving SVR. When initially building the multivariable logistic regression model, all variables with p-values < 0.2 were included in the initial multinomial logistic regression model. Once all variables were included, various nested multivariable regression models were made by using stepwise, manual, backwards selection principals with a stay criterion of $p < 0.2$. This approach was used until the final model contained only clinically important covariates and covariates significantly associated with the outcome achieving SVR. Although the covariates of age and sex were not statistically significant (i.e., p-values exceeded 0.5) covariates with the outcome of interest, previous research has demonstrated that both are covariates that may impact a patient's likelihood of achieving SVR, and therefore were deemed as clinically significant and were included in the model.

In the per-protocol SVR model, all but one telemedicine patient received Direct Acting Antiviral treatments, causing telemedicine patients to experience an overall SVR rate of 100%, which was far superior than the SVR rates observed among outpatient clinic and mixed delivery

patients. Due to this, in the per-protocol SVR model, HCV care delivery method could not be included in the final multivariable logistic regression model, as it resulted in invalid coefficient and odds ratio estimates. Clinic allocation however was included in the intent-to-treat model, and therefore for this model confounding and effect modification of the primary predictor of HCV care delivery method was assessed. Potential confounding between the primary predictor of interest, HCV care delivery method and all covariates on the outcome of achieving SVR was assessed using two variable logistic regression models. As the change in the beta coefficient for the variable of HCV care delivery method did not exceed 20% in any of the two variable logistic regression models, it was determined that the relationship between HCV care delivery method and achieving SVR was not confounded by any of the selected covariates. Effect modification was assessed by incorporating interaction terms between all covariates and the primary predictor of HCV care delivery method in the multinomial logistic regression model. As none of the interaction p-values exceeded 0.05, this indicated that no effect modification was occurring between HCV care delivery method and the selected covariates.

3.13.4 Assessing the Fit of The Multinomial Logistic Regression Model Using Per-Protocol Analysis

Model fit of the multivariable logistic regression model was assessed for patient and clinic characteristics associated with achieving per-protocol SVR using five strategies: 1) assessment for goodness-of-fit (i.e., Hosmer-Lemeshow test), 2) assessment for model discrimination (i.e. C-statistic), 3) visual inspection of observations using influence plots, 4) visual inspection of observations with high leverage, and 5) visual inspection of the Q-Q plots of residuals.

Model fit statistics demonstrated that the final model containing age, sex, HCV genotype, and treatment allocation had acceptable discrimination (0.788) and acceptable goodness-of-fit ($p = 0.509$). Comparison between the full and nested multivariable logistic regression models was additionally assessed using a likelihood ratio statistic. Results of the likelihood ratio test supported that the selected nested model was a better fit than the other larger models ($p = 0.12$). Fit statistics for each multiple logistic regression model can be found in **Appendix H.**

Visual inspection of influence plots demonstrated that the observation residuals had normal distribution. Five observations within the model were found to have high leverage, where high leverage was defined as having an h-statistic > 0.2. A sensitivity analysis was performed and removing the observations did not result in significant changes in beta coefficients, therefore the decision was made to keep the observations in the model to allow for the most representative model of the patients presenting to TOHVHP for HCV care.

The plotted QQ of the residuals demonstrated a slight deviation from normality. Upon further investigation, was noted that 42 of the 855 individuals had residuals that did not fit the model well. Upon further investigation, it was noted that 83% (35 of 42) of these individuals had received Direct Acting Antiviral treatments, which were highly predictive of treatment success, potentially leading the model to be skewed. However, these data points only represented ~5% of the overall sample, and it was decided to accept the model and to understand the limitation, meaning that the model may not be able to best determine likelihood achieving SVR for ~ 5% of the TOHVHP patient population. Based this, the final multiple logistic regression model was selected to represent variables associated with achieving SVR for all treatment regimens. Additionally, to solve the issue of skewed, a sub-analysis was performed using only patients who were treated with Direct Acting Antiviral treatments.

3.13.5 Assessing the Fit of The Multinomial Logistic Regression Model Using Intention To Treat Analysis

Model fit of the multivariable logistic regression model was assessed for patient and clinic characteristics associated with achieving intent-to-treat SVR using five strategies: 1) assessment for goodness-of-fit (i.e., Hosmer-Lemeshow test), 2) assessment for model discrimination (i.e. C-statistic), 3) visual inspection of observations using influence plots, 4) visual inspection of observations with high leverage, and 5) visual inspection of the Q-Q plots of residuals.

Model fit statistics demonstrated that the final model, containing age, sex, HCV care delivery method, HCV genotype, and treatment allocation had acceptable discrimination (0.732) and acceptable goodness-of-fit ($p = 0.825$). Comparison between the full and nested multivariable logistic regression models was additionally assessed using a likelihood ratio statistic. Results of the likelihood ratio test failed to supported that the selected nested model was a better fit than the other larger models ($p = 0.003$), however the model was used regardless due to having acceptable discrimination and goodness of fit. Fit statistics for each multiple logistic regression model can be found in **Appendix H.**

Visual inspection of influence plots demonstrated that the observation residuals had normal distribution. No observations within the model were found to have high leverage, where high leverage was defined as having an h-statistic > 0.2, therefore all observations remained in the model.

The plotted QQ of the residuals demonstrated a slight deviation from normality. Upon further investigation, was noted that 102 of the 907 individuals had residuals that did not fit the model well. Upon further investigation, it was noted that 71% (72 of 907) of these individuals

had received Direct Acting Antiviral treatments, which were highly predictive of treatment success, potentially leading the model to be skewed. However, these data points only represented ~11% of the overall sample, and it was decided to accept the model and to understand the limitation, meaning that the model may not be able to best determine likelihood achieving SVR for ~ 11% of the TOHVHP patient population. Based this, the final multiple logistic regression model was selected to represent variables associated with achieving SVR for all treatment regimens. Additionally, to solve the issue of skewed, a sub-analysis was performed using only patients who were treated with Direct Acting Antiviral treatments.

3.14. Ethical Considerations

Individuals who participated in the TOHVHP and OTN consented to share their personal information (Ottawa Health Science Network REB 2004-196). Data received from these individuals were restricted for use by study personnel and Dr. Cooper's research team members. Any physical recordings of patient PATMRN numbers were locked in a locked file cabinet that only the MSc student, Candis Lepage, had access to at the end of each night. Upon completion of the thesis analyses, physical recordings of patient PATMRNs were disposed and destroyed according to Ottawa Hospital – General Campus protocols. Research ethics board approval was already achieved prior to the start of this thesis. An amendment to the REB approval was sought to grant Candis Lepage access to Dr. Cooper's TOHVHP Database Project Data through the Ottawa Hospital Research Institute Research Ethics Board.

CHAPTER 4: OVERVIEW OF TOHVHP PATIENT POPULATION

4.1. Overview of the TOHVHP Patient Population Characteristics

The Ottawa Hospital Viral Hepatitis Program (TOHVHP) was evaluated for patients who used TOHVHP at least once to receive HCV care between January 1, 2012 and December 31, 2016. Comparisons between telemedicine, outpatient clinic, and mixed delivery patients in Tables 1 – 6 were made using Chi-Square analysis for categorical variables and ANOVA analysis for continuous variables using SAS 9.4 statistical software.

After inclusion and exclusion criteria previously stated in this thesis were applied, the patient population used for analysis included 1,454 patients who had used TOHVHP at least once for HCV care between January 1, 2012 and December 31, 2016. A total of 106 patients had received their HCV care exclusively via telemedicine as part of the Ontario Telemedicine Network through TOHVHP. Additionally, 1,267 received their HCV care exclusively via TOHVHP outpatient clinic at Ottawa Hospital – General Campus and 81 through a mixture of both outpatient clinic and telemedicine visits, known as mixed delivery (Figure 2).

The three HCV care delivery patient populations were comparable in age, sex distribution, and proportion of individuals experiencing the greatest quintile of material and social deprivation. When comparing telemedicine, outpatient clinic, and mixed delivery patients on socioeconomic factors, telemedicine patients (compared to outpatient clinic and mixed delivery patients) were more likely to be Indigenous (10% vs. 2% vs. 4%, $p < 0.0001$) and have not graduated high school (17% vs. 11% vs. 14%, $p < 0.0001$). Telemedicine patients were also less likely to reside in urban areas (2% vs. 5% vs. 75%, $p < 0.0001$) (Table 1).

Table 1. Population characteristics for telemedicine, outpatient clinic, and mixed delivery patients - Socioeconomic factors**.**

Socioeconomic Factor	Telemedicine N = 106			Clinic N = 1267			Mixed Delivery N = 81			P-value
	n (N)	Mean/ %	SD	n (N)	Mean/%	SD	n (N)	Mean/ %	SD	
Age [A]	106	48.2	11.4	1261	49.3	11.6	81	50.9	10.6	0.2
Sex										0.7
Male	72 (106)	67.9		804 (1261)	63.8		53 (81)	65.4		
Female	34 (106)	32.1		453 (1261)	35.9		28 (81)	34.6		
Race										<.0001
Caucasian	74 (106)	69.8		877 (1267)	69.2		66 (81)	81.5		
Black	2 (106)	1.9		96 (1267)	7.6		1 (81)	1.2		
Asian	0 (106)	0		90 (1267)	7.1		1(81)	1.2		
Indigenous	11 (106)	10.4		27 (1267)	2.1		3 (81)	3.7		
Hispanic	0 (106)	0		1 (1267)	0.08		0 (81)	0		
Other	1 (106)	0.9		20 (1267)	1.6		1 (81)	1.2		
No High School Diploma [B]	18 (104)	17.3		132 (1238)	10.7		11 (78)	14.1		<.0001
Housing Suitability [C]	101	97.1		1169 (1238)	94.4		75 (78)	96.2		<.0001
Suitable	(104)	2.9		69 (1238)	5.6		3 (78)	3.8		<.0001
Unsuitable	3 (104)									
Geographic Area Classification										<.0001
Rural	42 (106)	39.6		164 (1267)	12.9		36 (81)	44.4		
Intermediate	59 (106)	55.7		91 (1267)	7.2		37 (81)	45.7		
Urban	2 (106)	1.8		951 (1267)	75.1		4 (81)	4.9		
Greatest Material Deprivation	33 (106)	31.1		275 (1276)	21.7		17 (81)	20.9		0.2
Greatest Social Deprivation	19 (106)	17.9		282 (1267)	22.2		20 (81)	24.7		0.3

[A] Age at first entry into TOHVHP HCV Care

[B] Proportion of individuals of without a high school diploma was obtained by linking TOHVHP postal codes with 2016 Statistics Canada Census Information through the use of Statistics Canada 2016 Postal Code Conversion file. Average proportion for each clinic was used.

[C] Proportion of individuals with suitable and not suitable housing was obtained by linking TOHVHP postal codes with 2016 Statistics Canada Census Information through the use of Statistics Canada 2016 Postal Code Conversion file. Average proportions for each clinic was used.

When comparing HCV care delivery groups on clinical characteristics, telemedicine patients (compared to outpatient clinic and mixed delivery patients) were more likely to have HCV genotype 3-infections (23% vs. 16% vs. 16%, p = 0.03). Telemedicine patients were also less likely to be co-infected with HIV (1% vs. 6%, p = 0.008) than outpatient clinic patients and

less likely to have cirrhosis of the liver (9% vs. 16% vs. 30%, p = 0.0007) and to have undergone a liver biopsy (11% vs. 38% vs. 30%, p < 0.0001) than both outpatient clinic and mixed delivery patients. The three HCV care delivery patient populations were comparable on the proportion of patients co-infected with HBV (Table 2).

Table 2. Population characteristics for telemedicine, outpatient clinic, and mixed delivery patients - Clinical characteristics**.**

Clinical Characteristic	Telemedicine N = 106		Clinic N = 1267		Mixed Delivery N = 81		P-value
	n (N)	%	n (N)	%	n (N)	%	
HCV Genotype [A]							0.034
1	68 (106)	64.2	824 (1267)	65.0	61 (81)	75.3	
2	6 (106)	5.7	101 (1267)	7.9	5 (81)	6.2	
3	26 (106)	22.6	205 (1267)	16.2	13 (81)	16.0	
4	2 (106)	1.9	74 (1267)	5.8	0 (81)	0	
Mixed	0 (106)	0	20 (1267)	1.6	0 (81)	0	
HIV Positive							0.008
Yes	1 (106)	0.9	76 (1267)	6.0	0 (81)	0	
No	105 (106)	99.1	1191 (1267)	94.0	81 (81)	100	
HBV Positive							0.09
Yes	2 (106)	1.9	13 (1267)	1.0	0 (81)	0	
No	100 (106)	94.3	1142 (1267)	90.2	74 (81)	69.8	
Unknown	1 (106)	0.9	36 (1267)	2.8	6 (81)	5.7	
Biopsy							<.0001
Yes	12 (106)	11.3	483 (1267)	38.1	24 (81)	29.6	
No	94 (106)	88.7	784 (1267)	61.9	57 (81)	70.4	

[A] Excludes individuals without HCV genotyping and those with a viral load to low to determine the infecting HCV genotype

When comparing HCV care delivery groups on self-reported mental health history at patient intake, telemedicine (compared to outpatient clinic and mixed delivery patients) were more likely to have a history of depression (41% vs. 25% vs. 15%, p = 0.0002), a history of schizophrenia (6% vs. 1% vs. 0%, p = 0.0001), and a history of anxiety disorder (29% vs. 16%

vs. 10%, p = 0.0004). The three HCV care delivery patient populations were comparable in terms of history of post-traumatic stress disorder (PTSD), personality disorder, and bipolar disorder (Table 3).

Table 3. Population characteristics for telemedicine, outpatient clinic, and mixed delivery patients - Self reported history of mental illness.

Mental Illness	Telemedicine N = 106		Clinic N = 1267		Mixed Delivery N = 81		P-value
	n (N)	%	n (N)	%	n (N)	%	
PTSD [A]							0.3
Yes	1 (106)	0.9	29 (1267)	2.3	0 (81)	0	
No	105 (106)	99.1	1238 (1267)	97.7	81 (81)	100	
Schizophrenia							0.001
Yes	6 (106)	5.7	17 (1267)	1.3	0 (81)	0	
No	100 (106)	94.3	1250 (1267)	98.7	81 (81)	100	
Depression							0.0002
Yes	43 (106)	40.6	322 (1267)	25.4	12 (81)	14.8	
No	63 (106)	59.4	945 (1267)	74.6	69 (81)	85.2	
Personality Disorder							0.2
Yes	1 (106)	0.9	2 (1267)	0.2	0 (81)	0	
No	105 (106)	99.1	1265 (1267)	99.8	81 (81)	100	
Bipolar Disorder							0.2
Yes	4 (106)	3.8	47 (1267)	3.7	0 (81)	0	
No	102 (106)	96.2	1220 (1267)	96.3	81 (81)	100	
Anxiety Disorder							0.0004
Yes	31 (106)	29.2	201 (1267)	15.9	8 (81)	9.9	
No	75 (106)	70.8	1066 (1267)	84.1	73 (81)	90.1	

[A] PTSD = Post Traumatic Stress Disorder

When comparing HCV care delivery groups on self-reported risk factors for HCV exposure at patient intake, telemedicine patients (compared to outpatient clinic and mixed delivery patients) were more likely to have a history of injection drug use (73% vs. 56% vs. 61%, p < 0.0001), have tattoos (55% vs. 41%. 47%, p < 0.0001), and had previously been incarcerated (46% vs. 37% vs. 42%, p < 0.0001). Telemedicine patients were also less likely to

have received blood products (14% vs. 15% vs. 23%, p = 0.0001) and have piercings (24% vs. 33% vs. 26%, p < 0.0001). The three HCV care delivery patient populations were comparable in terms of the proportion of patients that engaged in high-risk sex. Although statistically significant, the absolute difference in history of intranasal cocaine use was small between HCV care delivery models and likely inconsequential (Table 4).

Table 4. Population characteristics for telemedicine, outpatient clinic, and mixed delivery patients - Self reported history of HCV risk factors**.**

HCV Risk Factors	Telemedicine N = 106		Clinic N = 1267		Mixed Delivery N = 81		P-value
	n (N)	%	n (N)	%	n (N)	%	
IV Drug Use							<.0001
Yes	77 (106)	72.6	703 (1267)	55.5	49 (81)	60.5	
No	25 (106)	23.6	551 (1267)	43.5	29 (81)	35.8	
Unknown	4 (106)	3.8	13 (1267)	1.0	3 (81)	3.7	
High-Risk Sex [A]							0.05
Yes	4 (106)	3.8	105 (1267)	8.3	11 (81)	13.6	
No	102 (106)	96.2	1152 (1267)	90.9	68 (81)	83.9	
Unknown	0 (106)	0	10 (1267)	7.8	2 (81)	2.5	
Received Blood Products							0.0001
Yes	15 (106)	14.2	192 (1267)	15.1	19 (81)	23.4	
No	79 (106)	74.5	1027 (1267)	81.0	54 (81)	66.7	
Unknown	12 (106)	11.3	48 (1267)	3.9	8 (81)	9.9	
Cocaine Snorting							<.0001
Yes	52 (106)	49.0	595 (1267)	47.0	38 (81)	46.9	
No	43 (106)	40.6	648 (1267)	51.1	37 (81)	45.7	
Unknown	11 (106)	10.4	24 (1267)	1.9	6 (81)	7.4	
Tattoos							<.0001
Yes	58 (106)	54.7	525 (1267)	41.4	38 (81)	46.9	
No	39 (106)	36.8	715 (1267)	56.4	35 (81)	43.2	
Unknown	9 (106)	8.5	27 (1267)	2.2	8 (81)	9.9	
Piercings							<.0001
Yes	25 (106)	23.6	416 (1267)	32.8	21 (81)	25.9	
No	70 (106)	66.0	822 (1267)	64.9	51 (81)	63.0	
Unknown	11 (106)	10.4	29 (1267)	2.3	9 (81)	11.1	
Prison							<.0001

Yes	49 (106)	46.2	474 (1267)	37.4	34 (81)	42.0
No	46 (106)	43.4	768 (1267)	60.6	41 (81)	50.6
Unknown	11 (106)	10.4	25 (1267)	2.0	6 (81)	7.4

[A] High-risk sex encompassed both individuals who engaged in high-risk heterosexual intercourse and men who have sex with men.

When comparing HCV care delivery groups on baseline clinic laboratory results, telemedicine patients, compared to outpatient clinic and mixed delivery patients had slightly lower baseline Fibroscan scores measured by transient elastography (15.9 kPa vs. 16.6 kPa vs. 18.6 kPa, p <0 .0001), however all HCV care delivery groups has an average of F4 Fibroscan score. The three HCV care delivery populations were comparable on baseline ALT values and baseline HCV viral load (Table 5).

Table 5. Population characteristics for telemedicine, outpatient clinic, and mixed delivery patients - Baseline HCV clinical measurements

Baseline Variables	**Telemedicine N = 106**		**Clinic N = 1267**		**Mixed Delivery N = 81**		**P-Value**
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	
ALT (IU/L) **[A]**	100	95 (90)	1246	97 (87)	79	120 (113)	0.07
HCV Viral Load (IU/mL)	97	3.2^{e+6} (5.4^{e+6})	1125	4.8^{e+6} (1.9^{e+7})	77	4.2^{e+6} (7.8^{e+6})	0.6
Fibroscan Score (kPa)**[B]**	26	15.9 (12.8)	487	16.6 (14.9)	48	18.6 (14.4)	<.0001

[A] Baseline ALT values
[B] Fibrosis based using treatment as the unit of measurement

Although it appears that HCV antiviral treatment uptake is higher among outpatient clinic patients compared to both telemedicine and mixed delivery patients, this may be due to the TOHVHP telemedicine program not being established until spring 2013 and fully operational until 2014. When controlling for treatment initiation year using Cochran-Mantel Haenszel statistic to account for the difference in both the establishment of HCV care delivery models and

the availability of different treatments during the included time period of this thesis (2012 to 2016), treatment uptake was comparable between HCV care delivery methods (p = 0.25) (Table 6).

Table 6. Population characteristics for telemedicine, outpatient clinic, and mixed delivery patients - HCV treatment initiations.

Clinical Characteristic	Telemedicine N = 106		Clinic N = 1267		Mixed Delivery N = 81		P-value
	n (N)	%	n (N)	%	n (N)	%	
Treatment Initiation [A]	37 (106)	34.9	815 (1267)	64.3	62 (81)	76.5	<.0001

[A] Measured as every receiving an HCV treatment regimen.

When comparing HCV care delivery groups by HCV treatment regimen, telemedicine, outpatient clinic, and mixed delivery patients experienced high rates of SVR for interferon-Direct Acting Antiviral combination therapies and Direct Acting Antiviral therapies. When controlling for treatment allocation using a Cochran-Mantel-Haenszel test, SVR rates did not significantly differ by HCV care delivery method, however the sample size may have been too small to detect small differences due to limited power (p = 0.93).

Table 7. Population characteristics for telemedicine, outpatient clinic, and mixed delivery patients - HCV treatment allocations.

Clinical Characteristic	Telemedicine N = 106		Clinic N = 1267		Mixed Delivery N = 81		P-value
	n (N)	%	n (N)	%	n (N)	%	
SVR by Treatment [A]							
Interferon							
Yes	0 (0)	0	134 (211)	63.5	4 (5)	80.0	*0.93

No	0 (0)	0	77 (211)	36.5	1 (5)	20.0
Interferon + Direct Acting Antivirals						
Yes	1 (1)	100.0	76 (83)	91.6	3 (3)	100.0
No	0 (0)	0	7 (83)	8.4	0 (3)	0
Direct Acting Antivirals	26 (26)	100.0	440 (472)	93.2	44 (47)	93.6
Yes	0 (26)	0	32 (472)	6.8	3 (47)	6.4
No						

[A] 7 clinic patients had unknown treatment and were excluded from analysis.
* Significance when controlling for treatment allocation, p-value calculated using Cochran-Mantel-Haenszel Test.

When comparing overall per-protocol SVR rates for all treatment regimens by HCV care delivery groups, telemedicine patients experienced higher SVR rates compared to outpatient clinic and mixed delivery patients (p = 0.02). It should be noted however that the sample size for telemedicine in this thesis might have been too small to detect small differences in SVR rates due to limited power (Table 8).

Table 8. Population characteristics for telemedicine, outpatient clinic, and mixed delivery patients - Overall sustained virologic responses for all HCV treatment types.

Clinical Characteristic	**Telemedicine N = 106**		**Clinic N = 1267**		**Mixed Delivery N = 81**		**P-value**
	n (N)	**%**	**n (N)**	**%**	**n (N)**	**%**	
SVR [A, B]							
Yes	27 (27)	100	655 (773)	84.7	51 (55)	92.7	0.02*
No	0 (27)	0	118 (773)	15.3	4 (55)	7.3	

[A] Based on the results of an individual's last HCV treatment regimen, not controlling for treatment allocation.
[B] SVR was calculated according to per-protocol analysis, including only individuals that successfully completed their treatment regimen and have a minimum of 3 months post-treatment blood work confirming SVR. Excludes individuals lost to follow-up or pending SVR results at time of analysis
* Significance calculated using Fisher's exact test as more than 50% of cells had expected counts less than 5.

CHAPTER 5: RESULTS OF THE PRINCIPAL COMPONENT ANALYSIS

Using the indictors for the proportion of people living alone, the proportion of individuals married, divorced, or separated, the proportion of individuals without a high school diploma, the proportion of lone-parent families, the employment-to-population ratio, and the average household income, two factor components to represent material and social deprivation indices were extracted. The first component combined the indicators of marital status and living alone (social component) and the second component combined the indicators of having a high school education, employment status, average household income, and family structure (material component). A value from these components was created to represent the level of deprivation for TOHVHP patients. Quintiles (20% increments) were calculated for each deprivation indices, with the lowest quintile representing the greatest level of deprivation and used in all logistic regression and Kaplan-Meier analyses (Appendix I).

The principal component analysis demonstrated a two-factor component structure was acceptable for the TOHVHP patient population. The indicators of not having a high school diploma, employment-to-population ratio, and average household income loaded as anticipated onto the material deprivation factor and the indicators of living alone and single-marital status loaded as anticipated onto the social deprivation factor. However, the indicator of single parent family equivalently loaded onto both the material and social deprivation factor. The social deprivation component summarized approximately one-fifth (18%) of the variation associated with the six indicators whereas the material deprivation component summarized more than half (56%) of the variation associated with the six indicators. Overall, both components demonstrated that the factors accounted for 74% of the cumulative variation associated with the six indicators selected for this study. When comparing the proportion of patients experiencing the greatest

amount of social and material deprivation, results demonstrated that the proportion of patients experiencing the greatest amount of social and material deprivation was comparable between HCV care delivery methods.

CHAPTER 6: OBJECTIVE ONE RESULTS

6.1. Retrospective Analysis of TOHVHP Database Project Data for Patient Retention

6.1.1 Comparing Lost to Follow-Up Rates Between HCV Care delivery Populations

A patient was defined as being lost to follow up if the patient: 1) failed to return for SVR blood work after a minimum of 3 months post treatment completion, 2) was lost from the clinic during their treatment regimen, or 3) had pending SVR blood work at time of analysis. The population analyzed consisted of 899 patients who had initiated treatment within TOHVHP and had known treatment initiation and completion dates on file. Proportions of patients lost to follow up by HCV care delivery method were presented as frequencies and compared using Chi-Square analysis.

When comparing all patient who initiated treatment within TOHVHP and had known treatment initiation and completion, lost to follow-up rates for telemedicine, outpatient clinic, and mixed delivery patients were 27% (10/37), 5% (42/800) and 11% (7/62) respectively. Telemedicine patients, compared to outpatient clinic and mixed delivery patients experienced significantly higher lost to follow up rates (Table 9, Figure 3).

Table 9. Proportion of patients lost to follow up by HCV care delivery method.

	Telemedicine N = 37		**Clinic N = 800**		**Mixed Delivery N = 62**		**P-value**
	n (N)	**%**	**n (N)**	**%**	**n (N)**	**%**	
Loss To Follow Up	10 (37)	27	42 (800)	5	7 (62)	11	*<.0001

* Significance calculated using Fisher Exact Test as more than 50% of cells had expected counts less than 5.

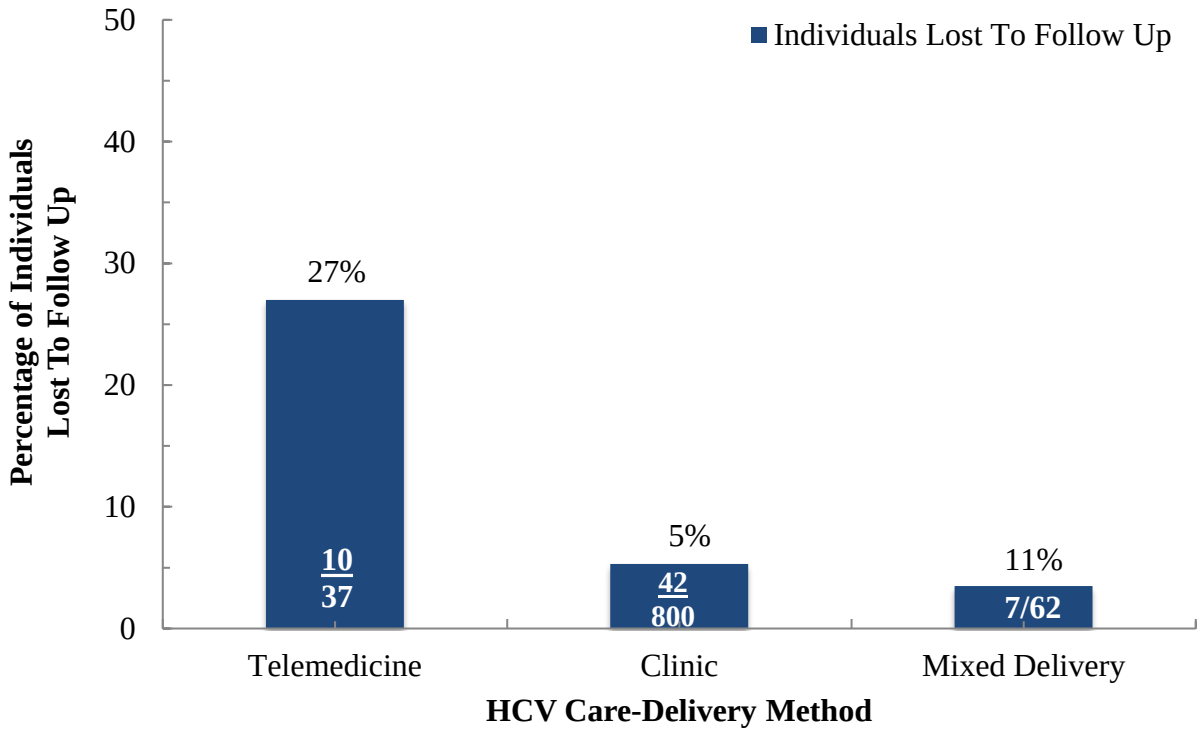

Figure 3. Lost to follow up rates by HCV care delivery method.

One of the focuses of this thesis was to assess the TOHVHP telemedicine program for patient retention among Indigenous patients accessing HCV care. When comparing all patients who self-identified as Indigenous and initiated treatment within TOHVHP, the lost to follow-up rate for telemedicine was 25% (1/4) whereas the lost to follow-up rate for outpatient clinic patients was 12% (2/17). None of the three patients who self-identified as Indigenous who received HCV care via mixed delivery were lost to follow-up. Although lost to follow-up rates did not statistically differ between HCV care delivery methods ($p = 0.66$), loss to follow up rates did appear to disproportionately affect telemedicine patients (27% vs. 12%), however due to a small sample size ($n = 21$) was too small to formulate any definitive conclusions regarding the

use of telemedicine for patient retention among TOHVHP who identified as Indigenous (Figure 4).

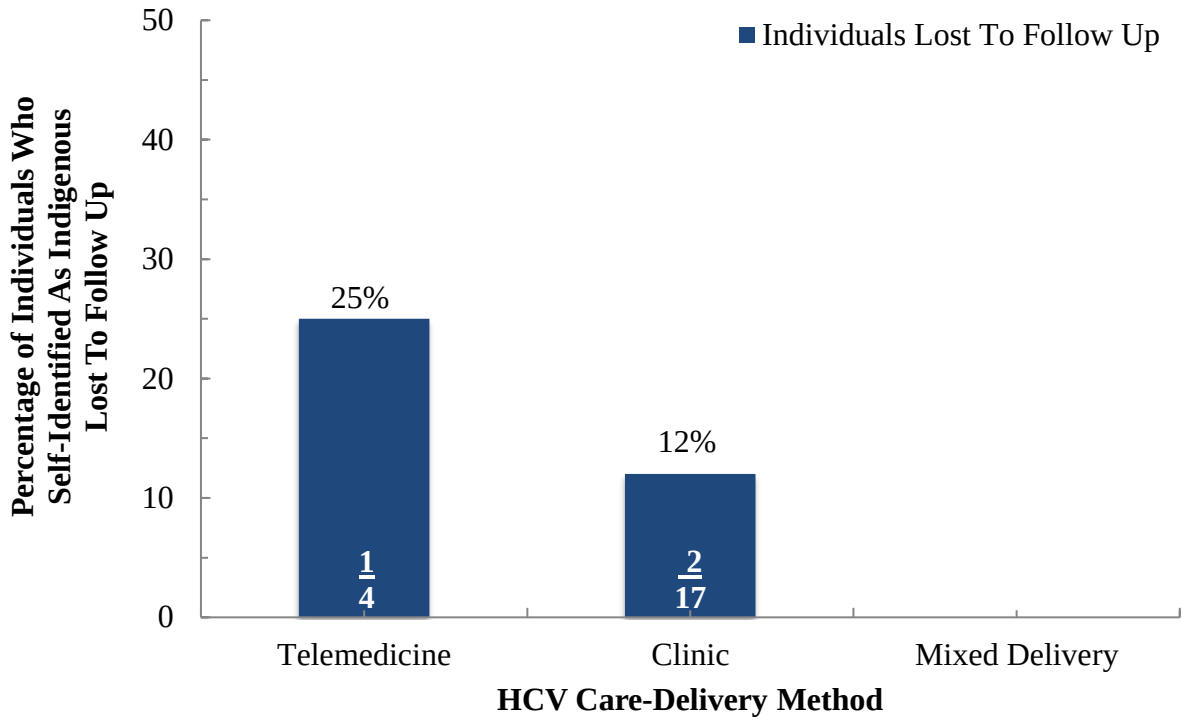

Figure 4. Lost to follow up rates among patients who self-identified as Indigenous by HCV care delivery method.

