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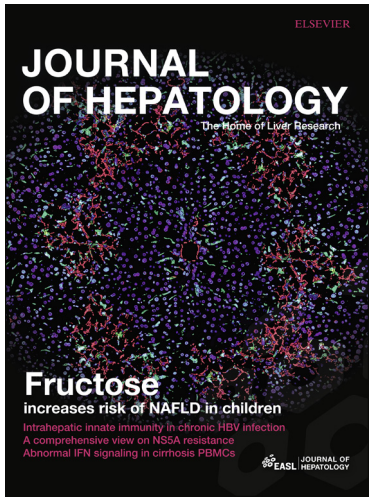

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PII: S0168-8278(18)32288-8
DOI: https://doi.org/10.1016/j.jhep.2018.07.025
Reference: JHEPAT 7060

To appear in: *Journal of Hepatology*

Received Date: 3 May 2018
Revised Date: 20 June 2018
Accepted Date: 20 July 2018

Please cite this article as: Rossi, C., Butt, Z., Wong, S., Buxton, J., Islam, N., Yu, A., Darvishian, M., Gilbert, M., Wong, J., Chapinal, N., Binka, M., Alvarez, M., Tyndall, M., Krajden, M., Janjua, N., The BC Hepatitis Testers Cohort Team, Hepatitis C Virus Reinfection after Successful Treatment with Direct-Acting Antiviral Therapy in a Large Population-Based Cohort, *Journal of Hepatology* (2018), doi: https://doi.org/10.1016/j.jhep.2018.07.025

Hepatitis C Virus Reinfection after Successful Treatment with Direct-Acting Antiviral Therapy in a Large Population-Based Cohort

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Running head: HCV reinfection post DAA treatment

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Keywords: Hepatitis C, Direct-Acting Antiviral, Reinfection, Injection Drug Use, Epidemiology, Canada

Word Count: 3,828

Number of Tables and Figures: 4 Tables and 2 Figures

Authors Contributions

NJ, SW, AY, MA, MK participated in the data acquisition. NJ conceived the analysis presented in this paper. CR and NJ designed the study. CR performed analyses guided by NJ and wrote the first draft of the paper and incorporated revisions. All authors contributed in the interpretation of results, manuscript preparation and revisions. All authors read and approved the final manuscript.

Financial Support Statement:

This work was supported by British Columbia Centre for Disease Control and the Canadian Institutes of Health Research [Grant # NHC – 142832 and PHE-141773]. Carmine Rossi is supported by a Canadian Institutes of Health Research (CIHR) and Canadian Network on Hepatitis C (CanHepC) Postdoctoral Fellowship Award. Maryam Darvishian is supported by a CanHepC and Michael Smith Foundation for Health Research Postdoctoral Fellowship Award.

Declaration of interests

MK has received grant funding via his institution from Roche Molecular Systems, Boehringer Ingelheim, Merck, Siemens Healthcare Diagnostics and Hologic Inc.

Abstract

Background & Aims: Direct-acting antiviral therapies (DAA) are an important tool for hepatitis C virus (HCV) elimination. However, reinfection among people who inject drugs (PWID) may hamper elimination targets. We therefore estimated HCV reinfection rates among DAA-treated individuals, including PWIDs.

Methods: We analyzed data from the BC Hepatitis Testers Cohort which included ~1.7 million individuals screened for HCV in British Columbia, Canada. We followed HCV-infected individuals treated with DAAs who achieved a sustained virologic response (SVR) and had ≥1 subsequent HCV RNA measurement to April 22nd, 2018. Reinfection was defined as a positive RNA measurement after SVR. PWIDs were identified using a validated algorithm and classified based on recent (<3 years) or former (≥3 years before SVR) use. Crude reinfection rates per 100 person-years (PYs) were calculated. Poisson regression was used to model adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CI).

Results: Of 4,114 individuals who met inclusion, most were male (n=2,692, 65%), born before 1965 (n=3,411, 83%) and were either recent (n=875, 21%) or former PWIDs (n=1,793, 44%). Opioid-agonist therapy (OAT) was observed in 19% of PWIDs. We identified 40 reinfections during 2,767 PYs. Reinfection rates were higher among recent (3.1/100 PYs; IRR: 6.7, 95% CI: 1.9, 23.5) and former PWIDs (1.4/100 PYs; IRR: 3.7, 95% CI: 1.1, 12.9) than non-PWIDs (0.3/100 PYs). Among recent PWIDs, reinfection rates were higher among individuals born after 1975 (10.2/100 PYs) and those with co-infected with HIV (5.7/100 PYs). Only one PWID receiving daily OAT developed reinfection.

Conclusions: Population-level reinfection rates remain elevated after DAA therapy among PWIDs because of ongoing exposure risk. Engagement of PWIDs in harm-reduction and support services is needed to prevent reinfections.

Abstract word count: 275 words

Lay Summary:

We estimated HCV reinfection rates after successful treatment with direct-acting antiviral therapies. Our findings showed that the risk of reinfection was highest among people with recent injection drug use. Among people who inject drugs, daily use of opioid-agonist therapy was associated with a lower risk of reinfection.

Highlights

- DAA therapies are an important component of HCV elimination strategies.
- Larger population-level reports of reinfection rates after DAA therapy are lacking.
- HCV reinfection rates remain elevated among people who recently injected drugs.
- Opioid-agonist therapy mitigates reinfection risk.

Background

Chronic hepatitis C virus (HCV) is associated with substantial morbidity and mortality, with > 71 million people infected worldwide in 2015 [1]. In 2013, an estimated 700,000 deaths globally were attributed to HCV-related liver disease sequelae, namely cirrhosis and hepatocellular carcinoma [2]. Mortality is expected to increase as many individuals infected with HCV decades ago are aging and at high risk of chronic liver disease [3, 4]. With the introduction of highly effective and well-tolerated, all-oral direct-acting antiviral (DAA) therapies to treat chronic HCV infection[5, 6], there has been renewed optimism regarding the ability to reduce the HCV disease burden and improve treatment outcomes in traditionally difficult to treat or cure populations. This includes those co-infected with HIV[7] as well as people who inject drugs (PWID) [8].

