



## Barriers associated with the treatment of hepatitis C virus infection among illicit drug users

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### Abstract

**Background:** Illicit drug users account for the majority of cases of HCV in the developed world, but few have received treatment.

**Methods:** We evaluated barriers to initiating HCV treatment – including general treatment willingness – and factors associated with these among HCV infected illicit drug users. Participants were recruited via convenience sampling from two community clinics in Canada. Individuals age >18 years with a history of illicit drug use completed interviewer-administered surveys. Those reporting positive HCV testing underwent additional questioning on willingness, uptake and barriers to treatment for HCV.

**Results:** Of 188 HCV positive illicit drug users, 16% ( $n=30$ ) received treatment for HCV. Factors associated with a decreased treatment uptake included current heroin use and HIV/HCV co-infection. Among those not having received therapy, 77% (117/153) indicated a willingness to receive treatment. Factors associated with treatment willingness included not being infected with HIV, having not recently used drugs by injection and having reported physical health problems. Among those not having sought treatment ( $n=107$ ), the major reasons for not doing so were: lack of information about HCV or knowledge that treatment was available (23%), the absence of symptoms (20%) and the perceived side effects of treatment (14%).

**Conclusions:** Among illicit drug users attending inner city clinics, we have observed a low uptake of HCV treatment, but a high willingness to receive therapy. An increased focus on improving education about the long-term consequences of HCV and the availability of effective treatment are important components for expanding HCV treatment among illicit drug users.

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**Keywords:** Hepatitis C virus; Illicit drug users; Treatment; Willingness; Barriers; Uptake; Injection drug users

### 1. Introduction

In North America, Europe and Australia, >50% of prevalent and >75% of incident Hepatitis C virus (HCV) infections are associated with injection drug use (Shepard et al., 2005). Among long-term injection drug users (IDUs), the prevalence of HCV is 64–94% (Diaz et al., 2001; Patrick et al., 2001). Among those infected with HCV, the majority will develop persistent,

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chronic infection. Without treatment, fibrosis may develop over decades, potentially leading to cirrhosis, end-stage liver disease, hepatocellular carcinoma or death (Seeff, 2002). In Canada, a significant increase in HCV-related morbidity, mortality and economic cost burden indicators are expected for the coming years, constituting a major public health issue (El Saadany et al., 2005; Krahn et al., 2004).

Over the past decade, treatment for HCV – specifically combination treatment consisting of pegylated interferon and ribavirin – has been shown to be highly effective, achieving viral clearance rates (depending on genotype) between 55 and 85% (Fried et al., 2002; Manns et al., 2001). Until recently, HCV treatment guidelines in North America categorically excluded illicit drug users from consideration, citing concerns about adherence, susceptibility for side effects (e.g., depression), and re-infection risks (NIH, 1997). Several successful HCV treatment studies involving illicit drug users over the past years have challenged this paradigm (Backmund et al., 2001; Grebely et al., in press; Matthews et al., 2005; Sylvestre, 2005). Concretely, current HCV treatment guidelines in North America have now been revised to now stipulate consideration of treatment for HCV in this population on a “case-by-case” basis (Seeff and Hoofnagle, 2003; Sherman et al., 2004).

Despite these new considerations, several indicators suggest that few illicit drug users have received HCV treatment to date. In Vancouver, during the period 2000–2005 only 1.1% of a population of 1361 HCV antibody positive inner city residents reported having received treatment for HCV infection, despite it being freely available to them (Grebely et al., 2006). Similarly, in Australia only 4% of 2500 current IDUs attending needle exchange programs in 2003 had been treated for HCV, with only 0.6% actually on treatment at the time of the survey (NCHECR, 2003).

In some cases, this may be due to resource limitations. At the same time, specific factors intrinsic to the illicit drug user population are influencing willingness or actual efforts for HCV treatment among illicit drug users may be at play. Large proportions of high-risk drug user populations remain uneducated about basic HCV risks and disease specifics, or are unaware of their disease status (Doab et al., 2005; Strauss et al., 2007). Several studies have indicated that between 50 and 80% of HCV infected drug users would be somewhat or strongly willing to undergo HCV treatment under the right circumstances (Doab et al., 2005; Fischer et al., 2005b; Stein et al., 2001; Strathdee et al., 2005). Specific enquiries have suggested that concerns about potential treatment side effects (e.g., depression) or requirements of simultaneous addiction treatment may reduce interest in HCV treatment, while perceptions of likely health complications from HCV, access to regular health or addiction care, and readiness for change concerning drug use are factors that have been associated with higher levels of interest in HCV treatment (Doab et al., 2005; Fischer et al., 2005b; Strathdee et al., 2005).