6.1.2 Comparing Time Until Treatment Initiation Between HCV Care delivery Populations

Time until treatment was defined as the period of time from a patient's first encounter with TOHVHP to the start of their first recorded HCV treatment regimen. Time until treatment initiation analysis excluded individuals who initiated their treatment regimen outside of TOHVHP, had unknown treatment regimens and who had unknown treatment initiation/ completion dates, resulting in an analysis population of 791 individuals. Time until treatment

initiation comparisons were assessed using a Kruskall-Wallis analysis and presented as median days until treatment and range.

Telemedicine patients compared to outpatient clinic patients experienced comparable wait times for initiating HCV treatment ($p = 0.41$). Telemedicine patients waited a median of 424 days (range: 134 – 4004 days) to initiate treatment whereas outpatient clinic patients waited a median of 513 days (range: 0 – 6921 days) waiting to initiate treatment. Mixed delivery patients experienced the shortest wait times, as patients on waited a median of 323 days (range: 62 – 4873 days) to initiate their HCV treatment regimen (Table 10).

Table 10. Time spent from TOHVHP first encounter until initiation of first HCV treatment regimen by HCV care delivery method.

	Telemedicine		**Clinic**		**Mixed Delivery**		**P-Value**
	n	**Median (Range)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	
Days Until Treatment	25	424 (134, 4004)	710	513 (0, 6921)	55	323 (62, 4873)	0.41*

* Significance measured using Kruskall Wallis test for non-parametric data.

6.1.3 Follow Up-Time by HCV Care Delivery Method

The primary outcome was overall patient retention in HCV care (time from entry into TOHVHP HCV Care to achievement of SVR) based on clinic allocation. Date of achieving SVR was represented as a patient's HCV treatment completion date plus 90 days. Patient retention time analysis excluded individuals who initiated their treatment regimen outside of TOHVHP, had unknown treatments, and who had unknown treatment initiation and/or completion dates, resulting in an analysis population of 791 individuals. Patient retention time comparisons were assessed using a Kruskall-Wallis analysis and presented as median days of patient retention and

range. The primary exposure of interest was HCV care delivery method of telemedicine, outpatient clinic, or mixed delivery.

For all 791 eligible patients, median patient retention time from entering the TOHVHP to achievement of SVR was 715 days (range: 141 days – 7096 days). When assessing patient retention time by HCV care delivery method, telemedicine patients compared to outpatient clinic and mixed delivery patients, spent equivalent time in HCV care ($p = 0.19$). For telemedicine patients, median patient retention time was 586 days (range: 383 – 4171 days), compared to outpatient clinic patients where median patient retention time was 785 days (range: 141 – 7096 days) and mixed delivery patients where median patient retention time was 558 days (247 – 5046 days) (Table 11).

Table 11. Follow up time by HCV care delivery method.

	Telemedicine N = 25		**Clinic N = 710**		**Mixed Delivery N = 55**		**P-Value**
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	
Patient Retention Follow Up Time	586	383 - 4171	785	141 - 7096	558	247 - 5046	0.19*

* Significance measured using Kruskall Wallis test for non-parametric data.

As treatment duration varied dependent on a patient being prescribed interferon based treatments (average 24 – 48 weeks) or Direct Acting Antiviral treatments (average 8 – 12 weeks), analyses comparing patient retention time were further broken into two groups: patients receiving interferon based therapies (including interferon-Direct Acting Antiviral combination treatments) and patients receiving exclusively Direct Acting Antiviral treatments. Additionally, as many patients had been exposed to multiple treatments prior to achieving SVR, primarily due to low cure rates and high treatment discontinuation rates associated with the adverse events

experienced using interferon treatments, two additional analyses were performed to control for previous treatment exposure, one for patients who were treatment naïve (i.e., had never been previously treated for their HCV infection) and one for patients who were treatment experienced. For the analyses presented in Table 12 - 14, the last treatment on file was used to calculate patient retention time. Patient retention time by treatment allocation and HCV care delivery method comparisons were assessed using a Kruskall-Wallis analysis and presented as median days of patient retention and range. The primary exposure of interest was HCV care delivery method of telemedicine, outpatient clinic, or mixed delivery.

Analysis included 211 treatment naïve patients prescribed interferon-based therapies. No telemedicine patients who initiated HCV treatment within the TOHVHP were prescribed interferon-based therapies. For outpatient clinic patients, the median patient retention time was 610 days (range: 141 - 4263 days) whereas for mixed delivery patients, the median patient retention time was 544 days (278 - 1051 days). Patient retention time was comparable between outpatient clinic and mixed delivery patients (p = 0.23) (Table 12).

Table 12. Follow up time for treatment naive patients receiving interferon-based and interferon-Direct Acting Antiviral treatments by HCV care delivery method**.**

	Clinic N = 203		**Mixed Delivery N = 8**		**P-Value**
	Median	**Range**	**Median**	**Range**	
Patient Retention Follow Up Time	610	141 - 4263	544	278 - 1051	0.23*

* Significance measured using Kruskall Wallis test for non-parametric data.

Due to the time of telemedicine program implementation coinciding with the approval of Direct Acting Antiviral treatments, no TOHVHP mixed delivery patients were treated with

multiple rounds of interferon-based therapies. Thirty-two outpatient clinic patients received multiple interferon treatment rounds. Median patient retention time was 3006 days (range: 180 - 4965 days).

When assessing treatment naïve patients prescribed Direct Acting Antiviral therapies, the analysis included 455 patients. When assessing patient retention time by HCV care delivery method, retention time for treatment naïve patients prescribed Direct Acting Antiviral therapies was comparable (p = 0.96). For telemedicine, median patient retention time was 586 days (range: 383 - 4171 days), compared to outpatient clinic where median patient retention time was 715 days (range: 183 - 7096 days) and mixed delivery where median patient retention time was 615 days (253 - 5046 days) (Table 13).

Table 13. Follow up time for treatment naive patients receiving Direct Acting Antiviral treatments by HCV care delivery method**.**

	Telemedicine N = 22		**Clinic N = 392**		**Mixed Delivery N = 41**		**P-Value**
	Med (days)	**Range**	**Med (days)**	**Range**	**Med (days)**	**Range**	
Patient Retention Follow Up Time	586	383 - 4171	715	183 - 7096	615	253- 5046	0.96*

* Significance measured using Kruskall Wallis test for non-parametric data.

When assessing treatment treatment-experienced patients prescribed Direct Acting Antiviral therapies, the analysis included 92 patients. When assessing patient retention time by HCV care delivery method, mixed delivery patients compared to telemedicine and outpatient clinic patients, spent less time in HCV care (p = 0.01). For telemedicine, median patient

retention time was 877 days (range: 444 - 3717 days), compared to outpatient clinic where median patient retention time was 2522 days (range: 257 - 6383 days) and mixed delivery where median patient retention time was 512 days (247 - 1278 days) (Table 14).

Table 14. Follow up time for treatment-experienced patients receiving Direct Acting Antiviral treatments by HCV care delivery method.

	Telemedicine N = 3		**Clinic N = 83**		**Mixed Delivery N = 6**		**P-Value**
	Med (days)	**Range**	**Mean (days)**	**Range**	**Mean (days)**	**Range**	
Patient Retention Follow Up Time	877	444 - 3717	2552	118 - 6383	512	247 - 1278	0.01*

* Significance measured using Kruskall Wallis test for non-parametric data

6.1.4 Patient Retention Status by HCV Care Delivery Method

Comparisons of patient retention status by HCV care delivery method were assessed using Chi-Square analysis and presented as frequencies. The primary exposure of interest was HCV care delivery method of telemedicine, outpatient clinic, or mixed delivery. Analysis included 899 individuals with known treatment initiation/completion dates. When comparing HCV care delivery populations on patient retention status (i.e., retained in HCV care vs. lost from HCV care), telemedicine patients were more likely to be lost to follow up than outpatient clinic and mixed delivery patients ($p < 0.0001$) (Table 15).

Table 15. Comparison of patient retention status among patients who initiated treatment within TOHVHP by HCV care delivery method.

	Telemedicine N = 37		**Clinic N =800**		**Mixed Delivery N = 62**		**P-Value**
	n (N)	%	n (N)	%	n (N)	%	
Retained In HCV Care	27 (37)	73.0	761 (800)	95.1	55 (62)	88.7	<.0001
Lost from HCV Care	10 (27)	27.0	39 (800)	4.9	7 (62)	11.3	

6.1.5 Factors Associated with Patient Retention in HCV Care

Comparisons of patient retention considering patient demographics between telemedicine, outpatient clinic, and mixed delivery patient were conducted. Chi-Square analysis was used for categorical variables and ANOVA analysis was used for continuous variables. All comparisons were done using SAS 9.4 statistical software. Analysis included 899 patients with known treatment initiation/completion dates.

When comparing patients retained in HCV care to patients lost to follow up, patients retained in care were more likely to live in rural areas (70.9% vs. 54.7%, $p = 0.003$), have greater social deprivation (25.3% vs. 12.2%, $p = 0.03$), and report suitable housing (95% vs. 92.8%, $p < 0.0001$). Patients retained in HCV care were less likely to have not graduated high school (11.0% vs. 14.3%, $p < 0.0001$). Although statistically significant, the absolute differences in age and housing suitability were small between HCV care delivery models and likely inconsequential.

When considering patient retention, patient populations were comparable by Indigenous race, sex, HCV genotype, co-infected with HIV and HBV, treatment allocation, history of mental illness, history of injection drug use, history of engaging in high risk sex, history of receiving blood products, history of intranasal cocaine use, having piercings, history of incarceration, and proportion experiencing the greatest quintile of material deprivation (Table 16)

Table 16. Patient characteristics associated with retention in HCV care until SVR blood work at 3 months post treatment completion.

	Patients Retained In Care N = 843)		**Patients Lost from HCV Care N = 56)**		**P-Value**
	n (N)	%	n (N)	%	
Sex					0.6
Male	559 (843)	66.3	39 (56)	69.6	
Female	284 (843)	33.7	17 (56)	30.4	
Age at Assessment	50.97	10.16	47.57	10.17	<.0001
HCV Genotype					0.3
1	610 (843)	72.3	37 (56)	66.1	
2	62 (843)	7.3	2 (56)	3.6	
3	118 (843)	13.8	13 (56)	23.2	
4	45 (843)	5.3	2 (56)	3.6	
Mixed	9 (683)	1.3	1 (56)	1.8	
HIV Co-infected	47 (843)	5.6	3 (56)	5.4	1.00
HBV Co-infected	6 (843)	0.7	0 (56)	0	1.00
Treatment Allocation					0.50
IFN	206 (843)	24.4	10 (56)	17.9	
IFN-DAA	87 (843)	10.3	7 (56)	12.5	
DAA	545 (843)	64.6	39 (56)	69.6	
History of Mental Illness	172 (843)	20.4	11 (56)	19.6	0.9
History of Injection Drug Use	447 (843)	53.0	36 (56)	64.3	0.1
History of High Risk Sex	91 (843)	10.8	8 (56)	14.3	0.4
History of Blood Products	153 (843)	18.1	14 (56)	25.0	0.2
History of Cocaine	370 (843)	43.9	32 (56)	57.1	0.05
History of Tattoos	323 (843)	38.3	30 (56)	53.6	0.02
History of Piercings	242 (843)	28.7	15 (56)	26.8	0.75
History of Incarceration	295 (843)	35.0	24 (56)	42.9	0.23
No High School Diploma	93 (843)	11.0	8 (56)	14.3	<.0001
Geographical Area					0.003
Rural	146 (808)	18.1	10 (53)	18.9	
Intermediate	89 (808)	11.0	14 (53)	26.4	
Urban	573 (808)	70.9	29 (53)	54.7	
Greatest Material Deprivation	187 (798)	23.4	16 (49)	32.7	0.2
Greatest Social Deprivation	202 (798)	25.3	6 (49)	12.2	0.03
Suitable Housing	801 (843)	95.0	52 (56)	92.8	<.0001
Not Suitable Housing	42 (843)	5.0	4 (56)	7.1	<.0001

Analysis of patient and clinic characteristics associated with patient retention was conducted using simple logistic regression models, with the primary predictor being HCV care

delivery method. HCV care delivery method was significantly associated with decreased odds of patient retention (clinic $p < 0.0001$ and mixed delivery $p = 0.05$). Having an HCV genotype 3-infection, having tattoos, not having graduated high school, and living in an intermediate geographic area was significantly associated with decreased odds of patient retention. Age at assessment and experiencing the greatest quintile of social deprivation were significantly associated with increased odds of patient retention. Identifying as Indigenous was not associated with patient retention (Table 17).

Table 17. Results from all simple logistic regression models. Reported are maximum likelihood estimates, standard errors, odds ratios with 95% confidence intervals, and p-values of all potential associated variables with the outcome of patient retention**.**

Variable	Coefficient (SE)	Odds Ratio (95% CI)	P-Value
Care Delivery Method (REF: Clinic)			
Telemedicine	- 1.98 (0.41)	0.14 (0.06, 0.31)	<.0001
Mixed Delivery	- 0.91 (0.43)	0.40 (0.17, 0.94)	0.04
Indigenous	- 0.83 (0.64)	0.44 (0.13, 1.52)	0.19
Female Sex	0.15 (0.29)	1.17 (0.65, 2.10)	0.6
Age	0.03 (0.01)	1.03 (1.00, 1.06)	0.02
HCV Genotype (REF: GENO 1)			
2	0.65 (0.74)	1.91 (0.45, 8.11)	0.38
3	- 0.58 (0.34)	0.56 (0.29, 1.08)	0.08
4	0.33 (0.74)	1.39 (0.32, 1.08)	0.66
Mixed	- 0.59 (1.07)	0.55 (0.07, 4.49)	0.58
HIV Co-Infection	-0.04 (0.61)	1.04 (0.31, 3.46)	0.9
History of Mental Illness	0.05 (0.35)	1.05 (0.53, 2.07)	0.9
History of IVDU	- 0.47 (0.29)	0.63 (0.36, 1.10)	0.10
History of High Risk Sex	- 0.32 (0.40)	0.73 (0.33, 1.58)	0.42
History of Cocaine Use	- 0.53 (0.28)	0.59 (0.24, 1.01)	0.06
History of Tattoos	- 0.62 (0.28)	0.54 (0.31, 0.93)	0.03
History of Incarceration	- 0.33 (0.28)	0.72 (0.42, 1.24)	0.24
Blood Recipient	- 0.41 (0.32)	0.67 (0.35, 1.25)	0.20
History of Piercings	0.09 (0.31)	1.01 (0.59, 2.03)	0.76
No High School Diploma	-3.18 (1.38)	0.04 (0.003, 0.63)	0.02
Area Classification (REF: Urban)			
Rural	- 0.30 (0.38)	0.74 (0.35, 1.55)	0.4

Intermediate	- 1.13 (0.34)	0.32 (0.16, 0.63)	0.001
Greatest Material Deprivation	- 0.38 (0.32)	0.69 (0.37, 1.28)	0.2
Greatest Social Deprivation	0.97 (0.44)	2.65 (1.11, 6.31)	0.03
Suitable Housing	1.07 (2.37)	2.92 (0.03, 303.84)	0.65
Unsuitable Housing	- 1.69 (2.23)	0.18 (0.02, 14.49)	0.45

As seen in the second column of Table 18, HCV care delivered via TOHVHP telemedicine and mixed delivery was significantly associated with decreased odds of patient retention. Potential covariates of age at assessment (OR = 1.05, 95% C.I. 1.02 – 1.08) and having experienced the greatest quintile of social deprivation (OR = 2.57, 95% C.I. 0.68 – 2.48) were significantly associated with increased odds of patient retention. After adjustment for the covariates of sex, age, and having experienced the greatest quintile of social deprivation, HCV care delivery via TOHVHP telemedicine and mixed delivery remained significantly associated with decreased odds of patient retention. However, the associations between HCV care delivery via both the TOHVHP outpatient clinic (OR = 0.13, 95% C.I. 0.06 – 0.31) and mixed delivery (OR: 0.31, 95% C.I. 0.13 – 0.74) and odds of patient retention were slightly attenuated. Retention was similar by sex in this model (Table 18).

Table 18. Odds ratios [95% C.I.s] of HCV care delivery method and potential covariates among those retained in HCV care.

Variable	**Unadjusted Odds Ratio (95% C.Is)**	**Adjusted Odds Ratios (95% C.Is)**	**P-Value**
Care Delivery Method (Ref: Clinic)			
Telemedicine	0.14 (0.06, 0.31)	0.13 (0.06, 0.31)	<.0001
Mixed Delivery	0.40 (0.17, 0.94)	0.31 (0.13, 0.74)	0.009
Female Sex		1.30 (0.68, 2.48)	0.4
Age		1.05 (1.02, 1.08)	0.003
Greatest Social Deprivation (Ref: Norm)		2.57 (1.06, 6.26)	0.04

CHAPTER 7: OBJECTIVE TWO RESULTS

7.1 Retrospective Analysis of TOHVHP Database Project Data for Proportion of Patients Initiating HCV Treatment and Patient Characteristics Associated with HCV Treatment Initiation

7.1.1 Proportion of Patients Initiating HCV Treatment by Treatment Regimen and Care delivery Method

A total of 35% (n = 37/106) of telemedicine patients initiated HCV treatment. For telemedicine patients, 8% (3/37) of patients initiated interferon-based (n = 1) and interferon-Direct Acting Antiviral (n = 2) combination HCV treatment regimens and 92% (34/37) of patients initiated Direct Acting Antiviral treatment regimens. For the other two HCV care delivery methods, a total of 64% (n = 808/1267) of outpatient clinic patients and 76% (n = 62/81) of mixed delivery patients initiated treatment. Although it appears that treatment initiation rates are disproportionately low among telemedicine patients, when controlling for the year of treatment initiation using Cochran-Mantel-Haenszel statistic to account for the later establishment of the telemedicine program and difference in available HCV treatment regimens, treatment uptake did not statistically differ by HCV care delivery method ($p = 0.24$). It should be noted however that the sample size for telemedicine in this thesis might have been too small to detect small differences in treatment initiation rates due to limited power

For outpatient clinic patients, 38% (308/808) initiated Direct Acting Antiviral HCV treatments and 62% (500/808) initiated interferon treatment regimens. For mixed delivery

patients, 16% (10/62) patients initiated interferon-based treatment and 84% (52/62) initiated Direct Acting Antiviral treatments (Figure 5).

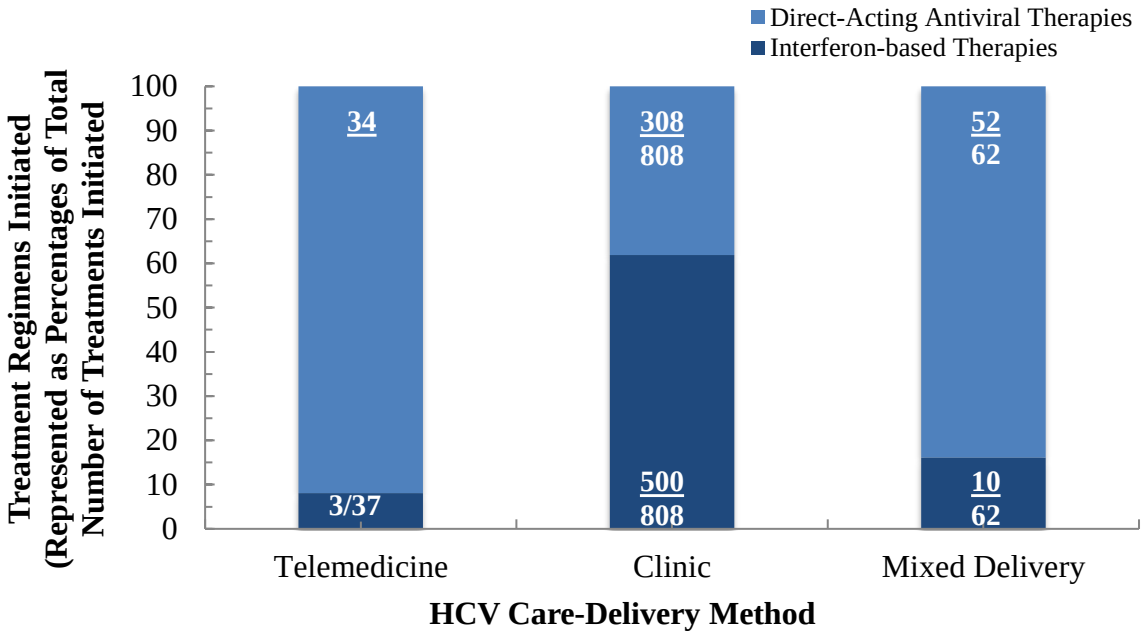

Figure 5. Overall percentage of telemedicine, outpatient clinic, and mixed delivery patients who initiated HCV treatment represented by treatment regimen.

One of the focuses of this thesis was to assess the TOHVHP telemedicine program for treatment initiation among Indigenous patients accessing HCV care. For TOHVHP patients who self-identified as Indigenous, a total of 59% (n = 24/41) initiated HCV treatment. A total of 36% (4/11) of telemedicine patients initiated HCV treatment. For telemedicine patients, 100% (4/4) of patients initiated Direct Acting Antiviral treatment regimens. For the other two HCV care delivery methods, a total of 63% (n = 17/27) of outpatient clinic patients and 100% (n = 3/3) of mixed delivery patients initiated treatment. For outpatient clinic patients, 18% (3/17) initiated interferon-based HCV treatments and 82% (14/17) initiated Direct Acting Antiviral treatment regimens. For mixed delivery patients, 100% (3/3) of patients initiated Direct Acting Antiviral

treatments. Although treatment initiation rates among patients who self-identified as Indigenous did not significantly differ by HCV care delivery method (p = 0.10), the sample size (n = 24) was too small to form any definitive conclusions regarding the use of telemedicine for treatment initiation among TOHVHP patients who identified as Indigenous (Figure 6).

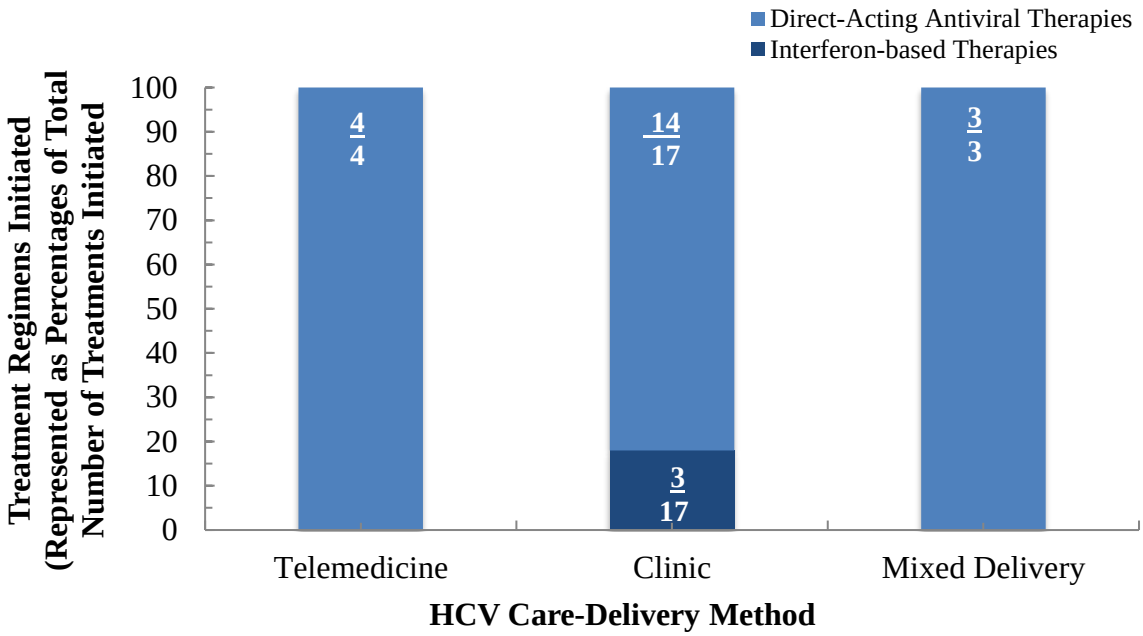

Figure 6. Overall percentage of telemedicine, outpatient clinic, and mixed delivery patients who self-identified as Indigenous and initiated HCV treatment represented by treatment regimen.

7.1.2 Characteristics of Patients Initiating HCV Treatment by Treatment Regimen

Comparisons of treatment initiation rates between telemedicine, outpatient clinic, and mixed delivery patients were performed with Chi-Square analysis using SAS 9.4 statistical software and presented as frequencies. Analysis included a total of 1447 patients and excluded 7 patients whose treatment was not recorded in patient files. Telemedicine patients were more

likely to have not initiated treatment compared to outpatient clinic and mixed delivery patients (65.1% vs. 35.9% vs. 23.5%, p <.0001) and less likely to have initiated interferon-based therapies (2.8% vs. 24.4% vs. 12.3%, p <.0001) (Table 19).

Table 19. Comparison of treatments initiated among patients with known treatments within TOHVHP by HCV care delivery method.

	Telemedicine N = 106		**Clinic N = 1260**		**Mixed Delivery N = 81**		**P-Value**
	n (N)	%	n (N)	%	n (N)	%	
No Treatment	69	65.1	452	35.9	19	23.5	<.0001*
Interferon-based Treatments	3	2.8	308	24.4	10	12.3	
Direct Acting Antiviral Treatments	34	32. 1	500	39.7	52	64.2	

* Significance measured using Fisher Exact test.

Comparisons between telemedicine, outpatient clinic, and mixed delivery patients were performed using Chi-Square analysis for categorical variables and ANOVA analysis for continuous variables using SAS 9.4 statistical software. Analysis included 1447 patients who whose treatment type was known and excluded 7 patients whose treatment was not recorded in patient files.

Individuals who initiated Direct Acting Antiviral treatments compared to individuals initiating interferon-based treatment and those not initiating HCV treatment were older at TOHVHP assessment (52.2 vs. 48.3 vs. 46.7 years, p < 0.0001), and were more likely to have HCV genotype 1-infections (75% vs. 63% vs. 57%, p = 0.0002), had engaged in high risk sex (13% vs. 7% vs. 4%, p < 0.0001), and had received blood products (25% vs. 7% vs.11%, p < 0.0001). Although statistically significant, there were no clinically relevant differences in housing suitability between treatment allocation groups.

Those who did not initiate treatment compared to those who initiated interferon-based and Direct Acting Antiviral treatments were more likely to have a history of mental illness (49% vs. 38% vs. 11%, $p < 0.0001$), history of injection drug use (62% vs. 54% vs. 54%, $p = 0.01$), history of intranasal cocaine use (52% vs. 43% vs. 46%, $p = 0.03$), have tattoos (49% vs. 37% vs. 40%, p 0.0006), have piercings (38% vs. 28% vs. 28%, $p = 0.001$), and had previously been incarcerated (43% vs. 34% vs. 36%, $p = 0.01$). Those who did not initiate treatment were less likely to have cirrhosis (F4) of the liver (10% vs. 44% vs. 41%, $p < 0.0001$) and had lower baseline ALT (84 IU/L vs. 107 IU/L vs. 105 IU/L, $p < 0.0001$). Patient populations were comparable on the proportion of patients co-infected with HIV, proportion of patients having a high school diploma, geographic area of residence, proportion of individuals experiencing the greatest quintile of material and social deprivation, and suitable housing (Table 20).

Table 20. Patient's personal and clinical characteristics associated with initiating HCV treatment among TOHVHP patients.

	Initiation of Interferon Regimen N = 321)		**Initiation of DAA Regimen N = 586)**		**No HCV Treatment N = 540)**		**P-Value**
	n (N)	%	n (N)	%	n (N)	%	
Sex							0.02
Male	224 (321)	69.8	380 (586)	64.8	320 (540)	59.3	
Female	97 (321)	30.2	206 (586)	35.1	210 (540)	38.9	
Age	48.3 (8.9)		52.2 (10.5)		46.7 (13.2)		< .0001
HCV Genotype [A]							0.0002
1	202 (321)	62.9	437 (586)	74.6	309 (540)	57.2	
2	24 (321)	7.5	40 (586)	6.8	48 (540)	8.9	
3	59 (321)	18.4	74 (586)	12.6	111 (540)	20.6	
4	17 (321)	5.3	30 (586)	5.1	29 (540)	5.4	
Mixed	5 (321)	1.6	5 (586)	0.9	10 (540)	1.9	
HIV Co-Infection							0.4
Yes	22 (321)	6.8	28 (586)	4.8	27 (540)	5.0	
No	299 (321)	93.2	558 (586)	95.2	513 (540)	95.0	
Viral Load (IU/mL)	3.8^{+6} (7.2^{+6})		4.9^{+6} (2.3^{+6})		4.9^{e+6} (1.4^{e+6})		< .0001

Baseline ALT (IU/L)	107 (97)		105 (91)		84 (79)		< .0001
Fibro Scan [B]							< .0001
F0 – F1	12 (52)	23.1	125 (516)	24.2	225 (321)	70.1	
F2	6 (52)	11.5	94 (516)	18.2	42 (321)	13.1	
F3	11 (52)	21.2	83 (516)	16.1	21 (321)	6.5	
F4	23 (52)	44.2	214 (516)	41.5	33 (321)	10.3	
History of Mental Illness							< .0001
Yes	121 (321)	37.7	66 (586)	11.3	265 (540)	49.1	
No	200 (321)	62.3	520 (586)	88.7	275 (540)	50.9	
History of IVDU	172 (321)	53.6	319 (586)	54.4	336 (540)	62.2	0.01
History of High Risk Sex	22 (321)	6.9	77 (586)	13.1	21 (540)	3.9	< .0001
History of Cocaine	138 (321)	42.9	268 (586)	45.7	278 (540)	51.5	0.03
History of Tattoos	119 (321)	37.1	235 (586)	40.1	265 (540)	49.1	0.0006
History of Incarceration	110 (321)	34.3	213 (586)	36.3	233 (540)	43.1	0.01
Previous Blood Recipient	21 (321)	6.5	146 (586)	24.9	59 (540)	10.9	< .0001
History of Piercings	91 (321)	28.3	166 (586)	28.3	203 (540)	37.6	0.001
No High School Diploma	37 (319)	11.7	62 (567)	10.9	61 (528)	11.6	0.3
Area Classification							0.17
Rural	54 (321)	16.8	105 (586)	17.9	82 (540)	15.2	
Intermediate	37 (321)	11.5	66 (586)	11.3	84 (540)	15.6	
Urban	221 (321)	68.8	387 (586)	66.1	347 (540)	64.3	
Greatest Material Deprivation	76 (321)	23.7	129 (586)	22.0	119 (540)	22.0	0.99
Greatest Social Deprivation	84 (321)	26.2	127 (586)	21.7	108 (540)	20.0	0.23
Housing Suitability							
Suitable	301 (319)	94.3	539 (567)	95.1	501 (528)	94.9	0.05
Not Suitable	18 (319)	5.7	28 (567)	4.9	27 (528)	5.1	0.04

[A] Genotypes 5 and 6 represented within genotype 1 due to similar behaviour to treatment

[B] Pre-Treatment Fibro Scan Fibrosis score by transient elastography

In the unadjusted logistic regression models, the primary predictor of HCV care delivery method was significantly associated with the outcome of initiating interferon-based treatment regimens (clinic $p < 0.0001$). Individuals receiving HCV care via telemedicine or mixed delivery were less likely to initiate HCV treatment compared to outpatient clinic patients. Identifying as Indigenous, female sex, having a history of mental illness, having a history of injection drug use, having a history of intranasal cocaine use, having tattoos, previous incarceration, and having received blood products were also significantly associated with decreased odds of initiating a interferon-based HCV treatment regimen. Older age, higher baseline ALT, ever having a liver

biopsy, and having a pre-treatment fibrosis score greater than F2 were significantly associated with increased odds of initiating an interferon-based HCV treatment regimen (Table 21).