However, as HCV infection does not result in sterilizing immunity, individuals with ongoing risk activities remain vulnerable to reinfection following cure of their initial infection [9]. Thus, reinfection after successful HCV treatment is an important public health issue and may impact efforts to control HCV transmission [10, 11]. PWIDs have been shown to be adherent to DAA treatments and can be effectively cured [12, 13]. However, concerns about reinfection risk impacts clinical decision-making regarding treatment of PWIDs[14, 15] who remain at risk of ongoing transmission. Although, reinfection is a major concern in the DAA era, estimates of reinfection rates have been limited to the interferon era where treatment was largely restricted to motivated patients who would most likely benefit from therapy and reinfection rates were low [16-20]. As DAAs have mitigated concerns related to compliance and adherence among PWIDs with ongoing injection behaviours, it has been postulated that reinfection rates with DAAs may be higher than during the interferon era [21]. However, population-level data on reinfection following successful DAA treatment is scarce [11].

The objective of the current study was to assess HCV reinfection rates in a population-based cohort of HCV-infected individuals who initiated all-oral DAA therapy in British Columbia (BC), Canada, with an emphasis on those identified as PWIDs.

Materials and methods

Study population

BC is a Canadian province with 4.8 million inhabitants. All residents of BC are registered in the publicly funded Medical Services Plan that acts as a single-payer system and covers services provided by fee for service practitioners including general practices and private laboratories. In 2016, an estimated 55,000 individuals were infected with HCV. Until March 2017, public reimbursement for DAA treatment in BC was restricted to patients, including PWIDs, with at least moderate fibrosis (METAVIR stage ≥ F2). Between April 2017 and March 2018, access was expanded to include individuals with comorbidities such as HIV co-infection, diabetes, chronic kidney disease, or any other condition that could accelerate disease progression or necessitate early treatment [22]. Starting March 2018, treatment is available to anyone with HCV with regardless of fibrosis level.

We utilized data from the British Columbia Hepatitis Testers Cohort (BC-HTC) which includes all individuals tested for HCV or HIV at the British Columbia Centre for Disease Control Public Health Laboratory (BCCDC-PHL) or who have been reported to public health as a confirmed case of HCV, HIV, hepatitis B or active tuberculosis (Supplementary Table 1). Using a unique personal health number, these data were linked with data on medical visits, hospitalization records, prescription drug dispensations, and deaths. All dispensed medications including HCV treatments and opioid-agonist therapy (OAT) are recorded in a central system called PharmaNet, included in the cohort. The BCCDC-PHL is a centralized laboratory responsible for performing nearly all serologic testing (95%)

and all confirmatory HCV RNA testing and HCV genotype testing in BC. Further information about the BC-HTC, including methodology and data linkages have previously been published [23, 24].

This analysis included all HCV-positive individuals successfully treated with an all-oral, interferon-free, DAA regimen and who had at least one valid HCV RNA measurement after achieving a sustained virologic response (SVR, see Case definitions). DAA therapy became available in BC on January 23rd, 2014. HCV RNA laboratory results were available until April 22nd, 2018. To allow sufficient follow-up time to observe reinfection events, we, therefore, included individuals who initiated treatment until July 15th, 2017.

Data linkage to establish the BC-HTC was performed under the auspices of the BCCDC's public health mandate. This study was reviewed and approved by the Behavioral Research Ethics Board at the University of British Columbia (H14-01649).

Case definitions

SVR was assessed using the first available HCV RNA measurement obtained between a minimum of 10 weeks to a maximum of 52 weeks after the end date of the last DAA prescription (i.e. SVR date). Individuals with a negative or undetectable HCV RNA test were considered to have achieved SVR. HCV RNA measurements were determined using the Abbott Real-Time Reverse Transcriptase polymerase chain reaction assay, with a lower limit of detection of 12 IU/mL. We selected a minimum of 10 weeks to define SVR because in the clinical setting, physician appointments are not always scheduled at exactly 12 weeks [25]. Only the first DAA treatment episode was considered in this analysis. Reinfection was defined as a single positive HCV RNA test measured after SVR. The date of reinfection was calculated as the midpoint between the last negative and first positive HCV RNA

measurement. Reinfections were considered to be persistent if they did not result in spontaneous clearance within six months of reinfection [18].

We assessed the following factors and their association with the risk of HCV reinfection: age at treatment initiation, birth cohort, sex, year of HCV diagnosis, HIV co-infection, injection drug use, OAT use, problematic alcohol use, and major mental illness.

Injection drug use, problematic alcohol use, and major mental illness were defined based on international classification of diseases (ICD) diagnostic or procedure codes, or fee item codes from a medical-services plan (medical visits), discharge abstract database (hospital admissions), or prescription database, as applicable (Supplementary Table 2). HIV diagnosis was based on serologic testing as per provincial guidelines, a record in the provincial HIV/AIDS reporting system, or three medical visits or an admission to hospital with a HIV-related diagnostic code. Assessment of OAT was based on the record of dispensed prescriptions in the centralized prescription database, PharmaNet, which records all prescriptions dispensed in the province. For the primary analysis, we utilized a more sensitive algorithm to identify PWIDs that included injection-related infections (>90% sensitivity) in addition to a medical visit or hospital admission for major drug-related diagnoses [26]. More specific algorithms to identify PWIDs were explored in sensitivity analyses. We further classified PWIDs based on when the latest definition-specific administrative record was observed. Individuals with major drug or injection-related diagnoses in the last three years prior to SVR were considered to be recent PWIDs and those with diagnoses more than three years prior were considered to be former PWIDs. OAT use was assessed only among former or recent PWIDs and was classified as daily (≥ 84 daily dispensations) or non-daily use (< 84 dispensations), in the 12 weeks prior to SVR. This time period

was selected to correspond to OAT use since the end of therapy. Presence or absence for all of these covariates were assessed prior to the SVR date.

