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Transitioning from interferon-based to direct antiviral treatment options: A potential shift in barriers and facilitators of treatment initiation among people who use drugs?

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ABSTRACT

Background: Multiple barriers for accessing hepatitis C virus (HCV) treatment were identified during the interferon-based (IFN) treatment era for people who inject drugs (PWID). Whether these barriers persist since the introduction of IFN-free direct-acting antiviral (DAA) agents in Canada remains to be documented. This study examined temporal trends in HCV treatment initiation and associated factors during the transition from INF-based to all-oral DAA regimens.

Methods: The study population was drawn from a prospective cohort of PWID in Montreal, Canada. At three-month/one-year intervals between 2011 and 2017, participants with chronic HCV infection completed an interviewer-administered questionnaire on socio-demographic characteristics, drug use and health service utilisation, including HCV treatment. Time-updated Cox multivariate regression models, stratified by DAA + INF (2011-2013) and all-oral DAA (2014–2017) availability periods, were conducted to examine associations between time to HCV treatment initiation and associated barriers and facilitators.

Results: Of 308 participants (85% male, median age 42 [IQR: 33, 50]), 80 (26%) initiated HCV treatment during 915 person-years (PY). Incidence rates increased from 1.6 /100 PY (95%CI:0.9–2.6) in 2011 to 12.7 (10.6–15.1) in 2017 (p-trend = 0.0012). In multivariate analyses, visiting a primary care physician (2011–2013: aHR = 3.63[1.21–10.9]; 2014–2017: 2.52[1.10–5.77]) and frequent injection (0.23[0.05–0.99] and 0.49[0.24–0.99]) were consistently associated with treatment initiation. Participants aged > 40 (2.27[1.24–4.13]), receiving opioid agonist therapy (OAT) (2.17[1.19–3.94]), and reporting prior HCV treatment (3.00[1.75–5.15]) were more likely to initiate treatment in the all-oral DAA period.

Conclusion: Treatment initiation increased between 2011 and 2017, but still remains low among PWID. Primary care visiting was a key facilitator regardless of the period, while engagement in OAT and health services, indicated by prior HCV treatment, increased the likelihood of treatment initiation in the DAA era. These findings suggest that access to health services is essential but not enough to scale up treatment in this population.

Introduction

Hepatitis C virus (HCV) is a global public health threat. Although HCV incidence has been declining steadily in Canada (Canadian Liver Foundation, 2013; Trubnikov, Yan, & Archibald, 2014), the associated burden continues to grow (Canadian Liver Foundation, 2013; Krajden et al., 2010; Myers et al., 2014). Injection drug use accounts for the majority of HCV cases (Public Health Agency of Canada, 2014b) and HCV burden (Degenhardt et al., 2016) in this setting. A 2011 national community-based study found that although over 90% of people who inject drugs (PWID) had been screened for HCV antibodies, fewer than 10% of those with a self-reported infection had ever initiated treatment (Public Health Agency of Canada, 2014a). Prior to 2014, the majority of Canadian government-subsidised HCV treatment regimens included

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pegylated interferon (IFN), with or without ribavirin, which carried significant side effects and had sub-optimal sustained viral response (SVR) rates (Kohli, Shaffer, Sherman, & Kottilil, 2014; Raza, Mittal, & Sood, 2013). HCV treatment has since been transformed by the introduction of IFN-free direct-acting antiviral (DAA) agents, with eight to 12 week all-oral regimens achieving SVR rates of over 95% with few or no side effects (Falade-Nwulia et al., 2017). These IFN-free DAA regimens have been approved by Health Canada and become increasingly available since 2014 (Chen et al., 2017; Falade-Nwulia et al., 2017; Jakobsen et al., 2017). Access to HCV treatment was initially offered only to patients with fibrosis score of F2 or higher, and eligibility criteria were gradually extended until the removal of all restrictions in March 2018.