Table 21. Results from all simple logistic regression models. Reported are maximum likelihood estimates, standard errors, odds ratios with 95% confidence intervals, and p-values of all potential associated variables among patients who initiated interferon-based treatments.

Variable	Treatment Allocation	Coefficient (SE)	Odds Ratio (95% CI)	P-Value
Care Delivery Method (REF: Clinic)				
Telemedicine	IFN	- 2.75 (0.59)	0.06 (0.02, 0.21)	< 0.001
Mixed Delivery	IFN	- 0.26 (0.39)	0.77 (0.35, 1.68)	0.52
Indigenous	IFN	-1.21 (0.63)	0.29 (0.09, 1.03)	0.05
Female Sex	IFN	-0.42 (0.15)	0.66 (0.49, 0.89)	0.006
Age	IFN	(0.00)	1.01 (1.00, 1.02)	0.05
HCV Genotype (REF: GENO 1)				
2	IFN	-0.27 (026)	0.76 (0.45, 1.29)	0.31
3	IFN	-0.21 (0.18)	0.81 (0.57, 1.17)	0.27
4	IFN	-0.11 (0.32)	0.89 (0.48, 1.67)	0.73
Mixed	IFN	-0.27 (0.56)	0.76 (0.26, 2.27)	0.63
HIV Co-Infection	IFN	0.33 (0.29)	1.38 (0.78, 2.49)	0.3
HBV Co-Infection	IFN	0.09 (0.57)	1.09 (0.36, 3.28)	0.9
Viral Load	IFN	-6.1E-9 (7.1E-9)	1.00 (1.00, 1.00)	0.4
Baseline ALT	IFN	0.003 (0.00)	1.003 (1.00, 1.01)	0.0002
Liver Biopsy	IFN	2.09 (0.16)	8.09 (5.91, 11.10)	<.0001
Pre Treatment Fibrosis Score (Ref: F0-F1)				
F2	IFN	0.98 (0.53)	2.68 (0.95, 7.53)	0.06
F3	IFN	2.28 (0.48)	9.82 (3.87, 24.95)	<.0001
F4	IFN	2.57 (0.40)	13.07 (7.62, 28.73)	<.0001
History of Mental Illness	IFN	-0.46 (0.14)	0.63 (0.47, 0.83)	0.001
History of IVDU	IFN	-0.36 (0.14)	0.70 (0.53, 0.93)	0.01
History of High Risk Sex	IFN	0.59 (0.32)	1.82 (0.98, 2.26)	0.06
History of Cocaine Use	IFN	-0.34 (0.14)	0.71 (0.54, 0.94)	0.02
History of Tattoos	IFN	-0.49 (0.14)	0.61 (0.46, 0.81)	0.0006
History of Incarceration	IFN	-0.38 (0.15)	0.69 (0.52, 0.92)	0.01
Blood Recipient	IFN	-0.56 (0.26)	0.57 (0.34, 0.96)	0.03
History of Piercings	IFN	-0.42 (0.15)	0.66 (0.49, 0.88)	0.006
No High School Diploma	IFN	0.009 (0.78)	1.00 (0.22, 4.66)	0.99
Area Classification (REF:				

Urban)				
Rural	IFN	0.03 (0.19)	1.03 (0.71, 1.52)	0.9
Intermediate	IFN	-0.37 (0.21)	0.69 (0.45, 1.06)	0.09
Greatest Material Deprivation	IFN	0.02 (0.17)	1.02 (0.73, 1.43)	0.9
Greatest Social Deprivation	IFN	0.29 (0.17)	1.33 (0.96, 1.86)	0.09
Suitable Housing	IFN	-0.89 (1.18)	0.41 (0.04, 4.14)	0.45
Unsuitable Housing	IFN	1.16 (1.15)	3.18 (0.33, 30.35)	0.32

Analysis of patient and clinic characteristics associated with initiating a Direct Acting Antiviral HCV treatment was restricted to patients initiating treatment between January 1, 2014 and December 31, 2016. This time restriction period was chosen as telemedicine delivered HCV care, one of the main predictors of our analysis, although initiated within TOHVHP in Spring 2013, was not fully established within communities until 2014. As current best practice HCV treatment recommendations include treating patients with Direct Acting Antiviral therapies, analysis was restricted to allow for the best representation of both available Direct Acting Antiviral treatments as well as availability of the TOHVHP telemedicine program.

In the unadjusted logistic regression models, the primary predictor of care delivery method was significantly associated with the outcome of initiating Direct Acting Antiviral treatment regimens. Hepatitis C Virus care delivery via telemedicine was associated with decreased odds of initiating treatment, whereas HCV care delivery via mixed delivery was associated with increased odds of initiating treatment. Having an HCV genotype 2-infection or HCV genotype 3-infection, having a history of injection drug use, having tattoos, having a history of intranasal cocaine use, previously being incarcerated, having piercings, and having a history of mental illness were associated with decreased odds of initiating Direct Acting Antiviral HCV treatment regimens. Older age, higher baseline ALT, having ever had a liver biopsy, having a pre-treatment fibrosis score more than F1, co-infection with HBV, having engaged in high-risk sex, and having ever received blood products were significantly associated

with increased odds of initiating Direct Acting Antiviral HCV treatment regimens. Identifying as Indigenous was not associated with decreased odds of initiating Direct Acting Antiviral HCV treatment regimens (Table 22).

Table 22. Results from all simple logistic regression models. Reported are maximum likelihood estimates, standard errors, odds ratios with 95% confidence intervals, and p-values of all potential associated variables among patients who initiated Direct Acting Antiviral treatments between January 1, 2014 and December 31, 2016**.**

Variable	Treatment Allocation	Coefficient (SE)	Odds Ratio (95% CI)	P-Value
Care Delivery Method (REF: Clinic)				
Telemedicine	DAA	0.82 (0.22)	0.44 (0.29, 0.68)	0.0002
Mixed Delivery	DAA	0.89 (0.26)	2.45 (1.43, 4.21)	0.0001
Indigenous	DAA	0.13 (0.33)	1.14 (0.59, 2.18)	0.7
Female Sex	DAA	-0.19 (0.12)	0.83 (0.65, 1.05)	0.1
Age	DAA	0.04 (0.00)	1.04 (1.03, 1.06)	< .0001
HCV Genotype (REF: GENO 1)				
2	DAA	-0.53 (0.27)	0.59 (0.38, 0.92)	0.02
3	DAA	-0.75 (0.17)	0.47 (0.34, 0.66)	<.0001
4	DAA	-0.31 (0.27)	0.73 (0.43, 1.24)	0.25
Mixed	DAA	-1.04 (0.55)	0.35 (0.12, 1.05)	0.06
HIV Co-Infection	DAA	-0.05 (0.28)	0.95 (0.55, 1.64)	0.9
HBV Co-Infection	DAA	2.31 (1.06)	10.03 (1.27, 79.41)	0.03
Viral Load	DAA	-26E-12 (3.3E-9)	1.00 (1.00, 1.00)	0.9
Liver Biopsy	DAA	0.89 (0.14)	2.44 (1.86, 3.22)	<.0001
Pre Treatment Fibrosis Score (Ref: F0-F1)				
F2	DAA	1.39 (0.22)	4.03 (2.64, 6.16)	<.0001
F3	DAA	1.96 (0.27)	7.11 (4.20, 12.04)	<.0001
F4	DAA	2.46 (0.22)	11.67 (7.62, 17.89)	<.0001
History of Mental Illness	DAA	-2.03 (0.16)	0.13 (0.09, 0.18)	<.0001
History of IVDU	DAA	-0.32 (0.12)	0.73 (0.57, 0.92)	0.008
History of High Risk Sex	DAA	1.32 (0.25)	3.74 (2.27, 6.15)	<.0001
History of Cocaine Use	DAA	-0.23 (0.12)	0.79 (0.63, 1.0)	0.05
History of Tattoos	DAA	-0.36 (0.12)	0.69 (0.55, 0.88)	0.003
History of Incarceration	DAA	-0.28 (0.12)	0.75 (0.59, 0.96)	0.02
Blood Recipient	DAA	0.99 (0.17)	2.71 (1.95, 3.76)	<.0001

History of Piercings	DAA	-0.42 (0.13)	0.66 (0.51, 0.84)	0.001
No High School Diploma	DAA	-0.91 (0.68)	0.40 (0.11, 1.53)	0.18
Area Classification (REF: Urban)	DAA	0.14 (0.16)	1.15 (0.93, 1.59)	0.4
Rural	DAA	-0.35 (0.18)	0.70 (0.49, 1.00)	0.05
Intermediate				
Greatest Material Deprivation	DAA	0.01 (0.15)	1.01 (0.76, 1.35)	0.9
Greatest Social Deprivation	DAA	0.17 (0.15)	1.12 (0.84, 1.51)	0.4
Suitable Housing	DAA	1.97 (1.11)	7.14 (0.82, 62.49)	0.08
Unsuitable Housing	DAA	-1.73 (1.07)	0.18 (0.02, 1.46)	0.11

A multivariable logistic regression model was used to assess the association between HCV care delivery method and covariates on the outcome of initiating interferon-based treatment regimens. As seen in the fourth column of Table 23, after adjustment for the covariates of age, sex, having a liver biopsy, pre-treatment FibroScan scores, and baseline ALT, HCV care delivery was no longer significantly associated with the outcome of initiating an interferon-based treatment regimen. Having ever had a liver biopsy (OR: 3.57, 95% C.I. 1.70, 7.47), having a pretreatment Fibroscan score of F3 (OR: 9.97, 95% C.I. 3.52 – 28.24) or F4 (OR: 8.51, 95% C.I. 3.41 – 21.24), and baseline ALT (OR: 1.01, 95% C.I. 1.00 – 1.01) were associated with increased odds of initiating interferon-based treatment regimens. Identifying as Indigenous was not associated with decreased odds of initiating interferon-based treatments (Table 23).

Table 23. Odds ratios [95% C.I.s] of HCV care delivery methods and potential covariates among patients initiating interferon-based or interferon-DAA based HCV treatments regimens.

Variable	Treatment Allocation	Unadjusted Odds Ratio (95% C.Is)	Adjusted Odds Ratios (95% C.Is)	P-Value
Care Delivery Method (Ref: Clinic)				
Telemedicine	IFN	0.06 (0.02, 0.21)	0.29 (0.06, 1.35)	0.11
Mixed Delivery		0.77 (0.35, 1.68)	0.46 (0.07, 3.03)	0.42
Female Sex	IFN		0.85 (0.40, 1.79)	0.66
Age	IFN		1.01 (0.96, 1.04)	0.67

Baseline ALT	IFN	1.01 (1.00, 1.01)	0.007
Liver Biopsy	IFN	3.57 (1.70, 7.47)	0.0008
Pre-treatment FibroScan			
F2	IFN	2.89 (0.97, 8.63)	0.06
F3	IFN	9.97 (3.52, 28.24)	<.0001
F4	IFN	8.51 (3.41, 21.24)	<.0001

A multivariable logistic regression model was used to assess the association between HCV care delivery method and covariates on the outcome of initiating Direct Acting Antiviral treatment regimens. As seen in the fourth column of Table 24, after adjustment for the covariates of sex, age, having ever had a liver biopsy, having a pre-treatment Fibro Scan, baseline ALT, history of mental illness, and having a history of engaging in high-risk sex, HCV care delivery via telemedicine remained significantly associated with the outcome of initiating a Direct Acting Antiviral treatment regimen. Having a HCV genotype 2-infection (OR: 0.50, 95% C.I. 0.26, 0.96), genotype 3-infection (OR: 0.53, 95% C.I. 0.32, 0.89), or genotype 4-infection (OR: 0.41, 95% C.I. 0.20, 0.88), and having a history of mental illness (OR: 0.17, 95% C.I. 0.11, 0.26) were associated with decreased odds of initiating Direct Acting Antiviral treatment regimens. Having ever had a liver biopsy (OR: 2.07, 95% C.I. 1.35, 3.18), having a pretreatment Fibroscan score of F2 (OR: 3.19, 95% C.I. 1.92, 5.30) or F3 (OR: 6.95, 95% C.I. 3.73 – 12.96) or F4 (OR: 9.58, 95% C.I. 5.79 – 15.86), and having a history of engaging in high-risk sex (OR: 2.30, 95% C.I. 1.16 – 4.56) were associated with increased odds of initiating Direct Acting Antiviral treatment regimens.

Once adjusted for covariates, HCV care via telemedicine was associated with decreased odds of initiating a Direct Acting Antiviral-based HCV treatment, however the relationship was attenuated (OR = 0.37, 95% C.I. 0.19 – 0.71), whereas the association between HCV care via mixed delivery was no longer significantly associated with increased odds of initiating a Direct

Acting Antiviral HCV treatment. Identifying as Indigenous was not associated with decreased odds of initiating Direct Acting Antiviral treatments (Table 24).

Table 24. Odds ratios [95% C.I.s] of HCV care delivery methods and potential covariates among patients initiating Direct Acting Antiviral treatment regimens between January 1, 2014 and December 31, 2016.

Variable	Treatment Allocation	Unadjusted Odds Ratio (95% C.Is)	Adjusted Odds Ratios (95% C.Is)	P-Value
Care Delivery Method (Ref: Clinic)				
Telemedicine	DAA	0.44 (0.29, 0.68)	0.37 (0.19, 0.71)	0.003
Mixed delivery	DAA	2.45 (1.43, 4.21)	1.32 (0.56, 3.10)	0.53
Female Sex	DAA		1.10 (0.75, 1.61)	0.64
Age	DAA		1.01 (0.99, 1.03)	0.29
Genotype (Ref: 1)				
2	DAA		0.50 (0.26, 0.96)	0.04
3	DAA		0.53 (0.32, 0.89)	0.02
4	DAA		0.41 (0.20, 0.88)	0.02
Mixed	DAA		0.26 (0.05, 1.56)	0.14
Liver Biopsy	DAA		2.07 (1.35, 3.18)	0.0008
Pre-treatment FibroScan				
F2	DAA		3.19 (1.93, 5.30)	<.0001
F3	DAA		6.95 (3.73, 12.96)	<.0001
F4	DAA		9.58 (5.79, 15.86)	<.0001
History of High Risk Sex	DAA		2.30 (1.16, 4.56)	0.02
History of Mental Illness	DAA		0.17 (0.11, 0.26)	<.0001

CHAPTER 8: OBJECTIVE THREE RESULTS

8.1 Retrospective Analysis of TOHVHP Database Project Data for Proportion of Patients Achieving SVR and Patient Characteristics Associated with Achieving SVR

8.1.1 Proportion of Patients Achieving HCV Cure by Treatment Regimen and Care delivery Method Using Per-Protocol Analysis

When using the per-protocol SVR definition, the overall SVR rate was 100% (27/27) for telemedicine patients, 86% (655/768) for outpatient clinic patients, and 93% (51/55) for mixed delivery patients. To address the differences between treatment regimen cure rates, treatment allocation was controlled for using Cochran-Mantel-Haenszel statistic. Although it appears that telemedicine patients achieved superior SVR rates, when controlling for treatment allocation, the likelihood of achieving SVR did not statistically differ by HCV care delivery method ($p = 0.43$). It should be noted however that the sample size for telemedicine in this thesis might have been too small to detect small differences in SVR rates due to limited power (Table 25).

Table 25. Per-protocol SVR rates by HCV care delivery method.

HCV Care Delivery Method	Achieved SVR	No SVR	SVR %	P-Value
Telemedicine	27	0	100	0.03
Clinic	655	118	86	
Mixed Delivery	51	4	93	

Due to the differences in cure rates between interferon and Direct Acting Antiviral treatments, treatment specific per-protocol SVR rates by HCV care delivery method were

calculated. For interferon treatment regimens, per-protocol SVR rates for outpatient clinic and mixed delivery patients was 64% (134/211) and 80% (4/5), respectively. No telemedicine patients were prescribed an interferon treatment regimen. For interferon-Direct Acting Antiviral combination therapies, SVR rates were 100% (1/1) for telemedicine patients, 92% (76/83) for outpatient clinic patients, and 100% (3/3) for mixed delivery patients. For Direct Acting Antiviral treatment regimens, SVR rates were 100% (26/26) for telemedicine patients, 93% (440/472) for outpatient clinic patients, and 94% (44/47) for mixed delivery patients (Figure 7).

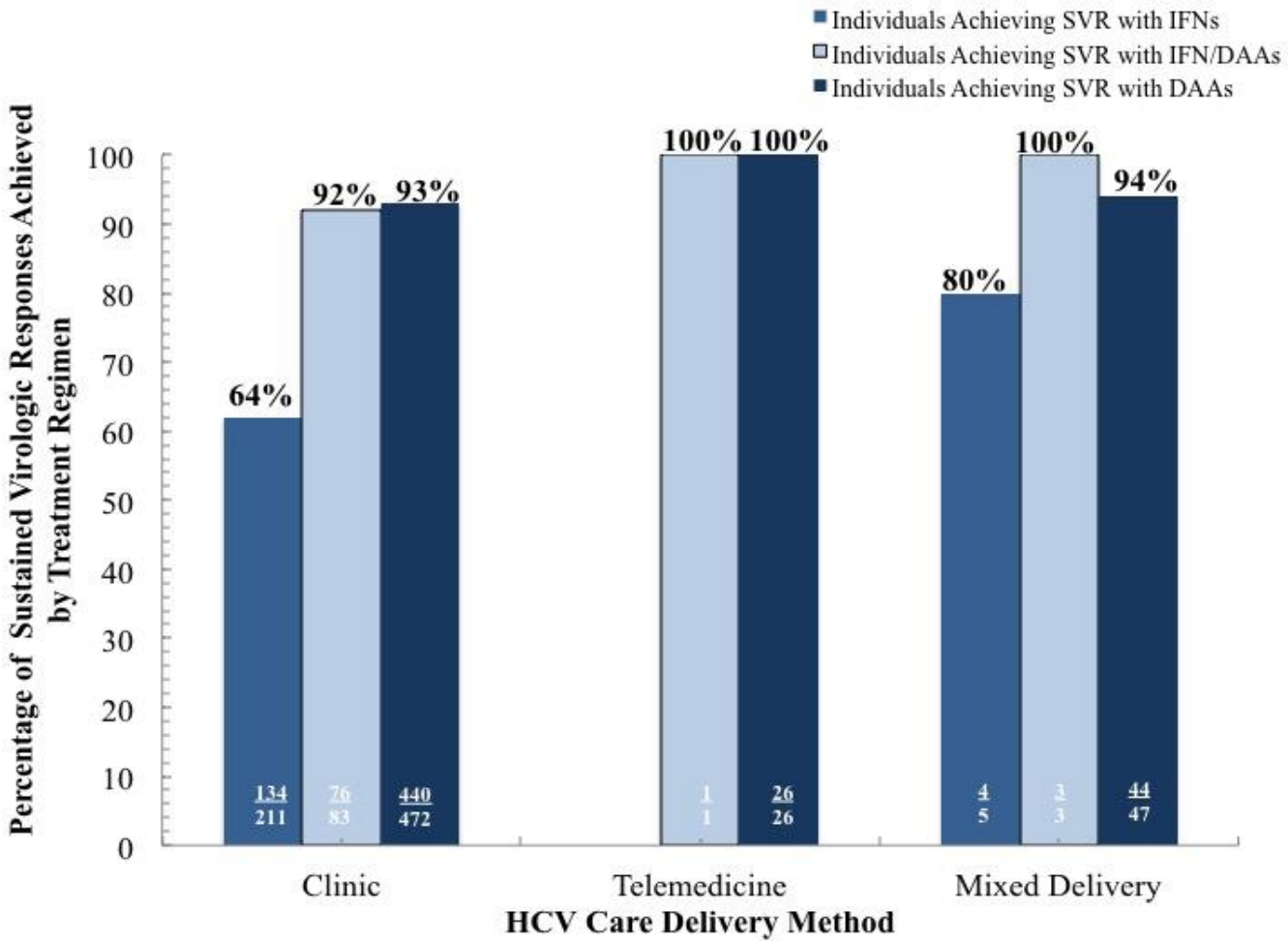

Figure 7. Overall percentage of HCV cure, using per-protocol SVR definition, for telemedicine, outpatient clinic, and mixed delivery patients represented by treatment regimen.

One of the focuses of this thesis was to assess the TOHVHP telemedicine program for SVR rates among Indigenous patients accessing HCV care When comparing patients who self-identified as Indigenous (n = 21) on per-protocol SVR rates, all (3/3) telemedicine patients who initiated HCV treatment achieved SVR. For the other two HCV care delivery methods, overall per-protocol SVR rates were 87% (13/15) for outpatient clinic patients and 100% (3/3) mixed delivery patients. Although once controlled for treatment allocation the likelihood of achieving SVR among patients who self-identified as Indigenous did not statistically differ by HCV care delivery method ($p = 0.10$), the sample size (n = 21) was too small to form any definitive conclusions regarding the use of telemedicine for achieving SVR among TOHVHP patients who identified as Indigenous.

Treatment specific per-protocol SVR rates by HCV care delivery method were also calculated for patients who self-identified as Indigenous. For interferon treatment regimens, per-protocol SVR rates for outpatient clinic patients were 33% (1/3). No telemedicine or mixed delivery patients were prescribed an interferon-based treatment regimen. Additionally, no patients who self-identified as Indigenous were prescribed interferon-Direct Acting Antiviral combination therapies. For Direct Acting Antiviral treatment regimens, SVR rates were 100% (3/3) for telemedicine patients, 100% (12/12) for outpatient clinic patients, and 100% (3/3) for mixed delivery patients (Figure 8).

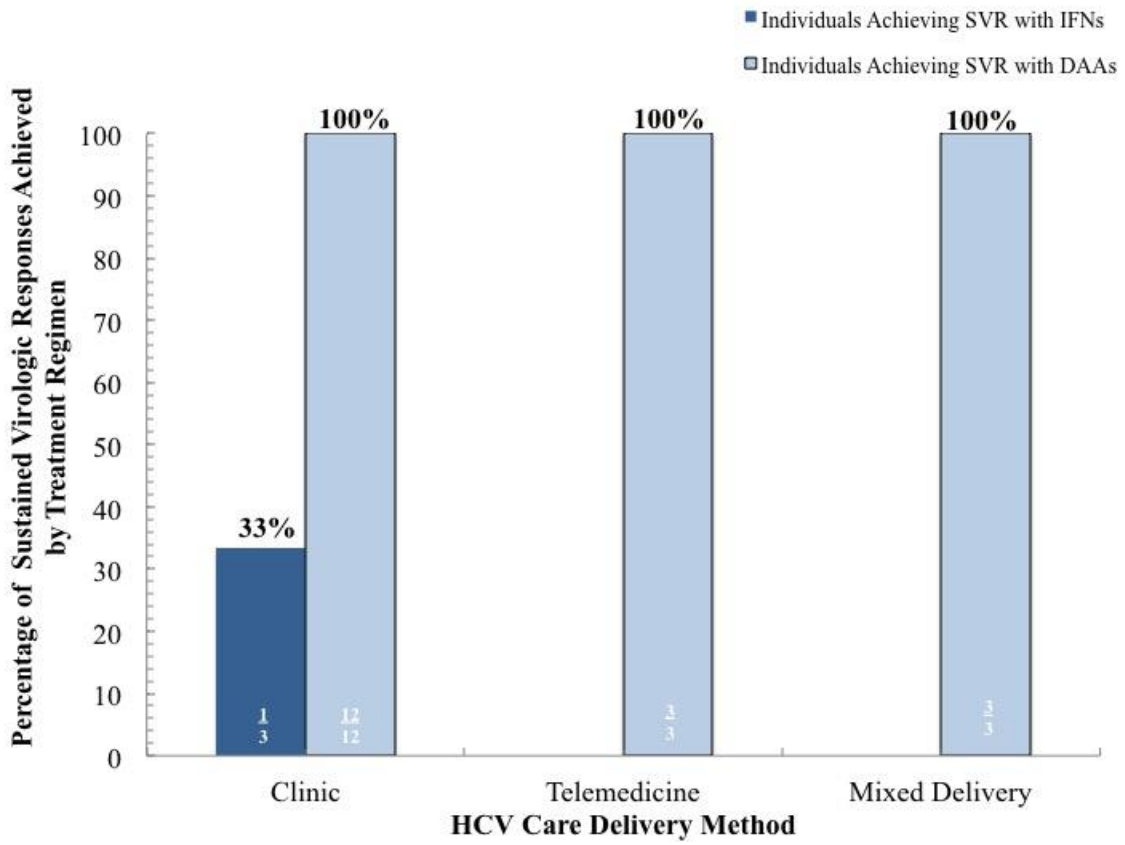

Figure 8. Overall percentage of HCV care, using per-protocol SVR definition, for telemedicine, outpatient clinic, and mixed delivery patients who self-identified as Indigenous represented by treatment regimen.

8.1.2 Proportion of Patients Achieving HCV Cure by Treatment Regimen and Care delivery Method Using Intent-to-treat Analysis

Using the intent-to-treat SVR definition, the rate of SVR were 76% (28/37) for telemedicine patients, 80% (655/815) for outpatient clinic patients, and 83% (51/62) for mixed delivery patients. The likelihood of achieving SVR did not statistically differ by HCV care delivery method (p = 0.72). It should be noted however that the sample size for telemedicine in

this thesis might have been too small to detect small differences in SVR rates due to limited power (Table 26).

Table 26. Intent-To-Treat SVR rates by HCV care delivery method**.**

HCV Care Delivery Method	Achieved SVR	No SVR	SVR %	P-Value
Telemedicine	28	9	76	
Clinic	655	160	80	0.72
Mixed Delivery	51	11	83	

Treatment specific intent-to-treat SVR rates by HCV care delivery method were also calculated. For interferon treatment regimens, intent-to-treat SVR rates were 0% (0/1) for telemedicine patients, 61% (134/221) for outpatient clinic patients, and 80% (4/5) for mixed delivery patients. For interferon-Direct Acting Antiviral combination therapies, SVR rates were 50% (1/2) for telemedicine patients, 87% (76/87) for outpatient clinic patients, and 60% (3/5) for mixed delivery patients. For Direct Acting Antiviral treatment regimens, SVR rates were 79% (27/34) for telemedicine patients, 88% (440/550) for outpatient clinic patients, and 85% (44/52) for mixed delivery patients (Figure 9).

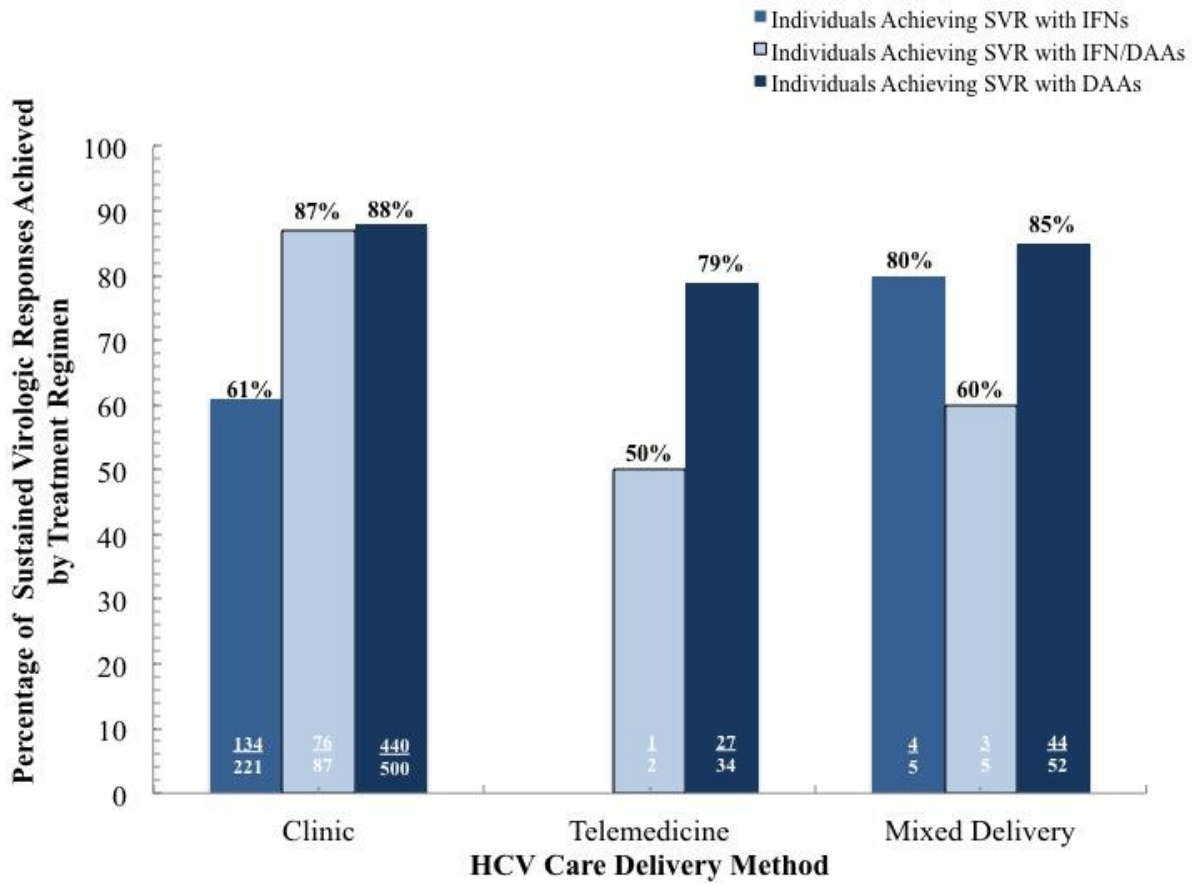

Figure 9. Overall percentages of HCV cure, using intent-to-treat SVR definition, for telemedicine, outpatient clinic, and mixed delivery patients represented by treatment regimen.

When comparing intent-to-treat SVR rates among patients who self-identified as Indigenous (n = 24), 75% (3/4) of telemedicine patients who initiated HCV treatment achieved SVR. For the other two HCV care delivery methods, overall intent-to-treat SVR rates were 76% (13/17) for outpatient clinic patients and 100% (3/3) mixed delivery patients. Although the likelihood of achieving SVR among patients who self-identified as Indigenous did not statistically differ by HCV care delivery method (p = 0.63), the sample size (n = 24) was too

small to form any definitive conclusions regarding the use of telemedicine for achieving SVR among TOHVHP patients who identified as Indigenous.

Treatment specific intent-to-treat SVR rates by HCV care delivery method were also calculated for patients who self-identified as Indigenous. For interferon treatment regimens, intent-to-treat SVR rates for outpatient clinic patients were 33% (1/3). No telemedicine or mixed delivery patients were prescribed an interferon treatment regimen or interferon-Direct Acting Antiviral combination therapies. For Direct Acting Antiviral treatment regimens, SVR rates were 75% (3/4) for telemedicine patients, 86% (12/14) for outpatient clinic patients, and 100% (3/3) for mixed delivery patients (Figure 10).