Statistical analysis

We compared demographic and risk factor characteristics between included and excluded patients (i.e. those without post-SVR measurements) who achieved SVR. Included individuals were followed from the SVR date until reinfection or their last negative HCV RNA measurement. We calculated incidence rates per 100 person-years (PYs) of follow-up for overall and persistent HCV reinfections and corresponding 95% confidence intervals (CIs), assuming a Poisson distribution. Cumulative incidence curves compared the risk of reinfection by PWID status. Poisson regression was used to model both age and sex-adjusted incidence rate ratios (IRRs) as well as fully-adjusted IRRs for overall and persistent reinfection risk factors. All tests were two-sided at a significance level of 0.05. All analyses were performed using SAS version 9.4 (Cary, NC, USA). For further details regarding the materials used, please refer to the CTAT table.

Results

Between January 23rd, 2014 and July 15th, 2017, 5,292 individuals treated with all-oral DAA therapy achieved SVR. Of these individuals, 4,114 had at least one post-SVR HCV RNA measurement and were included in this analysis (Figure 1). Excluded individuals who also achieved SVR, but did not have a post-SVR HCV RNA measurement, were younger, more likely to be recent or former PWIDs or be on OAT, more likely to have a history of problematic alcohol consumption, and less likely to be HIV co-infected (Supplementary Table 3).

Overall, most individuals were male (65%), Caucasian (92%), were between the ages of 45 and 64 (median age 60 years, interquartile range [IQR]: 54, 64) and were PWIDs (65%), with either recent

(21%) or former history (44%) of injection (Table 1). Since completion of DAA therapy, OAT use was identified in 513 patients (19% of all PWIDs, n = 2,668). Individuals were treated predominately with sofosbuvir/ledipasvir (61%) or sofosbuvir plus ribavirin (17%) and the majority were HCV treatment-naive (77%). Participants were followed for a total of 2,766.8 PYs. The median follow-up time was 123 days (IQR: 84, 357) and the median time to the first post-SVR HCV RNA measurement was 86 days (IQR: 82, 106). Only 39% of participants had ≥ 2 post-SVR HCV RNA measurements. Among those testing more than once during study follow-up, the median time between HCV RNA measurements was 182 days (IQR: 90, 275).

HCV reinfection

During post-SVR follow-up, we identified 40 reinfections, of which 33 (83%) were persistent. Among the persistent reinfections, four were subsequently retreated and achieved SVR again. Comparison of pre-treatment and reinfection HCV genotypes are provided in Supplementary Table 4. The overall and persistent reinfection rates were 1.44 (95% CI: 1.03, 1.97) and 1.19 per 100 PYs (95% CI: 0.82, 1.68), respectively (Table 2). We observed higher overall and persistent reinfection rates among younger individuals (< 45 years), those born after 1975, males, recent PWIDs, and those with major mental illness, problematic alcohol consumption and HIV co-infection.

Reinfections among PWID

Among recent PWIDs, 21 reinfections were detected during 674.3 PYs of follow-up, yielding a reinfection rate of 3.11 per 100 PYs (95% CI: 1.93, 4.76). Of these, 18 were persistent reinfections (rate 2.67 per 100 PYs, 95% CI: 1.58, 4.22). Reinfection rates were highest among recent PWIDs born after 1975 (10.2 per 100 PYs, 95% CI: 3.74, 22.2; Table 3), those with HIV co-infection (5.67 per 100 PYs, 95% CI: 2.59, 10.8) and those with problematic alcohol use (4.55 per 100 PYs, 95% CI: 2.35,

7.94). There was only one reinfection observed among PWIDs who used OAT daily in the previous 12 weeks prior to SVR. Among recent PWIDs, the cumulative risk of both overall and persistent reinfection initially increased rapidly in the first 36 weeks after SVR, with reinfection being less common afterwards (Figure 2). The cumulative risk of reinfection at 52 weeks post-SVR was higher among recent PWIDs (2.8% overall and 2.3% for persistent reinfection), than among former (1.2% overall and 1.1% for persistent reinfection) or non-PWIDs (0.2% overall and 0.1% for persistent reinfection).

Factors associated with reinfection

In the multivariable Poisson model, PWIDs with recent (IRR 6.7, 95% CI: 1.9, 23.5) and former use (IRR 3.7, 95% CI: 1.1, 12.9) had a significantly elevated risk of overall reinfection (Table 4). Major mental health illness, problematic alcohol use, or HIV co-infection were not associated with HCV reinfection after SVR. Results were consistent when the analysis was restricted to persistent reinfections. In an analysis restricted to PWIDs, daily OAT use was associated with a non-significant reduction in the risk of reinfection (IRR 0.7, 95% CI: 0.1, 5.6).

Sensitivity analyses

Crude HCV reinfection rates were equally elevated among recent PWIDs regardless of the algorithm used to identify them (Supplementary Table 5). These rates ranged between 2.74 (95% CI: 1.63, 4.34) to 5.61 per 100 PYs (95% CI: 3.21, 9.11). Crude reinfection rates were highest among recent and former PWIDs identified using the most specific administrative database algorithm that required two medical services visits with only injection drug use-related codes. Results were also consistent with persistent HCV reinfection rates. In the multivariable Poisson model, recent PWIDs remained associated with overall reinfection, with IRRs ranging from 3.7 (95% CI: 1.5, 9.2) to 5.6 (95% CI: 2.3,

13.8). Model results were also consistent when persistent reinfections were examined (Supplementary Table 6) and when the main analysis was restricted to those who had SVR assessed at least 12 weeks after treatment (Supplementary Table 7) .

