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Research paper

Variation in hepatitis C virus treatment uptake between Canadian centres in the era of direct-acting antivirals

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ABSTRACT

Background: Patients co-infected with HIV and hepatitis C virus (HCV) are a priority target for HCV treatment. The simplicity and efficacy of direct-acting antivirals (DAA) should help overcome patient, provider, and structural barriers to scaling up treatment.

Methods: We estimated between-centre variation in DAA treatment uptake among 1734 patients enrolled at the 18 centres of the Canadian Co-Infection Cohort—a prospective cohort of adults co-infected with HIV and HCV. We then compared this variation to that observed during the interferon era. Time to treatment uptake was modeled using a Weibull time-to-event model adjusting for centre and patient characteristics thought to have an impact on treatment initiation in the DAA era.

Results: At the time of administrative censoring (December 31, 2016), 981 cohort participants were eligible for second-generation DAA therapy (HCV RNA positive after November 21, 2013) of whom 278 initiated DAAs (16 patients per 100 person-years). Patients with low monthly income, Indigenous ethnicity, recent injection drug use, HCV genotype 3, or unknown HCV genotype were less likely to start treatment. After adjusting for patient characteristics, the estimated between-centre variance (σ^2) was 0.29 (95% credible interval [CrI]: 0.09-0.89), considerably lower than during the interferon era (σ^2 = 0.87, 95% CrI: 0.49–1.5). This between-centre variance was further reduced by the addition of centre-level effects for jurisdiction (σ^2 = 0.15, 95% CrI: 0.02-0.60).

Conclusion: Much of the variation in treatment uptake between centres can now be attributed to regional differences. This suggests that after the introduction of DAAs, treatment barriers have shifted towards prescribing and reimbursement restrictions based on liver fibrosis, which vary by jurisdiction. The removal of these restrictions, however, will need to be paired with strategies to overcome patient-level barriers, which continue to prevent marginalized people and active substance users from accessing treatment.

Introduction

People co-infected with hepatitis C virus (HCV) and HIV represent a priority group to target for HCV elimination efforts. Co-infection increases progression to cirrhosis, end-stage liver disease, and liver cancer, the primary causes of death among co-infected persons (Klein et al., 2014), and successful treatment improves these health outcomes (Rein, Wittenborn, Smith, Liffmann, & Ward, 2015). Injection drug use,

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a pathway for infection common to both viruses, continues to drive incident cases of HCV, especially when there is poor access to harm-reduction services. HCV infections also occur through sexual transmission among HIV-positive men who have sex with men (MSM) and may now be involving HIV-negative MSM (Richardson, Fisher, &, Sabin, 2008; Charre et al., 2018; Boerekamps, Wouters et al., 2018; McFaul et al., 2015). Epidemiologic studies have also identified HIV infection to be a biologic risk factor for the transmission and acquisition of HCV independently of behavioural risk factors (Taylor, Swan, & Mayer, 2012). Elimination of HCV among HIV-infected persons therefore represents a prerequisite to reaching HCV elimination goals more broadly.

Because of their HIV infection, co-infected patients are more likely to be tested for HCV and linked to care, which are important first steps in the care cascade for HCV treatment (Cachay et al., 2014; Sacks-Davis et al., 2018). In a recent review, more than 50% of diagnosed co-infected patients have been linked to care worldwide—much higher linkage rates than seen in HCV mono-infection (Sacks-Davis et al., 2018). Despite this, historically, treatment rates have been very low in co-infected populations (Mehta et al., 2006; Fleming, Craven, Thornton, Tumilty, & Nunes, 2003; Grebely et al., 2008). The complexity and need for specialized expertise, poor tolerability, and lack of effectiveness of interferon-based regimens have been important factors preventing wider treatment uptake (Myers, Ramji, Bilodeau, Wong, & Feld, 2012). We found that, in the interferon era, providers had diverse opinions about treatment eligibility and that treatment uptake was highly variable between treatment centres (Young et al., 2013). Clinicians were divided on whether or not to offer treatment to those consuming drugs or alcohol, having psychiatric comorbidities, and those with a history of re-infection with HCV.

Understanding patient, provider, and structural barriers to treatment in the DAA era is important because eliminating HCV in co-infected populations requires wider treatment uptake. These barriers should lessen with the ease of use and improved effectiveness of DAAs. Patients once considered difficult to treat, such as those co-infected with HIV and substance users, achieve high cure rates, both in clinical trials (Wyles et al., 2015; Sulkowski et al., 2015; Dore et al., 2016; Grebely et al., 2018) and in real-world studies (Sogni et al., 2016; Ingiliz et al., 2016; Berenguer et al., 2018). However, people living with HIV − HCV co-infection are often marginalized, stigmatized, and have competing priorities (e.g., active injection drug use, food insecurity) that may continue to be barriers to treatment in the DAA era (Cox et al., 2017; Wansom et al., 2017). Such patients may have difficulty remaining engaged in care.

An additional barrier unique to DAAs is their high cost, which has led to the imposition of prescribing and reimbursement restrictions based on clinical and behavioural criteria (Barua et al., 2015; Marshall et al., 2018). Recent pricing agreements and generics have allowed many countries to offer greater access to DAAs, which might allow for more widespread treatment in the absence of additional barriers (Andrieux-Meyer, Cohn, de Araújo, & Hamid, 2015; Hajarizadeh, Grebely, Matthews, Martinello, & Dore, 2017). Indeed, rates of HCV treatment have increased substantially in Canada since the introduction of DAAs (Saeed et al., 2017). However, within Canada there are regional differences in reimbursement criteria, based on liver fibrosis levels, which may impact treatment uptake (Marshall et al., 2016).