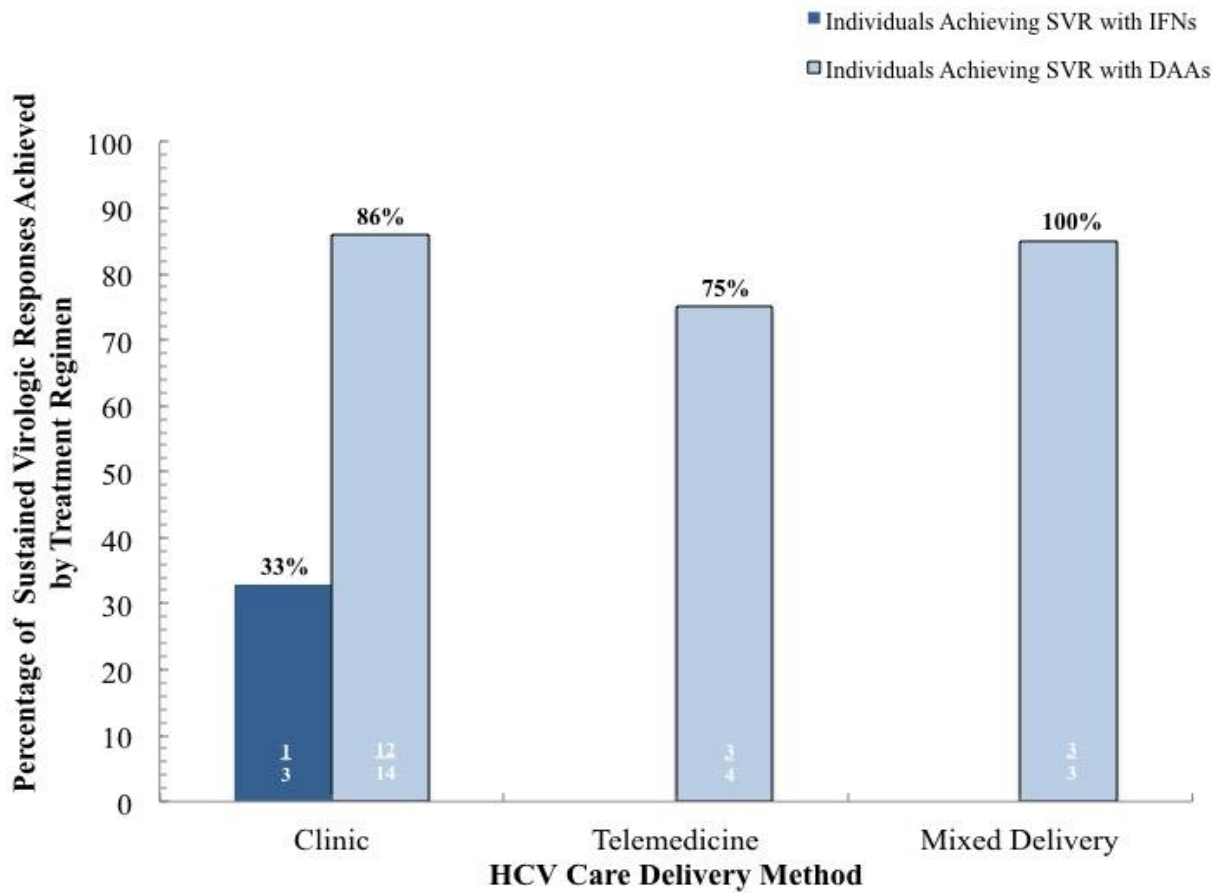

Figure 10. Overall percentage of HCV cure, using intent-to-treat SVR definition, for telemedicine, outpatient clinic, and mixed delivery patients who self-identified as Indigenous represented by treatment regimen.

8.1.3 Assessing Patient and Clinic Characteristics Associated with Achieving HCV Cure by Treatment Regimen and Care delivery Method Using Per-Protocol Analysis

Per-protocol SVR analysis was used for the analysis represented in Table 27. Per-protocol SVR included only those individuals who successfully completed their treatment regimen and had a minimum of 3 months post-treatment blood work confirming SVR. This analysis included 855 individuals. Comparisons between telemedicine, outpatient clinic and mixed delivery patients were made using Chi-Square analysis for categorical variables and T-tests for continuous variables using SAS 9.4 statistical software.

When comparing patients who achieved SVR to those who did not achieve SVR, patients that achieved SVR were older (51.4 years vs. 48.5 years, $p = 0.003$) and had higher baseline ALT (108 U/mL vs. 90 U/mL, $p = 0.009$). Patients who achieved SVR compared to those who did not achieve SVR were also more likely to be infected with genotype 1 (72.4% vs. 61.4%, $p < 0.0001$) and had received Direct Acting Antiviral therapies (69.6% vs. 28.7%, $p < 0.001$). Patients who achieved SVR compared to those who did not achieve SVR were also less likely to have a pre-treatment Fibroscan score of F4 (40.9% vs. 54.3%, $p < 0.0001$). Although statistically significant, the absolute difference in suitable housing was small between HCV care delivery models and likely inconsequential (Table 27).

Patient who achieved SVR were also less likely to be co-infected with HIV (4.8% vs. 9.8%, $p = 0.02$), have a history of mental illness (18.0% vs. 35.2%, $p < 0.0001$), have tattoos

(42.9% vs. 47.5%, p = 0.02), had been previously incarcerated (36.6% vs. 46.7%, p = 0.003), and to have not graduated high school (10.9% vs. 12.4%, p <0.0001). Although statistically significant, there was no clinically relevant difference in housing suitability HCV care delivery methods. Patient populations were comparable in terms of proportion of individuals who were Indigenous, sex, co-infection with HBV, baseline HCV viral load, having undergone a liver biopsy, previous treatment exposure, history of injection drug use, history of engaging in high risk sex, history of intranasal cocaine use, having piercings, geographic area of residence, and proportion of people experiencing greatest level of material and social deprivation (Table 27).

Table 27. Patient and clinical characteristics associated with achieving SVR.

Variable	Achieved SVR (n = 733)		No SVR (n = 122)		P-Value
	n (N)	%	n (N)	%	
Indigenous					0.53
Yes	19 (641)	2.9	2 (107)	1.9	
No	622 (641)	97.1	105 (107)	98.1	
Sex					
Male	480 (733)	65.5	87 (122)	71.3	0.21
Female	253 (733)	34.5	35 (122)	28.7	
Age	51.4 (10.2)		48.5 (9.4)		0.003
HCV Genotype					< .0001
1	531 (733)	72.4	75 (122)	61.4	
2	59 (733)	8.0	3 (122)	2.5	
3	88 (733)	12.0	31 (122)	25.4	
4	22 (733)	3.0	12 (122)	9.8	
Mixed	9 (733)	1.2	0 (122)	0	
HIV Co-Infection					
Yes	35 (733)	4.8	12 (122)	9.8	0.02
No	698 (733)	95.2	110 (122)	90.2	
HBV Co-Infection					
Yes	5 (733)	0.7	1 (733)	1.4	0.59
No	670 (733)	91.4	108 (733)	14.7	
Viral Load	4.9^{+6} (2.1^{+7})		2.7^{e+6} (1.4^{e+6})		0.29
Baseline ALT	108 (97)		90 (60)		0.009
Liver Biopsy					
Yes	337 (733)	46.0	66 (122)	54.1	0.09
No	396 (733)	54.0	56 (122)	45.9	

Treatment Start Fibrosis score by transient elastography					< .0001
F0 – F1	118 (493)	23.9	9 (35)	25.7	
F2	91 (493)	18.5	3 (35)	8.6	
F3	82 (493)	16.6	4 (35)	11.4	
F4	202 (493)	40.9	19 (35)	54.3	
Treatment Group					<.0001
IFN	138 (733)	18.8	78 (122)	63.9	
IFN-DAA	80 (733)	10.9	7 (122)	5.7	
DAA	510 (733)	69.6	35 (122)	28.7	
Previous Treatment Exposure					0.30
Naïve	603 (733)	82.3	105 (122)	86.1	
Multiple	130 (733)	17.7	17 (122)	13.9	
History of Mental Illness					
Yes	132 (733)	18.0	43 (122)	35.2	< .0001
No	601 (733)	82.0	79 (122)	64.8	
HCV Risk Factors					
History of IVDU	382 (733)	52.1	72 (122)	59.0	0.2
History of High Risk Sex	78 (733)	10.6	13 (122)	10.7	0.99
History of Snorting Cocaine	315 (733)	42.9	59 (122)	48.4	0.27
History of Tattoos	268 (733)	36.6	58 (122)	47.5	0.02
History of Incarceration	242 (733)	33.0	57 (122)	46.7	0.003
Previous Blood Recipient	146 (733)	19.9	7 (122)	5.7	0.0002
History of Piercings	202 (733)	27.6	42 (122)	34.4	0.12
No High School Diploma	78 (715)	10.9	15 (121)	12.4	<.0001
Area Classification					0.05
Rural	138 (703)	19.6	12 (117)	10.3	
Intermediate	75 (703)	10.7	14 (117)	11.9	
Urban	490 (703)	69.7	91 (122)	74.6	
Greatest Material Deprivation	154 (648)	23.8	36 (112)	32.1	0.06
Greatest Social Deprivation	179 (648)	27.6	28 (112)	25.0	0.56
Housing Suitability					
Suitable	679 (715)	95.0	114 (121)	94.0	<.0001
Not Suitable	36 (715)	5.0	7 (121)	6.0	<.0001

The following analysis was conducted to assess the association of covariates on the outcome of achieving SVR using a per-protocol SVR definition. Although this thesis focuses on HCV care delivery method as a predictor of clinical outcomes, this variable was unable to be included in the per-protocol SVR logistic regression model as including it caused instability of the model. This was due to the fact that receiving telemedicine was completely predictive of achieving SVR due to the small sample size, lack of utilization of inferior interferon-based

treatments, and the almost exclusive use of DAA-based treatment regimens with known high cure rates.

In the unadjusted logistic regression model, having HCV genotype 3-infection and HCV genotype 4, being co-infected with HIV, having a history of mental illness, having tattoos, previous incarceration, and having unsuitable housing were significantly associated with decreased odds of achieving SVR. Receiving interferon-Direct Acting Antiviral combination therapies or exclusively Direct Acting Antiviral therapies, having previously receiving blood products, and living in a rural area were significantly associated with increased odds of achieving SVR. Identifying as Indigenous was not associated with achieving SVR (Table 28).

Table 28. Results of all simple logistic regression models for all predictors. Reported are maximum likelihood estimates, standard errors, odds ratios with 95% confidence intervals, and p-values of all potential predictors among patients who achieved SVR using per-protocol analysis.

Variable	Coefficient (SE)	Odds Ratio (95% CI)	P-Value
Indigenous (Yes vs. No)	0.47 (0.75)	1.60 (0.37, 6.99)	0.53
Female Sex	0.27 (0.21, 1.59)	1.31 (0.86, 1.99)	0.21
Age	0.03 (0.009)	1.03 (1.01, 1.05)	< 0.0001
HCV Genotype (REF: GENO 1)			
2	1.02 (0.60)	2.78 (0.85 9.09	0.09
3	- 0.91 (0.25)	0.40 (0.25, 0.65)	0.0002
4	- 0.95 (0.36)	0.39 (0.19, 0.79)	0.008
HIV Co-Infection			
Yes vs. No	- 0.78 (0.35)	0.46 (0.23, 0.91)	0.03
HBV Co-Infection			
Yes vs. No	0.22 (1.1)	1.24 (0.14, 10.72)	0.84
Viral Load	3.72E-8 (2.24E-8)	1.000 (1.00, 1.00)	0.09
Baseline ALT	0.003 (0.001)	1.003 (1.00, 1.005)	0.06
Liver Biopsy	- 0.33 (0.19)	0.72 (0.49, 1.06)	0.09
Fibrosis score by transient elastography (Ref: F4)			0.31
F0-F1	0.21 (0.42)	1.23 (0.54, 2.81)	

F2	1.05 (0.63)	2.85 (0.82, 9.88)	
F3	0.66 (0.57)	1.93 (0.64, 5.84)	
Treatment Group (REF: IFN)			
IFN-DAA	1.87 (0.42)	6.46 (2.84, 14.68)	<.0001
DAA	2.11 (0.22)	8.23 (5.30, 12.79)	<.0001
Previous Treatment Exposure			0.30
(REF: Naïve)	0.29 (0.28)	1.33 (0.77, 2.29)	
Multiple			
History of Mental Illness			
Yes vs. No	-0.91 (0.21)	0.40 (0.27, 0.61)	< 0.0001
History of IVDU (Yes vs. No)	-0.28 (0.19)	0.75 (0.51, 1.12)	0.16
History of High Risk Sex (Yes vs. No)	-0.001 (0.32)	0.99 (0.54, 1.86)	0.99
History of Cocaine Use (Yes vs. No)	-0.22 (0.19)	0.81 (0.55, 1.18)	0.27
History of Tattoos (Yes vs. No)	-0.45 (0.19)	0.64 (0.43, 0.94)	0.02
History of Incarceration (Yes vs. No)	-0.58 (0.19)	0.56 (0.38, 0.83)	0.004
Blood Recipient (Yes vs. No)	1.41 (0.40)	4.09 (1.86, 8.95)	0.0004
History of Piercings (Yes vs. No)	-0.32 (0.21)	0.73 (0.48, 1.09)	0.12
No High School Diploma	- 1.55 (1.04)	0.21 (0.03, 1.64)	0.14
Area Classification (REF: Urban)			
Rural	0.76 (0.32)	2.14 (1.14, 4.01)	0.02
Intermediate	-0.005 (0.31)	0.99 (0.54, 1.84)	0.99
Greatest Material Deprivation	-0.42 (0.22)	0.66 (0.43, 1.02)	0.06
Greatest Social Deprivation	0.13 (0.23)	1.14 (0.72, 1.82)	0.56
Suitable Housing	2.82 (1.57)	16.83 (0.78, 363.26)	0.07
Unsuitable Housing	- 2.97 (1.52)	0.05 (0.003, 1.01)	0.05

When assessing all treatment regimens using per-protocol analysis, after adjustment for sex and age, having HCV genotype 2-infections (OR: 4.61, 95% C.I. 1.35 -15.79), receiving interferon-Direct Acting Antiviral combination therapies (OR: 6.38, 95% C.I. 2.75, - 14.85), and receiving Direct Acting Antiviral therapies (OR: 8.40, 95% C.I. 5.27 – 13.38) were significantly associated with increased odds of achieving SVR, whereas having HCV genotype 4-infections (OR: 0.45, 95% C.I. 0.21 – 1.00) was significantly associated with decreased odds of achieving SVR (Table 29).

Table 29. Adjusted logistic regression model. Presented are odds ratios [95% C.I.s] and p-values for patients who achieved SVR for all treatment regimens using per-protocol analysis.

Variable	Odds Ratios (95% C.Is)	P-Value
Female Sex	1.18 (0.74, 1.89)	0.50
Age	1.01 (0.99, 1.04)	0.32
HCV Genotype (REF: GENO 1)		
2	4.61 (1.35, 15.79)	0.01
3	0.64 (0.37, 1.11)	0.11
4	0.45 (0.21, 1.00)	0.05
Treatment Group (REF: IFN)		
IFN-DAA	6.38 (2.75, 14.85)	< .0001
DAA	8.40 (5.27, 13.38)	< .0001

When assessing only patients who received Direct Acting Antiviral therapies between January 1, 2014 and December 31, 2016, after adjustment for sex and age, having a HCV genotype 3-infection (OR: 0.37, 95% C.I. 0.16 – 0.85) was significantly associated with decreased odds of achieving SVR (Table 30).

Table 30. Adjusted logistic regression model. Presented are odds ratios [95% C.I.s] and p-values for patients who achieved SVR and received Direct Acting Antivirals using per-protocol analysis.

Variable	Odds Ratios (95% C.Is)	P-Value
Female Sex	1.19 (0.57, 2.49)	0.64
Age	1.02 (0.99, 1.05)	0.24
HCV Genotype (REF: GENO 1)		
2	2.04 (0.27 15.59)	0.49
3	0.37 (0.16, 0.85)	0.02
4	0.47 (0.13, 1.69)	0.25

8.1.4 Assessing Patient and Clinic Characteristics Associated with Achieving HCV Cure by Treatment Regimen and Care delivery Method Using Intent-to-treat Analysis

The following analysis was conducted to assess the association of covariates on the outcome of achieving SVR using an intent-to-treat SVR definition. In the unadjusted logistic regression model, HCV care delivery method was not associated with the outcome of achieving SVR. Having a HCV genotype 3-infections or genotype 4-infections, history of mental illness, history of injection drug use, history of intranasal cocaine use, having tattoos, having previously been incarcerated, not having graduated high school, living in a rural area, experiencing the greatest quintile of material deprivation, and having unsuitable housing were associated with decreased odds of achieving SVR. Older age, higher baseline viral load, and having ever received blood products were associated with increased odds of achieving SVR. Identifying as Indigenous was not associated with decreased odds of achieving SVR (Table 31).

Table 31. Results of all simple logistic regression models for all predictors. Reported are maximum likelihood estimates, standard errors, odds ratios with 95% confidence intervals, and p-values of all potential predictors among patients who did and did not achieve SVR using intent-to-treat analysis.

Variable	Coefficient (SE)	Odds Ratio (95% CI)	P-Value
Clinic Allocation (REF: Clinic)			
Telemedicine	- 0.27 (0.39)	0.76 (0.35, 1.64)	0.48
Mixed Delivery	0.12 (0.34)	1.13 (0.58, 2.22)	0.72
Indigenous (Yes vs. No)	- 0.08 (0.51)	0.92 (0.34, 2.51)	0.87
Female Sex	0.26 (0.18)	1.29 (0.91, 1.85)	0.16
Age	0.03 (0.008)	1.03 (1.01, 1.05)	0.0002
HCV Genotype (REF: GENO 1)			
2	0.91 (0.48)	2.48 (0.98, 6.33)	0.06
3	- 0.89 (0.21)	0.41 (0.27, 0.62)	<.0001

4	- 0.70 (0.34)	0.50 (0.26, 0.96)	0.04
HIV Co-Infection			0.06
Yes vs. No	- 0.59 (0.32)	0.55 (0.29, 1.03)	
HBV Co-Infection			
Yes vs. No	- 0.20 (1.09)	0.82 (0.09, 7.04)	0.24
Viral Load	4.78E-8 (2.04E-8)	1.00 (1.00, 1.00)	0.02
Baseline ALT	0.001 (0.001)	1.001 (1.00, 1.003)	0.20
Liver Biopsy	0.04 (0.17)	1.04 (0.75, 1.45)	0.08
Fibrosis score by transient elastography (Ref: F4)			0.48
F0 – F1	0.13 (0.32)	1.13 (0.61, 2.12)	
F2	0.62 (0.41)	1.86 (0.83, 4.18)	
F3	0.29 (0.38)	1.34 (0.63, 2.84)	
Treatment Group (REF: IFN)			
IFN-DAA	1.30 (0.32)	3.69 (1.97, 6.90)	< 0.0001
DAA	1.48 (0.18)	4.39 (3.06, 6.29)	< 0.0001
Previous Treatment Exposure (REF: Naïve)			0.39
Multiple	0.19 (0.23)	1.22 (0.78, 1.91)	
History of Mental Illness (Yes vs. No)	-0.72 (0.19)	0.49 (0.34, 0.70)	0.0001
History of IVDU (Yes vs. No)	-0.36 (0.17)	0.69 (0.49, 0.97)	0.03
History of High Risk Sex (Yes vs. No)	-0.11 (0.26)	0.90 (0.54, 1.50)	0.69
History of Cocaine Use (Yes vs. No)	-0.33 (0.17)	0.72 (0.52, 0.99)	0.05
History of Tattoos (Yes vs. No)	-0.48 (0.17)	0.62 (0.45, 0.86)	0.004
History of Incarceration (Yes vs. No)	-0.53 (0.17)	0.59 (0.42, 0.82)	0.002
Blood Recipient (Yes vs. No)	0.69 (0.25)	2.00 (1.22, 3.29)	0.006
History of Piercings (Yes vs. No)	-0.19 (0.18)	0.82 (0.58, 1.17)	0.27
No High School Diploma	- 2.77 (1.34)	0.06 (0.00, 0.87)	0.04
Area Classification (REF: Urban)			
Rural	0.51 (0.25)	0.67 (0.42, 1.08)	0.05
Intermediate	- 0.39 (0.24)	1.66 (1.01, 2.74)	0.10
Greatest Material Deprivation	- 0.38 (0.19)	0.68 (0.47, 0.99)	0.05
Greatest Social Deprivation	0.36 (0.21)	1.43 (0.95, 2.17)	0.09
Suitable Housing	2.40 (1.39)	11.06 (0.73, 168.48)	0.08
Unsuitable Housing	- 2.77 (1.34)	0.06 (0.01, 0.87)	0.04

When assessing all treatment regimens using an intent-to-treat analysis, after adjustment for sex and age, having HCV genotype 3-infections (OR: 0.57, 95% C.I. 0.36 – 0.89) and receiving HCV-care via telemedicine (OR: 0.44, 95% C.I. 0.20 – 0.99) were associated with decreased odds of achieving SVR. Having genotype 2-infections (OR: 3.46, 95% C.I. 1.30 – 9.21), receiving interferon-Direct Acting Antiviral combination therapies (OR: 3.55, 95% C.I.

1.84 – 6.84), and receiving Direct Acting Antivirals (OR: 4.55, 95% C.I. 3.06 – 6.76) were associated with increased odds of achieving SVR (Table 32).

Table 32. Adjusted logistic regression model. Presented are odds ratios [95% C.I.s] and p-values for patients who achieved SVR for all treatment regimens using intent-to-treat analysis.

Variable	Unadjusted Odds Ratios (95% C.Is)	Adjusted Odds Ratios (95% C.Is)	P-Value
Clinic Allocation (REF: Clinic)			
Telemedicine	0.76 (0.35, 1.64)	0.44 (0.20, 0.99)	0.05
Mixed delivery	1.13 (0.58, 2.22)	0.74 (0.36, 1.53)	0.42
Female Sex		1.19 (0.81, 1.76)	0.37
Age		1.02 (0.99, 1.04)	0.06
HCV Genotype (REF: GENO 1)			
2		3.46 (1.30, 9.21)	0.01
3		0.57 (0.36, 0.89)	0.01
4		0.54 (0.26, 1.09)	0.09
Treatment Group (REF: IFN)			
IFN-DAA		3.55 (1.84, 6.84)	0.0002
DAA		4.55 (3.06, 6.76)	<0.0001

When assessing only patients who received Direct Acting Antiviral therapies between January 1, 2014 and December 31, 2016, after adjustment for sex and age, HCV care delivery method was not associated with the outcome of achieving SVR. Having HCV genotype 3-infections (OR: 0.39, 95% C.I. 0.21, 0.72) was associated with decreased odds of achieving SVR (Table 33).

Table 33. Adjusted logistic regression model. Presented are odds ratios [95% C.I.s] and p-values for patients who achieved SVR and received Direct Acting Antivirals using an intent-to-treat analysis**.**

Variable	Unadjusted Odds Ratios (95% C.Is)	Adjusted Odds Ratios (95% C.Is)	P-Value
Clinic Allocation (REF: Clinic)			
Telemedicine	0.76 (0.35, 1.64)	0.55 (0.22, 1.35)	0.19
Mixed delivery	1.13 (0.58, 2.22)	0.69 (0.31, 1.57)	0.38
Female Sex		1.32 (0.77, 2.27)	0.31
Age		1.01 (0.99, 1.05)	0.08
HCV Genotype (REF: GENO 1)			
2		2.10 (0.49, 9.05)	0.32
3		0.39 (0.21, 0.72)	0.002
4		0.71 (0.23, 2.15)	0.54

CHAPTER 9. DISCUSSION

It is suggested that providing HCV care via telemedicine has the potential to address various barriers (i.e., geographic, financial, socioeconomic) that impact an individual's ability to initiate, adhere, and successfully complete HCV treatment and achieve HCV cure. We sought to evaluate the relatively new HCV telemedicine program operating through The Ottawa Hospital Viral Hepatitis Program to assess whether patients receiving telemedicine-delivered HCV care were able to achieve similar clinical outcomes compared to patients receiving traditionally delivered (i.e., via the Ottawa Hospital – General Campus) HCV care.

9.1. Performance Of TOHVHP Telemedicine Program

We evaluated the TOHVHP to examine the overall performance and ability of the telemedicine program to attract patients facing barriers to engaging in traditionally delivered HCV care. TOHVHP telemedicine patients compared to TOHVHP patients receiving HCV care delivery via traditional care delivery methods, such as at the Ottawa Hospital – General Campus outpatient clinic, were more likely to have not graduated high school, have a history of mental illness including depressive disorder, anxiety disorder, and schizophrenia, resided in more rural areas, had engaged in high risk behaviors for acquiring HCV including injection drug use and intranasal cocaine use, and had previously been incarcerated.

Indicators of lower socioeconomic status such as limited education is a known barrier to engaging in HCV care as individuals' may not be aware of their ongoing engagement with risk behaviors for acquiring HCV, particularly among high risk populations such as people who inject drugs [19]. This limited knowledge may therefore not only impair the individual from engaging

with HCV care, as they are unaware of their HCV positive status, but may also negatively impact an individual's desire to seek out HCV treatment, due to known difficulties associated with historical interferon-based therapies [4,19]. Presence of mental illness has also been well documented as a barrier for individuals to successfully engage in healthcare as individuals who are experiencing psychiatric illnesses may have inherent distress regarding the healthcare system, poor relationship with healthcare providers, decreased functional ability, and may be unable to rationalize the need to get treatment for their chronic HCV infection [4,58].

Engagement in HCV-risk factors such as ongoing and previous drug use, particularly injection drug use, is also a known barrier for patients to engage with HCV care. Individuals with active or a history of substance use may experience disproportionate rates of mental illness which may further negatively impact their ability to engage in HCV care [4,59,60]. Individuals who inject drugs may also face increased stigmatization from providers, family, or peers which may impact their desire to engage in HCV care [31,61]. Finally, people who inject drugs as well as individuals living in rural areas have difficulty accessing traditionally delivered HCV care in urban centralized, specialty care centers, therefore limiting their ability to engage in HCV care [4,31].

Overall, TOHVHP telemedicine program successfully engaged patients facing the above known barriers to linking with traditionally delivered HCV care.

9.2. Objective 1: Comparing Patient Retention Between Telemedicine and Traditional HCV Care Delivery Patients

We used TOHVHP Data Base Project Data to: 1) compare lost to follow up rates by HCV care delivery method, 2) compare time spent in HCV care by HCV care delivery method, and 3)

identify patient and clinical factors associated with patient retention in HCV care. It was hypothesized that TOHVHP telemedicine patients would experience similar patient retention compared to TOHVHP patients receiving HCV care via traditionally delivered HCV care.

9.2.1. Comparison of Lost To Follow Up Rates by HCV Care Delivery Method

We found that TOHVHP telemedicine patients were disproportionately affected by lost to follow up rates compared to TOHVHP patients receiving HCV care via traditionally delivered HCV care. Lost to follow up rates by HCV care delivery method were 27% for telemedicine patients, 5% for outpatient clinic patients, and 11% for mixed delivery patients (Table 9). Although it appears lost to follow up rates were disproportionately high among telemedicine patients, rates were only slightly higher than the 20% lost to follow up rate observed among marginalized population prescribed Direct Acting Antiviral treatments in primary healthcare settings [62]. Sub-analysis of patient retention among Indigenous patients suggested that lost to follow up rates disproportionately affected telemedicine patients. However the available sample size was too small to make definitive conclusions regarding patient retention among Indigenous patients engaged in TOHVHP telemedicine program (Figure 4).

9.2.2. Comparison of Time Spent in HCV Care by HCV Care Delivery Method

We found that patient retention time by HCV care delivery method was comparable between telemedicine, outpatient clinic, and mixed delivery patients (Table 11). Although not significant, the slightly shorter time in HCV care among telemedicine patients compared to outpatient clinic, may be largely due to the majority of patients being treated with shorter

duration, Direct Acting Antiviral treatment regimens (8-12 weeks duration) and the lack of prescribing interferon-based therapies (24-48 weeks duration) among this patient population.

9.2.3. Evaluation of the Association between HCV Care Delivery Method and Patient Characteristics On Patient Retention

In the unadjusted logistic regression model, HCV care delivery method was significantly associated with the outcome of patient retention in HCV care. Once adjusted for clinically significant variables including age and sex, and the potential confounder of social deprivation on the outcome of patient retention within TOHVHP using a multivariate logistic regression model, we found that telemedicine and mixed delivery patients experienced a disproportionately high proportion of individuals not retained in HCV care. Telemedicine patients had 0.87-decreased odds (OR: 13, 95% C.I. 0.06 – 0.31) of being retained in TOHVHP HCV care whereas mixed delivery patients had 0.69-decreased odds (OR: 0.31, 95% C.I. 0.13 – 0.74) of being retained in TOHVHP HCV care (Table 18).

Results also surprisingly demonstrated that patients experiencing the greatest amount of social deprivation had 2.57-increased odds (OR: 2.57, 95% C.I. 1.06 – 6.26) of being retained in TOHVHP HCV care (Table 18). This result was unanticipated as it is hypothesized that patients experiencing the greatest level of social deprivation, an indicator of low socio-economic status, [63] would face additional barriers to continuous engaging with HCV care. However, this result may be because the TOHVHP clinic has supports in place, including social workers and psychologist to provide additional support to individuals with both unstable housing and limited social support systems in order to improve patient retention. Results from a British Columbia Cohort of individuals living with HCV found that experiencing the greatest level of social

deprivation was not associated with a patient's likelihood of being retained in HCV care [32]. In contrast, a cohort study assessing the HCV care continuum in France found similar results to our study, where patients experiencing the greatest level of social deprivation with more likely to be engaged in HCV specialty care and initiate HCV treatment in bivariate analysis [64]. This discrepancy in the association between social deprivation and patient retention in HCV care within our study and previously published literature could be due to: 1) the type of deprivation indices used, 2) the limitations of using Statistics Canada Population Census Data for a unique, patient-level analysis, and/or 3) an indication of selection bias/channeling bias within the clinic due to the additional supports offered to clients.

Deprivation indices encompass a variety of indicator variables used to capture social and material deprivation including indicators of deprivation of physical goods (i.e., suitable housing, television, car, ability to participate in leisure activities, ability to take holidays, and access to residential recreational programs) and indicators that measure an individual's lack of social relationships/networks [65,66]. The French study used a unique type of deprivation index called the EPICES score whereas both the Canadian cohort study and our study used deprivation indices based off of Townsend indices [32,64,66]. The EPICES index encompassed 11 questions measuring financial stability (health insurance, engagement with the welfare system, inability to buy basic needs), housing stability (homeownership), expendable funds (participation in sports, attending movies, taking holidays) and richness of social networks (living as a couple, recent visits with family members, ability of family or friends to help with financial or stressful situations) [64]. The Townsend- based indices used in the Canadian cohort study and our study only used two higher level indicators to measure material deprivation (encompassing the proportion of people without a high school diploma, employment to population ratio, and average personal income) and social deprivation (encompassing the proportion of people who are separated, divorced or widowed, the

proportion of people who are in single parent families, and the proportion of people living alone) [32,65]. In addition to the influence that the variation of variables used within the deprivation indices could have on the association between social deprivation and patient retention, an issue with our own deprivation indictor for social deprivation may have also contributed to the observed discrepancy. Although the Canadian cohort and our study used the same deprivation index measures, our study found that one of the social deprivation indicators, the proportion of people living in single-parent families, for our patient population was more representative of material deprivation than social deprivation, which could have resulted in the different outcome for the association between social deprivation and patient retention than that observed in the Canadian cohort study. This dual indication of material and social deprivation for the proportion of single parent families among Canadian populations has been previously observed [65].

The discrepancy may also be due to inherent limitations of using higher, non-discrete population-level data from the Statistics Canada Population Census to build a social deprivation index for a patient population experiencing a high degree of marginalization. By using a social deprivation index that is not measured on an individual level and does not encompass housing stability (i.e., residential mobility), it could underestimate [67] or overestimate, particularly based on the importance of housing stability on clinical outcomes [62,68], the effect of social deprivation on health outcomes among this unique, highly marginalized population.

Finally, the positive association between experiencing the greatest level of social deprivation and increased retention in HCV care may be due to patients placing an increased emphasis on self-care to address their chronic HCV infection and an inherent selection bias within the TOHVHP clinic. Once a patient enters the TOHVHP for HCV care, providers, including nurses, physicians, and social workers, assess the patient for potential indicators of social deprivation including their current employment status, marital status, housing status, and

by assessing any social supports the patient may have to help them with their HCV care. If a patient is identified as being socially deprived, the TOHVHP clinical team will discuss with the patient what resources they may need to help them successfully complete their HCV treatment and provide the patient with any additional support such as outreach case workers and psychologist, that they may need. Additionally, the clinical team will schedule the patient for more frequent follow up visits using both in clinic visits and telephone follow up with an outreach nurse. This identification of patients who may need additional supports early in a patient's HCV care by the TOHVHP clinical team may therefore contribute to the positive association between a patient experiencing social deprivation and increased likelihood of being retained in HCV care. Additionally, research has found that the social nature of injection drug use can encourage high-risk injecting practices and co-dependent substance use due to individuals feeling the need to demonstrate reciprocation (i.e., pooling for substances) and trust (i.e., sharing of equipment, allowing others to prepare the substance for injection) in injecting partnerships, particularly in sexual relationships [69,70]. Due to a majority of our patient population having a history of injection drug use, it can be hypothesized that experiencing the greatest level of social deprivation may demonstrate that participants may be starting life as a single, independent person, and therefore may be removing themselves from environments where drug use or HCV risk factors may be more prominent, or removing themselves from past relationships to put their health, primarily their HCV infection as a priority.