Discussion

This paper reports the incidence of HCV reinfection in a large, real-world setting following the introduction of DAA therapies. To our knowledge, this is the first study of HCV reinfection post-DAA therapy in a representative and well-defined population. We found that the incidence of reinfection is higher among recent PWIDs and of note, those who used OAT continuously after completing HCV treatment, had a lower reinfection rate. These results highlight the need for engaging PWIDs with ongoing risk in harm reduction and prevention services following treatment to reduce reinfection risk to achieve World Health Organization (WHO) HCV elimination goals [27].

There is limited data on HCV reinfection following successful HCV treatment with DAAs. An early meta-analysis of five studies, comprising 131 current or former PWIDs (range 9 to 42 participants) treated with interferon-based therapies, reported a pooled reinfection rate of 2.4 per 100 PYs [16]. More recently, a review of low and high-risk HCV mono-infected patients also treated primarily with interferon-based therapies, estimated reinfection rates of 0.19 and 2.2 per 100 PYs, respectively, although estimates in these studies ranged considerably [17]. Additional studies have reported interferon era reinfection rates that range between 4.9 and 15.5 per 100 PYs for those with ongoing injection exposure following treatment [18, 28, 29]. We recently reported reinfection rates of 1.00 and 2.11 per 100 PYs, overall and for PWIDs, respectively, in BC, following successful interferon-based therapy [20]. Our current estimates of the reinfection rate following DAA therapies, overall (1.44 per 100 PYs), and among recent PWIDs (3.11 per 100 PYs) is slightly higher than previous estimates from

the interferon era in the same population [20]. However, when we use the same PWID definition as the interferon analysis, we find that our reinfection estimate among recent PWIDs is considerably higher (4.99 per 100 PYs, Supplementary Table 5). In the interferon-era, PWIDs were less likely to be treated and those who were treated were likely not engaging in risky injecting behaviours, thus resulting in lower HCV reinfection rates [21, 24]. The introduction of all-oral DAA therapies have mitigated concerns related to HCV treatment duration and compliance, and have increased the number of current and former PWIDs who are eligible and willing to initiate treatment [30]. However, given the fibrosis restrictions in place in BC during the study period, our population likely represents one with more advanced liver disease and a relatively lower risk for HCV reacquisition. Thus, as treatment is expanded to everyone, including younger PWIDs with higher risk injecting behaviours, reinfection rates could likely increase.

Other studies have reported higher HCV reinfection rates after DAA therapy among PWID and other high-risk populations, including men who have sex with men (MSM) [31, 32]. In a German population-based registry of 2,074 DAA treated patients (37% PWIDs, 12% MSM), the overall reinfection rate was 1.8 per 100 PYs [31]. In an analysis of 199 current or former PWIDs enrolled in the C-EDGE Co-Star trial, the reinfection rate was 2.3 per 100 PYs. As with the current study, more than 50% of reinfections occurred within one year of SVR in both of these settings. These data suggest that reinfection rates in our study are similar, though comparison is difficult due to differences in study populations and definitions.

As expected, recent PWIDs had the highest reinfection rates. Among recent PWIDs, males, those with younger age, more recent HCV diagnosis, problematic alcohol use, and HIV co-infection had higher reinfection rates. Of note, there was only one reinfection identified among PWIDs engaged with OAT.

These findings confirm the need for harm-reduction and additional support strategies in reducing the risk of reinfection and the future liver disease burden among people with ongoing injecting behaviours with specific emphasis on younger, male PWIDs with problem alcohol use or HIV co-infection [33]. As with primary HCV infection, a myriad of single and multicomponent prevention strategies have been suggested to reduce ongoing exposure [10]. These include provision of OAT and high-coverage needle-syringe programs (NSP)[34], as well as psychotherapy and peer-based drug cessation programs for stimulant use [35]. In our previous study, we have shown significant effect of OAT and psychotherapy in reducing risk of reinfection among PWIDs treated with interferon [20]. Furthermore, additional strategies such as reducing stigma and discrimination associated with injecting behaviours, promotion of mental health services[20], linkages to social services improving food, housing and job security, may also reduce HCV reinfection following successful treatment [36]. As PWIDs with ongoing risk have multiple co-occurring conditions such as HIV co-infection, mental illness, and problematic alcohol use, integration of HCV care within multidisciplinary settings that offer both addiction, mental health and clinical and social work/services have been recommended [37]. With the ongoing opioid-related epidemic in North America, integrated services are expected to improve overall health and survival of PWIDs.

This study utilized administrative-linked data to identify PWIDs with both recent and former injection exposure. Given the challenges associated with assessing substance and harm-related exposures using health services data, we employed a range of previously validated PWID definitions from the BC-HTC, however, it is unlikely that any approach would capture all injection drug users in the province [26]. Our primary analysis relied on a highly sensitive definition which included injection-related infections that would capture the most PWIDs in the province who would not be identified uniquely with major injectable drug or addiction-related diagnoses [38]. This provided a more conservative estimate of the

rate of HCV reinfection among PWIDs. Indeed, our alternative definitions that provided greater specificity, but lower sensitivity, yielded reinfection rates that were 80% higher among recent PWIDs. These findings suggest that HCV reinfection rates may be higher among those seeking care for specific drug or harm-related diagnoses and thus these individuals would benefit from interventions such as OAT and NSP that could be provided or referred to at the point-of-care. Alternatively, however, it is possible that these individuals may be more closely monitored for reinfection, given their ongoing risk behaviours, and this is reflected in their higher reinfection rates.

A major strength of the current study included the use of administrative-linked data which allowed us to capture all DAA treatment initiators, as well as OAT use, in a well-defined study population. Furthermore, given centralized HCV RNA testing at BCCDC-PHL, the frequency and timing of RNA measurements reflects the real-world clinical management of HCV-infected individuals post-SVR. This has resulted in increased generalizability of our findings to other jurisdictions in Canada and abroad. Lastly, to date, this is the largest and only population-based study of HCV reinfection rates after SVR with all-oral, interferon-free therapies [11]. Using linked laboratory and administrative data has provided a strong foundation for population-level monitoring of HCV reinfection rates, which will help support the program planning required to achieve WHO HCV elimination goals. This framework also demonstrates a proof of concept that could be applied in other settings with similar population-based data sources for monitoring reinfection rates in the entire population.

