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Original article

Identifying gaps in the treatment of hepatitis C in patients co-infected with HIV in Edmonton, Alberta

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ABSTRACT

Introduction: With the availability of direct-acting antivirals, Hepatitis C (HCV) is now considered a treatable disease. Patients who are co-infected with human immunodeficiency virus (HIV) and HCV represent an ideal patient population to treat for HCV, as (1) patients are routinely taking medication for HIV, and therefore would be able to complete HCV drug regimens, and (2) HIV infection has been shown to increase HCV disease progression.
Objective: We sought to determine the occurrence of HCV co-infection among HIV patients in our provincial cohort, determine whether they received treatment for HCV, and identify currently viremic patients who can be linked to care.
Materials and methods: HCV laboratory testing data (HCV antibody and HCV RNA) and HCV medication dispensation data was collected for all HIV positive patients. Current and previous HCV infection and treatment was assessed. Chart reviews were conducted for HCV viremic patients to assess their HIV care and social determinants.
Results: Of the 2417 HIV positive patients, 392 (16.2%) were identified as being co-infected with HCV. 198 (50.5%) of the HIV-HCV co-infected patients received HCV treatment and 232 (59.2%) were not viremic on the most recent HCV RNA test. 99 (69.2%) had a suppressed HIV infection suggesting they are active in their HIV care and good candidates for HCV treatment.
Conclusion: Despite the availability of direct-acting antivirals, many patients who are co-infected with HIV and HCV are not being treated for HCV. Routine surveillance of HIV-HCV co-infected patients could improve HCV treatment rates in a high-risk population.
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1. Introduction

In Canada, it is estimated that 20% of human immunodeficiency virus (HIV) patients are co-infected with hepatitis C virus (HCV) [1]. HIV-HCV co-infection is of particular concern as it is associated with an elevated risk of severe liver disease compared to those with only HCV infection [2,3]. Due to the increased risk of disease severity and common risk factors for both infections, it is recommended in Canada that all HIV patients are screened for HCV [4].

The ability to leverage the HIV cascade of care for treatment of HIV-HCV co-infected individuals is key to reducing HCV infection in this population [5]. The co-infected population is particularly at risk due to increased barriers to access care. Fortunately, when treatment is accessed, co-infected individuals have equivalent cure rates to mono-infected patients [6,7].

The emergence of direct-acting antiviral (DAA) therapy for HCV has greatly improved the treatment of HCV compared to previously available treatments, pegylated interferon (pegIFN) and ribavirin

Abbreviations: NAHP, Northern Alberta HIV Program; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NAT, nucleic acid test; RNA, ribonucleic acid; DAAs, direct-acting antivirals; pegIFN, pegylated interferon; RBV, ribavirin; ProvLab, Public Health Laboratory; EIA, enzyme immunoassay; OUD, opioid use disorder.

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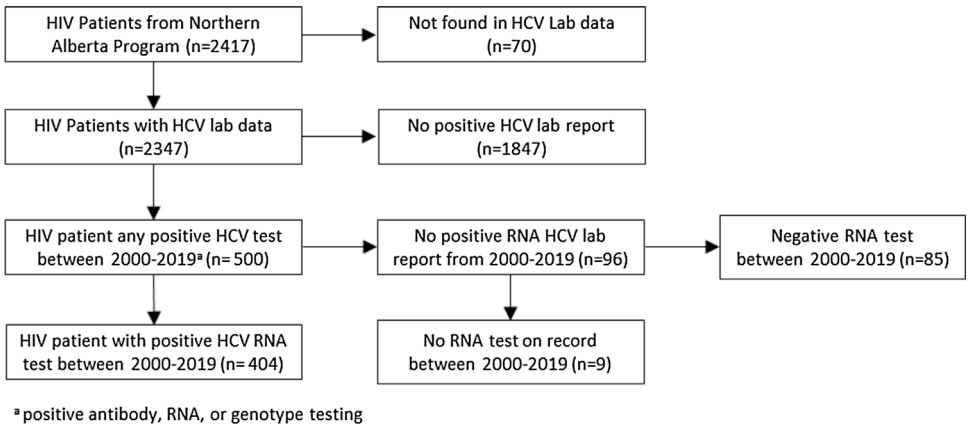

Fig. 1. Identification of the HIV-HCV co-infected cohort.
2417 patients in the Northern Alberta HIV Program were evaluated for the presence of an HIV-HCV co-infection. 404 patients were identified as having been HIV-HCV co-infected at some point between January 1, 2000 and December 31, 2019.