9.3. Objective 2: Comparing Treatment Initiation Rates Between Telemedicine and Traditional HCV Care Delivery Patients

We used TOHVHP Data Base Project Data to: 1) compare the proportion of patients initiating HCV treatment by HCV care delivery method, 2) identify patient and clinical factors associated with initiating interferon-based treatments, and 3) identify patient and clinical factors associated with initiating Direct Acting Antivirals. It was hypothesized that TOHVHP telemedicine patients would experience similar treatment initiation rates compared to TOHVHP patients receiving HCV care via traditionally delivered HCV care.

Due to vast differences regarding time of treatment regimen availability and limiting factors surrounding the use of interferon-based treatments for individuals with pre-existing mental health disorders, particularly depressive disorder, a multinomial logistic regression analysis was used to analyze the variables associated with the initiation of HCV treatment within the TOHVHP. The model included three outcomes, defined by the type of treatment initiated: 1) no treatment initiation, 2) initiation of interferon-treatment regimens (including interferon-Direct Acting Antiviral combination treatments), or 3) initiation of interferon-free Direct Acting Antiviral treatment regimens.

9.3.1. Proportion of Individuals Initiating Treatment by HCV Care Delivery Method

Upon initial review, we found that TOHVHP telemedicine patients had disproportionately low treatment initiation rates compared to TOHVHP patients receiving HCV care via traditionally delivered HCV care. Treatment initiation rates by HCV care delivery method were 35% for telemedicine patients, 64% for outpatient clinic patients, and 76% for mixed delivery patients (Table 19). Although it appears treatment initiation rates are

disproportionately low among telemedicine patients, once accounting for variation in HCV care delivery model establishment (i.e., TOHVHP telemedicine program was not established until late 2013) and the availability of various HCV treatment regimens (i.e., Direct Acting Antivirals not available until 2013), it was found that treatment uptake did not statistically differ by HCV-care delivery method[62]. It should be noted however that the sample size for telemedicine in this thesis might have been too small to detect small differences in treatment initiation rates due to limited power. Sub-analysis of treatment initiation rates among Indigenous patients found rates were similar among HCV-care delivery methods. However, the sample size was too small to make definitive conclusions regarding the telemedicine program for treatment uptake among Indigenous patients (Figure 6).

9.3.2. Evaluation of the Association between HCV Care Delivery Method and Patient Characteristics On Initiation of Interferon-Based Treatments

In the unadjusted logistic regression model, HCV care delivery was significantly associated with the outcome of initiating an interferon-based treatment, however this may be due to the non-existent use of interferon-therapies within the telemedicine group. Once adjusted for clinically significant variables including age and sex, and potential confounders of baseline ALT, having ever had a liver biopsy, and pre-treatment FibroScan scores on the outcome of initiating an interferon-based treatment within TOHVHP using a multivariate logistic regression model, we found that telemedicine and mixed delivery HCV care was not associated with decreased-odds of initiating an interferon-based treatment regimen (Table 21). The covariates of baseline ALT, having ever had a liver biopsy, and pre-treatment Fibroscan scores were significantly associated with initiating interferon-based treatment regimens (Table 21).

For every 1 IU/L increase in baseline ALT, the odds of initiating an interferon-based treatment increased 0.01x (OR: 1.01, 95% C.I. 1.00 – 1.01). Patients who ever had a liver biopsy had 3.57-increased odds (OR: 3.57, 95% C.I 1.70 – 7.47) of initiating interferon based treatments compared to patients who never had a liver biopsy. When comparing patients with moderate to advanced fibrosis (F2 – F4) to patients with minimal to no fibrosis (F0 –F1), the odds of initiating interferon-based treatments increased with increased presence of liver fibrosis. Patients with a F2, F3, and F4 baseline FibroScan score were nearly 3x more likely (OR: 2.89, 95% C.I. 0.91 – 8.63), 10x more likely (OR: 9.97, 95% C.I. 3.52 – 28.24), and 8.5x more likely (OR: 8.51, 95% C.I. 3.4` - 21.24) to initiate interferon-based therapies compared to patients with minimal to no fibrosis, respectively (Table 21).

Our results are consistent with current literature that support that increased ALT levels, having had a liver biopsy prior to the release of Fibroscan technologies, and increased fibrosis of the liver are positively associated with initiating a HCV treatment regimen. Abnormal ALT levels have been found to be associated with HCV treatment initiation. Research within a Danish cohort found that patients with ALT levels two-times the upper normal limit were more than 2x (RR: 2.17, 95% C.I. 1.64 – 2.87) more likely to initiate antiviral treatment [71]. Similar results supporting the relationship between elevated ALT levels and the initiation of antiviral treatments in patients living with chronic HCV were also observed in a Canadian cohort study where elevated ALT levels, defined as having an ALT level of more than 1.5x the upper normal limit, were associated with increased likelihood of initiating treatment [72].

Prior to the development of non-invasive FibroScan technologies, liver biopsies were viewed as the clinical gold standard for determining both the severity of a patient's liver disease and the appropriateness of initiating a patient on HCV antiviral therapies [73,74]. This supports the positive association between having ever had a liver biopsy and initiating treatment within the

TOHVHP cohort. Since late 2013, the TOHVHP had implemented new clinical standards that replaced invasive liver biopsies to determine the severity of a patient's liver disease with the use of FibroScan technology. The relationship between increased fibrosis of the liver being associated with HCV treatment initiation may be due to the high costs of Direct Acting Antivirals [75]. When Direct Acting Antiviral treatments first became available for use, many countries restricted their use to patients' with the most severe disease, defined as having a minimal liver fibrosis equivalent of F3, or F2 in Ontario, measured by FibroScan technology, until late 2015 [11]. Due to this cost-based barrier to accessing HCV treatment, individuals with moderate to advanced fibrosis (i.e., patients with stage 3 – 4 fibrosis) were more likely to initiate antiviral treatments compared to patients with mild liver disease (i.e., patients with stage 0 – 2 fibrosis) [76,77]. However in some studies there has been a noticeable uptake of treatment among patients with as little as stage 2 fibrosis as restrictions varied by country [73], supporting the results of our research model. This disproportional favor of initiating treatment among those living with severe liver disease is expected to decrease in Ontario because as of March 2018, the Ontario Drug Benefit Program expanded access to Direct Acting Antivirals and implemented a plan that permits physicians' to initiate antiviral treatment among all patients living with chronic hepatitis, regardless of their fibrosis score [75].

9.3.3. Evaluation of the Association between HCV Care Delivery Method and Patient Characteristics On Initiation of Direct Acting Antiviral Treatments

To account for a difference in treatment availabilities over time and the later establishment of the TOHVHP telemedicine program, a separate multivariate logistic regression model was performed and was restricted to patients who were prescribed Direct Acting

Antivirals between January 1, 2014 and December 31, 2016. In the unadjusted logistic regression model, HCV care delivery method was significantly associated with the outcome of initiating Direct Acting Antiviral treatments. Once adjusting in a multivariate logistic regression model for age sex, HCV genotype, ever having a liver biopsy, pre-treatment FibroScan score, history of engaging in high-risk sex, and history of mental illness, we found that telemedicine delivered HCV care remained associated with initiating Direct Acting Antiviral treatment uptake (Table 24). After adjustment for covariates, patients receiving HCV care via the TOHVHP telemedicine program had 0.63-reduced odds of initiating treatment compared to patients receiving traditional or mixed delivery care through TOHVHP (Table 24).

Similar to the multivariate logistic regression model evaluating patient and clinical factors associated with initiating any type of HCV treatment, the covariates of having ever had a liver biopsy and pre-treatment Fibroscan scores remained significantly associated with initiating Direct Acting Antiviral treatment regimens. Patients who ever had a liver biopsy had 2.07-increased odds (OR: 2.07, 95% C.I 1.35 – 3.18) of initiating Direct Acting Antiviral treatments. When comparing patients with moderate to advanced fibrosis (F2 – F4) to patients with minimal to no fibrosis (F0 –F1) to patients, the odds of initiating interferon-based treatments increased with increased fibrosis stage. Patients with a F2, F3, and F4 FibroScan score were nearly 3x more likely (OR: 3.19, 95% C.I. 1.93 – 5.30), 7x more likely (OR: 6.95, 95% C.I. 3.73 – 12.96), and 9.5x more likely (OR: 9.58, 95% C.I. 1.16 – 4.56) to initiate Direct Acting Antivirals compared to patients with minimal to no fibrosis (Table 24).

Unique to the model containing only those patients who initiated Direct Acting Antiviral therapies between January 1, 2014 and December 31, 2016, the covariates of HCV genotype, history of engaging in high-risk sex, and having a history of mental illness were significantly associated with initiating Direct Acting Antiviral treatment regimens. Patients with genotype 2-

infections had 0.50-decreased odds (OR: 0.50, 95% C.I. 0.26, 0.96) of initiating Direct Acting Antivirals whereas patients with genotype 3 or 4 infections had 0.47-decreased odds (OR: 0.53, 95% C.I. 0.32, 0.89) and 0.59-decreased odds (OR: 0.41, 95% C.I. 0.20, 0.88) decreased odds, respectively, of initiating Direct Acting Antivirals. Upon further investigation, it was found that low initiation rates for Direct Acting Antivirals among patients infected with genotype 2, 3, and 4-infections may be due to majority of these patients having minimal fibrosis of the liver (F1 or less measured by transient elastography). During the time period of this data analysis (2012 to 2016) Ontario government regulations required patients to have a Fibroscan score of F2 or higher to initiate Direct Acting Antivirals due to the high costs associated with the treatments. Of those who did not initiate treatment within TOHVHP, 62% of patients with genotype 2-infections, 71% of patients with genotype 3-infections, and 65% of patients with genotype 4-infections had pretreatment Fibroscan scores of F0 or F1 which is indicative of minimal liver damage. This rendered many patients relying on public drug insurance ineligible to receive Direct Acting Antivirals at the time and forcing them to wait until the treatment horizon changed in terms of public drug coverage policies[75].

Among TOHVHP patients, individuals with a history of engaging in high-risk sex were more than 2x (OR: 2.30, 95% C.I. 1.16 – 4.56) more likely to initiate Direct Acting Antivirals compared to individuals who did not have a history of engaging in high-risk sex (Table 24). Upon further investigation of this, we found that of those who initiated Direct Acting Antivirals and had a history of engaging in high-risk sex, 64% (n = 18/28) were co-infected with HIV. This increased treatment initiation within this particular sub-population may be due to both higher engagement of populations such as men who have sex with other men with the healthcare system and increased emphasis on treating HCV-HIV co-infected patients [11,14]. It had been found that individuals that engage in high-risk sex, such as men who have sex with other men, who are

living with co-infections of HIV and HCV are more likely to continuously engage with their healthcare providers and the healthcare system. This increased engagement may serve an additional opportunity for them to have a provider diagnosis and assess their HCV infection and may make it easier to facilitate them into continuous HCV specialty care, allowing for increased treatment uptake [11]. Patients living with HIV-HCV co-infections are also known to experience accelerated rates of liver fibrosis due to the nature of co-infections, which in turn increases a patients' risk of developing end-stage liver disease and hepatocellular carcinoma [11,12,74,77–80]. This increased risk has resulted in the development of clinical recommendations to treat all patients co-infected with HIV and HCV in order to improve both the patient's quality of life as well as reduce liver-related morbidity and mortality [11,77,79,80].

We also found that TOHVHP patients with a history of mental illness had 0.83-decreased odds (OR: 0.17, 95% C.I. 0.11 – 0.26) of initiating Direct Acting Antivirals compared to individuals without a history of mental illness (Table 24). Low treatment uptake within this group may have been because the majority of patients (76%) with a history of mental illness who did not initiate treatment had minimal fibrosis (F0 – F1), causing patients to have to wait to become eligible to receive Direct Acting Antivirals. Although the development of Direct Acting Antivirals has narrowed the gap for treating patients with existing psychiatric conditions, low treatment initiation rates may be indicative of providers determining patients were not ready to initiate treatment due to an ongoing uncontrolled psychiatric condition taking precedence over treating their HCV infection[75], which has been found in a previous San Francisco cohort study [81].

9.4. Objective 3: Comparing Sustained Virologic Response Rates Between Telemedicine and Traditional HCV Care Delivery Patients

We used TOHVHP Data Base Project Data to: 1) compare the proportion of patients achieving a sustained virologic response using per-protocol analysis by HCV care delivery method, 2) compare the proportion of patients achieving a sustained virologic response using intent-to-treat analysis by HCV care delivery method, 3) identify patient and clinical factors associated with achieving a sustained virologic response using per-protocol analysis and intent-to-treat analysis for all patients and any treatment regimen, and 4) identify patient and clinical factors associated with achieving a sustained virologic response using per-protocol analysis and intent-to-treat analysis for patients who were treated with Direct Acting Antivirals. It was hypothesized that TOHVHP telemedicine patients would experience similar sustained virologic response rates compared to TOHVHP patients receiving HCV care via traditionally delivered HCV care.

9.4.1. Proportion of Patients Achieving A Sustained Virologic Response According to Per-Protocol Analysis

In the analysis comparing the number of patients that achieved a sustained virologic response, according to per-protocol analysis, telemedicine delivered Direct Acting Antiviral treatments were able to achieve high sustained virologic response rates among patients facing identified barriers to traditionally delivered HCV care. Due to the TOHVHP telemedicine program not being established until the spring of 2013 and coinciding with the release of Direct

Acting Antiviral therapies, no telemedicine patients were prescribed solely interferon-based treatments.

Among patients prescribed interferon treatments, 64% (134/211) of outpatient clinic patients and 80% (4/5) of mixed delivery patients achieved SVR. With the development of HCV therapies combining both interferon and Direct Acting Antivirals, sustained virologic response rates improved compared to those observed when using solely interferon-based therapies. When comparing per-protocol SVR rates among patients who received interferon-Direct Acting Antiviral combination therapies, telemedicine (1/1) and mixed delivery (3/3) patients had a 100% SVR rate (1/1) compared to a 92% (76/83) SVR rate observed in outpatient clinic patients. Finally, when exclusively assessing SVR rates among patients who received Direct Acting Antivirals, telemedicine patients were able to achieve a 100% (26/26) cure rate compared to the 93% (440/472) cure rate among outpatient clinic patients and 94% (44/47) among mixed delivery patients (Appendix E).

When assessing overall SVR rates according to per-protocol analysis by HCV care delivery method; all 26 telemedicine patients (100%) who initiated treatment achieved sustained virologic response. This demonstrated that telemedicine delivered, Direct Acting Antivirals are capable of achieving high cure rates as seen in other cohort and clinical studies [62,77,82]. The other two HCV care delivery methods of outpatient clinic and mixed delivery also achieved high SVR rates of 86% (655/768) and 93% (51/55), respectively (Table 27). Although it appeared that telemedicine was able to achieve superior SVR rates compared to both outpatient clinic and mixed delivery patients this may be due to the use of superior Direct Acting Antiviral regimens among the telemedicine group (i.e. the most recently available DAA regimens are characterized by low pill count, better side effect profile and SVR rates over 95%). To account for this difference in prescribing, treatment allocation was controlled for using Cochran-Mantel-

Haenszel statistic to allow for accurate comparison of the association between HCV care delivery method and the likelihood of a patient achieving SVR. Once controlled for treatment allocation, the likelihood of achieving SVR did not statistically differ by HCV care delivery method ($p = 0.43$), supporting that telemedicine delivered HCV care is able to achieve similar HCV cure rates compared to those observed among patients receiving traditionally delivered HCV care (i.e., outpatient clinic and mixed delivery care), supporting this thesis hypothesis. It should be noted however that the sample size for telemedicine in this thesis might have been too small to detect small differences in SVR rates between HCV care delivery groups due to limited power.

When analyzing per-protocol SVR rates among Indigenous patients, it was found that SVR rates did not differ by HCV care delivery method ($p = 0.10$). However, the sample size was too small to formulate definitive conclusions regarding this effective of the TOHVHP telemedicine program to achieve SVR among Indigenous patients.

9.4.2. Proportion of Patients Achieving A Sustained Virologic Response According to Intent-to-treat Analysis

In the analysis comparing the number of patients that achieved a sustained virologic response, according to intent-to-treat analysis, telemedicine delivered Direct Acting Antiviral treatments are able to achieve high sustained virologic response rates among patients facing identified barriers to traditional delivered HCV care. Among patients prescribed interferon treatments, 0% (0/1) of telemedicine patients, 61% (134/221) of outpatient patients and 80% (4/5) of mixed delivery patients achieved SVR. When comparing intent-to-treat SVR rates among patients receiving interferon-Direct Acting Antiviral combination therapies, 50% (1/2) of

telemedicine patients, 87% (76/87) of outpatient clinic patients, and 60% (3/5) of mixed delivery patients achieved SVR. Finally, when exclusively assessing SVR rates among patients who received Direct Acting Antivirals, telemedicine patients were able to achieve a cure rate of 79% (27/34) compared to the 88% (440/550) cure rate among outpatient clinic patients and 85% (44/52) among mixed delivery patients (Figure 9).

When assessing overall SVR rates according to intent-to-treat analysis by HCV care delivery method; 28 of 37 (79%) telemedicine patients who initiated treatment achieved sustained virologic response. SVR rates using intent-to-treat SVR definition among telemedicine were slightly lower than those observed in both outpatient clinic and mixed delivery patients. The other two HCV care delivery methods of outpatient clinic and mixed delivery also achieved high SVR rates of 80% (655/815) and 83% (51/62), respectively (Table 26). Although it appeared that telemedicine patients were less likely to achieve SVR compared to both outpatient clinic and mixed delivery patients, SVR rates did not differ by HCV care delivery method ($p = 0.72$). It should be noted however that the sample size for telemedicine in this thesis might have been too small to detect small differences in SVR rates between HCV care delivery groups due to limited power. When analyzing intent-to-treat SVR rates among Indigenous patients, it was found that SVR rates did not differ by HCV care delivery method ($p = 0.63$). However, as previously described, the sample size was too small to draw definitive conclusions regarding the ability of the TOHVHP telemedicine program to achieve SVR among Indigenous patients

9.4.3. Evaluation of the Association between Patient Characteristics On Achieving A Sustained Virologic Response Among All Patients For Any Treatment Regimen

In the unadjusted logistic regression model using an intent-to-treat SVR definition for all treatment regimens, HCV care delivery via telemedicine was significantly associated with the outcome of achieving SVR. Once adjusted for clinically significant variables including age and sex, and potential confounders of HCV genotype and HCV treatment regimen on the outcome of achieving SVR within TOHVHP patients using a multivariate logistic regression model, we found that telemedicine delivered HCV care was associated with decreased-odds of achieving SVR when using an intent-to-treat SVR definition (Table 32). Using an intent-to-treat analysis, the covariates of HCV genotype and treatment allocation were significantly associated with initiating interferon-based treatment regimens (Table 32).

When applying per-protocol SVR definitions, it was found that HCV care delivery method (i.e., telemedicine vs. outpatient clinic vs. mixed delivery model) was a strong predictor of achieving SVR and could not be included in the model as its inclusion caused quasi-separation of the model, due to telemedicine patients receiving exclusively Direct Acting Antivirals with superior treatment outcomes. This illustrated that telemedicine patients are capable of achieving similar HCV cure rates as patients receiving HCV care via traditional care models (i.e., outpatient clinic and mixed delivery models). When controlling for clinically significant confounders of sex and age and the covariates of HCV genotype and assigned HCV treatment regimen, it was found that both HCV genotype and HCV treatment regimen were significantly associated with achieving per-protocol SVR (Table 29).

When assessing the relationship between HCV genotype and the likelihood of achieving SVR, it was found that having a genotype 3-infection was associated with decreased likelihood

of achieving HCV cure, however this association was not significant (p = 0.11). Individuals infected with a genotype 3-infection were 36% (OR: 0.64, 95% C.I. 0.37 – 1.11) less likely to achieve SVR when compared to individuals infected with a genotype 1-infection (Table 29).

Additionally, having a genotype 2-infection was associated with an increased likelihood of achieving SVR (p = 0.01). Results found that individuals infected with a genotype 2-infection were more than 4.5x (OR: 4.61, 95% C.I. 1.35 – 15.79) more likely to achieve SVR compared to individuals infected with a genotype 1-infection (Table 27). This high rate of SVR (i.e., more than 80%) among patients with genotype 2-infections has been previously documented in other clinical studies [83]

Treatment allocation was also significantly associated with achieving SVR. Once adjusted for age and sex, individuals who received a combination of interferon and Direct Acting Antiviral treatments were more than 6x (OR: 6.38, 95% C.I. 2.72 – 14.85) more likely to achieve SVR compared to individuals receiving solely interferon-based therapies. Patients who received exclusively Direct Acting Antivirals were nearly 8.5x (OR: 8.40, 95% C.I. 5.27 – 13.38) more likely to achieve SVR compared to individuals receiving solely interferon-based therapies (Table 29).

Results from the model also demonstrated that regardless of sex (p = 0.50) or age (p = 0.32) a patient had equal likelihood of achieving SVR, with proper adherence to the treatment regimen prescribed (Table 22). Additionally, the thesis sought to assess how identifying as Indigenous and/or having a history of mental health impacted a patient's ability to achieve SVR. Results demonstrated that when assessing for all treatment regimens, both identifying as indigenous and having a history of mental health were not associated with decreased likelihood of achieving SVR.

9.4.4. Evaluation of the Association between Patient Characteristics On Achieving A Sustained Virologic Response Among All Patients For Direct Acting Antiviral Treatment Regimen

A multivariate logistic regression model was used to evaluate potential patient level and clinical factors associated with achieving a sustained virologic response among patients receiving Direct Acting Antiviral treatment regimens. When using both an intent-to-treat SVR definition and a per-protocol SVR definitions, it was found that HCV care delivery method (i.e., telemedicine vs. outpatient clinic vs. mixed delivery model) was not significantly associated with the outcome of achieving SVR, supporting that telemedicine delivered Direct Acting Antivirals are capable of achieving similar HCV cure rates as those observed among patients receiving HCV care via traditional care models (i.e., outpatient clinic and mixed delivery models). When controlling for clinically significant variables of sex and age, the covariate of HCV genotype was found to be significantly associated with achieving SVR (Table 30).

When assessing the relationship between HCV genotype and the likelihood of achieving SVR, it was found that having a genotype 3-infection was significantly associated with decreased likelihood of achieving HCV cure ($p = 0.02$). Results found that individuals infected with a genotype 3-infection were 63% (OR: 0.37, 95% C.I. 0.16– 0.85) less likely to achieve SVR when compared to individuals infected with a genotype 1-infection (Table 30).

Hepatitis C Virus genotype as a predictor of SVR is a well documented phenomena [9]. Difficulty in treating HCV genotype 3-infections has been observed previously in the interferon-era. Although HCV cure rates have improved for patients living with genotype-3 infections with the invention of Direct Acting Antivirals, cure rates are still disproportionately low compared to those observed in genotype 1 and 2-infections [9,63,84–86]. Sub-optimal treatment outcomes even with the use of superior Direct Acting Antivirals among individuals living with HCV genotype

3-infections have been observed in many studies. Previous research, including the POSITRON, VALENCE, and ASTRAL-4 clinic trails, consistently found lower SVR rates between 62 – 85%, among individuals infected with genotype 3-infections, particularly among individuals who had failed a previous Direct Acting Antiviral treatment regimen and among individuals with cirrhosis of the liver [84].

This increased rate of treatment failure among individuals with genotype 3-infections is thought to be due to a combination of both host and virus factors. Genotype-3 infections have been found to be associated with increased presence of steatosis (i.e., accumulation of fat in the liver cells), accelerated rates of fibrosis of the liver, and increased viral-resistance to Direct Acting Antiviral treatments, all of which are associated with sub-optimal treatment outcomes [84,86]. Increased presence of steatosis has been found to be a negative predictor of SVR as it is associated with the increased production of pro-inflammatory cytokines, leading to increased fibrosis of the liver, decreasing the effectiveness of available HCV treatments [9,84].

Additionally, due to Direct Acting Antivirals acting on the process of viral replication instead of the host's immunity, there is increased risk of a patient developing resistance to Direct Acting Antivirals and failing their treatment regimen [84]. Resistance based substitution mutations in the NS5A and Y93H proteins, which play key roles in HCV RNA replication, have been found to be associated with decreased SVR rates of as low as 77% when using Direct Acting Antivirals among patients with genotype 3-infections [84,86].

Results from the model assessing only those patients who received Direct Acting Antivirals also demonstrated that regardless of sex ($p = 0.64$) or age ($p = 0.24$) a patient has equal likelihood of achieving SVR when using Direct Acting Antivirals, when medication is taken as prescribed (Table 28). Additionally, identifying as Indigenous and/or having a history of mental health were not associated with decreased likelihood of achieving SVR.

9.5. Using Per-Protocol Versus Intent To Treat Analysis For Comparing Sustained Virologic Response Rates Between Telemedicine and Traditional HCV Care Delivery Patients

In order to allow for clear evaluation of sustained virologic response rates among TOHVHP patients, both an intent-to-treat SVR definition and a per-protocol SVR definition were used. There are multiple advantages and drawbacks to using either definition when evaluating the TOHVHP telemedicine program for HCV cure rates. Applying an intent-to-treat definition for evaluating the TOHVHP telemedicine program controls for self-selection bias that may be introduced by patients removing themselves from the study (i.e., failing to return for scheduled appointments or for post treatment blood work). It also controls any attrition bias that may be introduced into the study as patients who successfully completed their treatment regimen may have better life circumstances (i.e., less substance use, suitable housing, decreased presence of mental illness) and therefore result in better clinical outcomes among this patient population. The use of intent-to-treat SVR definition also allows for the TOHVHP telemedicine program to be evaluated in terms of treatment outcomes in a real-world practice, where adherence to medication may be sub-optimal [87,88]. Alternatively, using a per-protocol definition for evaluating the TOHVHP telemedicine program allows for the evaluation of treatment efficacy, particularly among newer Direct Acting Antiviral treatments, when medication is taken and completed as prescribed. However, the use of per-protocol SVR definition may lead to overestimating the effect of either the HCV care delivery method or treatment allocation on achieving SVR [87,88].

The intent-to-treat SVR definition included all patients who initiated treatment within TOHVHP whereas the per-protocol SVR definition included only those patients who successfully completed their treatment regimen and returned for a minimum of 3 months post

treatment completion blood work to confirm they had achieved SVR. When applying an intent-to-treat SVR definition, SVR rates by HCV care delivery method were 76% (28/37) for telemedicine patients, 80% (655/815) for outpatient clinic patients, and 83% (51/62) for mixed delivery patients. Intent-to-treat SVR rates did not statistically differ by HCV care delivery method. It should be noted however that the sample size for telemedicine in this thesis might have been too small to detect small differences in SVR rates between HCV care delivery methods due to limited power in the study. Alternatively, when applying a per-protocol SVR definition, SVR rates by HCV care delivery method were 100% (27/27) for telemedicine patients, 86% (655/773) for outpatient clinic patients, and 93% (51/55) for mixed delivery patients. Per-protocol SVR rates did not statistically differ by HCV care delivery method, again it should be noted that the sample size for telemedicine in this thesis might have been too small to detect small differences in SVR rates between HCV care delivery methods due to limited power in the study.

When comparing intent-to-treat SVR rates to per-protocol SVR rates, there were noticeable differences. Although SVR rates did not significantly differ by HCV care delivery, intent-to-treat SVR rates were noticeable lower for telemedicine patients compared to when using a per-protocol SVR definition (76% vs. 100%). This demonstrated that using per-protocol analysis potentially caused a possible overestimation of the SVR rates among the TOHVHP telemedicine patient population. However, these decreased SVR rates observed for telemedicine patients when using an intent-to-treat definition is not thought to be due to telemedicine HCV care delivery being an inferior HCV care delivery model. This is because when using multinomial logistic regression models for intent-to-treat SVR, our research found that neither telemedicine nor mixed delivery patients were less likely to achieve SVR compared to outpatient clinic patients once adjusting for known clinically significant demographics and covariates

(Table 31). It is instead hypothesized that the lower rates of SVR among telemedicine patients may be due to the increased prevalence of known barriers to engaging in HCV care (i.e., presence of mental illness, substance use, and rural residence) among telemedicine patients that make it difficult to successfully complete their HCV care.

9.6. Issues Using Statistics Canada Data With TOHVHP Patient Population

Upon analysis and consultation with a University of Ottawa data analyst, it was determined that information for 15 of the 1,454 patients postal codes were not available within the 2016 Statistics Canada Census Data. These postal codes were verified using up-to-date patient information from the Ottawa Hospitals – General Campus OACIS software, however no inaccurate postal codes were identified. This suggests that these postal codes may have been: 1) recorded wrong during initial patient visits, 2) not updated in the event of a change of residence for a patient, 3) had been provided incorrectly by the patient, or 4) had been retired by Statistics Canada since 2015. The later explanation is less likely as the 2016 Postal Code Conversion File contained more than 848, 354 active postal codes and 2,302 previously retired postal codes, providing a large degree of representativeness for the Canadian population (Statistics Canada, 2017).

Although there are many benefits to using the Statistic Canada Postal Code Conversion file for generating population-level indicators of material and social deprivation, the limitations of the data source must be acknowledged. Due to the nature of mail delivery in rural areas, where mail is often delivered to a central post office for collection, the postal code used by the file may not necessary represent the actual residential location of patients who live in geographically rural areas. Additionally, the linkage between TOHVHP patient data and the Statistics Canada Postal

Conversion File was made using a single link indicator (SLI). A single link indicator is used to address issues with residential areas that have multiple postal code records. Due to this, the SLI used to generate the match between the TOHVHP patient populations' postal codes and Statistics Canada data was made on the underlying assumption that the SLI was representative of the geographic area with the desired postal code that encompassed the majority of residential housing, and therefore has some limitations as it may truly only partially correspond with the material and social indicators within the desired postal code [89].

9.7. Limitations and Results of The Primary Component Analysis

Using a primary component analysis, six socio-economic indicators were selected according to available literature on their association with either material or social deprivation. These indicators were: the proportion of individuals widowed, separated, or divorced, proportion of individuals living alone, proportion of lone-parent families, proportion of individuals without a high school diploma, employment-to-population ratio, and average household income. All variables captured individuals aged 15 years or older, and all except the proportion of lone-parent families were adjusted for the Canadian populations' age and sex composition. The indicator of mean household income was additionally adjusted for the economies scale, as previously described. Surprisingly, we found that what was intended to be an indicator of social deprivation, the proportion of people living in single-parent families, for our patient population, was also representative of material deprivation. This variable loaded equally onto both the material and social deprivation factors, which resulted in the social deprivation indicators encompassing the influence of primarily two variables instead of three, as originally intended (Appendix I). This dual indication of material and social deprivation for the proportion of single

parent families, although unanticipated, has been documented previously among Canadian populations [65].

9.8. Strengths of Thesis

There are clear strengths associated with this analysis. First, extensive care was taken to ensure the best quality of data to evaluate the TOHVHP dataset. The original two separate data files, one containing clinic patients and the other containing telemedicine patients, were individually reviewed. Data files were reviewed by confirming patient data against electronic medical records using the Ottawa Hospital OACIS program as well as using a physical patient chart review when required on various clinic variables to ensure data accuracy for the thesis. This resulted in the removal of patients who were not registered within the TOHVHP in both the clinic data file, were HCV RNA negative (i.e., spontaneously cleared the infection on their own), those mono-infected with HBV, and those who failed to attend any scheduled appointments. Noticeable outliers identified for both ALT values and Fibroscan (kPa) values were verified using electronic and physical patient chart review. All values were validated and the decision was made to keep these patients in the model in order to allow the models to be most representative of the patient population accessing HCV care at TOHVHP. Due to questions regarding the self-reported variables of highest level of education and housing stability from the TOHVHP Data Base Project, both of which are important measures of socio-economic status among marginalized populations, it was decided to used 2016 Statistics Canada population level data to capture the proportion of people without a high school degree as a proxy education indicator and the proportion of individuals with suitable and not suitable housing situations.