The results from this study should be interpreted cautiously in light of several limitations. First, we could not distinguish late relapse from true reinfection which would require sensitive sequencing methods or phylogenetic analyses data [39]. However, a study of trial populations demonstrated that <3% of all episodes of sequencing-confirmed late relapse occurred after 12 weeks post-treatment [40].

Based on these data it is probable that the recurrences of HCV RNA identified in this study are reinfections. This is also consistent with the fact that we found larger relative rates for HCV RNA recurrence among PWIDs with recent risks lends further credence these being reinfections as opposed to relapses [11].

Second, post-SVR follow-up after DAA therapy is limited. As a result, it is unclear if or how reinfection rates will change with further time since achieving SVR. It is conceivable that those who have the greatest probability of engaging in high-risk behaviour would become reinfected soon after SVR, and thus reinfection rates would decrease with time. It is also possible that risk factors are variable and high rates of reinfection may persist many years after SVR [19]. In addition, it is also important to note that we may have underestimated reinfection rates given that we excluded patients without subsequent HCV RNA measurements who were more likely to be younger, male and recent PWIDs. This highlights the need for continued engagement of treated HCV patients in clinical care to identify possible reinfection episodes.

Furthermore, although the median time to the first HCV RNA measurement after SVR was short, subsequent testing occurred approximately every six months, and thus it is possible that we may have underestimated the true incidence rate of reinfection following SVR given that we may have missed cases of spontaneous clearance after reinfection [41]. Recent evidence has suggested higher rates of spontaneous clearance among PWIDs who are repeatedly exposed to infections [42]. From a clinical standpoint, however, persistent reinfections are most relevant and, as others, we have attempted to characterize these reinfections separately from those that also spontaneous clear [18, 32]. Additionally, we may also have underestimated reinfection rates as we only included individuals who achieved SVR

and did not assess if those who we believe failed treatment were, in fact, quickly reinfected after end of treatment.

The results from this study have important implications for the management of HCV-infected individuals undergoing DAA therapy. With the lifting of fibrosis-related treatment restrictions in Canada in 2018 and the greater emphasis on treatment-as-prevention as a strategy for HCV elimination, a greater number of PWIDs will be receiving DAAs. This will result in treatment of younger PWID, many of whom will continue to be exposed to HCV through ongoing substance use and high-risk behaviours. Therefore it is imperative to minimize the risk of reinfection. Our data suggest that engagement into OAT reduces reinfection risk and this likely needs to be part of a comprehensive harm reduction programs that are offered with DAA therapies.

In conclusion, this is the first population-based study to address HCV reinfection in the DAA era and employed administrative-data linkages with near complete coverage to assess risk factors for HCV reinfection. We found that rates of HCV reinfection following successful treatment with DAA therapies are high among people with recent injection drug use exposure. Only one of the PWIDs who were on daily OAT developed reinfection, suggesting benefits of engagement in this strategy, although this requires further follow-up and a larger sample size to assess the long-term impact of OAT. Our results highlight the need for engagement of people with ongoing injecting risk in harm-reduction and support services to prevent reinfections following successful treatment. This population-level linked laboratory and administrative dataset provides a platform for comprehensive outcome evaluation during the DAA era.

Acknowledgements

We acknowledge the assistance of BCCDC, PHSA Performance Measurement and Reporting, Information Analysts, Ministry of Health Data Access, Research and Stewardship, MSP, DAD, Medical Beneficiary and Pharmaceutical Services program areas, BC Ministry of Health, BC Cancer Agency and their staff involved in data access, procurement and data management.

Disclaimer

All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

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Table 1: Baseline characteristics of participants for the analysis of HCV reinfection in British Columbia, Canada (n = 4,114)

	n (%) or median (IQR)
Age group	
< 45 years	294 (7%)
45 to 64 years	2,948 (72%)
≥ 65 years	872 (21%)
Median age (IQR), years	60 (54, 64)
Birth cohort	
< 1965	3,411 (83%)
1965 to 1974	487 (12%)
≥ 1975	216 (5%)
Year of HCV diagnosis	
1990-1997	1,099 (27%)
1998-2004	1,337 (32%)
≥ 2005	1,678 (41%)
Male gender	2,692 (65%)
PWIDs	
Recent (< 3 years before SVR)	875 (21%)
Former (≥ 3 years before SVR)	1,793 (44%)
No	1,446 (35%)

OAT, in previous 12 weeks, among recent or former PWIDs	513 (19%)
Any past major mental illness	1,245 (30%)
Any previous problematic alcohol use	998 (24%)
HIV co-infection	403 (10%)
HCV treatment experienced	960 (23%)
HCV treatment regimen	
Sofosbuvir/ledipasvir	2,497 (61%)
Sofosbuvir plus ribavirin	696 (17%)
Sofosbuvir/velpatasvir	393 (9%)
Ombitasvir/paritaprevir/ritonavir plus dasabuvir	375 (9%)
Other	153 (4%)
HCV genotype	
1	3,106 (75%)
2	316 (8%)
3	526 (13%)
Mixed/Other	166 (4%)

HCV, hepatitis C virus; IQR, interquartile range; OAT, opioid-agonist therapy; PWIDs, people who inject drugs; SVR, sustained virologic response.

