Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

# Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study

Nazrul Islam[1,2], Mel Krajden[2,3], Jean Shoveller[1,4], Paul Gustafson[5], Mark Gilbert[2,6], Jane A Buxton[1,2], Jason Wong[1,2], Mark W Tyndall[1,2], Naveed Zafar Janjua[1,2], the British Columbia Hepatitis Testers Cohort (BC-HTC) team*

1. School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada.
2. British Columbia Centre for Disease Control, Vancouver, BC, Canada.
3. Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada.
4. British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada.
5. Department of Statistics, University of British Columbia, Vancouver, BC, Canada.
6. Ontario HIV Treatment Network, Toronto, ON, Canada.

*Listed in the appendix



**Link to the published article**: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

**Author's academic degree(s):** Nazrul Islam, MBBS, MPH, MSc, Mel Krajden, MD, FRCPC, Jean A Shoveller, PhD; Paul Gustafson, PhD, Mark Gilbert, MD, MHSc, FRCPC, Jane A Buxton, MBBS, MHSc, FRCPC, Jason Wong, MD, MPH, FRCPC, Mark W Tyndall, MD, ScD, FRCPC, Naveed Z Janjua, MBBS, MSc, DrPH

*Address correspondence to*:

**Naveed Zafar Janjua**, MBBS, MSc, DrPH

Senior Scientist, Clinical Prevention Services, BC Centre for Disease Control
655 West 12th Avenue, Vancouver, BC V5Z 4R4
Tel: 604-707-2514, Fax: 604-707-2401
Email: naveed.janjua@bccdc.ca

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

## Contributors

NI, NZJ, MK, JS, PG, and MG conceptualised and designed the study. NI, NZJ, MK, JS, PG, MG, JAB, JW, and MWT were involved in acquisition, analysis, or interpretation of data. NI did the statistical analysis and wrote the first draft of the manuscript. All authors critically revised the manuscript for significant intellectual contents.

## Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not necessarily reflect the opinions or policies of the [British Columbia] Ministry of Health.

## Potential conflict of interest

MK has received grant funding via his institution from Roche Molecular Systems, Boehringer Ingelheim, Merck, Siemens Healthcare Diagnostics and Hologic Inc. PG has received consulting fees from ICON Plc and Biogen.

## Acknowledgments

This work was supported by the British Columbia Centre for Disease Control and Agencies contributing data to the study and the Canadian Institutes of Health Research (201503NHC-348216-NHC-ADWY-62134 & 201410PHE-337680-PHE-CAAA-179547). NI is supported by a Vanier Canada Doctoral Scholarship from the Canadian Institutes of Health Research. We thank the British Columbia Centre for Disease Control, Provincial Health Services Authority Performance Measurement and Reporting, Information Analysts, the British Columbia Ministry of Health Data Access, Research and Stewardship, and Medical Services Plan, Discharge Abstract Database, and Medical Beneficiary and Pharmaceutical Services programme areas, the British Columbia Ministry of Health, the British Columbia Cancer Agency and their staff involved in data access, procurement, and management. All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not necessarily reflect the opinions or policies of the British Columbia Ministry of Health.

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**ABSTRACT**:

**Background**

People remain at risk of reinfection with hepatitis C virus (HCV), even after clearance of the primary infection. We identified factors associated with HCV reinfection risk in a large population-based cohort study in British Columbia, Canada, and examined the association of opioid substitution therapy and mental health counselling with reinfection.

**Methods**

We obtained data from the British Columbia Hepatitis Testers Cohort, which includes all individuals tested for HCV or HIV at the British Columbia Centre for Disease Control Public Health Laboratory during 1990–2013 (when data were available). We defined cases of HCV reinfection as individuals with a positive HCV PCR test after either spontaneous clearance (two consecutive negative HCV PCR tests spaced ≥28 days apart without treatment) or a sustained virological response (SVR; two consecutive negative HCV PCR tests spaced ≥28 days apart 12 weeks after completing interferon-based treatment). We calculated incidence rates of HCV reinfection (per 100 person-years of follow-up) and corresponding 95% CIs assuming a Poisson distribution, and used a multivariable Cox proportional hazards model to examine reinfection risk factors (age, birth cohort, sex, year of HCV diagnosis, HCV clearance type, HIV co-infection, number of mental health counselling visits, levels of material and social deprivation, and alcohol and injection drug use), and the association of opioid substitution therapy and mental health counselling with HCV reinfection among people who inject drugs (PWID).