Second, additional care was taken to disentangle the effects of multiple care models being used to delivery HCV care for a single patients. Each file for patients originally flagged as having *ever* received telemedicine as a clinical intervention were personally verified to determine if the patients received their HCV care exclusively via telemedicine or if they had also received HCV care at the Ottawa Hospital – General Campus. This enabled us to understand the true clinical outcomes of patients receiving their care exclusively via telemedicine and compare them to patients who received HCV care via traditional and mixed delivery methods. This additional attention to the effects of the use of mixed interventions (i.e., both outpatient clinic care and telemedicine) for HCV care delivery has not yet been explored in previous telemedicine program evaluation literature.

Third, sustained virologic response rates by HCV care delivery method were calculated and presented using both intent-to-treat and per-protocol SVR definitions. The use of both analyses ensured our study presented a clear representation of SVR clinical outcomes in the TOHVHP patient populations, and applied CONSORT best practice guidelines for intervention [88] trials to allow for accurate and clear interpretation of the effects of telemedicine for HCV care delivery.

Lastly, the geographic reach of the telemedicine program was validated through linkage of patient postal codes with 2016 Statistics Canada Census Data using a Postal Code Conversion File. This confirmed that the telemedicine program was being accessed more by rural based patients, supporting the use of the TOHVHP telemedicine program to overcome geographic barriers to HCV care, as the model was intended.

9.9. Limitations of Thesis

There are several limitations that merit discussion. First, in an effort to increase the sample size of HCV antiviral treatment recipients, the inclusion criteria was changed from the originally intended of "all individuals ***who initiated HCV care*** in the TOHVHP between January 1, 2012 and December 31, 2016" to "all individuals ***who used*** the TOHVHP ***at least once*** between January 1, 2012 and December 31, 2016." Although this change in inclusion criteria did result in an increased sample size leading to increased power in the study, it caused issues due to comparing historical treatment options. This was an issue as treatments available for treating HCV have vastly changed over time (i.e., since 1990's use of interferon to 2015 introduction of Direct Acting Antivirals) as well as the eligibility criteria for treating patients for HCV having changed drastically due to the treatments accessible at the time. Although this was a limitation for this study, we addressed its effects in each of the three objectives.

For the patient retention model, separate models were developed to account for differences in HCV antiviral treatment durations (i.e., 24 – 48 weeks for interferon-based regimens vs. 8 – 12 weeks for Direct Acting Antivirals) and to account for the increased time patients (i.e., due to having multiple treatments) waited due to being either: 1) ineligible for the available treatment at the time or 2) having previously failed or had to terminate previously available interferon-based treatments. For the treatment initiation model, a multinomial logistic regression model was used to account for the differences in patient and clinical factors associated with initiating either an interferon-based treatment (including interferon-Direct Acting Antivirals combination therapies) or Direct Acting Antivirals. Finally, for the SVR model, two separate multivariate logistic regression models were used, one to assess patient factors associated with

achieving SVR for any treatment and one to assess patient factors associated with achieving SVR for exclusively Direct Acting Antiviral treatments.

Second, there are also limitations when using population-level Statistics Canada Census Data to create social and material deprivation indices. Although the smallest available unit, dissemination-area, was used for the linkage of 2016 Statistics Canada Census data to TOHVHP patient postal codes, there are limitations when using population-level as a proxy for patient-level deprivation. Due to the indices being created using this data, it is not an individual-level measure but instead is representative of a small geographic area, and therefore has been previously described to underestimate the effects of health inequity and the impact of socioeconomic factors, particularly among non-urban based populations [67]. The social and deprivation indices used in this model therefore should be used as a relative and not an absolute measure of the effects of social and material deprivation on TOHVHP clinical outcomes.

Third, there are limitations with this thesis due to the retrospective nature of data collection within the TOHVHP cohort. Individuals enrolled in the TOHVHP Data Base Project were asked a variety of questions regarding behaviors they had engaged in over their entire lifetime. Due to the long time frame required for individuals to recall their behavior, the data may have been negatively impacted by a potential recall bias by a participant's inability or unwillingness to disclose certain stigmatized behaviors, including incarceration, injection drug use, high risk sex, and intranasal cocaine use. Additionally, the results may have been impacted by the absence of data capturing important influencers for this study's outcomes including the proportion of patients who declined participation in the study, if a patient had private insurance, and if a patients was previously denied treatment based on funding, as well as the absence of potential unmeasured confounders, including variables to capture the quality of staff over time,

which may have impacted both treatment initiation rates and patient retention rates within the TOHVHP.

Fourth, there are both potential and real biases that impacted this study, including selection bias, differential loss to follow up bias, and channeling bias within the TOHVHP. Potential selection bias may have occurred on the patient level, as within the TOHVHP Data Base Project, there is no variable to capture demographic information and the proportion of individuals those who declined participating in the TOHVHP Data Base Project. This creates a potential selection bias as patients who volunteered to enter the TOHVHP Data Base Project may be inherently different, such as having higher socioeconomic status or more education, than those that declined participation and therefore may have biased the results, particularly for the measurements of material and social deprivation. Another form of bias that did impact our study was a differential loss to follow up bias. Individuals in our study who were lost to follow up were more likely to have not graduated high school ($p < 0.0001$) and were marginally more likely to have unsuitable housing ($p < 0.0001$) (Table 16). This indicates that those retained in HCV care in our study may inherently have more positive predictors for completing their HCV treatment regimen and achieving HCV cure. These positive predictors may include having stable housing, having a higher level of education, and higher socioeconomic status, which may bias the results, as our study may underrepresent the number of individuals in our study whom are facing known barriers to receiving HCV care. Another form of bias, known as a channeling bias also occurred within the TOHVHP. Channeling bias is a form of allocation bias that occurs in medical research where patients are allocated to a treatment group or intervention based on clinically relevant prognostic or baseline characteristics [90,91] . Due to the complex nature of treating patients living with chronic HCV who have cirrhosis of the liver, many of these patients were channeled into the out-patient care delivery group, in order to provide the patient with the necessary monitoring

and care required for their severity of disease, and therefore may have resulted in non-homogenous groups which may have biased the results. Misclassification, although possible to the retrospective nature of data collection of lifetime behaviors and history of mental illness are believed to have occurred independently of HCV care delivery allocation, and therefore are non-differential and would cause the study results to become more similar and are not believed to have been a significant issue.

Lastly, this thesis sought to better understand how clinical outcomes and engagement differed between Indigenous patients using telemedicine programs. Unfortunately, as only 2.8% (41/1454) of the patient population identifying as Indigenous, these analyses were limited due to limited power. All three objectives were assessed among a sub-population of TOHVHP patients who identified as identifying as Indigenous and we found that lost to follow up rates, treatment initiation rates, and SVR rates did not vary by HCV care delivery among Indigenous patients, which may suggest that telemedicine may be a successful means for providing HCV care to Ottawa's Indigenous population. However, there are limitations to this generalization as all analyses had small sample sizes, and therefore results should be interpreted with caution as the study lacked power and are not generalizable to other Canadian Indigenous populations. These results therefore are limited to the experiences of Indigenous patients involved with the TOHVHP telemedicine program.

9.10. Research Contribution to Existing and New Literature on Telemedicine Utilization Among Patients Living with Chronic Hepatitis C Virus

Although telemedicine is being widely used for the management of diseases, including infectious diseases such as HCV, there remains limited literature comparing clinical outcomes

achieved using telemedicine compared to the clinical outcomes observed using traditionally delivered HCV. The majority of available literature on the topic stems from evaluations of sustained virologic response rates among telemedicine patients in the United States and Australia. Additionally, there is limited literature evaluating other HCV clinical outcomes, including treatment initiation rates and patient retention between telemedicine and traditional HCV care delivery populations, which were explored in this thesis. This thesis therefore addresses the knowledge gap of the ability of telemedicine delivered HCV care to achieve important HCV clinical outcomes such as patient retention, treatment initiation, and sustained virologic response rates among a marginalized Canadian population.

Our study supports that telemedicine delivered HCV care is capable of achieving similar treatment initiation rates and sustained virologic response rates as those observed using traditional outpatient and mixed delivery for HCV care. It also highlights that lost to follow up rates disproportionately impact the TOHVHP telemedicine program. These increased lost to follow up rates may be due to both the relatively small available sample size of telemedicine patients and due to telemedicine patients experiencing known barriers to HCV care engagement such as history of mental illness, injection drug use, and limited education which make it difficult to adhere to HCV treatment regimens and continuously engage with their HCV circle of care.

Additionally, in a period of economic and financial stress regarding costs associated with the utilization of the Canadian healthcare system and the current shortage of healthcare providers in Canada, particularly in Ontario, telemedicine may be a means to mediate healthcare spending related to HCV. Our study found that TOHVHP mixed delivery patients, who received part of their care via the TOHVHP telemedicine network, compared to outpatient clinic patients required significantly shorter periods of time spent in HCV specialty care to achieve comparable

rates of HCV cure when using Direct Acting Antivirals. This suggests that HCV care that incorporates telemedicine services may be associated with decreased HCV related healthcare expenditure that is associated with prolonged engagement with HCV specialists and clinic operating costs as well as patient related healthcare costs associated with attending and traveling to their HCV appointments. This suggests that telemedicine delivered HCV care should be considered, when deemed appropriate by the provider and patient, in place of traditional outpatient clinic delivered HCV care to reduce Ontario healthcare expenditure associated with HCV.

9.11. Suggested Improvements and Considerations for the TOHVHP Telemedicine Program

Our research found that TOHVHP telemedicine patients faced barriers to engaging in traditionally delivered HCV care which included having limited education, having a history of mental illness, residing in more rural areas, having engaged in high risk behaviors for acquiring HCV including injection drug use and intranasal cocaine use, as well as having previously been incarcerated. Our research therefore highlights that additional improvements are required to ensure long-term efficacy and longevity of the TOHVHP telemedicine program.

In 2016, the World Health Organization initiated the global goal to eliminate viral hepatitis by the year 2030, which relies heavily on the ability to successfully diagnosis and initiate treatment among people who are both aware and unaware of their positive HCV status [34,92]. In order to this, alternative approaches to delivering HCV care, such as telemedicine models, must be explored to increase HCV specialty care access to patients living with HCV who may face these known barriers to engaging in HCV care. Although our research did not

assess the ability of our telemedicine program to diagnosis individuals living with HCV in Ottawa, we did find that although telemedicine delivered HCV care was able to achieve comparable treatment uptake and SVR rates to those observed among patients receiving traditionally delivered HCV care, disproportionality high lost to follow up rates affected our TOHVHP telemedicine patient population. This highlights the notion that in order to achieve the WHO's viral hepatitis elimination goal, additional delivery approaches must be taken to engage marginalized populations in HCV care in lieu of simply using superior treatment options and increasing access to HCV care through telemedicine within local healthcare and nursing centers.

The TOHVHP telemedicine patient population consisted of a large proportion of patients with genotype 3-infections compared to the outpatient clinic and mixed delivery patient populations (Table 2). It was also comprised of lower proportions of patients who had a liver biopsy (Table 2) and/or had ever received blood products (Table 4). These statistics indicate that the TOHVHP telemedicine program is serving a unique population of patients who have past or current substance use, which suggests that there is great potential for concurring mental illness among this population. The program is also serving patients who may have limited access to specialty care and may rely heavily on publically funded pharmaceutical insurance instead of privately funded medical coverage [75]. Due to this high representation of lower income, marginalized populations within the TOHVHP telemedicine program, the idea of integrating the TOHVHP telemedicine program into institutions with existing services targeting marginalized populations [75], including people who inject drugs, such as those offering mobile harm reduction services, needle exchange programs, and opioid replacement therapies, should be explored to improve TOHVHP telemedicine patient retention. Additionally, the program should, within financial constrictions, expand its capacity to offer a multidisciplinary HCV telemedicine team to include addiction specialists, peer workers, and social workers[75] to ensure the patients are

provided holistic HCV care that addresses both existing social determinants and concurrent mental illness that may impede a patient's ability to successfully engage with HCV care and complete their HCV treatment regimen.

Finally, although Indigenous Canadians represent a small proportion of the total Canadian population they are disproportionately at risk for bloodborne infections, including HCV[16,56,93,94]. The small proportion of Indigenous patients involved within both the TOHVHP outpatient clinic and telemedicine HCV programs indicate that additional approaches must be explored to increase engagement of Indigenous populations in Ottawa within the TOHVHP program. If possible, efforts should be made to integrate the TOHVHP telemedicine program and/or HCV specialty care into existing local Indigenous health centers, alongside their traditionally delivered medical care. This will allow for increased access to HCV specialty care among Ottawa's Indigenous population and create the opportunity for collaboration between HCV specialist and local physicians working in Indigenous health centers to allow continuity of healthcare for Indigenous persons with both local healthcare providers for which they are familiar and comfortable with, and the management of their HCV[75].

CHAPTER 10. CONCLUSION

Using a combination of patient-level and population-level data available from The Ottawa Hospital Viral Hepatitis Data Base Project and the 2016 Statistics Canada Census, we were able to address the three objectives of this thesis being: 1) retention in care, 2) proportion of patients initiating treatment, and 3) achieved HCV cure rates among patients receiving HCV care by either traditional HCV care-model delivery at the Ottawa Hospital – General Campus or telemedicine via the Ontario Telemedicine Network offered through The Ottawa Hospital Viral Hepatitis Program.

We found that TOHVHP telemedicine patients were able to achieve similar treatment initiation rates and SVR rates compared to TOHVHP outpatient clinic and mixed delivery patients. Evaluation of the program did demonstrate that patient retention is disproportionately lower among TOHVHP telemedicine patients, demonstrating that additional steps, such as increased involvement of outreach workers, familial support systems, local nurses, and appointment reminders, should explored to improve lost to follow up rates among this patient population as the telemedicine program continues to expand.

Overall, evaluation of TOHVHP telemedicine program patient outcomes provides crucial insight regarding the program effectiveness for HCV care delivery in Ontario. These research findings contribute evidence-based telemedicine knowledge that can inform the development of programs for other diseases across Canada impacting vulnerable and inaccessible populations.

COMPONENT TWO

AN EXPLORATORY QUALITATIVE PROTOCOL TELEMEDICINE EVALUATION IN FIRST NATIONS POPULATIONS IN SIOUX LOOKOUT REGION

Re: Access to HCV Care in Sioux Lookout Region: A Qualitative Study

CHAPTER 1. LITERATURE REVIEW/BACKGROUND INFORMATION

1.1. Hepatitis C Virus Among Indigenous Populations

Hepatitis C Virus in Indigenous populations is a multifactorial issue that stems from historical political factors including colonialism, socioeconomic marginalization, oppression, and increased prevalence of substance use suggested to be due to the widespread loss of cultural identity among Indigenous peoples living in Canada [16,93]. Indigenous Canadian individuals are consistently overrepresented in the total number of HCV infections diagnosed and underrepresented in healthcare resource allocations [94]. These populations in the past have had low engagement with traditional hospital and clinic-based care, resulting in sub-optimal treatment and health outcomes [95].

In Canada, individuals who identify as Indigenous are at higher risk for exposure to bloodborne pathogens including HCV due to the increased occurrence of unsafe injection practices, sharing of drug paraphernalia, and disproportionality high incarceration rates [94,95]. This increased risk of HCV exposure is also thought to be brought on by issues related to healthcare accessibility, high levels of poverty, sexual abuse, unique socio-economic factors, unique

barriers to engaging in health care brought on by geographic isolation, and the residual effects felt from historical and ongoing cultural oppression [96,97]. Oppression and trauma experienced by Indigenous people has resulted from numerous historical events such as the colonization of Canada, the implementation of the residential school system, and the "Sixties Scoop" [98]. The process of colonization in Canada resulted in the mass removal of Indigenous Canadians from their land and saw a blatant disregard for traditional values and customs. One of the major events during colonization was the establishment of the residential school system. Residential schools for Indigenous children operated from 1874 to 1996 and forcibly removed over 100 thousand Indigenous children from their families [98]. These schools were a means for the Canadian governments to instil Christianity into the children's lives and assimilate them into the European lifestyle by forcibly removing their language, culture, and identity [98]. In addition to these tactics used to assimilate Indigenous children, unorthodox punishment including emotional, physical, and sexual abuse was inflicted on many of the attending children [98,99].

What is known as the "Sixties Scoop" only increased the damage perpetuated by the residential school system. In 1951, the Federal Government of Canada took control from Indigenous families over the welfare of Indigenous children. During this time, a financial benefit was offered to provinces in order to help with the apprehension of Indigenous children [100]. This resulted in the mass removal of Indigenous children from their families, causing the number of Indigenous children in foster care to quickly rise from an estimated 1% to 40%, resulting in the overrepresentation of Indigenous children in the foster care system [98,99]. The combined effects of the abuse suffered at residential schools and the experience of being forcibly removed from one's biological family and community established the foundation for intergenerational trauma and its long lasting negative impact on Indigenous people's health throughout Canada.

The long lasting effects of historical trauma and systemic racism have created what is known as the Indigenous health gap, which has increased Indigenous Canadian's susceptibility to substance use, including injection drug use [16,93].This history of mistreatment of Indigenous peoples' by Euro-Canadian society, limited life opportunities, loss of Indigenous identity and culture, and ongoing systematic racism have led to unique socio-economic factors, negative health outcomes, and increased vulnerability to acquiring diseases among Indigenous peoples living in Canada [16,93,98,99,101]. Colonization has had long lasting negative impacts on Indigenous people's physical, social, and mental health. In addition to the extensive trauma suffered by Indigenous Canadian populations, the introduction to new and unfamiliar substances including alcohol, tobacco and illicit substances has had serious and profound effects on Indigenous peoples [16]. This increased presence of harmful substances coupled with the widespread loss of culture and Indigenous identity has fostered an environment for the development of substance addictions due to a high prevalence of mental health disorders, high levels of stress, low self-esteem, and unstable family dynamics [93].

This Indigenous health gap has strong effects on the rate of homelessness, poverty, substance use, and unsafe injection practices among Indigenous communities that in turn amplify the risk of acquiring bloodborne infections and create unique risk factors [16,98,99]. This association between the Indigenous health gap and increased substance use has been previously documented among Indigenous people living in Vancouver's Downtown East Side, a highly impoverished area of Canada. The Cedar Project, a Canadian study of individuals who self-identified as Indigenous living in Vancouver and Prince George, British Columbia, found that individuals who self-identified as Indigenous and had unstable housing, defined as single occupancy rooms, transitional living arrangements, or being homeless (i.e., shelters or homeless) were more likely to engage in injection drug use [100]. Furthermore, the association between an individual

experiencing trauma and its negative effects on family and cultural values, as well as the risk of acquiring blood-borne pathogens, has also been documented to foster the development of coping mechanisms, including self-medication through injection drug use. Of the 583 participants in the Cedar Project, 48% had experienced sexual abuse at least once in their lifetime. Of those that had been sexually abused, 38% were HCV positive, supporting the association between experiencing trauma and engaging in high risk behaviours for acquiring HCV ($p = 0.041$) [100,102]. This highlights how the Indigenous health gap is present in both urban and rurally situated Indigenous people's populations within Canada, demonstrating the complexity of disease among Indigenous peoples living in Canada regardless of their geographical location.

Finally, stigma, discrimination, and racism towards Indigenous populations in Canada is also known to increases an individual's vulnerability to acquire bloodborne infections as it has been found to negatively impacts both an individual's well-being and ability to engage with harm reduction strategies, which can contribute to engaging in known HCV risk behaviours [16,93,99,102,103]. All of this demonstrates that although Indigenous Canadians represent a small proportion of the total population, they are disproportionately at risk for bloodborne infections, including HCV due to the strong influence these unique risk factors have on their lives [16,56,93,94]. This increased prevalence of HCV affecting Indigenous populations in Canada poses a challenge to HCV care delivery given the rural and isolated geographical areas, as many of these individuals reside in areas that have limited available health care services [16,94].

1.2. Indigenous Populations and Health Services Access

Many Indigenous communities in Canada are classified as being remote or isolated [104]. A remote community is defined as a Indigenous community that is located 350 km from the nearest service site and has year-round road access, whereas isolated communities are defined as those

without year-round road access [105]. This presents an barrier for some patients with complex or chronic medical conditions as the majority of speciality care centres are located in urban areas throughout Southern Canada [104]. Parmar and colleagues found that Indigenous individuals were more likely to be lost to follow up, resulting in the premature termination of their HCV treatment and often had poor adherence to their prescribed treatment regimens (25% vs. 4.6%) [95]. This supports that alternative approaches should be explored to increase participation in HCV treatment and care in order to effectively provide medical services to Indigenous Canadian populations. Telemedicine has been suggested as an approach to provide HCV care to individuals facing traditional barriers to engaging in HCV care including geographic isolation, increased prevalence of substance use, co-existing mental illnesses, and the presence of socioeconomic stressors in attempts to overcome geographical and accessibility barriers [50,106].

1.3. Sioux Lookout Region

One particular Indigenous population in Canada that has utilized telemedicine for health care delivery to address accessibility barriers is Sioux Lookout region. Sioux Lookout is a region and Indigenous community in north-western Ontario situated on traditional Ojibway of Lac Suel First Nations territory [107]. The town of Sioux Lookout has a population of approximately 5,300 people and the surrounding 32 remote First Nations communities have a population of approximately of 30,000 people living in a geographical range of more than 385,000 km^2 [50,107]. Of the 32 communities within the Sioux Lookout region, only seven can be reached by road, causing many communities to have to be accessed by air, which can be both unreliable and expensive [50,108]. Currently in the region, a total of 25 communities have telemedicine videoconference capability in the local nursing stations of established health centres. Four telemedicine programs have been established including tele-counseling, tele-psychiatry, tele-

psychology, and telemedicine delivered HCV care [109]. The newest of these programs is the HCV telemedicine program where patients living with chronic HCV are initially linked with a physician to be seen in person at a clinic within the town of Sioux Lookout and then followed up for their HCV care and treatment via telemedicine in the community in which the patient resides. There is currently limited literature evaluating the telemedicine programs operating in Sioux Lookout. One available study within this region assessed the use of telemedicine to treat a broad range of infectious diseases. The researchers found that 98% of patients were satisfied with the use of telemedicine in nine evaluated areas. The three domains with less than 98% satisfaction ratings were picture quality of physician on the monitor, potential subsequent use of the telemedicine program, and if they would recommend telemedicine to others. Regardless, these three areas had satisfaction rates that were in the range of 90-96% [50].

This geographic area is of particular interest because it has a high prevalence of HCV when compared to the rest of Canada. According to a six-year study within Sioux Lookout First Nation Authority, the regional health authority providing health services to First Nations persons residing in Sioux Lookout region [110], on-reserve populations had nearly an 11x higher rate of HCV antibody-positive individuals compared to the rest of Ontario, including off-reserve Indigenous populations. This highlights how HCV disproportionately burdens this population [111]. The association between environmental factors such as inadequate housing, poverty, as well high levels of intergenerational trauma and limited access to harm reduction strategies, contribute to the increased susceptibility to acquire diseases, including HCV [16,50,111,112]. In addition, high prevalence of injection drug use among on-reserve populations has also been suggested to contribute to increased rates of new HCV infections [111]. Previous studies in urban Indigenous populations have also suggested that increased prevalence of injection drug use has also been found to be associated with decreased HCV treatment initiation, which can impede efforts to

increase treatment uptake amongst people living with HCV. The Community Health and Safety Evaluation (CHASE) study, which assessed health services uptake and health outcomes of residents living in Downtown Eastside Vancouver, Canada, found evidence of this, as of the individuals who used drugs in Vancouver between 2000 and 2004, only 1% initiated treatment [113].

1.4. Benefits of Using Telemedicine in Indigenous Communities

As previously described, many Indigenous populations in Canada have limited access to speciality care, which is problematic as HCV, if left untreated, can result in many complications with the potential to cause life-long HCV-morbidity or mortality [6,50,95]. The use of telemedicine in Sioux Lookout region highlights the potential benefit of telemedicine programs in addressing issues of health service access. These include mediating the need for arranged transportation from rural/isolated communities, reducing the time spent away from home for individuals receiving HCV treatment, decreasing wait times for specialty care, and increasing treatment uptake by making speciality care more accessible and therefore reducing the financial burden on the government and healthcare infrastructures [18,111]. Additionally, telemedicine within Indigenous populations in Canada has the ability to build community capacity by improving HCV knowledge among local primary care physicians and create the potential for earlier HCV diagnosis and treatment for individuals in the community who are unaware of their HCV positive status [51].

CHAPTER 2. STUDY RATIONALE

2.1. What concerns are being addressed?

Although there are many advantages to using telemedicine, consideration must be given to potential factors that may influence the success of the program when initiating it in or using it within Indigenous communities. Some studies have found telemedicine to have low utilization and satisfaction rates due to technological issues and concerns regarding patient confidentiality [52]. A review by the Infectious Disease Society of America found that encryption videoconferencing software could be used if there was a connection speed of at least 384 kbps, equivalent to high-speed Internet. Similar Internet speed was also found to be required for real-time telemedicine interactions between the provider and the patient [53]. Although Internet speed may not be an issue in more central or intermediate areas, it is a limitation for the use of telemedicine among remote and isolated Indigenous Canadian populations, as a large proportion are underserviced (low speed of 1.5 Mbs per household, consumer broadband) or still without access to internet [54,55]. Concerns have also been raised regarding patients being seen entering nursing stations with known HCV telemedicine services as it may result in the patients experiencing stigma among small, tight-knit communities. Additionally, the inability to have face-to-face interactions between the provider and the patient could negatively impact the patient's perception of their appointment experience due to the inability to recognize non-verbal cues, potential language barriers, and the inability to engage on an equal level with their provider.

A review of TeleMental Health in Canada's Indigenous population of northern Ontario found that individuals, although satisfied with the service, had concerns due to the lack of trust in an unknown provider, the provider's lack of acknowledgement of Indigenous cultural values

emphasizing face-to-face interactions in their own language, and lack of acknowledgement by the providing physician of important socio-economic factors at play (no clean, safe water, no power, no internet, and inadequate housing) by the inability to see the client in their natural setting [55]. These concerns raised highlight the need for telemedicine to be integrated in a manner that meets the local needs of the Indigenous communities. It also demonstrates that there are cultural safety concerns, determined by patients receiving the medical service, within the communities surrounding Sioux Lookout and thereby, the implementation of HCV Telemedicine must ensure community specific Indigenous cultural practices and traditions are integrated into the telemedicine program [50,56]. When all of these factors are achieved, telemedicine may then have the potential to be successful within Indigenous Canadian populations, such as Sioux Lookout region.

Engaging with the communities in Sioux Lookout region through semi-structured individual interviews will allow for a better insight into potential cultural safety issues from the patient's perspective that may be influencing the utilization of telemedicine as an HCV care delivery intervention for this population. Sioux Lookout Meno Ya Win Health Centre defines cultural safety as "a practice that is capable of delivering safe health care services to patients that understand and identifies clients' needs", which is ultimately determined as being culturally safe by the patient themself [114]. Utilizing qualitative research methods as a means of an exploratory telemedicine program evaluation will allow for researchers to gain an in-depth understanding of the perceptions and concerns of community members regarding the cultural safety of existing telemedicine programs serving communities in Sioux Lookout region. This will provide crucial insight as to the best approach to use and encourage the expansion of HCV-care via telemedicine within surrounding First Nation communities if appropriate when considering cultural factors.

This knowledge is critical to the success of telemedicine programs within Indigenous populations and could serve as a guide for assessing the cultural safety of other telemedicine programs.

2.2. Review of Cultural Safety and Telemedicine literature:

A comprehensive literature search was developed with an experienced library research personnel and the MSc student, Candis Lepage. All relevant literature found in the MEDLINE database was assessed. Reference lists of relevant studies were cross-referenced to include additional articles, not identified by the original search. Key indexed words for the search strategy included ("Cultural competency/or Health Services, Indigenous" or Cultural Safety" or "Cultural Sensitivity") and ("Videoconferencing" or "Telemedicine") and ("Indigenous populations" or "Indigenous"). A total of 34 texts were identified from the search, of which 12 full-text studies were deemed relevant to the research. Of those 12, only 8 directly addressed telehealth delivery among Indigenous populations and few directly evaluated the cultural safety of using these technologies.

Cultural safety among Indigenous populations, in the context of telemedicine and alternative health-care delivery platforms, is largely under-evaluated, with the majority of available literature originating from Alaska [115] and Australia [116,117]. A previous study evaluating the use of telemental health-care delivery among rural Indigenous Alaskan populations suggested that for telehealth delivery to be successful, providers need to be accepting of the incorporation of the traditional aspects of healing and treatment, be able to self-reflect upon their past issues with patients or particular populations, and acknowledge these issues upon first interaction with their patients. These actions, along with ensuring the continuity of a single healthcare provider for a patients' care, were suggested to be crucial to foster the development of trust, mutual respect, and open communication while using telehealth platforms [115,117,118]. Although one

Canadian study has evaluated the use of telemedicine among Indigenous populations in Quebec [119], it failed to evaluate cultural safety from the Indigenous perspective, demonstrating a key knowledge gap regarding cultural safety and the use of telehealth technologies among Indigenous Canadian populations.

Cultural safety guidelines emphasizing the requirement for culturally safe and competent health care have long been established within the field of nursing in New Zealand [120]. Cultural safety, as defined by the Nursing Council of New Zealand is:

> The effective nursing practice of a person or family from another culture, and is determined by that person or family. Culture includes, but is not restricted to, age or generation, sex, sexual orientation, occupation and socioeconomic status, ethnic origin or migrant experience, religious or spiritual belief, and disability (p. 7)

In addition to this, the nursing council emphasizes that cultural safety goes beyond both cultural awareness and sensitivity, and works to acknowledge past negative health care experiences for individuals. It also emphasizes the need for providers to acknowledge and reflect upon how their own cultural identity can, or has, impacted their ability to provide culturally safe and acceptable healthcare in the past [120].

Cultural safety is therefore the outcome achieved by the proper education of healthcare providers. It relies on a strong foundation of principles where providers are aware of inherent power imbalances between themselves and their patients as well as their own cultural biases that may impede the quality of their provided healthcare. It emphasizes that patients must have the autonomy and ability to openly express their concerns regarding their healthcare experiences, and highlights the need for providers to engage with patients on an equal-level to best understand how historical inequalities and socioeconomic factors can, and have, created inequalities within today's healthcare system [118,120].

Once this is achieved, health care providers are able to provide safe and effective services to patients from varying cultural backgrounds while simultaneously minimizing the risk for their patients to experience negative interactions with the healthcare system [120]. When applying the knowledge of cultural safety specifically to a review on how to create culturally safe care when using telemental health services among rural communities, it was highlighted that providers must be able to acknowledge that patients will come from a variety of backgrounds and face unique barriers to care [118]. It should also stressed that when using alternative healthcare delivery methodologies, adaptations and input must be sought from the individuals utilizing the service in order to allow for effective patient care across a variety of cultures and geographic locations [118,121,122].

As identified above, cultural safety embodies a variety of concepts that have largely been absent in current evaluations regarding the use of telemedicine within Indigenous Canadian populations. Data collection within communities in Sioux Lookout region will serve as an opportunity to perform a telemedicine program evaluation, utilizing qualitative methods, in order to provide insight and feedback, as well as identify any cultural safety issues may exist regarding the current use of telemedicine for HCV care delivery within this communities.

2.3.What are the research questions to be addressed?

Primary Question: Are there existing cultural safety concerns regarding the use of telemedicine to deliver HCV-care, and other healthcare to Indigenous communities within Sioux Lookout region in Northwestern Ontario.