(RBV) [8]. DAA therapy has been available in Canada since 2012 for HCV patients and was included in Alberta's publicly funded drug program for patients who met specific clinical eligibility requirements [9]. In April 2018, Alberta changed these requirements and DAAs became available to all HCV infected individuals regardless of their liver fibrosis status. With the increased availability of DAAs, the Alberta Health Services' Northern Alberta HIV Program (NAHP), a program that provides care to those with HIV through assessment, treatment, and education, has made it a priority to assess the HCV status of all their HIV patients. All HCV coinfected patients are linked to HCV care where they can be prescribed DAAs. This effort aligns with the World Health Organization's goal to eliminate hepatitis by 2030 [10].

This study aimed to determine the current proportion of HCV co-infection and the level of HCV treatment among patients amongst the Northern Alberta HIV population. In addition, patients eligible for HCV treatment were identified so that their HIV care providers can be encouraged to provide appropriate HCV care and treatment.

2. Materials and methods

2.1. Study population

The study population was made up of all patients in care at the Northern Alberta HIV Program (NAHP) between 2010 and 2019. HCV laboratory results from January 1, 2000 to December 31, 2019 were obtained from the Public Health Laboratory (ProvLab) and used to identify which HIV patients were co-infected with HCV (Fig. 1). Patients identified as having been HIV-HCV co-infected who were deceased or had their care relocated to a different health authority were excluded from the study.

2.2. Definition of HCV infection and laboratory algorithms

HCV positive individuals were defined as serology positive and nucleic acid positive. A two-step algorithm for testing was employed: first an enzyme immunoassay (EIA) screen was performed for anti-HCV antibodies (anti-HCV, Architect, Abbott, Abbott Park, IL, USA), which was confirmed either with a second EIA (HCV ULTRA, BioRad, Hercules, CA, USA; between 2010 and December 12, 2019), or directly by nucleic acid testing (NAT; HCV Qualitative, Roche, Basel, Switzerland; after December 12, 2019). For those specimens that were confirmed with a second EIA, NAT (HCV ribonucleic acid (HCV RNA)) was performed using a subsequent sample (RealTime HCV, Abbott Molecular, Chicago, IL, USA).

2.3. Creation of database and original data sources

Patients from the NAHP were linked to their laboratory data using their Alberta personal health number (PHN). Laboratory data for these patients from January 1, 2000 to December 31, 2019 was collected from the ProvLab, this included all anti-HCV and HCV RNA tests. Basic demographic information including date of birth and sex were also collected from the ProvLab database (Table 1). For patients where no HCV laboratory data was identified, additional laboratory data dating back to 1997 was searched to identify potential instances of testing. Data on HCV drug dispensation between May 26, 2005 and December 12, 2019 were also linked to the NAHP patients using the Alberta Pharmaceutical Information Network (PIN) database.

2.4. HCV cascade of care and definition of SVR

Previously infected HCV patients were defined as having (1) anti-HCV positivity and (2) an RNA positive between January 1, 2000 and December 31, 2019. Currently infected patients were defined by the most recent RNA test: a positive RNA (any value greater than the limit of detection) indicated active infection and negative (not detected) RNA indicated cleared or treated infection (Fig. 1). PIN data were used to identify which patients had received HCV treatment. Patients were considered to have an active HCV infection if HCV RNA was detected at their most recent test and they were not currently on treatment for HCV. Patients were considered to have achieved sustained virologic response (SVR) if HCV RNA was not detected at least 12 weeks following completion of their treatment. A patient was said to have treatment failure if HCV RNA was detected at least 12 weeks following completion of their treatment. If a patient had achieved SVR but later had a test result where HCV RNA was detected they were considered to have been re-infected (Fig. 2).