The objectives of this study were to: 1) estimate the residual variation in second-generation DAA treatment uptake in HIV − HCV co-infected patients across treatment centres in the Canadian Co-Infection Cohort after taking into account patient characteristics and region; and 2) compare the variation in DAA uptake with what was observed in the Cohort during the interferon era. We hypothesized that, after accounting for regional variation, treatment uptake in the DAA era would vary less by centre than during the interferon era.

Materials and methods

The Canadian Co-infection Cohort, established in 2003, is a prospective, multicentre cohort of HIV-positive adults with evidence of HCV infection (HCV antibody positive) enrolled from 18 HIV clinical care sites across Canada (Klein et al., 2010). Participating centres include tertiary care centres, community-based primary care clinics, and street outreach programs in Alberta, British Columbia, Ontario, Nova Scotia, Quebec, and Saskatchewan (Appendix A, Table 1). Enrolled patients, having given informed consent, were scheduled for visits every six months after the baseline assessment. Patient socio-demographic and behavioural characteristics were self-reported during the scheduled visits using standardized questionnaires, and blood specimens were collected for biochemical, hematologic, virologic, and immunologic analyses. HCV RNA was performed semi-annually for all participants as part of the study protocol. HCV treatment information was collected using standardized case report forms. The Canadian HIV Trials Network Community advisory committee and the institutional ethics boards of all participating centres have approved the use of data collected from cohort participants for research purposes.

Patient selection

The focus of this study was access to HCV treatment with second-generation DAAs, the first of which (simeprevir) was approved by Health Canada on November 21, 2013. Hence, only patients who were chronically infected (HCV RNA positive) on or after this date were selected for this study. Patients were excluded if they met any of the following criteria prior to November 21, 2013: 1) death, formal withdrawal from the cohort, or loss to follow-up (no visits for more than 1.5 years) or 2) prior use of a second-generation DAA (e.g., through participation in a clinical trial). Centres that recruited fewer than 15 participants were excluded due to the difficulty in estimating treatment rates for such small centres.

Second-generation DAAs were defined as any regimen approved by Health Canada during the study period (including those with pegylated interferon) containing at least one of the following: simeprevir, sofosbuvir, ledipasvir, velpatasvir, ombitasvir/paritaprevir/ritonavir, daclatasvir, grazoprevir, or elbasvir. Treatment could be open label or through a clinical trial.

Study design

Eligible patients were followed from November 21, 2013 or, if enrolled after that date, from the time of enrollment (index date). Study follow-up continued until they started a first second-generation DAA, or until they were censored for one of the following reasons: 1) spontaneous clearance of HCV infection (at least two consecutive tests more than six months apart where HCV RNA was undetectable without treatment), 2) death, 3) withdrawal from the cohort, 4) switching of study centres, 5) loss to follow-up, 6) starting an HCV treatment regimen that did not contain a second-generation DAA, or 7) the end of the study (administrative censoring on December 31, 2016). The exposure of interest was the centre where the patient was enrolled.

Statistical analysis

The time to HCV treatment initiation with a second-generation DAA was modeled using a Weibull time-to-event model with a normally distributed random effect for each cohort centre (as in Young et al., 2013). The variation between these centre effects gave an estimate of the residual variation in treatment uptake between centres after adjusting for patient characteristics. Centre effects were also ranked to illustrate the success of each centre in starting a reference patient on

treatment (a patient for whom all patient-level covariates took the value zero). To adjust for patient characteristics (and create this reference patient), the model included *a priori* selected patient-level covariates thought to have an impact on treatment initiation in the DAA era. All covariates were measured at the cohort visit closest to the index date. The following patient-level covariates were adjusted for: age (centered at 40), sex, Indigenous ethnicity, MSM, history of injection drug use (IDU), recent IDU within the past six months, recent alcohol consumption within the past six months, monthly income (≤ 1500 CAD), advanced liver fibrosis (based on an aspartate-to-platelet ratio index [APRI] greater than 1.5 at any time prior to the index date), undetectable HIV viral load (≤ 50 copies/ml), HCV genotype 3, and unknown HCV genotype.

Centre-level covariates such as region (i.e., province) and level of care (i.e., primary vs. tertiary centre) were included in subsequent analyses. When adjusting for province, British Columbia was used as the reference with individual indicators for Saskatchewan and Quebec, and a combined indicator for Alberta and Ontario. This reflects the regional differences in criteria for access to, and reimbursement of, DAA therapies for co-infected patients during the study period. Specifically, reimbursement criteria based on the level of liver fibrosis varied across provinces with Quebec having the most liberal policies (Marshall et al., 2016).

Finally, we compared our results to those we published during the interferon era. To do this we estimated an additional model where we substituted the covariates chosen for this study with the covariates used previously (Young et al., 2013).

We fitted this proportional hazards model using WinBUGS (Lunn, Thomas, Best, & Spiegelhalter, 2000), a Bayesian approach, because this allowed us to include both patient-level and centre-level covariates in the model (Stefanescu and Turnbull, 2006). We used uninformative prior distributions for all model parameters: prior distributions for covariate effects were specified as normal, centered at zero, with large variances, while prior distributions for centre effects were specified as normal, centered at zero, with a wide uniform distribution (i.e., over the range 0–1000) for its standard deviation (Gelman et al., 2003; Gelman, 2006).