2.4. Why is this study needed now?

Indigenous populations in Canada are grossly overrepresented in the number of chronic HCV infections. Engaging with communities within Sioux Lookout region through semi-structured individual interviews will allow for a better insight into potential cultural safety issues that may be influencing the utilization of telemedicine as a care delivery method. Utilizing qualitative research methods as a means of an exploratory telemedicine program evaluation will allow for researchers to gain an in-depth understanding of local community members' concerns regarding cultural safety and the utilization of telemedicine.

2.5. How will the results be used?

Study results will provide crucial insight as to the best approach to address current barriers to engaging with telemedicine for HCV care within the surrounding Sioux Lookout communities and assess if it is an appropriate care delivery method after considering cultural factors, community input, and review of physicians involved with remote HCV care.

CHAPTER 3: METHODOLOGY

3.1 Study Methodology

As there is limited existing literature and knowledge regarding community members' and physicians' perceptions of the HCV telemedicine program being used in Sioux Lookout region and limited resources in terms of both data collection time and financial support due to the structure of the University of Ottawa's MSc Epidemiology program guidelines, this research will be rooted in the notion of qualitative description. Qualitative description is a form of qualitative research where researchers use observations or semi-structured interviews to provide a low-inference summary of events of an informants' experiences using the informants' natural language [123]. According to Margarete Sandelowski, qualitative description is a useful form of qualitative research methodology that allows researchers involved in health care research to understand why individuals may or may not engage with certain health services [124].

Although qualitative description is more simplistic than applying alternative methodologies including phenomenology, grounded theory, or ethnography, it is a valuable qualitative methodology often used in health service research to capture patient's perceptions of real world experiences and allows researchers to understand the issue at hand directly from the patient's perspective through their own language [125–127]. Qualitative description is also often questioned for its rigor, however, in this qualitative study, we have incorporated methodological procedures noted in many other qualitative studies including purposeful sampling, adequate sample size, established participant recruitment, systematically collected data through audio recording, simultaneous transcription, and the use of thematic analysis by applying direct participant quotations by two researchers to avoid bias that may be introduced due to the close

involvement of the local interview facilitator throughout the data collection process and to minimize subjectivity in the interpretation of results [124,125,127].

There are many benefits to using qualitative description in the context of the Sioux Lookout HCV telemedicine program evaluation from the perspective of patients living in Sioux Lookout communities. First, it will ensure that the experience of community members utilizing the service are captured in their own language, thereby minimizing the potential misinterpretation from outside researchers [125]. Second, it will provide us with a rich description of the real world experiences of patients utilizing the service, which will help identify potential cultural safety issues specific to the Sioux Lookout HCV telemedicine program [125–127]. Third, where we are looking to understand: 1) the situation in Sioux Lookout and relevant factors that may be impacting the utilization of a telemedicine program among a highly stigmatized population of individuals living with HCV and 2) the unique concerns that that population may have, qualitative description is appropriate as we are not attempting to create a general theory or generalize the results to other HCV telemedicine programs operating in other Indigenous communities. Lastly, qualitative description has been demonstrated in previous studies to have the ability to successfully engage key stakeholders in order to address the concerns identified by patients utilizing the services, which could benefit not only the Sioux Lookout HCV telemedicine program but also providers involved with delivery of remote HCV care and their patients [126].

This study will be conducted as an exploratory, community-based program evaluation using the methodology of qualitative description in Sioux lookout region. Qualitative methodologies were selected for this component of the MSc thesis as it best allows researchers to understand human behavior and interactions while providing the most meaningful data to assess Sioux Lookout community members perceptions of the HCV telemedicine program [125]. Framing

this work as a community-based program evaluation is crucial to ensure that Sioux Lookout community members and providers who actively work in Sioux Lookout are continuously involved in the research process [128]. This will ensure that the results will help better understand how to improve telemedicine services for this community among individuals who are living with or have had risk factors for acquiring HCV. This exploratory research will be conducted using a common data collection method used in qualitative research of semi-structured interviews using open-ended question. Individual interviews have been previously applied to public health program evaluations and community based research and have been successful in capturing why a program is or is not working for a particular populations and for determining a program's effectiveness due to the ability to obtain meaningful responses by allowing participants to engage freely with researchers and not feel limited in their responses, which can occur when using some quantitative methodologies such as questionnaires [127,129–131].

3.2. Community Identification and Patient Recruitment

The research will consist of semi-structured interviews with health care providers and individuals within participating communities. Communities included in the study will be those in Sioux Lookout region that have high prevalence of chronic HCV, an established suboxone program, and have expressed community interest in participating in the study. Interviews will include individuals with prior usage of telemedicine, individuals with current and past risk factors for HCV recruited from local suboxone programs, healthcare providers involved with HCV care or telemedicine delivered healthcare, and local community members who have not utilized telemedicine previously. Individual interviews will be conducted instead of focus groups in order to protect the confidentiality of participants to the best of the researcher's abilities.

Interview participants will be identified using purposive sampling prior to interview commencement through the use of participant identification via outreach workers, HCV clinicians, and health care workers involved with the Suboxone programs, as well as through the use of recruitment posters placed in Suboxone program locations with an identified study phone number for participants to call to enroll in the study [124,127,132]. To be included in the study, participants must currently reside within one of the participating communities, be 18 years or older, and self-identify as Indigenous. Healthcare providers participating in the interviews must be involved with delivering remote care.

3.3. Individual Interview Structure and Participant Intake

Interviews will last approximately an hour and will explore: 1) perceptions surrounding the use of telemedicine, 2) identification of potential cultural safety issues with the current telemedicine program, and 3) discussion on how to improve any identified issues. Additionally, individual interviews will be conducted with health care providers within participating communities to assess: 1) the acceptability of telemedicine among providers, 2) their perceived acceptability among their patients, and 3) concerns they may have regarding the delivery of culturally safe care via telemedicine.

Individual interviews will allow for a more in-depth understanding of emerging cultural safety issues regarding the use of telemedicine and will provide participants an opportunity to discuss potentially more sensitive issues regarding the use of telemedicine, particularly in the context of HCV care, on a one-on-one basis and will ensure confidentiality is maintained. Either an external researcher or local facilitator from the Sioux Lookout First Nations Health Authority will administer the interviews. To ensure participants are comfortable and that their anonymity will be maintained, individuals will be given the choice of a facilitator for their interview.

Participants will be compensated $30.00 per interview for their time with the project, receive taxi chit or bus passes for transportation to and from the interview, and be offered food and beverage, as done in other research within Indigenous Canadian populations [133]. Although the above-mentioned honorarium has been used for participant compensation in previous studies within Indigenous Canadian populations, the exact honorariums for both the participants and an Indigenous facilitator will be determined through discussion with the Sioux Lookout First Nations Health Authority. After each interview, a debriefing session will take place between the facilitator and the MSc student, Candis Lepage, to determine if there are any practical issues with the thematic guides that need to be addressed. Recordings from the individual interviews will be transcribed verbatim.

To allow for a better understanding of the population in which the data is from, demographic information will be collected for all study participants. Demographic information collected will include age, sex, sexual identity, residential location, Indigenous identity, education, income, employment status, and information regarding previous telemedicine usage. Information will be obtained using an intake questionnaire prior to data collection (draft provided in **Appendix J**).

3.4. Participant Confidentiality and Study Ethics

Oral consent from the participant will be collected on an individual basis, prior to the commencement of the interview. Participants will be read a Participant Information and Consent Form (draft provided in **Appendix K** for community members and **Appendix L** for healthcare providers/agency workers). Participants will be informed of the purpose of the research, the potential benefits and risks of their participation in the study, their rights as research participants, how confidentiality will be maintained, and the anticipated duration of the interview. Participants

will be informed that they can withdraw their participation at any point in the interview. In order to maintain anonymity, the interview facilitator will sign the consent form on the participant's behalf while indicating verbal consent was given (draft of interview thematic guide in **Appendix K, L**).

Dr. Yoko Schreiber (U Ottawa, Department of Medicine), my second co-supervisor, has worked in Sioux Lookout region as an Infectious Disease Physician and has previously contacted local health authorities to discuss this MSc Epidemiology thesis protocol. To date, we have received feedback from Sioux Lookout First Nations Health Authority and local HCV-care providers on how to tailor this exploratory qualitative study to the specific and current community needs. Dr. Schreiber will also make future contact with additional local health care providers and community health representatives to further discuss recruitment strategies and how to best identify potential participants. The qualitative methods outlined above will serve as an exploratory program evaluation of the Sioux Lookout HCV Telemedicine Program that serves surrounding communities of Sioux Lookout Region for cultural safety. The data analysis will evaluate barriers for engaging with the existing telemedicine programs for individuals living in communities in Sioux Lookout region and determine how to ensure that HCV care delivery via telemedicine is delivered in a culturally safe and effective manner.

The interview thematic guide (drafts in **Appendix M and N**), intake questionnaire, and participant information and consent forms will first be reviewed by Sioux Lookout First Nations Health Authority and the community health representative. Any identified concerns with study documents will be discussed with all parties accordingly. Once finalized, the protocol will be presented to the Chiefs and Council. If approved, all study documents will then be sent for approval from the Ottawa University Research Ethics Board and SLMHC REB prior to the project initiation.

To ensure that data collection and research methods are conducted according to OCAP principles, Sioux Lookout First Nations Health Authority, Sioux Lookout First Nations Meno Ya Win Health Centre Research Ethics Board, and Chiefs and Council will be included with the research throughout the entire process (Office of Data Analysis, Research and Evaluation Administration on Children, 2016). The Sioux Lookout First Nation Health Authority has already been contacted by Dr. Yoko Schreiber, my co-supervisor, and has expressed interest in this project. The Sioux Lookout First Nation Health Authority will be consulted for approval of the research proposal and all study documents, including the individual interview thematic guides, intake questionnaire, and participant information and consent forms. All concerns raised by the Sioux Lookout First Nation Health Authority and community health directors will be addressed and the final approval of the Chiefs and Council will be sought prior to submitting the research protocol and study documents to the University of Ottawa Research Ethics Board and SLMHC REB. A research contract will also be drafted between SLFNHA, the participating communities, and the research team.

The main researcher, Candis Lepage, will continuously engage with Sioux Lookout First Nations Health Authority in order to actively identify any concerns with the study as they are presented. Sioux Lookout First Nations Health Authority and health directors will be consulted throughout the data analysis process and will be involved throughout the result interpretation process to ensure that the needs of the community are met (Office of Data Analysis, Research and Evaluation Administration on Children, 2016). Results from the study will be provided back to the community as soon as they are available and will be used in ways that the community feels will maximally benefit Sioux Lookout communities. Prior to the synthesis of study results and/or the distribution of results via publications, conferences, or presentations, Sioux Lookout First

Nations Health Authority, the health directors, and Chiefs and Council, will be contacted in order to grant permission for the use and dissemination of these data.

3.5. Participant Inclusion and Exclusion Criteria

Inclusion Criteria:

Individuals residing in communities surrounding Sioux Lookout region or those within these communities who are currently enrolled in a community-based buprenorphine-naloxone program, who are 18 years of age or older, and who self-identify as Indigenous. Healthcare provider will be eligible to participate if they are involved in existing telemedicine care delivery within Sioux Lookout communities.

Exclusion Criteria:

Individuals living within the Town of Sioux Lookout and healthcare providers not involved with existing telemedicine care delivery within Sioux Lookout communities

3.6. Participant Recruitment

3.6.1. Recruitment Process

Recruitment will occur through continuous engagement with community members including outreach workers, local health care providers, physicians working with individuals living with HCV, and Hepatitis C coordinators within the Sioux Lookout First Nations Health Authority. Engagement at the community-level with local leadership will ensure community

engagement throughout the project as well as provide better understanding of current community needs and suitability of the project for the community[118].

To ensure study results are representative to the population using telemedicine for HCV care, purposive sampling will be used. Recruitment will occur through the use of posters within locations offering suboxone programs within the community. Posters will contain an identified study phone number for participants to call to enroll in the study and information pamphlets providing information regarding the study. Additionally, peer-recruitment, coupled with snowball sampling to ensure sufficient sample size[134], will be used through outreach workers, HCV clinicians, and healthcare workers to identify participants within the suboxone program, as well as through word of mouth among those that access the suboxone program [124,127,132].

Participants will be recruited from communities in Sioux Lookout region that have high prevalence of chronic HCV, an established suboxone program, and have expressed community interest. Participants will be 18 years or older, reside in communities in Sioux Lookout region, are enrolled in a community-based suboxone program, which agreed to participate in the individual interview, and provided oral consent to participate in the individual interviews performed in the communities of Sioux Lookout region.

3.6.2. Recruitment Source

Recruitment will occur through established community-based buprenorphine-naloxone (suboxone) programs within First Nation communities within Sioux Lookout area[135]. To date, 22 of the 32 communities have established their own community-based suboxone programs, serving approximately 1,400 individuals, allowing for a large source population[135].

3.6.3. Rate of Recruitment

Recruitment will occur as a one-time event, spanning the time frame of two weeks within the identified communities surrounding Sioux Lookout. A previous study evaluating community-based suboxone programs in Northern Ontario Indigenous populations found that within six communities situated north of the Town of Sioux Lookout with a population of 4,388 individuals, a total of 526 patients were treated with buprenorphine-naloxone within a 3-year period[135]. Based off the numbers presented in the above review and information obtained through consultations with Sioux Lookout First Nation Health Authorities, it is estimated that within one community in Sioux Lookout region, there are approximately 200 individuals living with Hepatitis C Virus, of which 17 – 40 are estimated to be engaged and willing to participate.

3.6.4. Anticipated Sample Size

Based on the above outlined recruitment rates, it is expected that the final sample size will range from 17 to 40 participants.

3.6.5. Anticipated Loss To Follow Up

As data will be collected on a one-time-basis among Sioux Lookout community members, loss to follow up is not anticipated.

3.6.6. Anticipated Benefit to Participants

Participants will be compensated $30.00 for their time dedicated to the study for participating in the interview, will receive financial support for transportation to and from the study in the form of bus passes or taxi chits, and will receive food and beverages. Participation may allow researchers, physicians, and policy makers to understand the issues related to cultural

safety surrounding HCV care delivery using telemedicine in the future for rural, isolated, and Indigenous communities. It will also allow physicians to develop community tailored telemedicine practices that may benefits the communities within Sioux Lookout region.

3.6.7. Anticipated Risks for Participants

This study has risks, as with any study. Participants might find the interview questions are upsetting or distressing. Participants may not like the questions that are asked. Participants do not have to answer any question that makes them feel uncomfortable. Additionally, although the study will be conducted in Suboxone programs, separate from nursing centers in order to best protect the confidentiality of individuals living with Hepatitis C, absolute confidentiality cannot be promised, as individuals from the Suboxone programs may recognize participants of the study.

CHAPTER 4: DATA ANALYSIS STRATEGY

Qualitative data from participants will be analyzed using a thematic analysis approach. Data will be analyzed in an on-going and continuous process[136,137]. Master's student, Candis Lepage, as well as one additional external researcher, will read through the data to create codes for common themes raised in the interviews. Like codes will be grouped to identify key themes and patterns in the data. Analysis will also be conducted using NVivo for Mac and direct quotations from participants will be presented. Demographic information from the Sioux Lookout Intake forms will be compared using Chi-Square Tests and univariate analysis.

CHAPTER 5: PROJECT MANAGEMENT

No personal identifying information or personal health information will be collected for this study. All study documents, including the consent forms and the audio recording and notes, will not record a participant's name, address, or other identifying information. The Ottawa Hospital Research Institute may review relevant study records under the supervision of Candis Lepage and Dr. Yoko Schreiber's research staff for audit purposes only.

All paper records and voice recordings will be stored in a locked filing cabinet in an office. All records will be stored on an encrypted USB and will only be accessible by Candis Lepage, Dr. Schreiber, and Dr. Cooper. No identifiable information will be stored on any mobile devices. The study records will be kept for 10 years after termination of the study, as required by Ottawa Hospital Research Institute – Research Ethics Board. At the end of the storage time, all paper records will be shredded and all electronic records will be securely deleted. When we publish the results or present them at scientific meetings, no names or other information that could identify participants will be published or released.

CHAPTER 6: ETHICAL ISSUES

Research ethic board approval is being sought from all participating institutions including SLMHC Research Ethics Board, Chiefs and Council, and University of Ottawa Research Ethics Board. Research within Sioux Lookout will adhere to guidelines set forth by the Tri-Council policy statement 2: Research Involving the First Nations, Inuit and Métis Peoples of Canada. The research proposal, intake form, individual interview guides, and all information and consent forms will be submitted for review and approval to Sioux Lookout First Nation Health Authority and Chiefs and Council prior to submission to the University of Ottawa Research Ethics Board. Approval from both research ethic boards will be sought prior to study commencement. In preparation for data collection, the main researcher, Candis Lepage, has completed an Indigenous Cultural Safety course (Ontario Core ICS Health G-60901) to ensure the data is collected in a manner that is respectful to study participants and their culture.

Identifying personal information will not be collected in the intake form, interview questions, or participant information and consent form to allow for patient confidentiality to be maintained. Participants who do not wish to complete the intake questionnaire will still be able to participate in the interview. Participants will not be asked for their names at any point in the data collection process as the facilitator will sign on behalf of participants to maintain anonymity. Results from individual interviews will be presented in aggregate form to ensure that patients will not be able to be identified by their demographic information.

It is possible that the questions asked in the interviews will require recounting personal experiences, which could be unsettling or upsetting to participants. However, participants will be advised they do not have to answer any questions they do not wish and will be assured that they have the right to terminate the interview at any point during the interview process.

CHAPTER 7: KNOWLEDGE TRANSLATION STATEGY

Results obtained for this MSc thesis protocol for a qualitative exploratory study within communities of Sioux Lookout region will be shared both passively and actively with both the Sioux Lookout and scientific communities. Our knowledge translation strategy will consist of two components using an integrated knowledge translation and an end-of-project knowledge translation strategy. Integrated knowledge translation will be embodied as members of Sioux Lookout Health Authority, health directors, and Chiefs and Council will be actively involved with interpreting the knowledge gained from the interviews throughout the entire process. This will ensure that there is an equal partnership established between Sioux Lookout community and the researchers. This will also allow for the continuous refinement of interview questions and establishment of collective agreements on how best to disseminate the results to community members of Sioux Lookout region.

Knowledge translation will also occur at the end of the project through making the exploratory results gained from the research available to both knowledge users such as Sioux Lookout Health Authority, health directors, and Chiefs and Council, and the scientific community. The medium to reach these two audiences will be different. For local members such as Sioux Lookout Health Authority, health directors, Chiefs and Council, and community members engaged in the Suboxone programs, dissemination of results will take place through meetings and small, open, information sessions to allow for feedback from those who contributed to the research and to provide key stakeholders with information to bring about any needed changes required for the current HCV telemedicine program to become more culturally safe and accepted within the communities that use it. For the broader scientific community,

dissemination of results will occur through conference presentations addressing Indigenous health in Canada and through papers published in open access scientific journals.

CHAPTER 8: ANTICIPATED RESEARCH SIGNIFICANCE

Assessing the utility of telemedicine to engage, retain, and treat chronic HCV within Canada will provide crucial insight regarding program effectiveness for Canadians, rural, and Indigenous populations. Information gained regarding the cultural safety of telemedicine will allow HCV specialty care centers to tailor telemedicine programs to their local population, thereby increasing treatment initiation and adherence, leading to better health outcomes for all Canadians, including rural/Indigenous populations.

We hypothesize that the results from the qualitative data obtained from Sioux Lookout will support the future incorporation of telemedicine to manage HCV in Sioux Lookout in a way that abides by the CIHR Guidelines for Health Research Involving Indigenous people to ensure that the research findings are applied in a manner that abide by Indigenous values and traditions. These data obtained from Sioux Lookout participants can hopefully serve as a foundation and guideline of how to incorporate and tailor HCV Telemedicine programs according to other Indigenous populations' cultural beliefs and practices. These research findings will contribute evidence-based telemedicine knowledge that could inform the development of programs for other diseases across Canada impacting hard-to-reach populations.

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APPENDIX A. TOHVHP Data Base Project – Patient Consent Form

The Ottawa Hospital- General Campus
Division of Infectious Diseases
Viral Hepatitis Program
Data Base Project

CONSENT TO DATA COLLECTION

The objective of the Ottawa Hospital-General Campus Viral Hepatitis Program is to improve the care of patients with viral hepatitis. One important way to accomplish this is by undertaking research. For this reason, the Data Base Project was created. This Project involves the collection of information about patients to be made available to researchers in the future when new research questions have to be answered.

You are being asked to participate in this project because your doctors have determined that you have been infected with a hepatitis virus. Information about you and other patients with viral hepatitis will be collected and stored in a computer. Your participation in this project is **voluntary**.

Collection of Information

If you decide to participate in this program, when you first enroll, the clinic nurse and doctor will interview you to collect information about you and your illness. You will be asked about treatments that you might have had as well as information on your general state of health (ie: whether you have heart disease, diabetes, or other medical conditions), your ethnic background, and what risk factors you might have had in the past or have presently for acquiring viral hepatitis. As well, a physical examination will be performed. We will also collect blood test results, X-ray results and other test results. On subsequent visits we will collect more information including test results. We will also collect similar information from your medical records. These procedures are done routinely for all patients seen in the viral hepatitis clinic.

For the data base project, the data collected will not contain anything that could identify you personally such as name, initials, date of birth or hospital chart number. Each consenting participant will be assigned a unique study number (ie: 001, 002, 003, etc.). Access to the data base is restricted to several password protected computers within the viral hepatitis program. These computers are located in offices at the General Campus of the Ottawa Hospital under the control of Dr. Curtis Cooper and his staff. Requests for access to this information can be made by contacting Dr. Curtis Cooper.

Benefits

Your participation in this program may not provide you personally with any benefit. However, it will provide benefit to patients with viral hepatitis in general.

Confidentiality

Measures to protect the confidentiality of the information collected have been outlined above. No documents bearing your name will leave the Ottawa Hospital.

New Findings

New findings about viral hepatitis may occur at any time. The Data Base Project will provide information on new findings to all those that request them. If you do not request new information at this stage, you can request to be provided with new information at any later time.

Withdrawal

Joining in this project is voluntary. Choosing not to participate will not affect the quality of care you receive now or in the future at this institute. Your participation in this project in the future is also voluntary. You may withdraw from the project at any time for any reason. This will not affect the care that you receive from your doctor or the clinic that you attend. If you choose to withdraw from the project you can request that personal health information be discarded. Should you wish to withdraw, contact the site coordinator through Dr. Cooper's office at 613-737-8924. If you do not choose to have the information discarded it will continue to be stored and used as new technologies advance the field of hepatitis.

Commercial Value

It is possible that outside research organizations or commercial companies may want access to the data held by the Ottawa Hospital–General Campus Viral Hepatitis Program Data Base Project. The Viral Hepatitis Program may receive monetary reimbursement for such access. Any money obtained will be used to further the aims of the Ottawa Hospital Viral Hepatitis Program. You will not be paid for participation in this project. You will not share in any income that may arise out of this project. We will ask you to sign a waiver to any income that might be earned.

Contacts

Should any problems or questions arise during your participation in the project you may contact Dr. Curtis Cooper at 613-737-8924 or you may contact your usual physician. If you have questions about your rights as a research subject, you may contact the Ottawa Health Science Network Research Ethics Board at 613-798-5555 (ext. 16719).

Risks

There are no additional risks involved in participating in this project. There are no extra procedures done for the purposes of the data base project.

Subject Statement

I hereby voluntarily consent to participate in the Ottawa Hospital-General Campus Viral Hepatitis Program – Data Base Project. I have had ample time to review this

3 page consent form and consider all the information contained in it before signing this document. The project has been clearly explained to me and all of my questions have been answered to my satisfaction. I will receive a copy of this consent form.

_____
Patient's Name (print)

_____ _____
Patient's Signature Date (must be dated by patient)

_____ _____
Investigator / Designee Signature Date

OTTAWA HOSPITAL – GENERAL CAMPUS
VIRAL HEPATITIS PROGRAM
DATA BASE PROJECT

WAIVER OF FINANCIAL INTEREST

I hereby declare that I have read the Ottawa Hospital – General Campus Viral Hepatitis Program Data Base Project consent form and I understand it. I recognize that income may be derived by the Viral Hepatitis Program from my participation in the project. By signing below, I waive any financial claim to income that may derive from the use of data about me collected by the project. I will receive a copy of this consent form.

_____
Patient's Name (print)

_____ _____
Patient's Signature Date (must be dated by patient)

_____ _____
Investigator / Designee Signature Date

APPENDIX B. Signed Agreement for Access to 2016 PCCF and 2016 Statistics Canada Census Data

End-use Licence Agreement for Postal Code^{OM} Conversion Files

Restricted for use by University of Ottawa faculty, students, and staff

Terms of use:

1. The Licensee shall not lend, rent, lease, sublicense, distribute, make public, transfer or sell any part of the data product nor any right granted under this agreement to any person outside the licensed organization or to any other organization.

2. The Licensee shall not disassemble, decompile or in any way attempt to reverse engineer any part of the data product.

3. The Licensee shall not use any part of the data product to develop or derive any other data product or data service for external distribution or commercial sale.

4. The Licensee shall not use the data product other than for the purpose of matching Postal Code^{OM} data to geography in accordance with Appendix A.

5. The Licensee **shall not** use the data product for the following mail preparation purposes:
   (i) addressing mail;
   (ii) presorting addressed mail
   (iii) preparing unaddressed mail by householder count for delivery

6. The Licensee agrees not to merge or link the data product with any other databases in such a fashion that gives the appearance that the Licensee may have received, or had access to, information held by Statistics Canada about any identifiable individual, family, household, organization or business.

7. The Licensee is granted rights of use of the content of this data product for the purpose expressly described in the following **Appendix A**, and for no other purpose. In such cases, the source of the data must be acknowledged in all documents and communications by providing the following source citation at the bottom of each table and graph:

-------- APPENDIX A ----------

Approved Postal Code Data Matching Uses for University of Ottawa (DLI Accredited Canadian Post-secondary Institution)

Matching Postal Code^{OM} data to geography for:

1. **Teaching and learning purposes**.
   e.g.: Students can download PCCF on their laptop to do their assignments. This includes projects, maps, analytical papers, etc. Faculty can download and use the PCCF in teaching exercises.
2. **Research purposes**
   e.g.: Can be used in analysis to write articles that are published in journals. The data is not shared but the results are published. This also includes thesis for Masters or Doctorate where results are required to be public.
3. **Planning purposes**
   The institution can use the information in planning student recruitment activities or find out where these students are coming from.

APPENDIX C. Calculations for Proportions Included in the Primary Component Analysis

Measure (Proportion)	Formula Used
Persons without high school diploma	Number of people without a certificate or diploma / Total number of people reporting highest certificate achieved
Employment-to-Population Ratio	(Number of people employed/ Number of people in the labor force) / Total number of people 15 years of age and older
Mean Income	Average after tax income reported
People living alone	Number of one person households / Total number of private households
People separated, divorced or widowed	(Number of people who are separated + Number of people who are divorced + Number of people who are widowed) / Total number of people reporting marital status
Lone parent families	Number of long parent census families / Total number of census families
Suitable Housing	Number of people with suitable housing/ Total number of private households by housing suitability
Not Suitable Housing	Number of people with not suitable housing/ Total number of private households by housing suitability

APPENDIX D. TOHVHP Data Base Project Variable Definitions

Variable	Definition	Unit of Measurement
Race	Captured if the individual self-reported being Caucasian, Black, Asia, First Nation, Hispanic, or other	None
Education	Captured the highest level of education an individual completed. Options were less than high school, high school, college/some university, university undergrad, university graduate, or unknown	None
Housing	Captured an individual's housing status. Options were stable, unstable, or unknown	None
Sex	Captured if the individual self-reported being a male or female	None
HCV Genotype	Captured the individuals HCV genotype	None
Group HIV	Indicated if the individual had a HIV infection	True or False
Group HBV	Indicated if the individual had a HBV infection	True or False
fskpa	Fibro scan Kilopascal measurement (kPa)	kPa
ALT	Amount of alanine transaminase in the blood, measured at baseline TOHVHP clinic assessment	IU/L
Viral Load	HCV viral load	IU/mL
PTSD	Captured if the individual had a psychiatric history of post traumatic stress disorder	True or False
Anxiety	Captured if the individual had a psychiatric history of anxiety disorder	True or False
Schizophrenia	Captured if the individual had a psychiatric history of schizophrenia/schizoaffective disorder	True or False
Depression	Captured if the individual had	True or False

	a psychiatric history of depression	
Bipolar	Captured if the individual had a psychiatric history of bipolar disorder	True or False
IVDU	Captured if the individual had a history of intravenous drug use	Yes, No, or Unknown
Hetero	Captured if the individual had a history of high risk sex (opposite sex)	Yes, No, or Unknown
MSM	Captured if the individual had a history of high risk sex (same sex)	Yes, No, or Unknown
Blood	Captured if the individual had a history of receiving blood products	Yes, No, or Unknown
Snorting	Captured if the individual had a history of cocaine snorting	Yes, No, or Unknown
Tattoos	Captured if the individual had or has tattoos	Yes, No, or Unknown
Pierce	Captured if the individual had or has previous piercings	Yes, No, or Unknown
Prison	Captured if the individual had or has previous spent time in prison	Yes, No, or Unknown

APPENDIX E. Percentage of Variables Missing for Each Variable Used from TOHVHP Data Base Project Dataset

Variable	Percentage Missing (%)	Decision
Race	12.6	Keep
Education	89.6	Remove
Housing	74.8	Remove
Sex	0.7	Keep
HCV Genotype	3.4	Keep
GroupHIV	0	Keep
GroupHBV	5.5	Keep
fskpa	61.4	Keep with limitations
ALT	1.9	Keep
Viral Load	10.7	Keep
PTSD	0.0	Keep
Anxiety	0.0	Keep
Schizophrenia	0.0	Keep
Depression	0.0	Keep
Bipolar	0.0	Keep
IVDU	1.4	Keep
Hetero	0.8	Keep
Piercing	3.4	Keep
MSM	0.8	Keep
Blood	4.7	Keep
Snorting	2.8	Keep
Tattoos	3.0	Keep
Prison	2.8	Keep

APPENDIX F. Model Fit Statistics for Multivariable Logistic Regression Model Assessing Variables Association with Patient Retention in HCV Care.

Multiple multi-logistic regression models were run to produce the most-simple model with indications of a good fit. Model fit was assessed using calibration statistics and Hosmer-Lemeshow test statistic. The final model selected contained the variables of HCV care delivery method, greatest social deprivation, sex, and age. The model indicated acceptable calibration (c = 0.738) and a good fit for the data (p = 0.306) (Table 34).

Table 34. Results of the Hosmer-Lemeshow test and calibration statistics comparing model fit. Represented are the c-statistics and the p-value of the Hosmer-Lemeshow test.

Model	Calibration Statistic	P-value of the Hosmer-Lemeshow Test
Model 1 [A]	0.742	0.162
Model 2 [B]	0.737	0.552
Model 3 [C]	0.738	0.306

[A] Contained the variables sex, clinic, proportion of people who did not graduate high school, history of tattoos, proportion of individuals experiencing the greatest quintile of social deprivation, proportion of individuals experiencing the greatest quintile of material deprivation, age.
[B] Contained the variables sex, clinic, proportion of people who did not graduate high school, proportion of individuals experiencing the greatest quintile of social deprivation, proportion of individuals experiencing the greatest quintile of material deprivation, age.
[C] Contained the variables sex, clinic, proportion of individuals experiencing the greatest quintile of social deprivation, age.

Comparison of the multiple logistic regression models was compared using a likelihood ratio test p-value to compare model fit from the full to nested models to good model selection. It was confirmed based on the p – value that the third nested model containing sex, clinic, proportion of individuals experiencing the greatest quintile of social deprivation, and age had adequate goodness of fit and supported that the selection of the reduced model was sound (Table 35).

Table 35. Results of the likelihood ratio test comparing the original and nested models. Represented are the -2 log likelihood values and the p-values achieved when comparing the models for their fit.