**Findings**

5915 individuals with HCV were included in this study after clearance (3690 after spontaneous clearance and 2225 after SVR). 452 (8%) patients developed reinfection; 402 (11%) after spontaneous clearance and 50 (2%) who had achieved SVR. Individuals were followed up for a median of 5.4 years (IQR 2.9–8.7), and the median time to reinfection was 3.0 years (1.5–5.4). The overall incidence rate of reinfection was 1.27 (95% CI 1.15–1.39) per 100 person-years of follow-up over a total of 35 672 person-years, with significantly higher rates in the spontaneous clearance group (1.59, 1.44–1.76) than in the SVR group (0.48, 0.36–0.63). With the adjusted Cox proportional hazards model, we noted higher reinfection risks in the spontaneous clearance group (adjusted hazard ratio [HR] 2.71, 95% CI 2.00–3.68), individuals co-infected with HIV (2.25, 1.78–2.85), and PWID (1.53, 1.21–1.92) than with other reinfection risk factors. Among the 1604 PWID with a current history of injection drug use, opioid substitution therapy was significantly associated with a lower risk of reinfection (adjusted HR 0.73, 95% CI 0.54–0.98), as was engagement with mental health counselling services (0.71, 0.54–0.92).

**Interpretation**

The incidence of HCV reinfection was higher among HIV co-infected individuals, those who spontaneously cleared HCV infection, and PWID. HCV treatment complemented with opioid

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

substitution therapy and mental health counselling could reduce HCV reinfection risk among PWID. These findings support policies of post-clearance follow-up of PWID, and provision of harm-reduction services to minimise HCV reinfection and transmission.

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

## INTRODUCTION

Infection with Hepatitis C virus (HCV) is a major global public health problem.[1] In developed countries, the principal mode of HCV transmission is injection drug use (IDU).[2, 3] New direct-acting antivirals (DAA) are well-tolerated with higher cure rates (≥95%) and the introduction of these new treatments for HCV is expected to reduce morbidity and mortality. While majority of HCV cases will lead to chronicity, about a quarter clear the virus spontaneously.[4, 5] However, because neither spontaneous nor treatment-induced clearance of the virus confers immunity, reinfection remains a concern.[4, 6-9] The high cost of direct-acting antivirals poses concomitant concerns regarding potential reinfection risks, and these concerns have fuelled debates regarding approaches to scaling-up treatment access[10, 11] especially amongst high-risk groups (e.g., people who inject drugs [PWID]).[12-15]

Most studies assessing HCV reinfection rates were conducted in cohorts of such high-risk populations.[8, 16-30] Data from studies of HCV reinfection following spontaneous clearance [7, 18, 22, 25-31] or treatment-induced clearance (i.e., sustained virological response [SVR]) [8, 16-23, 32] show a wide range of reinfection estimates. These studies also only had a few reinfected cases limiting the ability of the investigators to assess the factors associated reinfection risks. Thus, the validity of the inferences drawn from these studies may be prone to greater uncertainties. Furthermore, factors increasing or reducing the risk of reinfection need to be assessed, to inform strategies to scale-up treatment for people with a potentially high risk of reinfection. Co-occurring risk factors such as injection drug use and mental illness are associated with increased risk of HCV infection, and thus addressing these conditions are paramount to reducing HCV reinfection risk.[33-35] In this study, we estimated the reinfection rate and assessed the association of intervention options including the role of opioid substitution therapy and mental health counselling with HCV reinfection risk among PWID. We hypothesised that engagement with these services would reduce HCV reinfection risk.

## METHODS

### Study Cohort

In this study, we estimated the reinfection rate and assessed the association of intervention options including the role of opioid substitution therapy and mental health counselling with HCV reinfection risk among PWID. We hypothesised that engagement with these services would reduce HCV reinfection risk (Supplementary Table 1). BCCDC-PHL is the centralised laboratory for most serology tests (95%), and all confirmatory tests in the province including HCV RNA (PCR) and genotype testing, and thus provides a unique tool to monitor and assess the association of HCV treatment and harm-reduction initiatives with clearance and reinfection. Details of the BC-HTC, including linkage, characteristics, and matching, have been reported previously.[36, 37]

Our analysis included all HCV-positive individuals who cleared their primary HCV infection spontaneously or achieved SVR after HCV treatment and who had at least one valid HCV PCR after spontaneous clearance or SVR. The laboratory results on HCV PCR were available until Dec 31, 2013. Therefore, to allow sufficient follow-up time to observe reinfections, we restricted the date of HCV spontaneous clearance up to Dec 31, 2012, and the treatment completion date up to July 16, 2012. The last date of follow-up was the date of reinfection for those who developed reinfection, and the last negative PCR on or before Dec 31, 2013, for those who did not develop reinfection. After applying these criteria, the enrolment period was Nov 07, 1992, to Dec 31, 2013.