Before being prescribed IFN-based treatment, individuals with confirmed chronic HCV infection had to undergo an extensive investigation, spanning several months, to determine HCV genotype, disease progression and presence of co-infection with HIV or hepatitis B (Canadian Task Force on Preventive Health Care, 2017). Low treatment uptake among PWID was thus found to result from multiple barriers at the patient, provider, and system levels (Treloar, Newland, Rance, & Hopwood, 2010). For those living with HCV, social vulnerabilities including unemployment, unstable housing conditions, current injection drug use, poverty and competing priorities, stigma, comorbidities, limited access to health insurance, and poor patient-provider relationships have been documented as barriers to treatment (Arain & Robaeys, 2014; Golden, Conroy, O'Dwyer, Golden, & Hardouin, 2006; Grebely, Oser, Taylor, & Dore, 2013; Janjua et al., 2017; Moirand, Bilodeau, Brissette, & Bruneau, 2007; Osilla et al., 2009; Treloar et al., 2010). Concerns about toxicity and side effects, inadequate treatment efficacy, and the impact of undergoing treatment on family or work responsibilities were further frequently reported barriers (Gidding et al., 2011; Swan et al., 2010; Treloar et al., 2010).

While the availability of IFN-free DAA therapies provides an opportunity to reverse an increasing trend of HCV-related morbidity and mortality in Canada (Falade-Nwulia et al., 2017; World Health Organization, 2016), the evidence supporting the actual impact of DAAs on reduction of HCV-related liver disease burden mostly comes from modelling studies and is currently scarce (Innes, Goldberg, Dillon, & Hutchinson, 2015). Clinical trials and observational studies demonstrate very high rates of treatment completion and favourable responses to DAA therapy among individuals with recent drug use (Cunningham et al., 2018; Hajarizadeh et al., 2018) and there is a growing consensus that treatment scale-up will be indispensable to reducing HCV burden among PWID (Cousien et al., 2016, 2017; de Vos, Prins, & Kretzschmar, 2015; Gountas et al., 2017; Hellard et al., 2014; Lima et al., 2015; Martin et al., 2013). Importantly, this requires rapidly identifying and treating active injectors as the population most likely to transmit the virus (Gountas, Sypsa, Blach, Razavi, & Hatzakis, 2018; Grebely et al., 2017). Yet despite steadily expanding eligibility for IFN-free DAAs in Canada, uptake among PWID remains insufficient to achieve national viral elimination targets (Gountas et al., 2018) and determinants of treatment initiation in this new therapeutic landscape are not well documented. Current strategies to increase treatment uptake among PWID rely on studies performed in the IFN era and therefore may be not applicable to the current DAA treatment era. Understanding the current context of HCV treatment initiation is essential to developing strategies to accomplish rapid treatment scale up in this heterogeneous and hard to reach population.

This study aimed to examine trends in rates of HCV treatment initiation and associated factors in the seven years surrounding introduction of IFN-free DAA therapy in Canada. We hypothesized that besides barriers related to social vulnerabilities and drug use patterns, access to health insurance through welfare, linkage to primary health care and opioid agonist therapy (OAT) may be also associated with treatment uptake in the context of new DAA treatment availability.

Methods

Study design and participants

The study participants were selected from the Hepatitis Cohort (HEPCO) an ongoing open prospective cohort study of PWID in Montréal, Québec, Canada, established in 2004, aimed to investigate factors associated with incident HCV infection and the natural history of HCV infection after seroconversion; secondary objectives were to estimate HIV incidence rates and examine access to care for HCV infection (Bruneau, Roy, Arruda, Zang, & Jutras-Aswad, 2012). Eligibility criteria for enrolment in HEPCO included: being aged 18 years or older, residency in the Greater Montréal area and self-reported drug injection within the past six months. Participants were recruited via street-level strategies such as word-of-mouth referral and community-based organizations.

Follow-up visits were scheduled to address primary and secondary aims of HEPCO, according to the participants' HCV infection status. HCV-RNA negative participants and those who seroconverted during follow-up were followed every three months in order to address the primary aims of the study. PWID infected with HCV (HCV antibody and RNA positive) at recruitment were followed at one year-intervals to address secondary aims. At baseline and at each follow-up visit, participants completed an interviewer-administered questionnaire, and venous blood samples were drawn for HCV-RNA and HIV antibody testing. The questionnaire elicited information on socio-demographic characteristics, drug use patterns and related behaviors, and healthcare service utilization, including HCV testing and treatment history, where appropriate. Participants were invited to return in two weeks to receive test results. Participants testing HCV-RNA positive or HIV infected were provided with post-test counseling and were systematically referred for medical follow-up and treatment assessment to the CHUM Addiction Medicine program, which offers multidisciplinary services for patients with drug-related problems, including hepatitis C and HIV treatment.