Sensitivity analysis

Sensitivity analyses included the following variations on the base model: 1) censoring patient follow-up when a patient started either an unapproved treatment or was treated within a clinical trial; 2) adding a patient-level covariate for previous unsuccessful HCV treatment; 3) adjusting follow-up time for those patients lost to follow-up; and 4) using weakly informative priors rather than uninformative priors to improve precision in estimates. These sensitivity analyses are described in detail in Appendix A.

Results

Among 1734 patients enrolled in the cohort at the time of administrative censoring, 981 met all eligibility criteria (Fig. 1). During a follow-up of 1776 person-years, 278 patients started a second-generation DAA (16 patients per 100 person-years). The regimens started (with or without ribavirin) were ledipasvir/sofosbuvir (n = 172), sofosbuvir (n = 28), paritaprevir/ritonavir/ombitasvir/dasabuvir (n = 19), simeprevir/sofosbuvir (n = 16), sofosbuvir with pegylated interferon (n = 11), daclatasvir/sofosbuvir (n = 8), elabasvir/grazoprevir (n = 7), daclatasvir with interferon-lambda (n = 3), daclatasvir with pegylated interferon (n = 2), sofosbuvir/velpatasvir (n = 1), simeprevir with pegylated interferon (n = 1), and 10 blinded or partially-blinded regimens initiated through DAA clinical trials. The remaining patients were censored due to spontaneous clearance of HCV infection (n = 9), death (n = 35), formal withdrawal from the cohort (n = 12), switching study centres (n = 1), loss to follow-up (n = 168), initiation

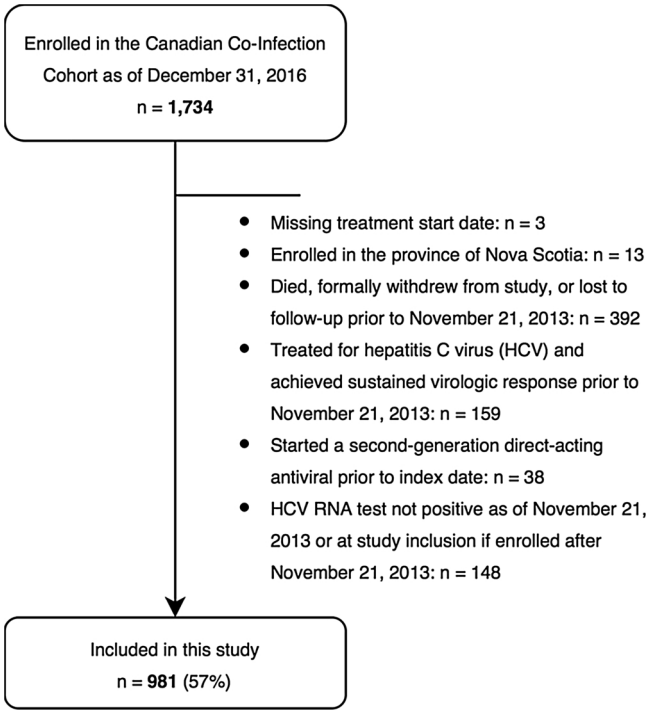

Fig. 1. Patient selection flow chart.

of an HCV treatment regimen that did not contain a second-generation DAA (n = 17), and administrative censoring (n = 461). Those lost to followup were less likely to be on antiretrovirals and more likely to have a diagnosis of end stage liver disease than those administratively censored (Appendix A, Table 3).

Compared to patients who remained untreated, patients starting treatment with second-generation DAAs were slightly older, were less likely to be female or of Indigenous ethnicity; less likely to report recent use of either injection drugs or opiate substitution therapy (OST); and more likely to have an undetectable HIV viral load (Table 1). Patients who started treatment had higher APRI scores and were more likely to have been previously diagnosed with end-stage liver disease or to have been previously treated during the interferon era. Among those not treated, 18% had unknown HCV genotype.

Multivariate analysis

Treatment uptake was more likely (hazard ratio > 1) in patients with the following patient-level characteristics: older age, MSM, advanced liver fibrosis, and undetectable HIV viral load (Table 2). In contrast, patients with low monthly income, Indigenous ethnicity, recent injection drug use, HCV genotype 3, or unknown HCV genotype were less likely to start treatment. In sensitivity analyses, the point estimates and credible intervals of the covariate effects were consistent across all model specifications (Table 2; Appendix A, Tables 2 and 4). Hazard ratios for treatment uptake in the 17 centres ranged between 0.4 (95% credible interval [CrI]: 0.2-0.8) and 2.2 (95% CrI: 1.2–4.1) for the centres least and most likely to treat patients, respectively (data not shown). These effects were similar in magnitude to the hazard ratios for the covariate effects, which ranged between 0.2 and 2.6 (Table 2).

Adjusting for patient characteristics, the estimated between-centre variance (σ^2) was 0.29 (95% CrI: 0.09-0.89). The between-centre variance was noticeably reduced by the addition of centre-level fixed effects for the provinces (σ^2 = 0.15, 95% CrI: 0.02-0.60). Apart from this change, the point estimates and credible intervals of the between-centre variance were consistent across sensitivity analyses (Table 2; Appendix A, Tables 2 and 4).

Table 1
Baseline characteristics of the Canadian Co-infection Cohort participants who started direct-acting antiviral treatment during follow-up compared to those who did not.