Data linkage to establish the BC-HTC was done under 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**

We used the definition of an HCV case as an individual who tested positive for either HCV antibody, had a valid HCV PCR result, or was reported as a case of HCV to public health.[36]

Spontaneous clearance was defined as two consecutive negative HCV-PCR tests, at least 28 days apart,[31] following HCV diagnosis without treatment. In the primary analysis, the date of spontaneous clearance was calculated as the midpoint between the last positive and first negative PCR after HCV diagnosis.[31] The first negative PCR date was used in a sensitivity analysis.

SVR was defined as two consecutive negative HCV-PCR tests, at least 28 days apart, 12 weeks after completion of interferon-based treatment.[38] For this analysis, data were available only for interferon-based treatments. In the primary analysis, the date of SVR was calculated as the midpoint between the treatment completion date and the date of the first negative PCR to assess SVR at 12 weeks after treatment (SVR12). The first negative PCR date was used in the sensitivity analysis.

Reinfection was defined as a positive HCV PCR after clearance (spontaneous or SVR). In the primary analysis, the date of reinfection was calculated as the midpoint between the last negative and first positive PCR after clearance.[31] The first positive PCR date after clearance was used in the sensitivity analysis.

We looked at the following factors and their association with risk of HCV reinfection: type of HCV clearance, age, birth cohort, sex, year of HCV diagnosis, HIV coinfection, the number of mental health counselling visits, use of opioid substitution therapy, injection drug use, problematic alcohol use, and levels of material and social deprivation.

HIV diagnosis was based on HIV lab tests as per provincial guidelines, recorded in the provincial HIV/ AIDS reporting system, or two medical visits or an admission to hospital with HIV-related diagnostic codes as described elsewhere.[36] The date of HIV diagnosis was the earliest date a person was diagnosed as having HIV. Mental health counselling, injection drug use, opioid substitution therapy, and problematic alcohol use were defined based on ICD diagnostic or procedure codes, or fee item codes from a medical-services plan (medical visits) or discharge abstract database (hospitalizations) or prescription database, as applicable (Supplementary Table 2). Assessment of opioid substitution therapy is based on the record of dispensed prescriptions in the centralised prescription database, PharmaNet, which records all prescriptions dispensed in the province. For the main analysis, mental health counseling was defined as any mental health counseling visit during the follow-up time. In the sensitivity analysis, it was defined as the number of visits per year during the follow-up to explore whether the level of engagement with healthcare services is associated with a reduction in reinfection risk. Material and social deprivation was based on Québec Index of Material and Social Deprivation.[39] We classified patients with missing information on material and social deprivation as unknown.

**Statistical analysis**

We assessed the profile of the overall cohort and by clearance status. We calculated incidence rates of HCV reinfection per 100 person-years of follow-up and corresponding 95% CIs, assuming a Poisson distribution. We explored bivariate relationships with Cox proportional hazards models, and calculated the unadjusted hazard ratios (HRs) with 95% CIs. Variables based on a priori hypotheses, and those significant at 0.10 in the univariate analysis were included in the multivariable models, and we calculated adjusted HRs with 95% CIs. Birth cohort, sex, and year of HCV diagnosis were included in all the models irrespective of their statistical significance in the univariate analysis; birth cohort and sex were added because they are established risk factors of HCV, and the year of HCV diagnosis was used to adjust for varying testing patterns over time. We also assessed variables in the final multivariable model of additional Cox proportional hazards models fitted separately in the spontaneous clearance and the SVR groups. Finally, the effects of mental health counselling and opioid substitution therapy were assessed in people with a history of injection drug use during the follow-up by fitting another Cox proportional hazards model. Since people can be on and off this type of therapy (defined as not taking opioid substitution therapy for more than 7 consecutive days), this variable was used as a time-varying covariate. We used HIV as a time-varying covariate in all the analyses. To assess the robustness of using midpoints as the date of HCV transitions, as used in the primary analysis, we also used the earliest date of transition in the sensitivity analysis. In observational studies, people who receive interventions are usually different from those who do not, which introduces treatment-indication bias or confounding by indication. To correct for treatment-indication bias, we applied inverse-probability-of-treatment weighting (IPTW). We computed propensity scores of receiving mental health counselling or opioid substitution therapy (at each time-point) using logistic regression. Propensity scores were used to construct the IPTW