Table 2: Crude HCV reinfection incidence rates, per 100 person-years, for overall and persistent HCV reinfection, after successful DAA therapy in British Columbia, Canada (n = 4,114)

		All reinfections		Persistent reinfections	
	Person-years	N	Rate (95% CI) *	N	Rate (95% CI) *
Overall	2,766.80	40	1.44 (1.03, 1.97)	33	1.19 (0.82, 1.68)
Age group					
< 45 years	216.24	9	4.16 (1.90, 7.90)	9	4.16 (1.90, 7.90)
45 to 64 years	2,026.04	29	1.43 (0.96, 2.06)	23	1.14 (0.72, 1.70)
≥ 65 years	524.52	2	0.38 (0.05, 1.38)	1	0.19 (0, 1.06)
Birth cohort					
< 1965	2,263.34	25	1.10 (0.71, 1.63)	19	0.84 (0.51, 1.31)
1965 to 1974	352.64	9	2.55 (1.17, 4.84)	8	2.27 (0.98, 4.47)
≥ 1975	150.81	6	3.98 (1.46, 8.66)	6	3.98 (1.46, 8.66)
Year of HCV diagnosis					
1990-1997	760.89	13	1.71 (0.91, 2.92)	9	1.18 (0.54, 2.25)
1998-2004	921.25	17	1.85 (1.07, 2.95)	14	1.52 (0.83, 2.55)
≥ 2005	1,084.43	10	0.92 (0.44, 1.70)	10	0.92 (0.44, 1.70)
Gender					
Male	1,805.26	32	1.77 (1.21, 2.50)	28	1.55 (1.03, 2.24)
Female	961.53	8	0.83 (0.36, 1.64)	5	0.52 (0.17, 1.21)
PWID					
Recent (< 3 years before SVR)	674.28	21	3.11 (1.93, 4.76)	18	2.67 (1.58, 4.22)
Former (≥ 3 years before SVR)	1,137.60	16	1.41 (0.80, 2.28)	13	1.14 (0.61, 1.95)

No	954.91	3	0.31 (0.06, 0.92)	2	0.21 (0.03, 0.76)
OAT, in previous 12 weeks, among recent or former PWIDs					
Daily use	52.59	1	1.90 (0.05, 10.6)	1	1.90 (0.05, 10.6)
Non-daily use	292.62	12	4.10 (2.12, 7.16)	12	4.10 (2.12, 7.16)
Any past major mental illness					
Yes	901.92	19	2.11 (1.27, 3.29)	16	1.77 (1.01, 2.88)
No	1,864.87	21	1.13 (0.70, 1.72)	17	0.91 (0.53, 1.46)
Any previous problematic alcohol use					
Yes	667.96	16	2.40 (1.37, 3.89)	13	1.95 (1.04, 3.33)
No	2,098.84	24	1.14 (0.73, 1.70)	20	0.95 (0.58, 1.47)
HIV Co-Infection					
Yes	378.44	13	3.44 (1.83, 5.87)	12	3.17 (1.64, 5.54)
No	2,388.36	27	1.13 (0.75, 1.64)	21	0.88 (0.54, 1.34)

* Rate per 100 person-years

CI, confidence interval; HCV, hepatitis C virus; OAT, opioid agonist therapy; PWIDs, people who inject drugs; SVR, sustained virologic response.

Table 3: Crude HCV reinfection incidence rates and 95% confidence intervals, per 100 person-years, for overall and persistent HCV reinfection among PWIDs (n = 2,668) *

	All PWIDs (n = 2,668)		Recent PWIDs (n = 875)		Former PWIDs (n = 1,793)	
	All reinfections	Persistent reinfections	All reinfections	Persistent reinfections	All reinfections	Persistent reinfections
Age group						
< 45 years	5.64	5.64	10.4	10.4	0	0
	(2.58, 10.7)	(2.58, 10.7)	(4.74, 19.7)	(4.74, 19.7)	(0, 5.07)	(0, 5.07)
45 to 64 years	2.00	1.55	2.26	1.69	1.83	1.46
	(1.32, 2.91)	(0.96, 2.38)	(1.17, 3.94)	(0.77, 3.21)	(1.02, 3.02)	(0.76, 2.56)
≥ 65 years	0.33	0.33	0	0	0.41	0.41
	(0, 1.85)	(0, 1.85)	(0, 6.58)	(0, 6.58)	(0.01, 2.27)	(0.01, 2.27)
Birth cohort						
< 1965	1.54	1.19	1.88	1.47	1.37	1.06
	(0.97, 2.34)	(0.69, 1.91)	(0.86, 3.58)	(0.59, 3.02)	(0.73, 2.35)	(0.51, 1.94)
1965 to 1974	3.26	2.90	4.35	3.63	2.17	2.17
	(1.49, 6.19)	(1.25, 5.71)	(1.60, 9.47)	(1.18, 8.46)	(0.45, 6.34)	(0.45, 6.34)
≥ 1975	5.42	5.42	10.2	10.2	0	0
	(1.99, 11.8)	(1.99, 11.8)	(3.74, 22.2)	(3.74, 22.2)	(0, 7.14)	(0, 7.14)
Year of HCV diagnosis						
1990-1997	2.04	1.36	2.22	1.78	1.93	1.10
	(1.05, 3.56)	(0.59, 2.68)	(0.72, 5.18)	(0.48, 4.55)	(0.77, 3.97)	(0.30, 2.82)
1998-2004	2.44	2.13	3.83	2.98	1.74	1.74
	(1.39, 3.96)	(1.17, 3.58)	(1.75, 7.27)	(1.20, 6.14)	(0.70, 3.58)	(0.70, 3.58)
≥ 2005	1.59	1.59	3.57	3.57	0.54	0.54