For the purpose of this study, participants infected with HCV (HCV-Ab and HCV-RNA positive) and who completed at least one follow-up visit between January 2011 and December 2017 were included in the present analysis.

Measures

The primary outcome of interest was time to self-reported date of HCV treatment initiation, confirmed with medical records when available, among participants infected with HCV. To identify eligible participants for this study, blood specimens yielding positive results for HCV antibodies using enzyme immunoassay (EIA, Abbott Laboratories, Chicago, Illinois, US) were further tested to detect the presence of hepatitis C virus. HCV-RNA testing was performed using the qualitative COBAS AMPLICOR HCV Test v2.0 (Roche Diagnostic Systems) up until 2013, and the COBAS Ampliprep/COBAS Taqman HCV Quantitative Test v2.0 (Roche Molecular Systems, CA, USA) or the RealTime HCV assay (Abbott) thereafter.

Primary exposure variable

We used date of treatment initiation as a proxy for the prevailing treatment environment. In Canada, the first DAAs became available in 2011; from 2011 to 2013, INF-based treatment were still widely prescribed. In 2014, the all-oral IFN-free regimens became available, and from that time, IFN-based regimens were no longer offered to patients in the province of Quebec. Thus, study period was classified as 1) 2011–2013, denoting a time frame of IFN-based regimens availability and 2) 2014–2017, denoting IFN-free, DAA-based era.

Potential correlates of time to HCV treatment initiation considered for the analyses were based on our hypotheses elaborated following a literature review of studies identifying factors associated with HCV treatment uptake among PWID (Arain & Robaeys, 2014; Gidding et al.,

2011; Grebely et al., 2013; Janjua et al., 2017; Treloar et al., 2010). These included socio-demographic characteristics, drug use patterns and measures of engagement with healthcare services. Socio-demographic characteristics included: age, sex, welfare as an income source, total monthly income (CAD$), and housing arrangements. Age was analyzed in binary form, categorized as ≤40 or > 40 years old, based on the average age of reaching stage 2 fibrosis due to HCV infection, as reported in the literature (Smith, Combellick, Jordan, & Hagan, 2015). This categorization was chosen to reflect differences in eligibility criteria for HCV treatment associated with progression of liver disease. Welfare as an income source was assessed in binary form (yes/no) in the previous three-month period. This variable was included to control for postulated differences in access to HCV treatment. In Quebec, people receiving welfare benefit from universal government health coverage, including HCV treatment (without co-payment). As with previous studies (Bruneau et al., 2012), unstable housing, assessed in reference to the past three months, was defined as living on the street, in shelters or apartment-hotels rented on a monthly basis, indicating rapid turnover compared to typical, 12-month rent-lease accommodations in Montreal. Drug use patterns were based on the types of drugs injected and the frequency of injection: cocaine and heroin injection were defined by use in the previous month, and analyzed as binary variables (yes/no). High frequency of injection, assessed in reference to the previous three months, was categorized as injecting, on average, every other day or more (i.e., injecting on ≥45 days, yes/no). Measures of engagement with healthcare services included three binary variables (yes/no): contact with a primary care physician (PCP) in the past three months, being currently enrolled in OAT and having previous HCV treatment experience. As previously (Artenie et al., 2015), contact with a PCP was defined as having visited a PCP in a clinic or local community health center at least once in the past three months. Receipt of OAT (yes/no) was defined as receiving methadone or buprenorphine/naloxone at each visit. Finally, a dichotomous variable denoting HIV serostatus was also included, as assessed by standard clinical serology testing (fourth-generation test including HIV-1, -2 and p24 antigen).

Statistical analysis

Descriptive statistics were used to characterize the study sample at baseline, overall and stratified by whether or not participants initiated HCV treatment over the study period. Bivariate associations between explanatory variables and HCV treatment initiation were tested using Chi-square or Fisher's exact tests for categorical variables, and the nonparametric Wilcoxon-Mann-Whitney test for continuous variables, given their non-normal distribution.