Given that illicit drug users are at the core of the present and future HCV epidemic in developed nations, any efforts to reduce the disease burden of HCV will include the development of systematic programs to increase treatment uptake in this group (Fischer et al., 2006). With these considerations in mind, we sought to evaluate barriers to initiating HCV treatment

– including general treatment willingness – within a cohort of HCV-infected illicit drug users recruited from two inner city community health clinics in Vancouver and Victoria, British Columbia, Canada.

## 2. Patients and methods

Study participants ( $n = 332$ ) were recruited from two inner city community health clinics (CHC) in Vancouver and Victoria between June and December 2006: both centres are multi-disciplinary health care facilities providing primary care, addiction services and treatment of infectious diseases predominantly to marginalized individuals. Inclusion criteria were age  $>18$  years and a history of illicit drug use. Study participants were recruited by way of convenience sampling from patients visiting the CHC study sites for health services. Interview staff approached as many patients as possible attending the CHC sites on study days (2–5 days/week), to secure verbal informed consent for study participation. Study participants then completed a short, interviewer-administered questionnaire (approximately 15–20 min in duration) in a private room. Participants received a \$5 honorarium for the completion of the interview. The study was approved by the University of British Columbia Clinical Research Ethics Board.

The questionnaire included sections covering socio-demographics, physical and mental health status, HCV and HIV status and treatment information, addiction treatment and illicit drug use behaviours. The questionnaire was comprised partly of items used and validated in large-scale cohort studies focusing on illicit opioid drug use as well as HCV care in marginalized populations (Fischer et al., 2005a,b) and partly of new items which were specifically created for this study. Based on our stated objectives, the present analysis was conducted with the 188 subjects who had self-reported currently being positive for HCV infection (57%) in the context of the study interview (the remaining 144 subjects completed the questionnaire and reported not being positive for HCV infection). Among this sub-sample, individuals who self-reported being positive for HCV infection were asked questions about whether they had ever sought treatment for HCV and whether treatment had ever been offered or received. Subjects not having sought, been offered or received treatment were further queried about the reasons why this had not occurred. Those with self-reported HCV clearance were excluded from this analysis. Among those having received treatment for HCV, information about the specific regimen that was received and the outcome of treatment was collected. Among individuals not having received treatment for HCV, an additional set of questions focused on HCV treatment motivation and willingness to receive treatment was administered. Treatment willingness was assessed by means of a 5-point Likert-like scale (‘definitely not willing’, ‘somewhat not willing’, ‘neither willing nor unwilling’, ‘somewhat willing’ or ‘definitely willing’), with willingness defined by an individual stating they were somewhat or definitely willing to consider it. Differences in the participants’ treatment willingness was furthermore examined for the following specific scenarios associated with HCV treatment: common adverse events (i.e., depression), requirement for weekly clinic visits, requirement for addiction treatment, requirement for liver biopsy and a hypothetical 50% success rate following treatment.

Further self-reported variables of interest in this analysis included age, sex, ethnicity, housing status, main income source in the past 30 days, having been arrested or detained in the past 12 months, general health, physical and mental health problems, HIV status, drug addiction treatment, current enrolment in opiate maintenance program, injection drug use, illicit drug use, needle and equipment sharing and combined illicit drug use. Temporary housing was defined as living in a boarding house, shelter, detoxification centre, group home or hospital. General health status was self-categorized as ‘excellent’, ‘very good’, ‘good’, ‘fair’ and ‘poor’. Self-reported illicit drug use in the past 30 days included the drug type, number of days and mode of use. For the present analysis, cocaine, heroin, speed, crack, cannabis and alcohol were considered. Combination drug use, injection drug use and needle and equipment sharing in the past 30 days were also considered in this analysis.

