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Low rate of reinfection among a cohort of people who use drugs successfully treated for hepatitis C virus infection in Vancouver, Canada

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ABSTRACT

Introduction: Concerns about reinfection may be limiting HCV treatment uptake among people who use drugs (PWUD), with rates of 17.1/100 person-years in some cohorts. The aim of this study was to evaluate reinfection following successful treatment for hepatitis C virus infection in a cohort of people who inject drugs in Vancouver, Canada.

Methods: We identified a cohort of HCV-infected PWUD treated at our centre. Following cure, patients were maintained in long-term follow-up in a multidisciplinary program to address their medical, psychological, social, and addiction-related needs. HCV RNA measurements were repeated every 6 months, and ongoing drug use was documented. The primary outcome of this analysis was the occurrence of reinfection.

Results: 243 recent PWUD (use within 6 months of treatment initiation) have achieved SVR and maintained in long-term follow-up. Ongoing drug use post-treatment was documented in 195 individuals. Key characteristics: mean age 53 years, 25% female, 78% treatment naïve, 17% cirrhotic. Reinfection occurred in 4 cases, all in patients with ongoing drug use. This incidence was 1.05/100 [95% 0.8–5.2] person years based on 379 person-years of follow-up in individuals currently using drugs.

Conclusion: Approaches including long-term maintenance in multidisciplinary care may optimize long-term outcomes of HCV treatment in PWUD.

Introduction

The World Health Organization has set the goal of eliminating hepatitis C virus (HCV) as a public health concern by 2030 (World Health Organization & World Health Organization, 2016). With the availability of safe, effective directly acting antiviral (DAA) therapy options with > 95% cure rate (Kish, Aziz, & Sorio, 2017), this has become a feasible goal, from a biological standpoint. However, these treatments must be made available to the people who need them, particularly those at high risk of infection, and ongoing transmission.

People who use drugs (PWUD) make up a significant proportion of new HCV cases in developed countries, while treatment rates remain extremely low for this population (Grebely et al., 2017). There are numerous reasons why PWUD are not receiving HCV therapy, including lack of systematic screening or access to the medical system, among many others (Sperle, Hedrich, Palczak, Singleton, & Zimmerman, 2018). Another reason may be that providers are unwilling to prescribe expensive HCV treatment to individuals who present a risk of reinfection (Asher et al., 2016; Edlin, 2002; Sperle et al., 2018). In a survey of clinicians who attended a large hepatology and gastroenterology meeting, 85% were unwilling to provide HCV treatment to infected individuals who had used drugs in the past 30 days (Asher et al., 2016), largely due to concern about reinfection. Despite PWUD being identified as a priority group to receive HCV treatment in most clinical guidelines (European Association for the Study of the Liver, 2018), such attitudes may limit treatment uptake, ultimately impeding the goal of HCV elimination.

Reinfection is a legitimate concern. The largest risk group for reinfection are PWUD, specifically those injecting drugs, and men who have sex with men (Martinello, Hajarizadeh, Grebely, Dore, & Matthews, 2017). Many cohorts in both the interferon and DAA eras report rates of reinfection from 2 to 6 per 100 person-years (PY), depending on the prevalence of ongoing risk behaviours (Aspinall et al., 2013; Midgard et al., 2016; Rossi et al., 2018, Simmons et al., 2016). The British Columbia Hepatitis Testers Cohort, a large, longitudinal observational cohort in British Columbia, recently reported a reinfection rate of 3.1/100 PYs among recent PWUDs. After stratifying by birth year after 1975, this rate increased to 10.2/100 PYs (Rossi et al., 2018).

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Rather than excluding individuals from receiving treatment, providers and institutions should develop strategies to mitigate the risk of reinfection. The aim of this paper is to evaluate the rate of reinfection following successful HCV treatment among a cohort of PWUD in Vancouver, Canada, who had access to long-term, multidisciplinary care.

Methods

Study definitions

Recent drug use: confirmed drug use within 6 month of HCV treatment initiation

Active/current drug use: confirmed drug use in the post-treatment period.

Reinfection: positive HCV RNA after achieving sustained virologic response.