Incidence of HCV treatment for the whole study period and each year separately was calculated using the person-time method, and 95% confidence intervals (CIs) were estimated based on the Poisson distribution. Trend analysis was conducted to examine changes in incidence rates by year of study visit using the Kendall rank correlation coefficient (Kendall, 1990), a nonparametric measure of the strength and direction of correlation between two variables. For HCV-infected participants at recruitment (HCV-Ab and HCV-RNA positive), the follow-up started at the time of study entry and for those seroconverted during the follow-up, at six months after seroconversion if they had at least two RNA-positive results. For all participants, the follow-up ended at the time of HCV treatment initiation or at the last study visit, whichever came first.

Univariate and multivariate Cox proportional hazards models were used to estimate associations between variables of interest and time to HCV treatment initiation. Except for age, gender and previous treatment experience, all variables were analyzed as time-updated covariates. Covariates considered for inclusion in the multivariable model demonstrated a marginal association with the outcome in univariate analyses ($p < 0.1$). A backward elimination approach was used to determine the final multivariable model; variables were retained if they demonstrated a statistically significant association with the outcome ($p < 0.05$). To assess whether determinants of HCV treatment initiation changed along with the shift in HCV treatment regimens observed over the study period, results of multivariable Cox regression analyses were stratified by study period (2011–2013 vs 2014–2017). Finally, a sensitivity analysis was conducted to account for differential follow-up intervals, by restricting the study sample to participants who were followed at three-month intervals (i.e. excluding participants HCV RNA + at enrolment who were followed at 12-month intervals).

Ethical considerations

The HEPCO study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and is approved annually by the Research Ethics Board of the Centre hospitalier de l'Université de Montréal. All participants sign an informed consent form, in accordance with the regulations of the Centre hospitalier de l'Université de Montréal.

Results

Participant characteristics

A flowchart describing participant inclusion criteria is presented in Fig. 1. Overall, 354 HCV RNA + HEPCO participants were eligible for this investigation over the seven-year period. Of these, 308 (87%) had at least one follow-up visit and formed the study sample. Except for being more likely to report high-frequency injection (44% vs. 32%, $p = 0.05$), no differences were observed between participants who did (n = 308, 87.0%) and did not (n = 46; 13.0%) have at least one follow-up visit.

Table 1 presents baseline characteristics of the 308 PWID who formed the study sample, globally and according to HCV treatment initiation. The majority were male (85%) and their median age was 42 (interquartile range (IQR): 33–50). Their median monthly income was

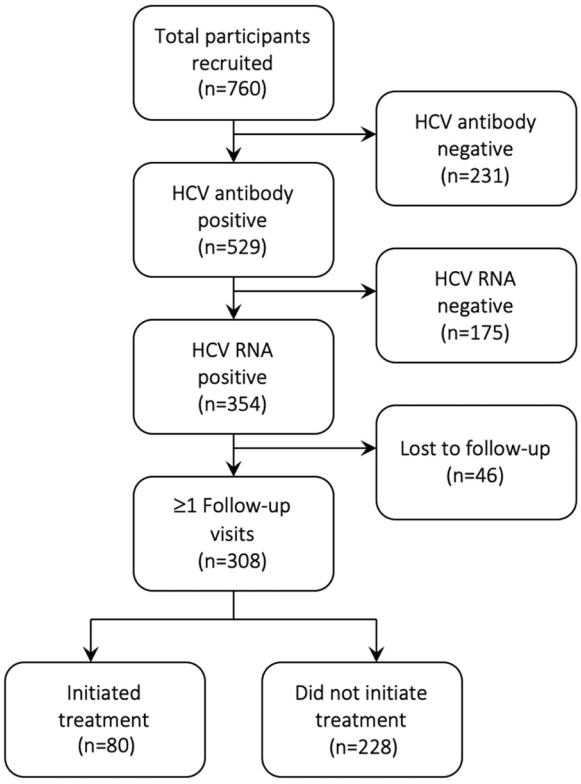

Fig. 1. Participants flow-chart diagram.

Table 1
Baseline characteristics of the study participants, overall and stratified according to HCV treatment initiation.