which were applied to the intervention (IPTW=1/ propensity score) and no-intervention (IPTW=1/[1 minus propensity score]) groups.[40, 41] We used IPTW-weighted Cox proportional hazards models to estimate the association of opioid substitution therapy and mental health counselling with reinfection risk among PWID. All the tests were two-sided at a significance level of 0.05. We did all analyses with SAS/STAT software version 9.4.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## RESULTS

After exclusion (14 excluded because they had two consecutive negative PCR tests, but the gap between the two tests was <28 days), we noted 5915 cases with at least one valid HCV PCR following primary clearance (3690 cases of spontaneous clearance, and 2225 cases of SVR), who were included in this analysis (Figure 1). These cases were followed up for a median of 5.4 years (IQR 2.9–8.7), and the median time to reinfection was 3.0 years (1.5–5.4). Individuals included in this study had a median of nine HCV PCR tests (IQR 6–12) with a median testing interval of 7.4 months (IQR 2.8–18.5). The median number of tests was eight (IQR 6–10) in individuals with spontaneous clearance and 10 (8–13) in those who achieved SVR. The median testing interval was 8.7 months (IQR 3.0–22.4) in those with spontaneous clearance, and 6.3 months (2.8–14.2) in those who achieved SVR.

452 (8%) of 5915 individuals developed reinfection: 402 (11%) of those who cleared the primary infection spontaneously, and 50 (2%) of those who achieved SVR after HCV treatment. The overall sample was predominantly young (3135 [53%] <45 years) at HCV clearance, born before 1965, and male (Table 1).

The overall reinfection rate was 1.27 (95% CI 1.15–1.39) per 100 person-years of follow-up over a total of 35 672 person-years, with higher rates (per 100 person-years) in the spontaneous clearance group (1.59, 1.44–1.76) than in the SVR group (0.48, 0.36–0.63) (Table 2). We noted higher rates of reinfection in people younger than 35 years, male participants, people coinfected with HIV, PWID, people with a history of problematic alcohol use, and those from the most deprived neighbourhoods, and lower rates in individuals who were engaged with mental health counselling services. For PWID, the incidence rates were 1.88 (95% CI 1.66–2.12) per 100 person-years for those who cleared their previous HCV episode spontaneously and 1.14 (0.77–1.63) per 100 person-years for those who achieved SVR. When we did an additional analysis using one negative PCR (i.e., less stringent criteria to define viral clearance) to define spontaneous clearance and SVR, we noted, as expected, that the rates of reinfection were higher

than these estimates (overall 2.42 [95% CI 2.29–2.56] per 100 person-years; PWID 3.34 [3.12–3.56]; and HIV-coinfected 4.17 [3.43–4.91] (Supplementary Table 3).

In the multivariable Cox proportional hazards model, birth cohort, female sex, spontaneous clearance, HIV-coinfection, and injection drug use were significantly associated with HCV reinfection (Table 3). After adjusting for other potential confounders, female patients had a significantly lower likelihood of HCV reinfection. Compared with the SVR group, the risk of HCV reinfection was nearly three times higher for the spontaneous clearance group. The adjusted likelihood of HCV reinfection was significantly higher among people coinfected with HIV and PWID (Table 3). In both the spontaneous clearance and the SVR groups, female patients had a lower likelihood of reinfection, whereas PWID and people coinfected with HIV had a higher likelihood of reinfection (Table 4).

In the adjusted Cox proportional hazards model restricted to current PWID (n=1604), PWID who were on opioid substitution therapy had a lower likelihood of HCV reinfection (Table 5) as did those who ever received mental health counselling services during the follow-up time. The interaction of opioid substitution therapy and mental health counselling was not significant (p=0.326; Supplementary Table 4).