Factors associated with having received HCV treatment and HCV treatment willingness were assessed using  $\chi^2$  or Fisher’s Exact Test, as appropriate. Multiple logistic regression models were fit with all variables of interest. These models were then subjected to backwards elimination. To assess if statistically signif-

Table 1

Baseline demographic characteristics of Canadian illicit drug users studied for uptake of, willingness and barriers to receive treatment for HCV infection ( $n = 188$ )

Characteristic <sup>a</sup>	$n = 188$ (%)
Mean age: years (S.D.)	43.6 (8.8)
Male sex	123 (65.4)
Aboriginal ethnicity	37 (19.7)
Unstable housing (temporary or homeless)	109 (58.0)
Social benefits as main source of income (in past 30 days)	171 (91.0)
Arrested or detained (in past 12 months)	57 (30.3)
“Fair” or “poor” self-reported general health	106 (56.4)
Physical health problems	161 (85.6)
Mental health problems	74 (39.4)
Ever tested positive for HIV infection	40 (21.3)
Ever been in drug addiction treatment	163 (86.7)
Currently enrolled in opiate maintenance treatment program	102 (54.3)
Ever injected drugs	178 (94.7)
Ever shared needles or injection equipment	162 (86.2)
Illicit drug use (in past 30 days)	146 (77.7)
Cocaine	62 (33.0)
Heroin	70 (37.2)
Speed	21 (11.1)
Crack	108 (57.4)
Cannabis	86 (45.7)
Alcohol	63 (33.5)
Combined drug use (in past 30 days)	82 (43.6)
Injection drug use (in past 30 days)	91 (48.4)
Needle or equipment sharing (in past 30 days)	15 (8.0)

<sup>a</sup> All characteristics are by patient self-report.

icant changes in the willingness for patients to undergo HCV treatment when specific different common scenarios are presented to the patient, McNemar's test was used. Statistically significant differences were assessed at a significance level of 0.05 and all reported  $P$ -values are two-sided.

### 3. Results

Key social, drug use and health characteristics of the analysis sample ( $n = 188$ ) are presented in Table 1.

Of the sample ( $n = 188$ ), 107 (56.9%) reported never having sought treatment for HCV infection and 96 (51.1%) reported having been offered treatment for HCV infection. In fact, 16.0% ( $n = 30$ ) reported previously ( $n = 26$ ) or currently ( $n = 4$ ) receiving treatment for HCV infection. Of those not initiating treatment for HCV ( $n = 158$ ), five refused to answer the questions about HCV treatment willingness. Of the remaining 153 subjects who had not received treatment, 76.5% ( $n = 117$ ) were either somewhat or definitely willing to receive such treatment.

To understand the factors associated with uptake of treatment for HCV infection, we compared the characteristics of individuals that previously or currently had ( $n = 30$ ) and had not ( $n = 158$ ) received such treatment (Table 2). In a multiple logistic regression analysis, HIV infection (adjusted odds ratio (AOR), 0.20; 95% CI, 0.04–0.88,  $P = 0.033$ ) and heroin use in the past 30 days (AOR, 0.34; 95% CI, 0.13–0.88,  $P = 0.027$ ) were both independently associated with a decreased uptake of treatment for HCV infection.

To investigate factors associated with willingness to receive treatment for HCV infection, we then compared the characteristics of untreated individuals that were willing ( $n = 117$ ) and not willing ( $n = 36$ ) to receive HCV treatment. In the univariate analysis (Table 3), willingness to receive treatment occurred more often in individuals self-reporting physical health problems. A decreased willingness to receive treatment was observed in individuals with HIV co-infection, current heroin use and current injection drug use. In a multiple logistic regression analysis (Table 4), the only factor independently associated with an increased willingness to receive treatment was the presence of physical health problems. Willingness to receive treatment was inversely associated with HIV infection and current injection drug use. Treatment willingness was not significantly influenced by any of the conditional treatment scenarios.

To further investigate barriers associated with seeking treatment for HCV infection, respondents who had not sought HCV treatment were asked why this was so. The major reasons (in decreasing frequency of response) were: lack of information/did not know that treatment was available ( $n = 25$ , 23.4%), absence of symptoms ( $n = 21$ , 19.6%), perceived side effects of treatment ( $n = 15$ , 14.0%), mild liver disease ( $n = 11$ , 10.3%), other medical co-morbidities ( $n = 8$ , 7.5%) and a lack of interest in treatment ( $n = 3$ , 2.8%). Individuals offered treatment for HCV, but in whom treatment was not initiated ( $n = 66$ ) were queried as to why this was so. Among respondents ( $n = 60$ ), treatment evaluation was ongoing in 16 (26.7%), concerns of treatment side effects were reported in 10 (16.7%), addictions issues were cited by 9 (15.0%), other medical contra-indications were present in 6 (10.0%) and 4 cited a lack of interest in treatment (6.7%).