2.5. Chart review for currently HIV-HCV co-infected patients

Patients who were identified as currently having an active HCV infection were further investigated by reviewing their chart information (Table 2). Additional data collection included aspartate transaminase (AST) to platelet ratio index (APRI) score, the use of antiretroviral therapy, HIV viral load, and information on particular social determinants such as opioid use disorder (OUD), heavy alcohol use, education, homelessness, and incarceration. A patient was flagged as having OUD if their chart indicated multiple prescriptions for opioid agonists and/or naloxone. This information

Table 1
Population demographics for HIV-HCV co-infected patients from the NAHP[a].

Characteristic	HIV-HCV Co-infected (n = 392)	Patients without active HCV infection (n = 232)	Patients with active HCV Infection (n = 143)	p-value
Sex			0.430[b]	
Male	266 (67.9)	160 (69.0)	93 (65.0)	
Female	126 (32.1)	72 (31.0)	50 (35.0)	
Age			<0.001[b]	
20–29	12 (3.1)	5 (2.2)	6 (4.2)	
30–39	44 (11.2)	18 (7.8)	21 (14.7)	
40–49	120 (30.6	56 (24.1)	61 (42.7)	
50–59	148 (37.8)	92 (39.7)	48 (33.6)	
60+	68 (17.4)	61 (26.3)	7 (4.9)	
Mean (SD)	50.5 (9.6)	52.8 (9.3)	47.3 (9.1)	<0.001[c]
Initial Diagnosis Year			<0.001[b]	
2000	22 (5.6)	15 (6.5)	6 (4.2)	
2001	24 (6.12)	17 (7.3)	7 (4.9)	
2002	29 (7.4)	25 (10.8)	3 (2.1)	
2003	23 (5.9)	16 (6.9)	6 (4.2)	
2004	26 (6.6)	22 (9.5)	4 (2.8)	
2005	21 (5.4)	16 (6.9)	5 (3.5)	
2006	23 (5.9)	15 (6.5)	8 (5.6)	
2007	29 (7.4)	14 (6.0)	14 (9.8)	
2008	18 (4.6)	13 (5.6)	5 (3.5)	
2009	29 (7.4)	14 (6.0)	14 (9.8)	
2010	15 (3.8)	10 (4.3)	5 (3.5)	
2011	15 (3.8)	7 (3.0)	8 (5.6)	
2012	14 (3.6)	4 (1.7)	8 (5.6)	
2013	12 (3.1)	7 (3.0)	3 (2.1)	
2014	21 (5.4)	8 (3.5)	11 (7.7)	
2015	15 (3.8)	11 (4.7)	4 (2.8)	
2016	14 (3.6)	6 (2.6)	8 (5.6)	
2017	17 (4.3)	5 (2.2)	11 (7.7)	
2018	21 (5.4)	7 (3.0)	11 (7.7)	
2019	4 (1.0)	–	2 (1.4)	

[a] Total HIV-HCV co-infected patients from the NAHP (n = 392), HIV-HCV co-infected patients who no longer have an active HCV infection (n = 232) and HIV-HCV co-infected patients with an active HCV infection (n = 143).
[b] Chi–square test.
[c] Wilcoxon rank-sum test.