Patient characteristic at beginning of study follow-up [a]	Started DAA during follow-up n = 278	Did not start DAA during follow-up n = 703
Age (years), median (Q1 ; Q3)	51 (46 ; 55)	47 (39 ; 53)
Female	23%	34%
Indigenous	8%	36%
MSM	33%	16%
History of IDU	74%	88%
Recent IDU	41%	58%
History of opiate substitution therapy [b]	9%	19%
Recent opiate substitution therapy	3%	10%
Recent alcohol consumption	56%	56%
Recent alcohol abuse	19%	13%
HCV duration (years), median (Q1 ; Q3)	16 (10 ; 21)	12 (6 ; 18)
HCV viral load (log_{10}), median (Q1 ; Q3)	6.1 (5.5 ; 6.6)	5.9 (5.0 ; 6.5)
HCV genotype	–	–
Genotype 1	79%	60%
Genotype 2	5%	4%
Genotype 3	12%	16%
Genotype 4	3%	1%
Genotype unknown	2%	18%
APRI > 1.5 [c]	42%	24%
Prior diagnosis of end-stage liver disease [d]	25%	9%
Previous HCV treatment	26%	12%
HIV duration (years), median (Q1 ; Q3)	17 (11 ; 23)	12 (6 ; 19)
On ART	95%	79%
HIV viral load ≤ 50 copies/ml	88%	67%
CD4 cell count, median (Q1 ; Q3)	480 (290 ; 650)	450 (280 ; 660)
Income ≤ 1500 CAD	72%	79%
Province	–	–
Alberta	1%	2%
British Columbia	24%	29%
Ontario	27%	23%
Quebec	46%	22%
Saskatchewan	1%	24%

APRI = aspartate-to-platelet ratio index, HCV = hepatitis C virus, DAA = direct-acting antivirals, CAD = Canadian dollars, MSM = males who have sex with males, IDU = injection drug use, Q1 = first quartile of distribution, Q3 = third quartile of distribution.

[a] Measured at the cohort visit closest to the beginning of study follow-up. Recent IDU, opiate substitution therapy, and alcohol consumption were patient reported behaviour in the 6 months prior to this cohort visit.

[b] History of methadone for addiction therapy was patient reported participation in a methadone program for drug addiction therapy any time during cohort follow-up (prior to start of study follow-up) or during the 6 months prior to cohort enrollment.

[c] As measured at any time prior to the beginning of study follow-up.

[d] Diagnosis of ascites, cirrhosis, portal hypertension, spontaneous bacterial peritonitis, encephalopathy, esophageal varices, hepatocellular carcinoma, or hepatorenal syndrome at any time prior to the beginning of study follow-up.

There was substantial uncertainty in estimates of centre effects and consequently in the rankings of centres with respect to their success at starting patients on treatment (Fig. 2). This uncertainty remained after adjustment for regional differences (Appendix A, Fig. 1). Nevertheless, patients treated at centres in Quebec were more likely to start treatment than those treated at centres in other provinces.

Comparing the DAA era with the interferon era

Differences are apparent when comparing results from the DAA era to those previously published for the interferon era. First, treatment uptake was lower in the interferon era (9 per 100 person-years) compared to the DAA era (16 per 100 person-years).

Second, in the interferon era, age was not associated with starting treatment, and women and patients with a longer duration of HCV infection were less likely to start treatment. In the DAA era, older patients, those with a longer duration of infection, and those on antiretroviral therapy were more likely to start treatment, while homeless patients were less likely to start treatment (Table 3). Patients with genotypes 2 and 3 were more likely to start treatment in the interferon era, while patients with genotype 3 were less likely to start treatment in the DAA era. However, in both eras, Indigenous patients and those with a history of crack or cocaine use were less likely to start treatment.

Third, after adjusting for patient characteristics, the between-centre variance was higher in the interferon era ($\sigma^2 = 0.87$, 95% CrI: 0.49–1.5) than in the DAA era ($\sigma^2 = 0.29$, 95% CrI: 0.09-0.89) as expected. In the interferon era, this variance remained high after adjusting for province ($\sigma^2 = 0.88$, 95% CrI: 0.44–1.6), but was reduced by this adjustment in the DAA era ($\sigma^2 = 0.15$, 95% CrI: 0.02-0.60). Note that this variance increased in the DAA era when estimated using interferon-era covariates ($\sigma^2 = 0.43$, 95% CrI: 0.16–1.24), and this illustrates that the choice of covariates is important when estimating the residual variation (Table 3).

Discussion

In the era of safe, effective, oral HCV treatments, we found that treatment uptake has increased substantially compared to the interferon era. Variation in treatment uptake between treatment centres has been reduced by approximately 70%, which suggests a more uniform approach to treatment across centres. This likely reflects the relative ease of using DAAs compared with interferon-based therapies and the general acceptance of the efficacy and benefits of treating co-infected persons for HCV with these medications. Variation between centres was further reduced when adjusting for province, which suggests regional differences in treatment access policies are now among the most important barriers to wider treatment uptake. Finally, the increases in treatment uptake we have observed belie the fact that there are still people being left behind. Recent substance users, Indigenous persons and, more broadly, those with lower socio-economic status all remained less likely to be treated in the DAA era.

Reaching the World Health Organization (WHO) elimination targets (90% reduction in new HCV infections and 65% reduction in mortality related to HCV) (World Health Organization, 2016) will require considerable scale up in HCV treatment, which will have to reach all populations affected. In particular, scale up in treatment will have to be aimed at those at risk of ongoing transmission (e.g., younger injection drug users with early fibrosis stage), those with advanced disease at imminent risk for liver related complications and death (Grebely, Matthews, Lloyd, & Dore, 2013), and those co-infected with HIV. All of those groups have traditionally failed to access treatment. A fundamental principle underpinning the WHO response to viral hepatitis, therefore, is the promotion of equity in health care. To increase treatment and reduce the burden of disease among key populations at risk for HCV, human-rights issues such as stigma, discrimination, social exclusion and poor access to services must be addressed.