	Overall, N (%) (n = 308)	Initiated treatment, N (%) (n = 80)	Did not initiate treatment, N (%) (n = 228)	P-value
Age (> 40 years)	165 (53.6)	46 (57.5)	119 (52.2)	0.59
Male sex	262 (85.1)	64 (80.0)	198 (86.0)	0.25
Monthly income [CAD$, Median (IQR)]	1000 (735, 1800)	900 (705, 1474)	1000 (750, 1946)	0.18
Unstable housing, past 3 months	120 (39.0)	27 (34.3)	93 (40.7)	0.44
High frequency of injection, past 3 months	141 (45.0)	28 (35.0)	113 (49.6)	0.06
Cocaine injection, past month	180 (58.4)	39 (48.6)	141 (61.8)	0.08
Heroin injection, past month	97 (31.5)	24 (30.0)	73 (32.0)	0.87
Currently enrolled in OAT	102 (33.1)	34 (42.5)	68 (30.0)	0.07
Contact with a PCP, past 3 months	205 (66.5)	62 (78.6)	143 (62.7)	0.02
Previous HCV treatment experience	63 (20.4)	35 (43.8)	28 (12.3)	< 0.01
HIV positive	13 (4.2)	3 (3.8)	10 (4.4)	1.00
Welfare as a source of income, past 3 months	248 (80.5)	65 (81.4)	183 (80.3)	0.96
One-year follow-up period (vs. three-month)	94 (31%)	21 (26.3)	73 (32.0)	0.34

Legend: PCP: primary care physician; OAT: opioid agonist therapy; IQR: interquartile range.

1000 $CAD IQR: 735–1800), 80% reported welfare as an income source and more than one-third reported past 3-month unstable housing (39%). Almost half (45%) of participants reported at least 45 days of injection in the past three months. Two-thirds reported contact with a PCP in the past three months and one- third were receiving OAT. Only 20% had previous HCV treatment experience.

A number of differences were noted between participants who did and did not initiate HCV treatment. Those who did were less likely to inject cocaine (48% vs. 61%, p = 0.08) and to report high frequency of injection (35% vs. 49%, p = 0.06). They were also more likely to have seen a PCP in the past three months (79% vs. 63%, p = 0.03), to receive OAT (42% vs. 30%, p = 0.07) and to have been previously treated for HCV infection (44% vs. 12%, p < 0.01).

HCV treatment incidence

Prior to HCV treatment initiation, participants contributed a total of 915.6 person-years of observation (mean duration between visits = 6.4 months). Overall, 214 PWID (69%) were followed at 3-month intervals and 94 (31%) were followed at 1-year intervals. A total of 80 PWID (26%) initiated treatment, for a global incidence rate of 7.5 per 100 person-years (95% CI: 7.0–8.1). HCV treatment initiation increased gradually between 2011 to 2017, from 1.6 (0.9, 2.6) in 2011 to 12.7 (10.6, 15.1) in 2017, with the exception of 2015 where a decrease was observed (p-value for trend = 0.0012). (Fig. 2).

Predictors of time to HCV treatment initiation

Table 2 presents the results of univariate and multivariable time-updated Cox regression models, globally and stratified by the period of participants follow-up (adjusted HRs only). In the global multivariable model, cocaine injection (aHR: 0.59; 95%CI: 0.37-0.93) and high frequency of injection (aHR: 0.48; 95%CI: 0.25-0.93) were negatively associated with HCV treatment initiation, whereas recent contact with a PCP (aHR: 2.89; 95%CI: 1.41–5.95), being enrolled in OAT (aHR: 1.67; 95%CI: 1.01–2.77) and previous HCV treatment experience (aHR: 2.37; 95%CI: 1.49–3.77) were positively related to the outcome. Older age was associated with greater treatment initiation, though this relationship was not statistically significant (aHR: 1.43; 95%CI: 0.88–2.35). Unstable housing was significantly associated with treatment initiation in univariate models, but not in multivariable analyses, and was therefore not retained in the final stratified models.

In the model stratified by study period, cocaine injection, high frequency of injection and recent contact with a PCP were associated with treatment initiation in the same directions and relatively similar strengths of association. In contrast, current OAT enrollment was associated with a two-fold increase in treatment initiation in the 2014–2017 period (aHR: 2.17; 95%CI: 1.19–3.94) but not in 2011–2013 (aHR: 0.98; 95%CI: 0.38–2.59). Similarly, previous HCV treatment experience was associated with a three-fold increase in treatment initiation in 2014–2017 (aHR: 3.00; 95%CI: 1.75–5.15) but not in the earlier time period (aHR: 1.31; 95%CI: 0.50–3.45). Older age was associated with greater treatment initiation in 2014–2017 (aHR: 2.27; 95%CI: 1.24–4.13). This association was reversed in the 2011-13 period (aHR: 0.58; 95%CI: 0.24–1.42).