Study setting

This study took place at the Vancouver Infectious Diseases Centre (VIDC). VIDC is a research and medical centre that delivers specialty healthcare, and focuses on diagnosis and treatment of chronic infectious diseases, with an emphasis on HCV and HIV.

All participants had access to a range of services, which aim to address individuals' medical, social, psychological, and addiction-related needs. These include: identification and intervention of all medical and psychiatric co-morbidities; assistance with government housing and income assistance applications; and provision of addiction treatment, including opioid substitution therapy (OST). All patients had access to snacks, refreshments, and meal supplements throughout the workweek, as necessary. Appointments for follow-up evaluation could be specifically scheduled, or patients could be evaluated within our weekly support group structure. Taken together, these measures were meant to coordinate HCV treatment with long-term engagement in care.

Study design

This study was a retrospective chart review of a cohort of recent or active PWUD who were successfully treated for HCV infection. Drug use was assessed by urine drug screen on an ongoing basis, as well as patient self-report. All patients who initiated HCV treatment at our centre between March 2014 to December 2018 were considered for inclusion. Following determination of cure (sustained virologic response at 12 weeks after treatment completion, SVR12), individuals were maintained in long-term follow-up, with ongoing access to our multidisciplinary program. HCV RNA measurements (Abbott RealTime HCV Viral Load Assay) were repeated every 6 months, more often if there was a clinical suspicion of acute hepatitis. Specific strategies to reduce loss to follow-up were implemented if patients did not present for scheduled appointments. This included contacting the patients' other service providers, known places of residence, and pharmacies where medications were known to be obtained.

All viremic patients were offered treatment per contemporary guidelines, and none were excluded due to ongoing drug use. Until April 2017, HCV treatment in British Columbia was limited to individuals with fibrosis levels at or above METAVIR stage F2. Between April 2017 and March 2018, individuals with certain co-morbidities (such as HIV co-infection) or demographic factors (females of reproductive potential) were eligible for treatment. As of March 2018, access to treatment has been expanded to all HCV RNA positive individuals.

Outcome

The primary outcome of this analysis was the incidence of reinfection.

Analysis

Data collected for patients who met the inclusion criteria included demographic variables, HCV infection status, treatment regimens, injection drug use history, follow-up duration, and incidence of reinfection. Reinfection was differentiated from relapse by genotyping and resistance profiles. The incidence of reinfection was calculated as the number of occurrences per 100 person years of follow-up and was reported with a corresponding 95% Wilson confidence interval (95% CI).

Results

467 patients were initiated on treatment during the stated period and considered for inclusion. At the time of analysis, 53 individuals remained on treatment or had not yet reached the SVR12 time-point, 25 had incomplete data (17 of whom had at least one recorded negative HCV-RNA, of which 9 were in the post-treatment period but prior to SVR12), two were deceased on treatment, two discontinued treatment due to side effects, one patient experienced a virologic relapse, one was a non-responder. Additionally, 21 have not undergone any post-SVR HCV RNA testing with our centre, and 119 had no history or no recent history of drug use and were excluded. 243 individuals were therefore considered for this analysis, defined as those with a demonstrated recent history of drug use, achieving SVR at our centre with DAA therapy, and maintained in long-term follow-up. These data are summarized in Fig. 1.

Key demographics of those included in the analysis are provided in Table 1.

The median duration of follow-up (follow up since achieving SVR12) is 714 (range 134–1841) days, with 86% followed > 1 year. Reinfection was observed in 4 cases, all of which occurred in patients with ongoing injection drug use. The rate of reinfection was 0.84/100 PYs, based on 474 PYs follow up in this cohort, and 1.05/100 PYs based on 379 PYs follow up in the subset ongoing active PWUD-only cohort.