### 4. Discussion

Effectively engaging marginalized individuals in HCV treatment is crucial for lowering the future HCV-related disease burden. The (self-reported) uptake of treatment for HCV infection in our study sample was 16%. This is higher than the rates previously reported among HCV-infected inner city residents in Vancouver (Grebely et al., 2006) and IDUs attending needle exchange programs in Australia (NCHECR, 2003), where only 1–4% have received HCV treatment. Our increased uptake may not be surprising given that the inner city community clinics from which respondents were recruited feature multi-disciplinary programs integrating general health, addiction and HCV treatment care. The study population – as recruited – may also represent a group that is relatively more engaged in basic health care by way of their relationship with and access to the community health clinics, thus, making them more likely to receive treatment for HCV.

Factors associated with decreased uptake of treatment for HCV infection in our study population included current heroin use and HIV/HCV co-infection. Current heroin use may be a proxy for acute intensive entrenchment in high-risk drug use, reducing the likelihood of engagement in health care. It may also be reflective of physician bias and a general reluctance to offer HCV treatment under such circumstances. Data from our centre (Grebely et al., in press-c) and others (Sylvestre et al.,



Table 2

Q4 Characteristics associated with having received treatment for HCV infection among illicit drug users (*n* = 188)

Characteristic	Treatment for HCV infection ( <i>n</i> = 30), <i>n</i> (%)	No treatment for HCV infection ( <i>n</i> = 158), <i>n</i> (%)	OR (95% CI)	<i>P</i> *
Mean age: years (S.D.)	46.1 (9.0)	43.1 (8.7)	–	0.10
Male sex	22 (73.3)	101 (63.9)	1.55 (0.65–3.71)	0.43
Aboriginal ethnicity	4 (13.3)	26 (16.5)	0.56 (0.18–1.72)	0.44
Unstable housing (temporary or homeless)	17 (56.7)	92 (58.2)	0.94 (0.43–2.06)	0.97
Social benefits as main source of income (in past 30 days)	29 (96.7)	141 (89.2)	3.50 (0.45–27.32)	0.32
Arrested or detained (in past 12 months)	8 (26.7)	49 (31.0)	0.81 (0.34–1.94)	0.80
“Fair” or “poor” self-reported general health	18 (60.0)	88 (55.7)	1.19 (0.54–2.64)	0.69
Physical health problems	26 (86.7)	135 (85.4)	1.11 (0.35–3.47)	0.99
Mental health problems	14 (46.7)	60 (38.0)	1.43 (0.65–3.14)	0.49
Ever tested positive for HIV infection	2 (6.7)	39 (24.7)	0.22 (0.05–0.96)	0.03
Ever been in drug addiction treatment	26 (86.7)	137 (86.7)	1.00 (0.32–3.14)	0.99
Currently enrolled in opiate maintenance treatment program	13 (43.3)	89 (56.3)	0.59 (0.27–1.30)	0.27
Ever injected drugs	29 (96.7)	149 (94.3)	1.75 (0.21–14.36)	0.99
Ever shared needles or injection equipment	24 (80.0)	136 (86.1)	0.65 (0.24–1.76)	0.40
Illicit drug use (in past 30 days)	20 (66.7)	126 (79.7)	0.51 (0.22–1.19)	0.18
Cocaine use	7 (23.3)	55 (34.8)	0.57 (0.23–1.41)	0.31
Heroin use	6 (20.0)	64 (40.5)	0.37 (0.14–0.95)	0.04
Crack use	11 (36.7)	93 (58.9)	0.40 (0.18–0.91)	0.03
Cannabis use	13 (43.3)	73 (46.2)	0.89 (0.41–1.96)	0.93
Alcohol use	7 (23.3)	56 (35.4)	0.55 (0.22–1.37)	0.28
Combined drug use (in past 30 days)	9 (30.0)	73 (46.2)	0.50 (0.22–1.16)	0.15
Injection drug use (in past 30 days)	10 (33.3)	81 (51.3)	0.48 (0.21–1.08)	0.11