Guidelines reflect these changing priorities and now recommend that all HIV − HCV co-infected patients be offered treatment, including people who inject drugs, irrespective of liver fibrosis stage (World Health Organization, 2016; American Association for the Study of the Liver & Infectious Disease Society of America, 2016; European Association for the Study of the Liver, 2017). Despite these guidelines, jurisdictional policies may lag and impede wider treatment uptake. The high cost of DAA treatments has led to the imposition, globally, of restrictions to reimbursement linked to liver fibrosis stage, health care provider type, and patient behaviour (e.g., substance use). As in many developed countries such as the United States or European countries, Canada has, until recently, imposed reimbursement restrictions linked to fibrosis stage for DAA prescriptions in order to contain the cost of treatment (e.g., limiting treatment to those with liver fibrosis stage ≥ F2) in all provinces except for Quebec (Marshall et al., 2016). About a third of Canadian provinces restricted prescriptions to specialists while

Table 2
Multivariate Weibull time-to-event model for direct-acting antiviral treatment uptake in the Canadian Co-infection Cohort during follow-up (n = 981).

	Hazard ratio (95% credible interval)		
Covariate at beginning of study follow-up [a]	Base model	Model with provinces	Model with level of care
Age (per 10 years)	1.2 (1.0 - 1.4)	1.2 (1.0 - 1.3)	1.2 (1.0 - 1.4)
Female	1.0 (0.7 ; 1.4)	1.0 (0.7 ; 1.4)	1.0 (0.7 ; 1.4)
Indigenous	0.5 (0.3 ; 0.8)	0.6 (0.3 ; 0.9)	0.5 (0.3 ; 0.8)
MSM	1.4 (1.0 ; 1.9)	1.5 (1.0 ; 2.0)	1.4 (1.0 ; 1.9)
History of IDU (but not recent)	0.9 (0.6 ; 1.3)	0.9 (0.6 ; 1.3)	0.9 (0.6 ; 1.3)
Recent IDU	0.7 (0.5 ; 1.0)	0.7 (0.5 ; 1.0)	0.7 (0.5 ; 1.1)
Recent alcohol consumption	0.9 (0.7 ; 1.1)	0.9 (0.7 ; 1.1)	0.9 (0.7 ; 1.1)
HCV genotype 3	0.7 (0.5 ; 1.0)	0.7 (0.5 ; 1.0)	0.7 (0.5 ; 1.0)
HCV genotype unknown	0.2 (0.1 ; 0.4)	0.2 (0.1 ; 0.4)	0.2 (0.1 ; 0.4)
APRI > 1.5 [b]	1.9 (1.5 ; 2.5)	1.9 (1.5 ; 2.4)	1.9 (1.5 ; 2.5)
HIV viral load ≤ 50 copies/ml	2.6 (1.8 ; 3.8)	2.5 (1.7 ; 3.7)	2.6 (1.8 ; 3.9)
Monthly income ≤ 1500 CAD	0.8 (0.6 ; 1.0)	0.8 (0.6 ; 1.0)	0.8 (0.6 ; 1.1)
Province (reference = British Columbia)	–	–	–
Saskatchewan	–	0.2 (0.1 ; 0.8)	–
Quebec	–	1.6 (0.8 ; 3.3)	–
Alberta and Ontario	–	0.8 (0.4 ; 1.6)	–
Primary care centre	–	–	0.6 (0.3 ; 1.3)
Estimated variance component			
Between-centre variance	0.29 (0.09 ; 0.89)	0.15 (0.02 ; 0.60)	0.25 (0.06 ; 0.86)

APRI = aspartate-to-platelet ratio index, HCV = hepatitis C virus, CAD = Canadian dollars, MSM = males who have sex with males, IDU = injection drug use.
[a] Measured at the cohort visit closest to the beginning of study follow-up. Age was centered at 40 years to create a reference patient. Recent IDU and alcohol consumption were patient reported behaviour in the 6 months prior to this cohort visit.
[b] As measured at any time prior to the beginning of study follow-up.