The age range of individuals who experienced reinfection was 38–67 years, with a mean age of 47 years. All subjects were male. Other characteristics identified in single patients included: HIV co-infection, cirrhosis, psychiatric co-morbidity, and homelessness. Regarding reinfection genotypes and timing, one patient was reinfected from genotype 1a to 3, discovered four weeks post-SVR; two patients were reinfected with their original genotype 1a, one discovered three weeks post-SVR, the other six months post-SVR; one patient was re-infected from genotype 3 to 1a, discovered 7 months post-SVR. In the case of the individual who experienced a reinfection three weeks post-SVR with the same genotype, reinfection was differentiated from a relapse based on the resistance profile of the isolates. Resistance testing of the first isolate at the beginning of treatment showed no resistance associated substitutions (RASs), and subsequent resistance testing showed the presence of an NS5A mutation which led to the conclusion of re-infection for this case. All re-infections were documented as persistent, and all 4 subjects will be offered re-treatment, with one individual having already initiated it.

Discussion

This paper describes the reinfection rate among people with and without confirmed drug use post-HCV treatment, in the context of a model of care which aims to address patients' multidisciplinary needs in an integrated manner. Those with confirmed drug use in the post-treatment period were younger, more often male, homeless, and with higher rates of psychiatric and HIV diagnoses, and polysubstance use. The few reinfected individuals were also younger and more often male. Younger age, in particular, has previously been correlated to higher rate of reinfection (Midgard et al., 2016; Rossi et al., 2018).

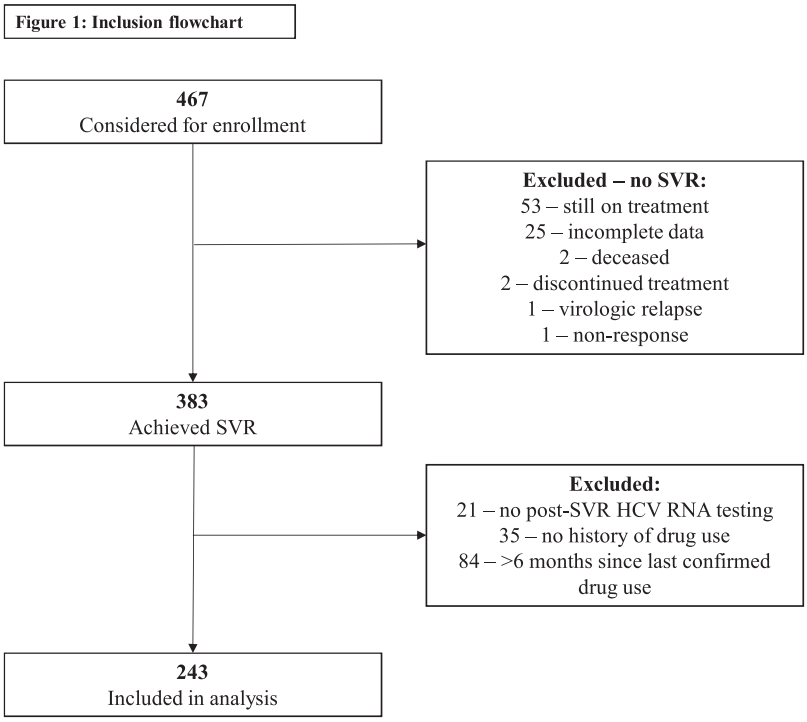

Fig. 1. Inclusion flowchart.

Table 1
Participant demographic and disease characteristics.

Characteristics	Total cohort, n (%)	Active drug use post-treatment, n (%)	No drug use post treatment, n (%)
Population size	243	195	48
Age (mean)	54	53	60
Sex			
Male	173 (71%)	146 (75%)	27 (57%)
Female	70 (29%)	49 (25%)	21 (43%)
HIV **co**-infection	34 (14%)	29 (15%)	5 (10%)
HCV treatment experienced	62 (26%)	43 (22%)	19 (39%)
Homeless	24 (10%)	23 (12%)	1 (2%)
On OST	116 (48%)	103 (53%)	13 (27%)
Psychiatric Diagnosis	109 (45%)	94 (48%)	15 (32%)
Cirrhosis	50 (21%)	33 (17%)	17 (35%)
Substances used			
Opiates only	59 (24%)	39 (20%)	12 (25%)
Cocaine only	30 (12%)	18 (9%)	12 (25%)
Amphetamines only	20 (8%)	12 (6%)	8 (17%)
Multiple	142 (58%)	126 (65%)	16 (33%)
Genotype			
1a	149 (61%)	123 (63%)	26 (54%)
1b	16 (7%)	10 (5%)	6 (13%)
3	58 (24%)	47 (24%)	11 (23%)
Other	19 (8%)	14 (7%)	5 (10%)