2005) suggest that although occasional drug use does not impact response to treatment for HCV infection, frequent illicit drug use may be associated with decreased response to therapy. It is not surprising that HIV/HCV co-infected subjects were less likely to receive treatment, given low rates of treatment uptake (0–4%)

observed among similar subjects in other cohorts (Fishbein et al., 2004; Hall et al., 2004; Mehta et al., 2006; Walley et al., 2005). Interestingly, in two of these studies only 33–46% were referred by physicians for HCV treatment evaluation (Fishbein et al., 2004; Mehta et al., 2006). Given that co-infection with HIV leads

Table 3

Characteristics associated with willingness to receive treatment for HCV infection among illicit drug users not having received treatment for HCV infection (*n* = 153)

Characteristic	Willing to receive HCV treatment ( <i>n</i> = 117), <i>n</i> (%)	Not willing to receive HCV treatment ( <i>n</i> = 36), <i>n</i> (%)	OR (95% CI)	<i>P</i> *
Mean age: years (S.D.)	42.8 (8.7)	43.3 (8.2)	–	0.77
Male sex	80 (68.4)	19 (52.8)	1.93 (0.90–4.14)	0.13
Aboriginal ethnicity	20 (17.1)	11 (30.6)	0.47 (0.20–1.10)	0.10
Unstable housing (temporary or homeless)	73 (62.4)	18 (50.0)	1.66 (0.78–3.52)	0.24
Social benefits as main source of income (in past 30 days)	102 (87.2)	34 (88.9)	0.40 (0.09–1.84)	0.36
Arrested or detained (in past 12 months)	34 (29.1)	10 (27.8)	1.07 (0.46–2.45)	0.99
“Fair” or “poor” self-reported general health	66 (56.4)	20 (55.6)	1.03 (0.49–2.20)	0.99
Physical health problems	106 (90.6)	26 (72.2)	3.71 (1.42–9.66)	0.01
Mental health problems	46 (39.3)	13 (36.1)	1.11 (0.51–2.43)	0.85
Ever tested positive for HIV infection	22 (18.8)	15 (41.7)	0.32 (0.14–0.73)	0.008
Ever been in drug addiction treatment	99 (84.6)	34 (94.4)	0.32 (0.07–1.47)	0.16
Currently enrolled in opiate maintenance treatment program	61 (52.1)	24 (66.7)	0.54 (0.25–1.19)	0.18
Ever injected drugs	109 (93.2)	35 (97.2)	0.39 (0.05–3.22)	0.69
Ever shared needles or injection equipment	103 (88.0)	29 (80.6)	1.78 (0.66–4.81)	0.26
Illicit drug use (in past 30 days)	92 (78.6)	31 (86.1)	0.59 (0.21–1.68)	0.47
Cocaine use	35 (29.9)	17 (47.2)	0.48 (0.22–1.02)	0.06
Heroin use	41 (35.0)	20 (55.6)	0.43 (0.20–0.92)	0.03
Crack use	64 (54.7)	26 (72.2)	0.46 (0.21–1.05)	0.08
Cannabis use	56 (47.9)	14 (38.9)	1.44 (0.67–3.09)	0.35
Alcohol use	42 (35.9)	12 (33.3)	1.12 (0.51–2.47)	0.84
Combined drug use (in past 30 days)	100 (85.5)	25 (69.4)	0.89 (0.42–1.87)	0.75
Injection drug use (in past 30 days)	53 (45.3)	25 (69.4)	0.36 (0.16–0.81)	0.01

Table 4

Multiple logistic regression of factors associated with willingness to receive treatment for HCV infection among illicit drug users not having received treatment for HCV infection ( $n = 153$ )

Characteristic	AOR	95% CI	P
Physical health problems	4.07	1.46–11.37	0.007
HIV infected	0.28	0.12–0.68	0.005
Drug use by injection (in past 30 days)	0.28	0.12–0.68	0.005

to rapid progression of liver disease (Benhamou et al., 1999), further strategies for improving the evaluation and referral of HIV/HCV co-infected illicit drug users for HCV treatment are urgently needed.

Among those who reported that they had not received therapy for HCV infection, three out of four (77%) indicated a willingness to do so, suggesting that an interest in treatment is not a sizeable barrier to treatment in this group. This is consistent with data from other studies (Doab et al., 2005; Fischer et al., 2005b; Stein et al., 2001; Strathdee et al., 2005). Our data further confirmed that treatment willingness remained high even when respondents were being made aware of potentially onerous conditions or less favorable outcomes of treatment.