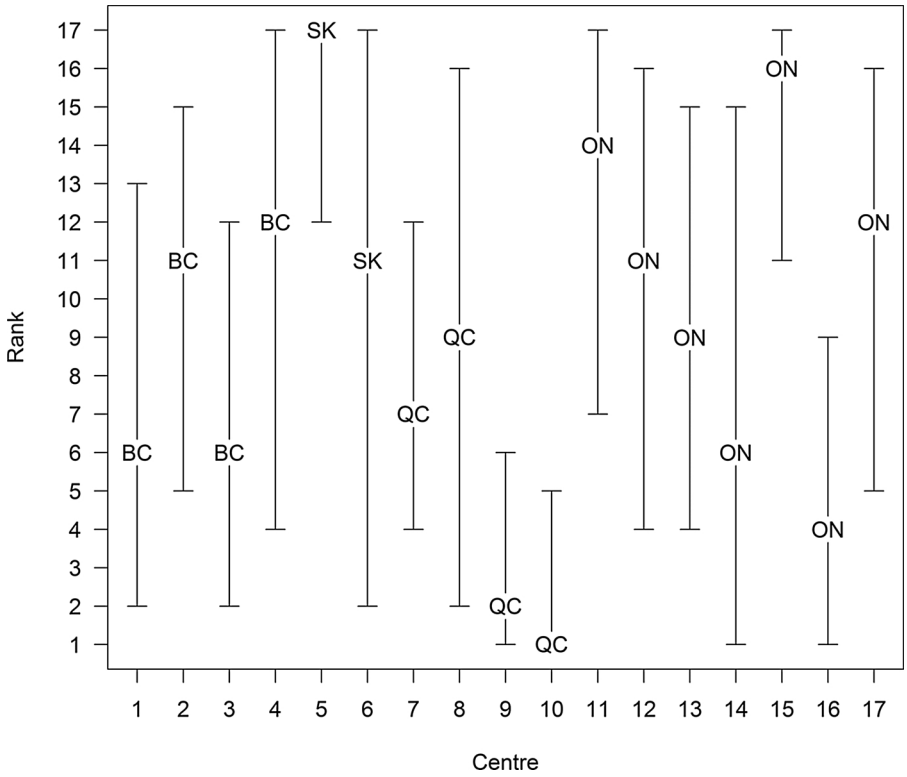

Fig. 2. Median centre ranks (with 95% credible intervals) for all 17 cohort centres included in the study. Ranks represent how successful (low rank best) centres were at starting patients on second-generation direct-acting antivirals during follow-up. Note: BC = British Columbia, SK = Saskatchewan, QC = Quebec, ON = Ontario and Alberta.

there were no restrictions related to alcohol or drug consumption (Marshall et al., 2016). In March 2017, the pan-Canadian Pharmaceutical Alliance secured a new pricing agreement with leading pharmaceutical companies making DAAs more affordable for public health plans in Canada (Government of British Columbia, 2017). Lower prices have allowed the removal of fibrosis restrictions in 2018 and should lead to the increased uptake and the broader public health benefits seen in other countries (Canadian AIDS Treatment Information Exchange, 2018; Government of British Columbia, 2018; Government of Prince Edward Island, 2018; Ontario Public Drug Programs, 2018). However, during this study's observation period, fibrosis restrictions were in place in all participating provinces, with the exception of Quebec. As a consequence, in our cohort, there has been a notable shift in the DAA era, to treating older patients with advanced liver disease. Warehousing of patients for whom interferon was not considered safe or effective and for whom treatment is now considered urgent most likely contributed

Table 3
Multivariate Weibull time-to-event model for treatment uptake in the Canadian Co-infection Cohort during follow-up – direct-activing antiviral era (n = 981) versus interferon era (n = 669).

Covariate at beginning of study follow-up [a]	Hazard ratio (95% credible interval)		
	Base model with DAA era covariates	Base model with interferon era covariates	Previously published (Young et al., 2013) (interferon era)
Age (per 10 years)	1.2 (1.0 ; 1.4)	1.2 (1.0 ; 1.4)	0.9 (0.8 ; 1.1)
Female	1.0 (0.7 ; 1.4)	0.9 (0.6 ; 1.2)	0.6 (0.4 ; 0.9)
Indigenous	0.5 (0.3 ; 0.8)	0.5 (0.3 ; 0.8)	0.6 (0.3 ; 1.1)
MSM	1.4 (1.0 ; 1.9)	–	–
History of IDU (but not recent)	0.9 (0.6 ; 1.3)	–	–
Recent IDU	0.7 (0.5 ; 1.0)	–	–
History of crack or cocaine use	–	0.6 (0.5 ; 0.9)	0.6 (0.4 ; 0.9)
Recent alcohol consumption	0.9 (0.7 ; 1.1)	0.9 (0.7 ; 1.1)	0.9 (0.7 ; 1.2)
HCV genotype 2 or 3	–	0.9 (0.6 ; 1.2)	1.8 (1.2 ; 2.6)
HCV genotype 3	0.7 (0.5 ; 1.0)	–	–
HCV genotype unknown	0.2 (0.1 ; 0.4)	–	–
Duration of HCV infection (per 10 years)	–	1.3 (1.1 ; 1.5)	0.8 (0.7 ; 1.0)
APRI > 1.5 [b]	1.9 (1.5 ; 2.5)	–	–
HIV viral load ≤ 50 copies/ml	2.6 (1.8 ; 3.8)	–	–
On antiretroviral therapy	–	2.2 (1.4 ; 4.1)	1.2 (0.8 ; 1.9)
CD4 cell count (per 100 cells/μL)	–	1.0 (1.0 ; 1.0)	1.1 (1.0 ; 1.1)
Monthly income ≤ 1500 CAD	0.8 (0.6 ; 1.0)	–	–
Currently homeless	–	0.6 (0.4 ; 1.0)	0.9 (0.5 ; 1.5)
Psychiatric diagnosis	–	1.1 (0.8 ; 1.5)	1.2 (0.9 ; 1.6)
Estimated variance component			
Between-centre variance	0.29 (0.09 ; 0.89)	0.43 (0.16 ; 1.24)	0.87 (0.49 ; 1.5)

APRI = aspartate-to-platelet ratio index, HCV = hepatitis C virus, DAA = direct-acting antivirals, CAD = Canadian dollars, MSM = males who have sex with males, IDU = injection drug use.

[a] Measured at the cohort visit closest to the beginning of study follow-up. Age was centered at 40 years to create our reference patient. Recent IDU and alcohol consumption were patient reported behaviour in the 6 months prior to this cohort visit.

[b] As measured at any time prior to the beginning of study follow-up.

to this shift.

We also observed a shift from treating predominantly HCV genotype 3 in the interferon era to genotype 1 in the DAA era. This was expected, given the greater efficacy of early DAA therapies for genotype 1 infections (Majumdar, Kitson, & Roberts, 2016; Berden et al., 2017). Sofobuvir/velpatasvir was only approved in Canada towards the end of the study period and glecaprevir/pibrentasvir was not yet approved. The recent availability of these pan-genotypic regimens will remove this barrier in the near future.