	(0.73, 3.01)	(0.73, 3.01)	(1.44, 7.35)	(1.44, 7.35)	(0.07, 1.95)	(0.07, 1.95)
Gender						
Male	2.49	2.16	3.82	3.37	1.71	1.45
	(1.68, 3.56)	(1.41, 3.17)	(2.23, 6.12)	(1.89, 5.57)	(0.91, 2.93)	(0.72, 2.59)
Female	1.15	0.82	1.74	1.31	0.79	0.53
	(0.46, 2.37)	(0.27, 1.92)	(0.47, 4.46)	(0.27, 3.82)	(0.16, 2.31)	(0.06, 1.90)
Any past major mental illness						
Yes	2.53	2.13	3.02	3.02	2.15	1.43
	(1.52, 3.95)	(1.22, 3.46)	(1.45, 5.56)	(1.45, 5.56)	(0.98, 4.07)	(0.52, 3.11)
No	1.70	1.41	3.20	2.33	0.97	0.97
	(1.00, 2.68)	(0.79, 2.33)	(1.60, 5.73)	(1.01, 4.59)	(0.39, 2.01)	(0.39, 2.01)
Any previous problematic alcohol use						
Yes	2.69	2.19	4.55	3.41	1.21	1.21
	(1.54, 4.37)	(1.17, 3.74)	(2.35, 7.94)	(1.56, 6.48)	(0.33, 3.10)	(0.33, 3.10)
No	1.72	1.48	2.19	2.19	1.49	1.11
	(1.07, 2.63)	(0.88, 2.34)	(1.00, 4.16)	(1.00, 4.16)	(0.77, 2.60)	(0.51, 2.12)
HIV Co-Infection						
Yes	3.97	3.67	5.67	5.04	2.38	2.38
	(2.12, 6.80)	(1.90, 6.41)	(2.59, 10.8)	(2.18, 9.93)	(0.65, 6.08)	(0.65, 6.08)
No	1.62	1.28	2.33	1.94	1.24	0.93
	(1.04, 2.41)	(0.77, 2.00)	(1.20, 4.07)	(0.93, 3.57)	(0.64, 2.16)	(0.42, 1.76)

* Rate per 100 person-years

HCV, hepatitis C virus; OAT, opioid-agonist therapy; PWIDs, people who inject drugs.

Table 4: Incidence rate ratios (IRRs) from Poisson regression models for overall and persistent HCV reinfection in British Columbia, Canada

	All reinfections		Persistent reinfections	
	Age and sex-adjusted IRR (95% CI)	Fully adjusted IRR * (95% CI)	Age and sex-adjusted IRR (95% CI)	Fully adjusted IRR * (95% CI)
PWID				
Recent (< 3 years before SVR)	8.0 (2.4, 26.9)	6.7 (1.9, 23.5)	9.7 (2.2, 42.3)	8.1 (1.8, 36.9)
Former (≥ 3 years before SVR)	4.1 (1.2, 14.2)	3.7 (1.1, 12.9)	5.0 (1.1, 22.0)	4.4 (1.0, 19.8)
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Any past major mental illness				
Yes	1.8 (0.9, 3.3)	1.1 (0.5, 2.1)	1.8 (0.9, 3.6)	1.1 (0.5, 2.3)
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Any previous problematic alcohol use				
Yes	1.8 (1.0, 3.4)	1.2 (0.6, 2.4)	1.7 (0.9, 3.5)	1.1 (0.5, 2.4)
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
HIV Co-Infection				
Yes	2.1 (1.1, 4.2)	1.6 (0.8, 3.3)	2.3 (1.1, 4.9)	1.8 (0.8, 3.7)

No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)

CI, confidence interval; IRR, incidence rate ratio; PWIDs, people who inject drugs; SVR, sustained virologic response.

* Models adjusted for age, sex and all other predictors shown in the table.

Figure legends

Fig. 1. Study participant selection flow chart. HCV, hepatitis C virus.

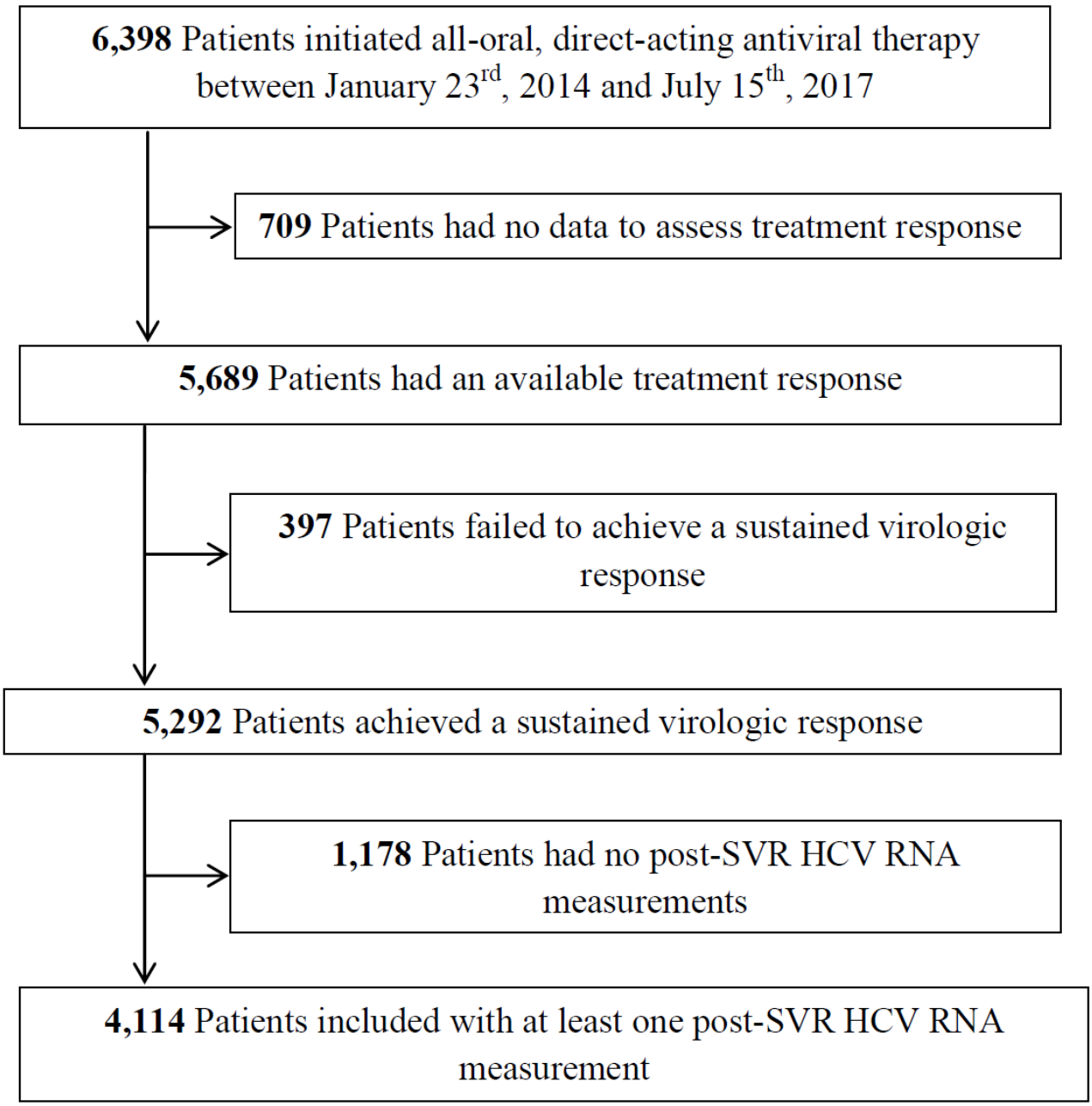
Fig. 2. Cumulative incidence curves for reinfection, by injection drug use history.