Results remained largely unchanged when restricting the study sample to participants followed at 3-month intervals (Supplemental Table 1).

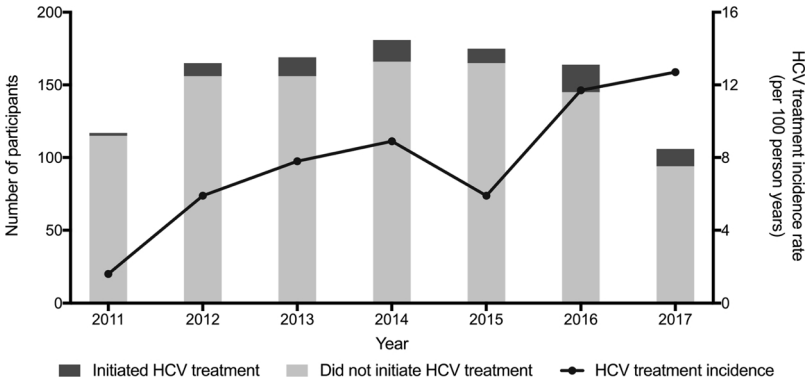

Fig. 2. Number of participants who initiated and did not initiate HCV treatment, and HCV treatment incidence rate among HCV-RNA positive people who inject drugs, 2011-2017.

Table 2
Cox proportional hazards analysis of HCV treatment initiation among 308 HCV-RNA positive people who inject drugs, overall and stratified by the period of follow-up (2011–2013 and 2014–2017).

	Global		Study period	
Characteristic	uHR (95% CI)	aHR (95% CI)	2011-2013 aHR (95% CI)	2014-2017 aHR (95% CI)
Age (> 40 vs < = 40)	1.22 (0.78, 1.91)	1.43 (0.88, 2.35)	0.58 (0.24, 1.42)	**2.27 (1.24, 4.13)**
Male sex	0.73 (0.42, 1.29)	0.82 (0.46, 1.45)	–	–
Monthly income (CAD $), past 3 months	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	–	–
Welfare as a source of income, past 3 months	1.90 (0.95, 3.81)	1.78 (0.87, 3.64)	–	–
Unstable housing, past 3 months	0.47 (0.27, 0.82)	0.67 (0.37, 1.19)	–	–
Cocaine injection, past month	0.50 (0.32, 0.77)	0.59 (0.37, 0.93)	**0.40 (0.18, 0.90)**	0.64 (0.37, 1.09)
High frequency of injection, past 3 months	0.39 (0.21, 0.72)	0.48 (0.25, 0.93)	**0.23 (0.05, 0.99)**	**0.49 (0.24, 0.99)**
Contact with a PCP, past 3 months	4.08 (2.04, 8.16)	2.89 (1.41, 5.95)	**3.63 (1.21, 10.89)**	**2.52 (1.10, 5.77)**
Currently enrolled in OAT	2.19 (1.40, 3.37)	1.67 (1.02, 2.77)	0.98 (0.38, 2.59)	**2.17 (1.19, 3.94)**
Previous HCV treatment experience	2.36 (1.50, 3.73)	2.37 (1.49, 3.77)	1.31 (0.50, 3.45)	**3.00 (1.75, 5.15)**

Legend: PCP: primary care physician; OAT: opioid agonist therapy; uHR: unadjusted hazard ratio; aHR: adjusted hazard ratio.

Discussion

This study examined trends in the annual rate of HCV treatment initiation and associated factors in a population of community-based PWID in Montreal, Canada, during the seven years surrounding the introduction of interferon-free DAA-based treatment regimens. HCV treatment uptake increased steadily from 1.6 to 12.7 per 100 person-years between 2011 and 2017, with the exception of a dip in 2015. This marked increase reflects continued improvements in available treatment regimens and key changes in their financing and reimbursement under the Quebec Provincial Health Insurance Plan over this time period. In 2012, HCV-infected individuals became eligible for improved IFN-based regimens (including Sofosbuvir). IFN-free DAAs were first introduced in 2014, but subsidized treatment was only available to individuals with moderate to severe fibrosis (≥F2) until 2018 (Marshall et al., 2016). The decrease in the rate of HCV uptake in 2015 likely indicates the 'warehousing' of individuals with limited fibrosis awaiting coverage for IFN-free therapy (McGregor, McManus, Hajarizadeh, & Gray, 2016; Schanzer et al., 2018). Altogether, only 26% of participants initiated treatment during the study period. Thus, while treatment uptake is improving, it remains suboptimal in this population, despite treatment referral procedures available as part of the study protocol.