Our data imply that liberalizing fibrosis restrictions ought to substantially reduce an important structural barrier to treatment uptake. The appreciably lower between-centre variation, in the DAA era, after adjusting for region—an effect not seen in the interferon era—suggests that regional differences in reimbursement criteria were a major barrier to wider treatment uptake during the study period. Quebec, the jurisdiction with centres most likely to start DAAs, had the most liberal reimbursement policies, allowing for the treatment of all co-infected patients regardless of fibrosis stage since 2015 with no explicit restrictions to re-treatment or type of provider able to prescribe therapy.

Several modelling studies have illustrated the importance of removing fibrosis restrictions for reducing HCV incidence, prevalence, and mortality to levels consistent with elimination (National Academies of Sciences, Engineering, and Medicine, 2017; Razavi et al., 2017; Cousien et al., 2017). Most new infections occur among younger, more recently infected individuals with early or limited fibrosis who drive the continued epidemic. Therefore, focusing treatment on those with fibrosis stage of F2 or greater, while reducing liver mortality, will have minimal impact on new infections (National Academies of Sciences, Engineering, and Medicine, 2017).

Of the relatively few countries considered to be on track to eliminate HCV (> 7% treated per year), all have in common the removal of fibrosis restrictions to DAA reimbursement (Polaris Observatory, 2018). For example, uptake of HCV treatment has increased substantially in Australia, Egypt, France, Georgia, the Netherlands, Morocco, Portugal, and Scotland after universal access to HCV treatment was implemented (World Health Organization, 2017). In Australia, a trend towards the treatment of younger people has recently been observed, suggesting that removing fibrosis restrictions will allow access to DAAs for individuals at higher risk for infection transmission, if no other restrictions are in place (Hajarizadeh et al., 2017). In the Netherlands, the universal availability of DAAs has led to rapid uptake among HIV-positive MSM (Boerekamps, Newsum et al., 2018). This has been temporally associated with a 50% reduction in acute HCV incidence in this group, which suggests that wider uptake can impact incident HCV infections among HIV-infected people, even in the short term (Boerekamps, van den Berk et al., 2018).

Unfortunately, disease-based restrictions remain common in Europe (in 2017, nearly half of the European countries/jurisdictions restricted DAAs to persons ≥ F2 fibrosis) and in almost all American states (Marshall et al., 2018; Barua et al., 2015; Ooka, Connolly, & Lim, 2017). Nearly all these jurisdictions additionally require a specialist to prescribe DAA therapy (Marshall et al., 2018; Ooka et al., 2017). Furthermore, as a recent WHO progress report highlights, high prices for HCV drugs remain a significant barrier in many upper-middle-income countries that lack access to generic DAAs. These countries represent about 38% of people living with HCV globally (World Health Organization, 2018).

As competition and generics enable price reductions for DAAs, and fibrosis restrictions are progressively removed, access to treatment should extend to all key populations. However, our data (and that of others) suggest this does not happen in lock step. Despite the recent loosening of fibrosis restrictions in some American states, behavioural restrictions remain in place in most jurisdictions: 50% of American states continue to restrict treatment based on recent drug or alcohol use and 19 states require patients to pass drug screening tests (Ooka et al., 2017). Furthermore, many states continue to require that co-infected

patients receive antiretrovirals and have undetectable HIV RNA to be eligible for DAA therapy. Treatment rates in HIV−HCV co-infected patients have not increased in some American centres since the availability of DAAs (Cope, Glowa, Faulds, McMahon, & Prasad, 2016).

In Canada, there are no restrictions to reimbursement of HCV treatment related to substance use, other behaviours, or HIV therapy (Marshall et al., 2016). Even so, the high cost of treatment has led to restrictions on re-treatment of failures or re-infections in many provinces (Marshall et al., 2016). Even when not overtly prohibited (e.g., "one kick at the can" policies), moral judgments about who does and does not deserve treatment, given the cost to the health care system of re-treating, may enter into treatment decisions and lead to the withholding of treatment from substance users (Wolfe et al., 2015).

Indeed, we found that not all patients are being started on DAAs equally. As in the interferon era, recent drug or alcohol users, Indigenous people, and those with lower socio-economic status remain less likely to be treated. This finding is consistent with other studies. In Massachusetts and Maryland, where there are few restrictions to prescribing DAAs, active users of drugs or alcohol were far less likely to be prescribed DAAs (Clements et al., 2016; Wansom et al., 2017). Even where there is universal health care, such as in British Columbia, socio-economically marginalized people were less likely to receive DAAs (adjusted odds ratio for most deprived vs. most privileged: 0.71, 95% CI: 0.58-0.87) (Janjua et al., 2017). We also observed a shift to treating those receiving antiretrovirals and with well-controlled HIV infection, which suggests that patients who are considered more stable and more likely to adhere to DAAs are being preferentially treated. With no restriction to prescribing based on substance use or HIV therapy, lower treatment rates in these marginalized groups may not simply be related to providers' choice but to difficulties in keeping such patients engaged in care. We found that patients with unknown HCV genotypes were also less likely to be treated. Since genotype assessment is a first step in the evaluation of a patient for treatment, missing genotypes may reflect that such patients have not yet been considered for treatment or are less engaged in regular follow-up (Cachay et al., 2014; Wansom et al., 2017).