Model	-2 Log Likelihood Value	Df	P-value Comparing Model Fit
Nested Model 1 [B]	332.19	7	0.37
Nested Model 2 [C]	332.35	5	0.92
Full Model [A]	331.37	8	

[A] Contained the variables sex, clinic, proportion of people who did not graduate high school, history of tattoos, proportion of individuals experiencing the greatest quintile of social deprivation, proportion of individuals experiencing the greatest quintile of material deprivation, age.
[B] Contained the variables sex, clinic, proportion of people who did not graduate high school, proportion of individuals experiencing the greatest quintile of social deprivation, proportion of individuals experiencing the greatest quintile of material deprivation, age.

[C] Contained the variables sex, clinic, proportion of individuals experiencing the greatest quintile of social deprivation, age

APPENDIX G. Model Fit Statistics for Multivariable Logistic Regression Model Assessing Variables Association with HCV Treatment Initiation.

Initiating a Interferon Treatment (Included Exclusively Interferon and Interferon-Direct Acting Antiviral Combination Therapies)

Multiple multi-logistic regression models were run to produce the most-simple model with indications of a good fit. Model fit was assessed using calibration statistics and Hosmer-Lemeshow test statistic. The final model selected contained the variables of HCV care delivery method, presence of a liver biopsy, pretreatment Fibroscan score, age, sex, and baseline ALT. The model indicated exceptional calibration (c = 0.826) and a good fit for the data (p = 0.663) (Table 36).

Table 36. Results of the Hosmer-Lemeshow test and calibration statistics comparing model fit. Represented are the c-statistic and the p-value of the Hosmer-Lemeshow test.

Model	Calibration Statistic	P-value of the Hosmer-Lemeshow Test
Model 1 [A]	0.820	0.811
Model 2 [B]	0.841	0.442
Model 3 [C]	0.836	0.889
Model 4 [D]	0.826	0.524
Model 5 [E]	0.826	0.663

[A] Contained the variables of clinic, age, sex, identifying as Indigenous, history of injection drug use, history of engaging in high risk sex, history of intranasal cocaine use, previous tattoos, previous piercings, history of incarceration, history of mental illness, ALT, proportion of individuals experiencing the greatest quintile of social deprivation, proportion of individuals experiencing the greatest quintile of material deprivation, pretreatment Fibroscan score, and presence of having a liver biopsy.
[B] Contained the variables of clinic, age, sex, history of intranasal cocaine use, previous tattoos, history of mental illness, ALT, pretreatment Fibroscan score, and presence of having a liver biopsy.
[C] Contained the variables of clinic, age, sex, previous tattoos, history of mental illness, ALT, pretreatment Fibroscan score, and presence of having a liver biopsy.
[D] Contained the variables of clinic, age, sex, history of mental illness, ALT, pretreatment Fibroscan score, and presence of having a liver biopsy.
[E] Contained the variables of clinic, age, sex, ALT, pretreatment Fibroscan score, and presence of having a liver biopsy.

Comparison of the multiple logistic regression models was compared using a likelihood ratio test p-value to compare model fit from the full to nested models to good model selection. It was confirmed based on the p – value that the third nested model containing HCV care delivery method, presence of a liver biopsy, pretreatment Fibroscan score, sex, age and baseline ALT had adequate goodness of fit and supported that the selection of the reduced model was sound (Table 37).

Table 37. Results of the likelihood ratio test comparing the original and nested models. Represented are the -2log likelihood values and the p-values achieved when comparing the models for their fit.

Model	-2 Log Likelihood Value	Df	P-value Comparing Model Fit
Nested Model 1 [B]	204.49	12	0.000
Nested Model 2 [C]	206.46	11	0.160
Nested Model 3 [D]	209.24	10	0.095
Nested Model 4 [E]	212.16	9	0.087
Full Model [A]	852.75	19	

[A] Contained the variables of clinic, age, sex, identifying as Indigenous, history of injection drug use, history of engaging in high risk sex, history of intranasal cocaine use, previous tattoos, previous piercings, history of incarceration, history of mental illness, ALT, proportion of individuals experiencing the greatest quintile of social deprivation, proportion of individuals experiencing the greatest quintile of material deprivation, pretreatment Fibroscan score, and presence of having a liver biopsy.
[B] Contained the variables of clinic, age, sex, history of intranasal cocaine use, previous tattoos, history of mental illness, ALT, pretreatment Fibroscan score, and presence of having a liver biopsy.
[C] Contained the variables of clinic, age, sex, previous tattoos, history of mental illness, ALT, pretreatment Fibroscan score, and presence of having a liver biopsy.
[D] Contained the variables of clinic, age, sex, history of mental illness, ALT, pretreatment Fibroscan score, and presence of having a liver biopsy.
[E] Contained the variables of clinic, age, sex, ALT, pretreatment Fibroscan score, and presence of having a liver biopsy.

Initiating a Direct Acting Antiviral Treatment

Multiple multi-logistic regression models were run to produce the most-simple model with indications of a good fit. Model fit was assessed using calibration statistics and Hosmer-Lemeshow test statistic. The final model selected contained the variables of HCV care delivery genotype, history of mental illness, history of engaging in high-risk sex, presence of a liver biopsy, pretreatment Fibroscan score, sex, and age. The model indicated exceptional calibration ($c = 0.851$) and a good fit for the data ($p = 0.202$) (Table 38).

Table 38. Results of the Hosmer-Lemeshow test and calibration statistics comparing model fit. Represented are the c-statistic and the p-value of the Hosmer-Lemeshow test.

Model	Calibration Statistic	P-value of the Hosmer-Lemeshow Test
Model 1 [A]	0.863	0.607
Model 2 [B]	0.862	0.676
Model 3 [C]	0.861	0.586
Model 4 [D]	0.853	0.464
Model 5 [E]	0.851	0.202

[A] Contained the variables of clinic, genotype, history of injection drug use, history of engaging in high risk sex, history of intranasal cocaine use, history of receiving blood products, previous tattoos, previous piercings, history of incarceration, history of mental illness, ALT, sex, age, geographic area of residence, housing suitability, proportion of individuals who did not graduate high school, co-infection with HBV, pretreatment Fibroscan score, and presence of having a liver biopsy.

[B] Contained the variables of clinic, genotype, history of injection drug use, history of engaging in high risk sex, history of intranasal cocaine use, history of receiving blood products, history of incarceration, history of mental illness, ALT, sex, age, proportion of individuals who did not graduate high school, co-infection with HBV, pretreatment Fibroscan score, and presence of having a liver biopsy.
[C] Contained the variables of clinic, genotype, history of injection drug use, history of engaging in high risk sex, history of receiving blood products, history of incarceration, history of mental illness, ALT, sex, age, co-infection with HBV, pretreatment Fibroscan score, and presence of having a liver biopsy.
[D] Contained the variables of clinic, genotype, history of injection drug use, history of engaging in high risk sex, history of mental illness, ALT, sex, age, pretreatment Fibroscan score, and presence of having a liver biopsy.
[E] Contained the variables of clinic, genotype, history of engaging in high risk sex, history of mental illness, sex, age, pretreatment Fibroscan score, and presence of having a liver biopsy.

Comparison of the multiple logistic regression models was compared using a likelihood ratio test p-value to compare model fit from the full to nested models to good model selection. Although the p-values indicated that the nested model containing HCV care delivery method, presence of a liver biopsy, pretreatment Fibroscan score, sex, age and baseline ALT was no better of a fit than the large model, the decision was made to use the reduced model as it had good calibration and fit (Table 39).

Table 39. Results of the likelihood ratio test comparing the original and nested models. Represented are the -2 log likelihood values and the p-value achieved when comparing the models for their fit.

Model	-2 Log Likelihood Value	Df	P-value Comparing Model Fit
Nested Model 1 [B]	644.28	21	0.006
Nested Model 2 [C]	662.95	19	0.000
Nested Model 3 [D]	708.11	16	0.000
Nested Model 4 [E]	724.99	14	0.000
Full Model [A]	626.35	27	

[A] Contained the variables of clinic, genotype, history of injection drug use, history of engaging in high risk sex, history of intranasal cocaine use, history of receiving blood products, previous tattoos, previous piercings, history of incarceration, history of mental illness, ALT, sex, age, geographic area of residence, housing suitability, proportion of individuals who did not graduate high school, co-infection with HBV, pretreatment Fibroscan score, and presence of having a liver biopsy.
[B] Contained the variables of clinic, genotype, history of injection drug use, history of engaging in high risk sex, history of intranasal cocaine use, history of receiving blood products, history of incarceration, history of mental illness, ALT, sex, age, proportion of individuals who did not graduate high school, co-infection with HBV, pretreatment Fibroscan score, and presence of having a liver biopsy.
[C] Contained the variables of clinic, genotype, history of injection drug use, history of engaging in high risk sex, history of receiving blood products, history of incarceration, history of mental illness, ALT, sex, age, co-infection with HBV, pretreatment Fibroscan score, and presence of having a liver biopsy.
[D] Contained the variables of clinic, genotype, history of injection drug use, history of engaging in high risk sex, history of mental illness, ALT, sex, age, pretreatment Fibroscan score, and presence of having a liver biopsy.
[E] Contained the variables of clinic, genotype, history of engaging in high risk sex, history of mental illness, sex, age, pretreatment Fibroscan score, and presence of having a liver biopsy.

APPENDIX H. Model Fit Statistics for Multivariable Logistic Regression Model Assessing Variables Association with Achieving SVR.

Using Per-Protocol Analysis

Multiple multi-logistic regression models were run to produce the most-simple model with indications of a good fit. Model fit was assessed using calibration statistics and Hosmer-Lemeshow test statistic. The final model selected contained the variables of genotype, sex, age, treatment allocation, and history of incarceration. The model indicated excellent calibration (c = 0.801) and a good fit for the data (p = 0.9019) (Table 40).

Table 40. Results of the Hosmer-Lemeshow test and calibration statistics comparing model fit. Represented are the c-statistic and the p-value of the Hosmer-Lemeshow test.

Model	Calibration Statistic	P-value of the Hosmer-Lemeshow Test
Model 1 [A]	0.825	0.5745
Model 2 [B]	0.806	0.2287
Model 3 [C]	0.805	0.7261
Model 4 [D]	0.799	0.6591
Model 5 [E]	0.788	0.5088

[A] Contained the variables genotype, history of injection drug use, history of tattoos, history of incarceration, history of receiving blood products, sex, history of piercings, hiv status, treatment allocation, history of mental illness, age, material deprivation, proportion of individuals without a high school diploma, proportion of people with suitable housing, proportion of people with not suitable housing, geographic area, biopsy, viral load and baseline treatment fibrosis score by transient elastrography.
[B] Contained the variables of genotype, history of injection drug use, history of piercing, history of receiving blood products, sex, treatment allocation, presence of a liver biopsy, and age.
[C] Containing variables of genotype, sex, age, history of injection drug use, treatment allocation, history of piercing, history of receiving blood products
[D] Containing variables genotype, sex, age, history of injection drug use, history of receiving blood products, and treatment allocation
[E] Containing variables genotype, sex, age, and treatment allocation

Comparison of the multiple logistic regression models was compared using a p-value to compare model fit from the full to nested models. Although the final model indicated that the inclusion of tattoos made a better fit, after consultation with thesis supervisor, it was determined this may be due to the presence of patients having multiple risk factors for HCV. Exploratory analysis demonstrated that of those who had been incarcerated, 67% had tattoos; therefore the decision was made to remove it from the model to reduce redundancy (Table 41).

Table 41. Results of the likelihood ratio test comparing the original and nested models. Represented are the -2 log likelihood values and the p-value achieved when comparing the models for their fit.

Model	-2 Log Likelihood Value	Df	P-value Comparing Model Fit
Nested Model 1 [B]	556.262	13	0.0000

Nested Model 2 [C]	556.973	12	0.399
Nested Model 3 [D]	559.209	11	0.1348
Nested Model 4 [E]	565.034	8	0.12044
Full Model [A]	174.085	26	

Using Intent-To-Treat Analysis

Multiple multi-logistic regression models were run to produce the most-simple model with indications of a good fit. Model fit was assessed using calibration statistics and Hosmer-Lemeshow test statistic. The final model selected contained the variables of genotype, sex, treatment allocation, age, and clinic allocation. The model indicated acceptable calibration (c = 0.732) and a good fit for the data (p = 0.825) (Table 42).

Table 42. Results of the Hosmer-Lemeshow test and calibration statistic comparing model fit. Represented are the c-statistic and the p-value of the Hosmer-Lemeshow test.

Model	Calibration Statistic	P-value of the Hosmer-Lemeshow Test
Model 1 [A]	0.760	0.719
Model 2 [B]	0.737	0.319
Model 3 [C]	0.732	0.825

[A] Contained the variables of clinic allocation, genotype, history of injection drug use, history of tattoos, history of incarceration, history of receiving blood products, sex, hiv status, treatment allocation, history of mental illness, age, social deprivation, material deprivation, proportion of individuals without a high school diploma, proportion of people with suitable housing, proportion of people with not suitable housing, geographic area, biopsy, viral load, and ALT.
[B] Contained the variables of clinic allocation, genotype, sex, treatment allocation, age, proportion of people with suitable housing, proportion of people with not suitable housing, and geographic area.
[C] Contained the variables of clinic allocation, genotype, sex, treatment allocation, and age.

Comparison of the multiple logistic regression models was compared using a p-value to compare model fit from the full to nested models. Although the p-values indicated that the nested model was no better of a fit than the large model, the decision was made to use the reduced model as it had good calibration and fit (Table 43).

Table 43. Results of the likelihood ratio test comparing the original and nested models. Represented are the -2 log likelihood values and the p-value achieved when comparing the models for their fit.

Model	-2 Log Likelihood Value	Df	P-value Comparing Model Fit
Nested Model 1 [B]	767.00	13	0.0000
Nested Model 2 [C]	792.09	11	0.003
Full Model [A]	300.92	28	

[A] Contained the variables of clinic allocation, genotype, history of injection drug use, history of tattoos, history of incarceration, history of receiving blood products, sex, hiv status, treatment allocation, history of mental illness, age, social deprivation, material deprivation, proportion of individuals without a high

school diploma, proportion of people with suitable housing, proportion of people with not suitable housing, geographic area, biopsy, viral load, and ALT.
[B] Contained the variables of clinic allocation, genotype, sex, treatment allocation, age, proportion of people with suitable housing, proportion of people with not suitable housing, and geographic area.
[C] Contained the variables of clinic allocation, genotype, sex, treatment allocation, and age.

APPENDIX I. Results of Primary Component Analysis

Table 44. Indicators and variables included in the area-based material and social deprivation indexes for the TOHVHP cohort based from 2016 Statistics Canada Census Data.

	Index	
Indicator	**Material**	**Social**
Persons without a high school diploma	- 0.30	- 0.04
Employment/population	0.36	0.16
Average household income	0.30	- 0.02
Persons living alone	0.21	0.64
Persons separated, divorced, or widowed	0.07	0.52
Single-parent families	- 0.34	- 0.11
Explained Variance	56%	18%
Cumulative Variance	56%	74%

* Values in the table represent loadings and are to be interpreted as coefficient coefficients between indicator and components. Source: Canadian Census, 2016.

APPENDIX J. Sioux Lookout Participant Intake Form

Sioux Lookout Participant Intake Form (Questions to be approved by SLMHC Research Ethics Board, Chiefs and Council, and University of Ottawa Research Ethics Board)

The purpose of this form is to gather information about who is participating in the individual interviews to inform us of any concerns regarding the use of telemedicine and cultural safety to make sure we are accessing a wide variety and diverse group of people. The questionnaire is completely anonymous (your name will not be used) and you may choose to skip any questions you do not want to answer.

1. What is your age?

- ☐ 18-25
- ☐ 26-35
- ☐ 36-45
- ☐ 46-55
- ☐ 56-65
- ☐ 66-75
- ☐ 76 or more
- ☐ Do not wish to answer

2. What was your biological sex at birth?

- ☐ Female
- ☐ Male
- ☐ Do not wish to answer

3. What sex do you identify with now?

- ☐ Female
- ☐ Male
- ☐ Transgender (Male-to-Female)
- ☐ Transgender (Female-to-Male)
- ☐ Other
- ☐ Do not wish to answer

4. What is your sexuality?

- ☐ Straight
- ☐ Gay
- ☐ Bi-Sexual
- ☐ Two-Spirited
- ☐ Other
- ☐ Do not wish to answer

5. What is your residential location

- ☐ Within the Town of Sioux Lookout
- ☐ Community within Sioux Lookout Region

If you do not live within the Town of Sioux Lookout, can you state what community you are from? _____

6. What is your Identifying as Indigenous

Do you identify as identifying as Indigenous?

- ☐ Yes
- ☐ No
- ☐ Do not wish to answer

If yes, do you identify as:

(Select only one.)

- ☐ First Nations
- ☐ Inuit
- ☐ Metis
- ☐ Other _____

7. What is your highest level of education?

- ☐ No formal education
- ☐ Elementary School (Primary – Grade 6)
- ☐ Junior High School (Grade 7 – Grade 9)
- ☐ High School (Grade 10 – Grade 12)
- ☐ College / Trade School
- ☐ Some University
- ☐ Completed University
- ☐ Specialty Degree (i.e., Dentistry, Medicine, Law)
- ☐ Other (specify) _____
- ☐ Do not wish to answer

8. What is your employment status?

- ☐ Regular / Part-Time
- ☐ Casual / Part-Time
- ☐ Self-Employed
- ☐ Student
- ☐ Home-maker/parenting
- ☐ Disability Leave
- ☐ Unemployed
- ☐ Retired
- ☐ Do not wish to answer

9. What is your average annual household income?

- ☐ < $10,000
- ☐ $10,000 - $50,000
- ☐ $50,000 - $100,000
- ☐ > $100,000
- ☐ Do not know
- ☐ Do not wish to answer

10. Have you ever used telemedicine?

- ☐ Yes
- ☐ No

If yes, when was the last time you used telemedicine services?

- ☐ Less than 3 months
- ☐ 3 to 6 months
- ☐ 6 months to 1 year
- ☐ More than 1 year
- ☐ Do not wish to answer

APPENDIX K. Sioux Lookout Participant Information and Consent Form – Individual Interviews (Community Members)

Sioux Lookout – Participant Information and Consent Form: Individual Interview (Community Members)
(To be printed on letterhead)

Access to HCV Care in Sioux Lookout Region: A Qualitative Study

To be read to the participant before the commencement of interview.
Interviewer signs and dates two copies.
One copy offered to participant, one copy stays with interviewer.

Principal Investigator: Candis Lepage (MSc Epidemiology Candidate) Tel: ###-###-####

Participation in this study is voluntary. Please read this Participant Informed Consent Form carefully before you decide if you would like to participate.

BACKGROUND OF THE STUDY
This interview is part of a research study being conducted by University of Ottawa - MSc Epidemiology candidate, Candis Lepage.

The purpose of this research study is to evaluate if the current Hepatitis C Virus care delivery using telemedicine is culturally safe. We are doing this study because there is a lack of available HCV specialty care in rural, isolated, and Indigenous communities. We want to see if offering HCV care via telemedicine will help reduce the number of chronic HCV complications and improve treatment uptake in Indigenous communities. This interview will also serve as a means for us to understand if there are any concerns regarding telemedicine and telemedicine HCV-delivery.

STUDY PROCEDURES
You are being invited to participate in this interview based on your residential location in a community in Sioux Lookout region and your current or past participation in the local Suboxone program. You are being asked to participate in an interview to help understand current perceptions within the community regarding Hepatitis C Virus (HCV) care delivery using telemedicine. You are also being asked to participate in this interview to help us address any concerns there may be regarding telemedicine or telemedicine HCV-care delivery within your community.

The interview will be audio recorded. You can choose not to answer any questions, you can choose to stop the tape recorder at any time, and you can end your participation at any time.

STUDY DURATION
The entire study will last about one year. Participation in the interview will involve approximately one hour of your time.

BENEFITS
You will receive $30.00 for your participation in this study. Your participation may allow researchers, physicians, and policy makers to understand the issues related to cultural safety surrounding HCV care delivery using telemedicine in Indigenous communities. It will also allow physicians to develop community tailored telemedicine practices that may benefits the community.

POTENTIAL RISKS AND DISCOMFORTS
This study has risks, as with any study. You might find the interview questions and discussions upsetting or distressing. You may not like the questions that you are asked. You do not have to answer any questions that makes you uncomfortable.

DO I HAVE TO PARTICIPATE?
Your participation in this study is completely voluntary. You can choose not to participate in this study. You may decide not to be in this study, or to be in the study now, and then change your mind later and decide not to complete the interview.

CONFIDENTIALITY
No personal identifying information or personal health information will be collected for this study. All study documents, including this consent form and the audio recording and notes, will not record your name, address, or any other identifying information. This section of the consent form describes how the interview information will be used and shared. The Ottawa Hospital Research Institute may review relevant study records under the supervision of Candis Lepage and Dr. Yoko Schreiber's research staff for audit purposes only.

All paper records and voice recordings will be stored in a locked filing cabinet in an office. All records will be stored on an encrypted USB and only accessible by Candis Lepage, Dr. Schreiber, and Dr. Cooper. No identifiable information will be stored on any mobile devices. The study records will be kept for 10 years after termination of the study, as required by Ottawa Hospital Research Institute – Research Ethics Board. At the end of the storage time, all paper records will be shredded and all electronic records will be securely deleted. When we publish the results or present them at scientific meetings, no names or other information that could identify you will be published or released.

Although confidentiality will be maintained by all research members involved with the study, given the nature of recruitment within the local Suboxone programs, we cannot promise that confidentiality will be maintained on behalf of other individuals in the Suboxone program that may know you, although it will be requested.

QUESTIONS
Should you have any questions or need more information about anything to do with the study, please feel free to contact the Principal Investigator of the study. Her name is Candis Lepage. You can call Candis at ###-###-#### for any reason that has to do with you taking part in the study.

The Office of Research Ethics and Integrity at the University of Ottawa has reviewed the plans for this study. If you have any concerns about your rights as a research participant, you can call the Protocol Officer for Ethics in Research at the University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 154, Ottawa, ON K1N 6N5. Telephone: (613)-562-5387. Email: ethics@uottawa.ca.

Consent to Participate in Research

Access to HCV Care in Sioux Lookout Region: A Qualitative Study

Investigator or Delegate Statement
I confirm that:

- I have read each of the two pages of this Participant Information and Consent Form to the participant.
- To the best of my knowledge, the participant understands the nature, demands, risks and benefits involved in taking part in this study.
- The participant understands that although their confidentiality is maintained on behalf of the research personnel, that confidentiality cannot be promised on behalf of the participants, although it will be requested.
- The participant has had a chance to ask me any questions they have about the study.
- Their questions have been answered to their satisfaction and they have agreed to take part in the interview.
- I have offered the participant a copy of this Participant Information and Consent Form for their use.

Investigator/Delegate's Printed Name

Investigator/Delegate's Signature

Date

APPENDIX L. Sioux Lookout Participant Information and Consent Form – Individual Interviews (Healthcare Providers/Agency Workers)

Sioux Lookout – Participant Information and Consent Form: Individual Interview (Healthcare Providers/Agency Workers)
(To be printed on letterhead)

Access to HCV Care in Sioux Lookout Region: A Qualitative Study

To be read to the participant before the commencement of individual interview.
Interviewer signs and dates two copies.

One copy offered to participant, one copy stays with interviewer.

Principal Investigator: Candis Lepage (MSc Epidemiology Candidate) Tel: ###-###-####

Participation in this study is voluntary. Please read this Participant Informed Consent Form carefully before you decide if you would like to participate.

BACKGROUND OF THE STUDY
This interview is part of a research study being conducted by University of Ottawa - MSc Epidemiology candidate, Candis Lepage.

The purpose of this research study is to evaluate if the current Hepatitis C Virus care delivery using telemedicine is culturally safe. We are doing this study because there is a lack of available HCV specialty care in rural, isolated, and Indigenous communities. We want to see if offering HCV care via telemedicine will help reduce the number of chronic HCV complications and improve treatment uptake in Indigenous communities. This individual interview will serve as a means for us to understand provider's perspectives regarding telemedicine and telemedicine HCV-delivery.

STUDY PROCEDURES
You are being invited to participate in this individual interview based on your position as a provider in the residential location within Sioux Lookout and surrounding area in providing remote healthcare. You are being asked to participate in an individual interview to help understand provider's opinions regarding Hepatitis C Virus (HCV) care delivery using telemedicine within this community. You are also being asked to participate in an individual interview to help us address any concerns there may be regarding telemedicine or telemedicine HCV-care delivery within your community.

The individual interview will be audio recorded. You can choose not to answer any questions, you can choose to stop the tape recorder at any time, and you can end your participation at any time.

STUDY DURATION
The entire study will last about one year. Participation in the individual interview will involve approximately one hour of your time.

BENEFITS
You will receive $30.00 for your time in this study. Your participation may allow researchers, physicians, and policy makers to understand the issues related to cultural safety surrounding HCV care delivery using telemedicine in the future Indigenous communities. It will also allow physicians to develop community tailored telemedicine practices that may benefits the community.

POTENTIAL RISKS AND DISCOMFORTS
This study has risks, as with any study. You might find the interview questions and discussions upsetting or distressing. You may not like the questions that you are asked. You do not have to answer any question that makes you uncomfortable.

DO I HAVE TO PARTICIPATE?
Your participation in this study is completely voluntary. You can choose not to participate in this study. You may decide not to be in this study, or to be in the study now, and then change your mind later and decide not to complete the interview.

CONFIDENTIALITY
No personal identifying information or personal health information will be collected for this study. All study documents, including this consent form and the audio recording and notes, will not record your name, address, or any other identifying information. This section of the consent form describes how the interview information will be used and shared. The Ottawa Hospital Research Institute may review relevant study records under the supervision of Candis Lepage and Dr. Yoko Schreiber's research staff for audit purposes only.

All paper records and voice recordings will be stored in a locked filing cabinet in an office. All records will be stored on an encrypted USB and only accessible by Candis Lepage, Dr. Schreiber, and Dr. Cooper. No identifiable information will be stored on any mobile devices. The study records will be kept for 10 years after termination of the study, as required by Ottawa Hospital Research Institute – Research Ethics Board. At the end of the storage time, all paper records will be shredded and all electronic records will be securely deleted. When we publish the results or present them at scientific meetings, no names or other information that could identify you will be published or released.

QUESTIONS
Should you have any questions or need more information about anything to do with the study, please feel free to contact the Principal Investigator of the study. Her name is Candis Lepage. You can call Candis at ###-###-#### for any reason that has to do with you taking part in the study.

The Office of Research Ethics and Integrity at the University of Ottawa has reviewed the plans for this study. If you have any concerns about your rights as a research participant, you can call the Protocol Officer for Ethics in Research at the University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 154, Ottawa, ON K1N 6N5. Telephone: (613)-562-5387. Email: ethics@uottawa.ca.

Consent to Participate in Research

Access to HCV Care in Sioux Lookout Region: A Qualitative Study

Investigator or Delegate Statement
I confirm that:

- I have read each of the two pages of this Participant Information and Consent Form to the participant.
- To the best of my knowledge, the participant understands the nature, demands, risks and benefits involved in taking part in this study.
- The participant has had a chance to ask me any questions they have about the study.
- Their questions have been answered to their satisfaction and they have agreed to take part in the individual interview.
- I have offered the participant a copy of this Participant Information and Consent Form for their use.

Investigator/Delegate's Printed Name

Investigator/Delegate's Signature

Date

APPENDIX M. Sioux Lookout Individual Interviews (Community Members) Thematic Guide

Sioux Lookout – Individual Interview (Community Members) Thematic Guide

We are looking to evaluate the cultural safety of HCV – care delivery-using telemedicine Indigenous communities.

1. Can you please tell me what you have heard about telemedicine?

   Probes: Have you used telemedicine? Have your friends or family members used telemedicine? If yes, what was the reason for using telemedicine? What were your thoughts about this experience?

2. What do you think are possible **advantages** of using telemedicine services in Sioux Lookout region?

   Probes: What aspects of care do you think telemedicine improves? If so, why?

3. What do you think are possible **disadvantage** of using telemedicine services in Sioux Lookout?

   Probes: Have you ever experienced any difficulty using telemedicine? If yes, what were these? Have you ever felt as if telemedicine did not address external factors, including life situation such as housing? Financial issues? Limited resources? Lack of family support? If yes, what were these and how would do you feel these would be best addressed? Has there ever been a misunderstanding of cultural context of presenting illness or pathology? If so, what happened?

4. What do you think are possible **draws or reasons** why people may prefer to travel into the town of Sioux Lookout to receive their HCV care in person rather than use the telemedicine services in the communities?

   Probes: Do you have personal reasons why you may have chose or chosen to travel in town to receive your medical care? If yes, what are they? Do you feel there are factors external to the care delivery method, including life situations or available infrastructures that may draw people to making the travel into Town to receive their care? If so what are they?

5. What aspects of the current telemedicine program do you believe need to be improved in Sioux Lookout region?

   Probes: Have individuals in the community expressed concerns regarding the telemedicine services? If yes, what were they? When talking specifically about HCV care via telemedicine, are there any different aspects you feel need to be improved? If yes, what are they. How you do feel these can be improved? Linguistics (i.e., potential for misunderstanding prescribed treatment course or presenting symptoms)?

6. Can you please comment on if or how you believe telemedicine supports cultural traditions/beliefs within Sioux Lookout region?

   Probes: If yes, does it incorporate traditional values? Means of communication? Respect for traditional aspects of healing? If no, what values is it failing to support? Can you explain how

it does not support these? How do you feel these should be addressed? Have there ever been a time where treatment regimen was prescribed that did not respect your values/norms/morals? If so, what do you feel the treatment regimen did not respect? Has there been a time where there was a potential misunderstanding due to cultural habits or the lack of provider knowledge regarding cultural habits? If so, how did this impact your experience with telemedicine? How could this be fixed?

7. What do you think needs to be added with the telemedicine service to support community traditions and beliefs?

   Probes: Do you think there are things that needed to be added into telemedicine services to better serve and respect patients and cultural beliefs? If so, what? How would you want to see these be incorporated? What would you want emphasized? What is important for you in a medical technology such as telemedicine?

8. Are there any other comments you wish to provide?

   Probe: Is there anything we missed today? Is there anything you wish to clarify?

APPENDIX N. Sioux Lookout Individual Interviews (HealthCare Providers/Agency Workers) Thematic Guide

Sioux Lookout – Individual Interview Thematic Guide (HealthCare Workers/Agency Workers)

We are looking to evaluate the cultural safety of HCV – care delivery-using telemedicine in Indigenous communities.

1. Can you please explain use your experience with telemedicine as a provider?

   Probes: Do you use telemedicine with patients? If yes, please explain how. What were your thoughts about this experience?

2. What do you think are possible **advantages** of using telemedicine services in Sioux Lookout region?

   Probes: What aspects of care do you think telemedicine improves? If so, why?

3. What do you think are possible **disadvantage** of using telemedicine services in Sioux Lookout region?

   Probes: Have you ever experienced any difficulty using telemedicine with patients? If yes, what were these? Have you ever felt as if telemedicine did not address external factors in your patient's lives including housing? Financial issues? Limited resources? Lack of family support? If yes, what were these and do you think you could better address them in an in-patient appointment?

4. What aspects of the current telemedicine program do you believe need to be improved at Sioux Lookout region?

   Probes: Do you feel there are needed improvements in Telemedicine-care delivery? If yes, what were they? How you do feel these can be improved from a provider's prospective?

5. Can you please comment on if or how you believe telemedicine supports cultural traditions/beliefs within Sioux Lookout region?

   Probes: If yes, does it incorporate traditional values of your patients? Means of communication for patients? Respect for traditional aspects of healing? If no, what values is it failing to support? Have patients ever raised concerns of these issues when using telemedicine? Can you explain how it does not support these? How do you feel these should be addressed from a provider's prospective?

6. What do you think needs to be added with the telemedicine service to support community traditions and beliefs? What about for providing care for individuals living with HCV?
   Probes: Do you think there are things that needed to be added into telemedicine services to better serve and respect patients and cultural beliefs? If so, what? How would you want to see these are incorporated? What would you want emphasized? What do you feel is important for you as a provider to ensure telemedicine works and respects the culture of your patients?

7. Are there any other comments you wish to provide?
   Probe: Is there anything we missed today? Is there anything you wish to clarify?