Our study identified a number of factors likely to deter or enhance HCV treatment initiation among PWID. Visiting a PCP was positively associated with treatment initiation both pre- and post-introduction of IFN-free DAAs, while enrolment in OAT was a significant facilitator only in the IFN-free DAA era. Conversely, high frequency of drug injection and cocaine injection were inversely associated with treatment initiation in both periods, but appeared to exert a weaker influence (as indicated by hazard ratio point estimates closer to one) during the IFN-free DAA period. Other factors that were significantly and independently associated with HCV treatment initiation in the DAA-based IFN-free era included age and previous HCV treatment experience. Participants aged over 40 were roughly twice as likely to initiate treatment than those who were younger during this period, likely reflecting the initial targeting of DAA therapies towards individuals with more advanced liver disease (Iversen et al., 2019; Madden, Hopwood, Neale, & Treloar, 2018). It is also possible that younger individuals experiencing fewer clinical symptoms may have been less likely to seek out HCV care (Solund et al., 2018). Previous treatment experience likely acts as a proxy for HCV awareness, knowledge, and engagement with care systems, and may also reflect a need for treatment according to liver disease stage.

Our findings are consistent with many prior studies of HCV care in PWID. Visits to a PCP have been associated with increased awareness about HCV infection (Treloar et al., 2011), improved access to screening (Arain et al., 2016; Barocas et al., 2014), greater willingness to initiate HCV treatment (Strathdee et al., 2005), and greater linkage to specialist care (Stoove et al., 2005), while enrolment in OAT has been positively associated with access to a regular source of HCV care (Ti et al., 2018), likelihood of receiving pre-treatment liver disease assessment (Young et al., 2018), likelihood of treatment offer and acceptance (Moirand et al., 2007), and overall treatment uptake (Butler, Larney, Day, & Burns, 2018; Iversen et al., 2019). Our findings reiterate the central role that PCP play in the prevention, screening and management of HCV among PWID (Artenie, Bruneau, Levesque, & Wansuanganyi, 2014; Bechini et al., 2016; Murtagh et al., 2018), acting as a key resource throughout all stages of the HCV cascade of care. PCP with their increasingly holistic approach to the health needs of PWID, are an attractive alternative to specialist services. Access to primary care has been also shown to increase linkage to substance abuse treatment (Bachireddy, Weisberg, & Altice, 2015; Centers for Disease Control & Prevention, 2012; Morozova, Dvoriak, Pykalo, & Altice, 2017). Similarly, recent years have seen growing recognition of the role that OAT clinics can play in achieving linkage to HCV care (Des Jarlais et al., 2015; Perlman et al., 2015), and these provide the setting for the majority of innovative peer-support (Crawford & Bath, 2013; Keats et al., 2015; Treloar et al., 2015) and integrated care models emerging in the literature (Artenie et al., 2014; Read et al., 2017; Seidenberg, Rosemann, & Senn, 2013).

Our findings suggest that although access to primary care and OAT remain critical to expanding HCV treatment among PWID in the DAA era, treatment infrastructures have not yet been sufficiently mobilized to achieve widespread uptake. Of participants who did not initiate HCV treatment during the study period, there were around 60% of visits at which they reported accessing primary care services in the three months prior to a visit and 30% reported being currently on OAT. Although PCP were always allowed to prescribe HCV treatment in Montreal, the provision of HCV screening or treatment in primary care settings is not a universal practice (Bechini et al., 2016). Recent qualitative research from Australia suggests that provider-and system-level barriers persist even in the context of a national universal access policy for IFN-free DAA therapies (Madden et al., 2018). Among some PCP, there is a perception that provision of HCV care is not a core task of their practice. (Madden et al., 2018). This perception is likely to be partially attributed to limited education and training regarding HCV care among non-specialist physicians. A recent international study conducted among physicians working in clinics offering OAT documented low self-perceived competency related to HCV management and treatment among a substantial proportion of prescribers (Grebely et al., 2018).