There is mounting evidence that HCV treatment can be as successful in marginalized groups. For example, clinical trials of DAA therapy in OST and active drug users have demonstrated very high rates of sustained virologic response, on par with non-drug users (Dore et al., 2016; Litwin et al., 2017; Grebely, Mauss et al., 2016). Such results are increasingly being replicated in many real-world settings (Mason et al., 2017; Read et al., 2017; Grebely, Alavi et al., 2016). Indeed, attitudes towards treating substance users may be shifting. In a recent survey of Canadian infectious disease physicians, we found that most respondents had favourable attitudes towards treating substance users (Chan, Young, Cox, Nitulescu, & Klein, 2018). Of those surveyed, all current DAA prescribers agreed that patients with HCV who are actively injecting drugs should be offered HCV treatment and linked to harm-reduction services and OST, and 81% agreed that patients who become re-infected should be candidates for re-treatment. This differs starkly from a Canadian national survey, conducted before the DAA era predominantly among gastroenterologists and hepatologists, which found that fewer than 20% would prescribe HCV treatment to substance users using needle and syringe exchange services (Myles, Mugford, Zhao, Krahn, & Wang, 2011). Similarly, a recent survey at the American Association for the Study of Liver Diseases (AASLD) Liver Meeting found only a slight increase in the proportion of clinicians (from 10% in the interferon era to 15% in the DAA era) willing to treat PWID (Asher et al., 2016). Concerns over reinfection risk and cost of treatment were primary considerations for offering therapy. In our recent survey, prescribers identified poor access to harm-reduction services and mental-health treatment as the most important barriers to treatment for their patients (Chan et al., 2018). Additionally, most felt they had not received adequate training to manage patients who have substance abuse issues. This suggests a need for more training in addiction medicine and engaging more addiction physicians in HCV care. Indeed, OST was relatively low in our cohort with only 3% of DAA treated patients (and 10% of those not treated) reporting recent OST suggesting that co-localisation of addiction treatment services with HIV and HCV care is lacking in our cohort. In addition to removal of fibrosis restrictions, further policy changes that support delivery of addiction care to PWID living with HIV and HCV are needed in Canada.

A variety of tailored approaches for substance users are being evaluated to increase engagement and retention in HCV care (Litwin, 2016). For example, physical integration of treatment for substance use and HCV, virtual integration of behavioural and medical treatments via telemedicine, case management, outreach, peer navigation, and directly observed therapy are but some of the approaches that have been used successfully to increase engagement in care and treatment rates (Gonzalez, Fierer, & Talal, 2017; Read et al., 2017). As cost savings amount from price reductions in HCV therapy and from the reduced health expenditures associated with chronic HCV, resources will need to be shifted to support such innovative models of care and to address the wider social inequities that underlie poor health outcomes for many people living with HIV and HCV.

Our study has several strengths. First, we followed a large cohort of co-infected patients in both community-based and tertiary care settings during a period spanning two HCV treatment eras. Second, our prospectively collected patient-level data included demographic, behavioral, and clinical factors likely associated with HCV treatment uptake. Third, we modeled these data using methods that allow us to distinguish between patient- and centre-level effects. Fourth, our results were consistent across all sensitivity analyses. Accounting for level of care provided (primary vs. tertiary), adjusting for prior unsuccessful HCV treatment, or censoring patients if, and when, they started HCV treatments through clinical trials did not appreciably change results. Nonetheless, there is the potential for incomplete adjustment for patient characteristics that could lead to an overestimation of between-centre variance. As an illustration, when we used covariates more appropriate for the interferon era, the estimated between-centre variance increased substantially in the DAA era. Any incomplete adjustment would affect centres that had very different populations from the average, such as the two located in Saskatchewan. The HCV epidemic in this province is much more recent and disproportionately affects young, Indigenous people who inject drugs and who have many competing health and social concerns (Health Canada, 2015). Thus, for these patients or their providers, HCV treatment may not be the highest priority. Additionally, this province has very few providers of HCV treatment (personal communication, A. Wong). In light of these considerations, the estimated hazard ratio for Saskatchewan may be overly pessimistic.

Losses to follow-up were particularly high among patients with end stage liver disease who had high mortality and among patients with uncontrolled HIV—both groups who might be less likely to receive treatment. Censoring such patients might be informative as it might make centres with higher rates of loss to follow-up appear better at starting patients on treatment than they in fact were. To address this limitation, we conducted sensitivity analyses where study follow-up for those lost to follow-up was extended until administrative censoring. These analyses yielded estimated between-centre variances similar to that of our main analysis (see Sensitivity analysis 3 in Appendix A).

Finally, it should be noted cohort participants may not be perfectly representative of all Canadians co-infected with HIV and HCV. The CCC is open to all HIV-patients with evidence of HCV infection followed at participating sites without restriction and is estimated to include 23% of the total co-infected population in care in Canada. Since participants have access to universal healthcare, insurance does not restrict those who can attend clinics. However, our study population is not generalizable to those who have not been diagnosed or who have not been linked to care—estimated to be 15% and 10%, respectively, of the total co-infected population in Canada in 2016 (Janjua, personal communication, 2018).

Conclusions

There are compelling public health and health equity reasons for extending HCV treatment to all co-infected persons, a priority population previously considered difficult to treat. Our data suggest that jurisdictional policies restricting treatment to patients with advanced fibrosis remain an important barrier to treatment uptake in the DAA era. Reducing the price of HCV medications is a necessary first step to removing this barrier. Reducing DAA prices alone, however, will be insufficient to reach elimination targets. Substance users and marginalized people remained less likely to be treated in our study even after accounting for jurisdictional differences. Resources need to be redirected to support patients and providers to address unmet health and social needs which continue to stand in the way of universal treatment access. Only then can treatment be scaled up to reach high-risk transmitters and reduce incidence and prevalence so that elimination targets can be achieved.

Conflict of Interest Statement

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2018.08.012.

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