Factors associated with willingness to receive treatment for HCV infection reflected both physician and patient-related issues, such as HIV co-infection, recent abstinence from drug use and ongoing physical health problems. The observation that HIV/HCV co-infected illicit drug users are less willing to receive or accept treatment for HCV (Stein et al., 2001) (Fishbein et al., 2004) has been previously reported. This may reflect a negative experience with HIV therapy, a lack of interest in engaging in care for another chronic condition (which may currently be asymptomatic) or a desire to focus more on the HIV infection. The presence of ongoing health care problems, as reported by others (Strathdee et al., 2005) may mitigate this, while heavy ongoing drug use may further exacerbate it, whether or not HIV co-infection is present. Confirming this point, individuals that did not seek treatment for HCV were more often asymptomatic or fearful of possible side effects, quite apart from their reported lack of information about treatment and its availability. It has been demonstrated that IDUs told by a doctor that HCV can cause liver damage or cancer and IDUs with a higher perceived risk of developing cirrhosis or liver cancer were more likely to be interested in receiving treatment for HCV (Strathdee et al., 2005). Given the often asymptomatic nature of HCV-associated liver disease, illicit drug users may not be experiencing symptoms associated with liver disease and may not be actively seeking treatment for HCV due to a lack of knowledge about the potential long-term consequences of HCV and the availability of effective treatment.

As health care systems move forward to incorporate increased uptake of HCV treatment, it will be important to do so in a targeted way. The results of our study may help inform such an approach, initially targeting symptomatic individuals as well as those who are free from HIV infection and not deeply entrenched in current high-risk (injection) drug use. Implementing this approach within a multi-disciplinary program such as ours may increase the likelihood of success. Another strategy to con-

sider could include peer-support, coupled with directly observed therapy for the delivery of the medications in those requiring treatment (Grebely et al., in press-b, in press-c). Data from our centre have demonstrated the benefit of these approaches (Grebely et al., in press-b, in press-c).

Health care provider-related barriers to HCV treatment uptake must also be addressed. Many (especially non-specialist) physicians are not inclined or do not feel comfortable to provide HCV treatment care, especially to perceived 'difficult' patients such as active substance user populations (Litwin et al., 2007; Morrill et al., 2005; Thompson et al., 2005). Targeted physician education will go a long way towards addressing these systematic biases.

There are several limitations to the study methodology in this report. First, the results may not be generalizable to all other populations of illicit drug users in Canada or elsewhere. However, the demographic characteristics in this study population were similar to that of a large, community-based sample that we have previously described (Grebely et al., in press-a). Second, all data collected and analyzed were self-reported to enhance confidentiality between the research staff and subjects. Self-reports on drug use among illicit drug users have been demonstrated to be highly valid under appropriate study circumstances (Darke, 1998). Additionally, false-positive reporting of HCV status may occur, but appears to be less frequent than false-negative reporting (Best et al., 1999). In addition, testing and counseling for HIV and HCV infections are provided free of charge in Canada, with a high uptake of testing among high-risk individuals. We are therefore relatively confident of the validity of self-reported HCV and HIV infection status reported in our analyses. Third, the use of convenience sampling may have led to the inclusion of individuals that access care more frequently and are engaged in the healthcare system. Lastly, all interviews were face-to-face and may be associated with inherent interviewer bias and the tendency for participants to report socially desirable answers, although we took all reasonable measures to limit its impact, mainly by giving assurance to respondents that their answers will not affect their care and guaranteeing full data confidentiality.

In this study, we have demonstrated a low rate of current HCV treatment uptake likely associated with both patient and care provider characteristics, but with a significant potential for growth. Increased HCV treatment uptake could likely be accomplished by actively and systematically recruiting patients that we have identified as most receptive to considering treatment in the short-term into an environment that is most receptive to providing such treatment. Increasing the education of both patients and physicians on HCV and its treatment prospects will also be important in moving forward. Given that the successful reduction of the HCV disease burden in Canada crucially hinges on increased treatment uptake, such measures need to be expediently designed and evaluated.

### Conflict of interest

Authors J.G. and B.C. have consulted for pharma company Hoffmann-La Roche and Schering Canada. All other authors declare that they have no conflicts of interest.

## Q1 Uncited references

Feld and Hoofnagle (2005) and Pradat et al. (2002).

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