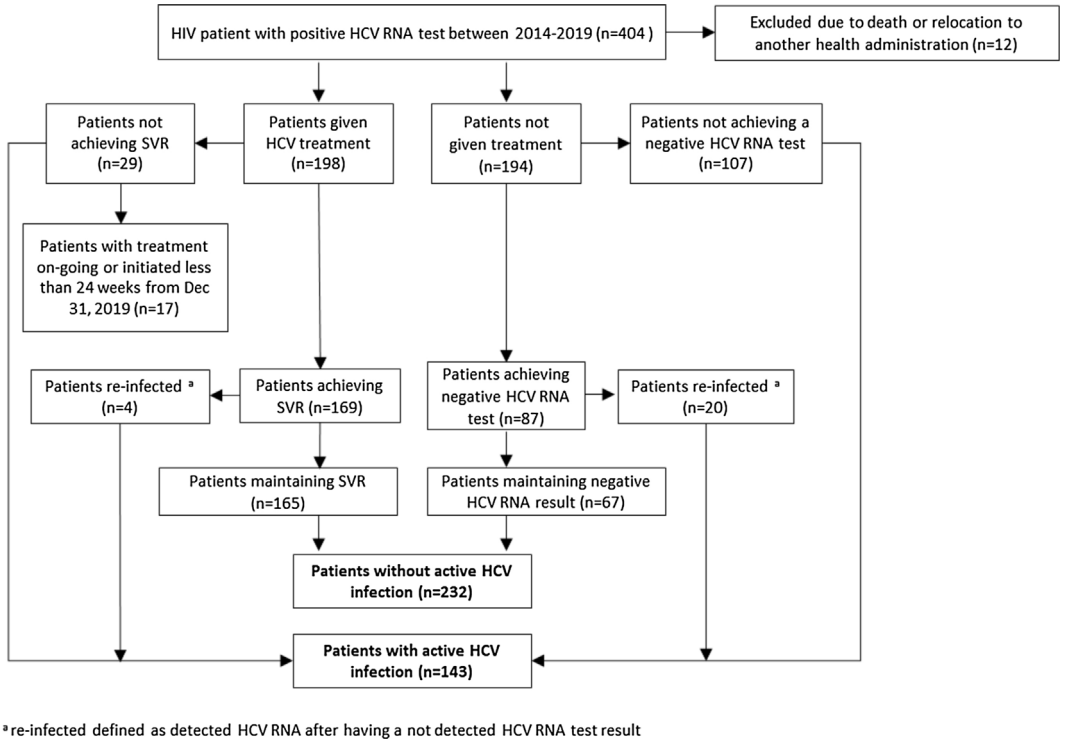

Fig. 2. Identification of HIV-HCV co-infected patients with active HCV infection.
404 HIV-HCV co-infected patients from the Northern Alberta HIV Program were assessed for the occurrence of HCV treatment as well as the current status of their HCV infection. 143 patients were found to currently have an active HIV-HCV co-infection.

Table 2
Characteristics of HIV-HCV co-infected patients from the NAHP with an active HCV infection (n = 143).

	Patients with Active Infection (n = 143) N (%)
APRI Score >1.5[a]	
Yes	8 (5.6)
No	109 (76.2)
Unknown	26 (18.2)
Failed HCV Treatment	2 (1.4)
ARV Therapy	126 (88.1)
HIV Viral Load <200 copies/mL	9 (69.2)
Opioid Use Disorder	125 (87.4)
Alcohol Use	20 (14.0)
Under-housed	23 (16.1)
Currently Incarcerated	103 (72.0)
Highest Education Level	
Incomplete High School	41 (28.7)
High School	12 (8.4)
Post-Secondary	6 (4.2)
Unknown	84 (58.7)
Ethnicity	
Black	2 (1.4)
Caucasian	43 (30.0)
Indigenous	85 (59.4)
Asian	1 (0.7)
Unknown	12 (8.4)

[a] Aspartate transaminase to platelet ratio index (APRI) score. An APRI score greater than 1.5 is an indicator of liver fibrosis.

was used to identify patients who are good candidates for future HCV treatment based on their ability to adhere to their HIV ARV therapy.

2.6. Statistical analysis

Patient characteristics were assessed using basic descriptive measures. Comparison of individual-level characteristics between those with HCV viremia and those no longer HCV viremic was done using chi–square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. The patient's age as of January 1, 2020 was used for the analysis. All analyses were conducted using STATA 15 (StataCorp. 2017. College Station, TX, USA).