In a population with confirmed ongoing risk of infection, we documented a low reinfection incidence rate of 1.05/100 person years, as compared to other studies within similar populations (Simmons, Saleem, Hill, Riley, & Cooke, 2016). This may relate to continued engagement in care after achievement of SVR, as well as programming which addresses upstream determinants of health, such as food security and housing. As programs to treat HCV-infected PWUD are expanded, approaches such as this must be included to optimize long-term outcomes in this population. Such programs will be especially useful in settings where HCV treatment scale up is not meeting the modelling targets for reduced reinfection rates, as is the case in Canada. Notably, all four reinfections occurred within a relatively short time post-SVR (three weeks to seven months). Follow-up of active PWUD from EOT to SVR12 and 12–24 weeks later may be a key time to prevent reinfection. This may also speak to the potential of a cohort effect in studies with higher reinfection rates but shorter term follow up.

This analysis presents the reinfection rate in a single arm study within a relatively small cohort, and therefore conclusions regarding causality between the multidisciplinary programming and the lower rate of reinfection can only be drawn with caution. While this cohort is made up mainly of individuals with ongoing risk behaviours, it is possible that they represent a subset of people who are more motivated to maintain their HCV cure. There may be a sampling bias, in self-selection of individuals who are choosing to engage in care in a long-term manner. However, many of our patients are recruited from community outreach programs, in which we provide point-of-care testing and linkage to care to individuals who are otherwise disengaged from healthcare services, therefore making up a population who could be considered at highest risk of re-infection. Additionally, our program has robust strategies to re-engage those who may be lost to follow up (particularly those with highest risk behaviors for HCV transmission). Taken together, these approaches serve to mitigate the risk of selection of patients with inherently lower risk of HCV reinfection in our long-term follow-up cohort. Nonetheless, this potential bias must be continuously acknowledged in analyses of this type.

Reinfection rates as high as 17.1/100 person-years have been reported in active PWUD who have received successful HCV treatment (Schulkind et al., 2018). While reinfection is to be anticipated in some cases, high rates of reinfection will hamper efforts to eliminate HCV in these key populations (Hickman, De Angelis, Vickerman, Hutchinson, & Martin, 2015). Treatment should not be withheld due to concerns of reinfection, but rather care should be provided to individuals in a manner which encourages reduction of risk factors. These include providing effective needle and syringe programs and education about highest risk behaviors. Especially for individuals at high risk of re-infection, models which integrate multidisciplinary programming, address upstream determinants of risk behaviours, and promote long-term

engagement in care, may reduce the frequency of behaviours that lead to reinfection. It may be beneficial to capitalize on the achievement of HCV cure to consolidate engagement in care and reduce the risk of reinfection by reducing high risk behaviours as part of a comprehensive intervention. This may help us address the goals of HCV control in this important population. From a broader perspective, this may also be an important tool for improvement of the quality of life and promotion of social integration of vulnerable inner-city residents. Longer term follow up is indicated to evaluate our model in terms of its ability to maintain aviremia in this population, both in the period directly after SVR, as well as in the long term.

CRediT author statement

Conceptualization – BC; Data curation, - BC, DT, AT, AA, JH, TM, Formal analysis; BC, JH; Funding acquisition – LC, RY, BC, JH; Investigation – BC, DT, JH; Methodology – BC, JH; Project administration – RY, LC; Supervision – BC; Validation – TM, AA, AT; Visualization – TM; Writing – original draft – JH, BC; review and editing – all authors. All authors have seen and approved the final version.

Statement on conflicts of interest

VIDC is partly supported by the Merck & Co, Gilead Sciences, AbbVie, and ViiV Healthcare. This analysis was conducted as part of VIDC's overall research program and no funding was specifically dedicated to it.

Individual authors conflicts:

AA– Travel grants from AbbVie and Merck & Co.

AT – Travel grants from AbbVie.

DT – Honoraria from Merck & Co.

JH – Travel grants from AbbVie.

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LC, RY, and TM report no conflicts.

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