The lower HCV treatment uptake observed in our study among cocaine injectors and PWID with high injection frequency relative to other PWID is worrisome, given that these populations have heightened risk

of HCV infection (Bruneau, Arruda, Zang, Jutras-Aswad, & Roy, 2019). The more limited opportunities for engagement in care available to stimulant users, compared to opioid users, may account for the observed inverse association between cocaine injection and treatment initiation. As mentioned, OAT has a well-recognized role in HCV prevention and care for people who inject opioids. In contrast, there are no registered pharmacological treatments to date for cocaine dependence, and psychosocial interventions generally show modest results (Penberthy, Ait-Daoud, Vaughan, & Fanning, 2010; Somaini et al., 2011). Altogether, our findings suggest that, in spite of universal access to DAA treatment among PWID, services are likely not to reach everyone equally, and efforts must be devoted to developing strategies adapted to the various needs of PWID.

Numerous studies have found that DAA IFN-free treatment is effective and well tolerated among PWID, with no association between drug injection and treatment non-adherence or failure (Hajarizadeh et al., 2018). Accordingly, treatment guidelines no longer include drug injection as a contraindication to HCV treatment (Shah et al., 2018; Treloar et al., 2015) and Canadian provinces do not explicitly exclude individuals with recent substance use from reimbursement for DAA therapy (Marshall et al., 2016). Nonetheless, an international study of clinicians found that only 15% were willing to prescribe these medications to active PWID, with willingness inversely related to injection frequency (Asher et al., 2016). Our findings suggest that current strategies continue to exclude individuals whose drug use is not medically stabilized, including stimulant users and those injecting with high frequency (Harris, Albers, & Swan, 2015). These are individuals with substantially elevated risk of HCV transmission (Bruneau et al., 2012) and innovative strategies, such as the integration of care systems within supervised injection sites (Høj, Minoyan, Artenie, Grebely, & Bruneau, 2018) or social network strategies to referral and treatment (Hellard et al., 2014) may be required.

This study provided an opportunity to describe the rate of HCV treatment initiation and to assess and contrast associated barriers and facilitators during the transition between IFN-based and DAA regimens in a community-based population of PWID. Our study also has limitations. First, we did not measure liver fibrosis stage, limiting our ability to control for discrepancies in eligibility and need for HCV treatment between the two eras. Second, we did not collect systematic information on the type of HCV treatment initiated by PWID, and used the date of treatment initiation as a proxy of prevailing treatment environment. Although we used a cut-off to distinguish between these two eras, it is likely that this transition was more gradual. Third, all participants received pre- and post-test counseling and treatment referrals, potentially resulting in overestimation of the rate of treatment initiation compared with the general population of PWID in Montreal. Fourth, self-report data may be affected by recall and social-desirability biases. Finally, participant recruitment took place through non-random sampling techniques, and results may not be generalizable to the entire population of PWID in Montreal.

Conclusions

Injection drug use is the primary source of HCV infection and related disease burden in Canada. Numerous studies have demonstrated that PWID can be successfully treated for HCV, and the rapid treatment initiation in conferring significantly better outcomes (Arain & Robaeys, 2014; Hajarizadeh et al., 2018). Yet, despite the availability of highly effective and tolerable IFN-free DAA therapies since 2014, the majority of HCV-positive PWID in Montreal remain untreated. Engagement in primary care and OAT remain key facilitators of treatment initiation in the IFN-free, DAA-based period, whereas high frequency of injection and cocaine injection appear to deter access. This highlights a need to better engage people who use drugs in substance use care, when appropriate, and to expand access and integration of HCV care within primary healthcare, particularly for individuals not eligible for OAT.

Contributors

IM conceptualized the study ideas, performed all statistical analysis and drafted the manuscript. JB provided guidance on all aspects of the study and is a key editor. GZ prepared the data and assisted with analyses. AA, NM, SH and BJ provided methodological guidance and editorial assistance. GBE, VML and DJA provided overall manuscript oversight and critical feedback. All authors have read and approved the final manuscript.

Conflict of interest

J.B. and V.M.-A. hold research grants: Gilead, Merck, Abbvie. Consultant: Gilead and Merck.

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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.2019.04.002.

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