2.7. Ethics

This study received ethics approval from the University of Alberta Health Research Ethics Board. Certification approval number is Pro00070515.

3. Results

In total, 2417 HIV positive patient records were examined. Of these, 404 (16.7%) were identified as having been co-infected with HCV at some point between January 1, 2000 and December 31, 2019. 12 of the HIV-HCV co-infected patients were excluded from additional analysis due to death or relocation. At the time of study 143 (35.4%) of the co-infected patients were currently viremic, 68% (n = 266) were male, and the mean age was 50.5 years (SD:9.6). Patients with HCV viremia (n = 143) were on average younger ($p < 0.001$) than patients who were no longer viremic for HCV (Table 1).

Of the 392 HIV-HCV co-infected patients, 198 (50.5%) received treatment for HCV. 29 (14.6%) patients received treatment, but did not achieve SVR. Of those, 17 (58.6%) were currently on treatment, or their treatment had ended less than 12 weeks from December 31, 2019 and therefore, SVR had yet to be determined (Fig. 2). Of the remaining 12 patients who did not achieve SVR, one received treatment in another province, and one did not complete their treatment regimen. The reason for the remaining 10 patients to not achieve SVR was unknown; no resistance testing was available. Of the treated patients who had sufficient time to achieve SVR (n = 181), 93.4% (n = 169) achieved SVR, while 4 of these patients later became re-infected (Fig. 2).

194 (49.5%) co-infected patients were identified as not having received HCV treatment. Of these, laboratory data indicate that 87 (44.8%) had a negative RNA HCV test following their initial positive RNA test and 67 (77.0%) of these patients remained HCV RNA negative at their most recent test date, suggesting a proportion of the patients who did not receive HCV treatment were not viremic at their most recent HCV RNA test despite not having any treatment on record (Fig. 2).

In total, 63.5% (n = 249) of the HIV-HCV co-infected patients were considered to no longer have an active HCV infection based on their most recent HCV RNA laboratory results or the fact that they were currently undergoing treatment.

3.1. HCV RNA positive cases

Chart reviews of the 143 patients with an active HCV infection found that 126 (88.1%) of these patients were on ARV therapy and 99 (69.2%) had an HIV viral load less than 200 copies/mL. 87.4% (n = 125) of the patients with an active HCV infection were identified as having opioid use disorder (OUD; Table 2). The majority of the patients with an active infection were either incarcerated (72.0%, n = 103) or identified as being under-housed (16.1%, n = 23). A large proportion of the patients with an active infection were identified as Indigenous, 59.4% (n = 85; Table 2).

4. Discussion

Our study found that of the 2417 HIV-positive patients examined, 97% were tested for HCV at some point during their care and 16.7% were HIV-HCV co-infected. Our proportion of co-infection was slightly lower than the estimated 20% prevalence of HCV co-infection among HIV patients in Canada in 2007 [1]. Injection drug use (IDU) as the transmission source for HIV has decreased in Alberta over the past few decades likely due to increased harm reduction interventions [11,12]. As the level of diagnostic screening has previously been identified as a gap in HCV treatment cascades [5], the high level of HCV screening in our HIV positive population is encouraging as it indicates appropriate patient management, and follows the World Health Organizations recommendation that all persons living with HIV be screened for HCV (WHO report) [13]. The number of first-time positive HCV diagnoses among HIV patients was lower in the years 2010–2019 compared to the years 2000–2009. This decrease in HCV diagnoses among HIV patient is likely due to increased HCV prevention efforts.