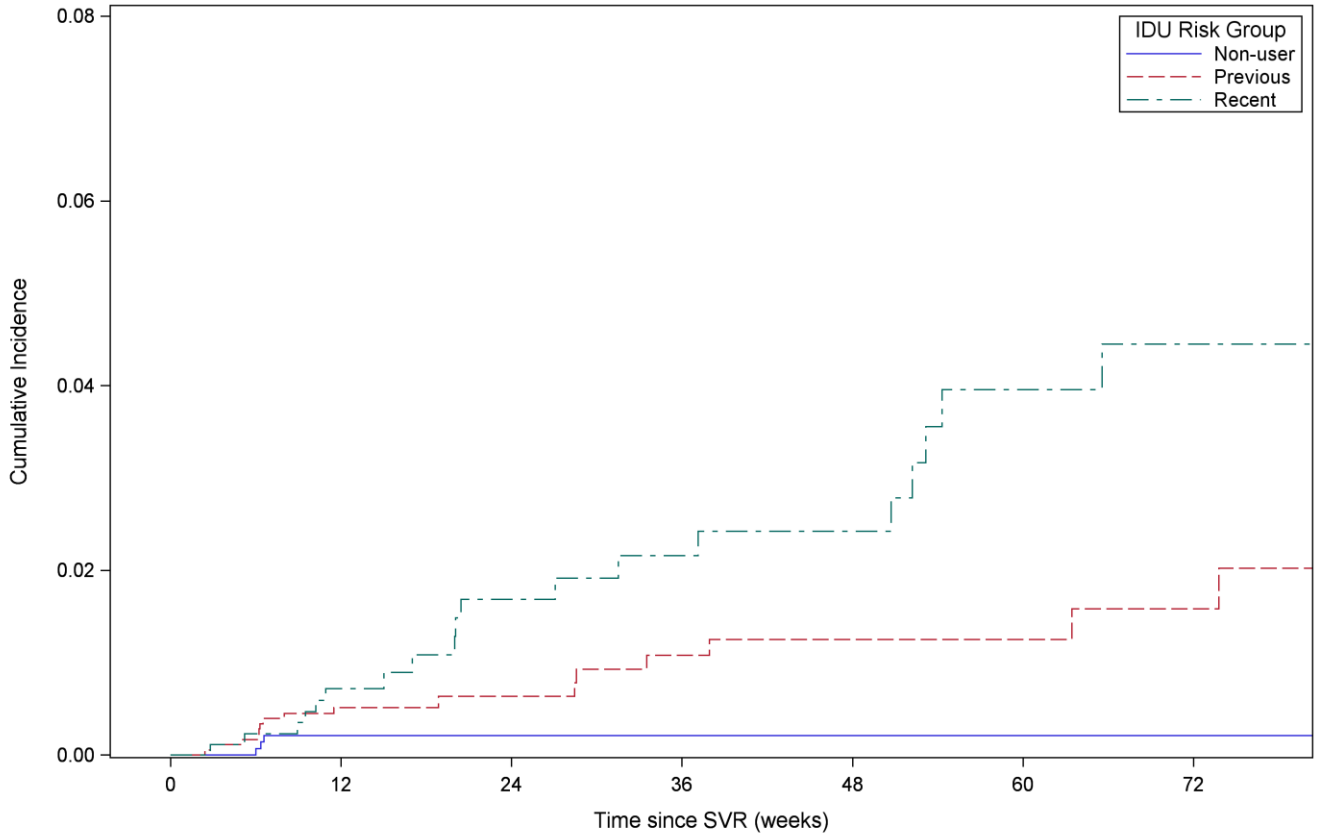
(A) All reinfections. Level of significance: $p < 0.001$ (Gray's K-Sample Test). (B) Persistent reinfections. Level of significance: $p < 0.001$ (Gray's K-Sample Test).

Hepatitis C Virus Reinfection after Successful Treatment with Direct-Acting Antiviral Therapy in a Large Population-Based Cohort

Highlights

- DAA therapies are an important component of HCV elimination strategies.
- Larger population-level reports of reinfection rates after DAA therapy are lacking.
- HCV reinfection rates remain elevated among people who recently injected drugs.
- Opioid-agonist therapy mitigates reinfection risk.


6,398 Patients initiated all-oral, direct-acting antiviral therapy between January 23rd, 2014 and July 15th, 2017
709 Patients had no data to assess treatment response
5,689 Patients had an available treatment response
397 Patients failed to achieve a sustained virologic response
5,292 Patients achieved a sustained virologic response
1,178 Patients had no post-SVR HCV RNA measurements
4,114 Patients included with at least one post-SVR HCV RNA measurement



Non-user	1446	1194	621	526	375	290	212
Previous	1793	1495	743	610	440	335	234
Recent	875	747	459	379	287	215	165