In our study, only half of HIV-HCV co-infected patients had received treatment for HCV. While underwhelming, this is better than the HCV cascade of care among the general population in both Alberta [14] and British Columbia, Canada [15,16]. HCV treatment among HIV positive patients is higher than the general population, as previous studies found just 12% of Albertans with HCV were prescribed DAAs with 3.4% being cured within 2 years of diagnosis and only 26% of British Columbians with chronic HCV were assessed for treatment [14,17]. Studies among Canadian HIV-HCV co-infected patients have also identified low rates of treatment initiation with just 21–48 % of HIV-HCV co-infected patients initiating HCV care [18,19]. While HIV patients are more often linked to HCV care than the general population, this remains an area for improvement. For

Alberta to reach the global goal of HCV elimination by 2030, rates of HCV treatment among HIV infected individuals will need to be significantly improved. In recent years, Alberta has made DAAs a part of their publicly funded provincial drug plan and reduced the eligibility restrictions so cost and eligibility should no longer be significant barriers to treatment. Both the availability of DAAs and the cost have previously been identified as gaps in HCV treatment. Particularly, this is seen in the US, where patients insured under state Medicaid were negatively associated with HCV treatment initiation [20]. As the cost of HCV drug regimens is now publicly funded, the noted discrepancy seen in our study between the number of patients with active HCV infection and those being treated, may be due to other factors including the difficulty of retaining patients in care, and having patients invested in their treatment.

Nearly 90% of HIV-HCV co-infected individuals in our study were on HIV ARV therapy (nearly 70% of them with suppressed viral load), which shows success in their HIV care, and an ability to complete an 8–12 week course of HCV treatment. As a follow-up to this study, the study investigators will be contacting the HIV-treating physicians of the HIV patients with an active HCV infection to ensure they are aware of their patient's HCV status and encourage them to refer these patients to HCV care, or treat HCV themselves, if it is within their scope of practice.

A large proportion of those who have an active HCV infection were identified as having OUD. Additional data from those who did receive HCV treatment are required to determine if this is a characteristic unique to those who have not been treated or if it is simply a result of OUD being a risk factor for HCV. Additional social determinants data should be collected for both those who have been and have not been treated to better identify correlates associated with not having HCV treatment. This would be beneficial in identifying trends among those who have not been treated which could have implications for future interventions aimed at ensuring all HCV patients are treated to achieve the goal of HCV elimination.

There are a few limitations to this study. First, there were patients within the NAHP HIV-positive population who did not have available HCV laboratory test data, this may be due to anonymous testing, not being an Alberta resident (and therefore not having an Alberta PHN to link their laboratory data), or being tested outside of Alberta. There was also a significant portion of patients who were identified as never receiving treatment yet were no longer viremic for HCV. It is possible that these patients received treatment in a setting not captured by the Alberta PIN database such as a federal corrections center, in an investigational drug-trial, or experienced spontaneous clearance. Spontaneous clearance generally occurs in approximately 25% of infected individuals, usually within 6 months of infection; however, this rate is even lower in individuals with HIV-HCV co-infection so it likely does not account for a significant portion of these cases [21,22]. The second limitation is that neither additional HIV care nor social determinant information for HIV-HCV co-infected individuals was collected, therefore comparisons of treated vs. not treated could not be made. The final limitation of this study is that we could not assess whether untreated patients had ever been offered and refused treatment or if they were assessed and determined not to be a candidate for treatment before the changes in eligibility criteria. This means that it is difficult to determine if the gap between positive HCV RNA test results and treatment is due to a failure of the care providers to offer treatment or patient-associated factors. While it is likely a combination of both, it would be beneficial to understand how many patients are refusing treatment, and why, as this would indicate a need for additional outreach efforts to identify the reasons for such refusal, and educate these individuals to encourage reconsideration.

5. Conclusions

Despite the availability of direct-acting antivirals, many patients who are co-infected with HIV and HCV are not being treated for HCV. This study highlights that routine surveillance of HIV-HCV co-infected patients could improve HCV treatment rates in a population who is at high risk for rapid HCV disease progression. We found that many of the currently HCV viremic patients were active in their HIV care (with suppressed HIV viral loads), suggesting that most patients could be reached, linked to HCV care, and be successfully treated.

Conflict of interest

The authors have no conflicts of interest to declare.

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