In our sensitivity analysis using the number of mental health counselling visits per year during the follow-up, 1185 (20%) participants had one visit or more per year during follow-up, 501 (9%) had one visit, and 684 (12%) had two or more visits per year. In the adjusted Cox proportional hazards model, compared with individuals who had no visits, those with one visit per year had a reduced risk of reinfection (adjusted HR 0.32, 95% CI 0.20–0.51) as did those with two or more mental health counselling visits (0.67, 0.48–0.93; Supplementary Table 5). The joint effect of opioid substitution therapy and mental health counselling was not significant as in the original analysis (p=0.885; Supplementary Table 4).

In our additional Cox proportional hazards models using single negative PCR for the assessment of clearance, we showed similar results to the main analysis (Supplementary Table 6). Our analysis using the earliest date of HCV transitions also yielded similar findings to those reported in the main analysis (Supplementary Table 7). In the IPTW analysis of mental health counselling, the adjusted HR was 0.70 (95% CI 0.58–0.84) for mental health counselling, and 0.71 (0.58–0.87) for opioid substitution therapy, and 0.71 (95% CI 0.59–0.86), and 0.73 (0.59–0.90), respectively, with IPTW of opioid substitution therapy receipt.

## DISCUSSION

In this study (to the best of our knowledge, the largest population-level study so far to characterise HCV reinfection risks after spontaneous clearance and SVR among individuals followed up for more than 19 years), the incidence rate of HCV reinfection was higher among individuals who cleared their primary infections spontaneously compared with those who achieved SVR after HCV treatment. The risk of HCV reinfection was much lower in female

individuals, and higher in individuals coinfected with HIV, and among PWID. Receiving opioid substitution therapy and being engaged with mental health counselling services were independently associated with a significantly lower likelihood of HCV reinfection among PWID. These findings have important implications for post-clearance follow-up, and interventions for prevention of reinfections in an era of direct-acting antivirals when HCV treatment is being scaled up to include PWID in many countries across the world.

Our estimate of the reinfection rate after SVR was 1.14 (95% CI 0.77–1.63) per 100 person-years among PWID, whereas estimates reported in earlier smaller studies were wider, ranging between 0–5 per 100 person-years.[8, 16-23, 32] Wider range of reinfection rates reported in these studies might be due to varying sample sizes and study populations, in addition to any differences in the availability of harm-reduction programmes and population risk activities.

The HCV reinfection rate among PWID in the spontaneous clearance group was 1.88 (95% CI 1.66–2.12) per 100 person-years in our study, with a higher estimate using single negative PCR for clearance. Earlier studies reported a wide range of estimates between zero and 46.8 per 100 person-years.[7, 18, 22, 25-31] The results from our study showed a lower reinfection rate in the SVR group compared with the spontaneous clearance group, which is consistent with findings from previous smaller reports, including a meta-analysis, although different from those from a recent study on HIV-positive men who have sex with men (MSM), in which reinfection rates were lower among those with spontaneous clearance. [4, 12, 42, 43] The difference in the reinfection rates between individuals who had spontaneous clearance and individuals who had a SVR is probably due to differences in their characteristics, including risk factors. Compared with the SVR group, participants in the spontaneous clearance group were younger (<45 years) with a significantly higher proportion of female individuals, PWID, people coinfected with HIV, a history of problematic alcohol use, and a lower socioeconomic status. People with HIV coinfection and substance use were less likely to be treated with interferon-based treatments because of potential toxicity, tolerability, and adherence concerns.[38] Thus, we see under-representation of PWID in the SVR group in our sample. Restriction to treatment accessibility has also been documented in other studies in Canada.[44, 45] Highly effective, well tolerated, direct-acting antivirals open up opportunities to reduce disease burden, and potentially reduce transmission providing overall population benefits in addition to individual health benefits, especially in PWID. However, as noted in the spontaneous clearance group, reinfection rates among PWID after SVR in the era of direct-acting antivirals could increase, unless accompanied by appropriate interventions to prevent reinfection. Future research will delineate this issue in terms of long-term benefit of treatment coupled with harm-reduction services.

Within the context of expansion of HCV treatment with direct-acting antivirals to high-risk populations such as PWID, the results from this study provide important evidence on the association of opioid substitution therapy and mental health counselling with HCV reinfection. Our data show that engagement with these harm-reduction initiatives is associated with

significant reductions in HCV reinfection risk. To our knowledge, this is the first study to examine the association of mental health counselling with HCV reinfection risk among PWID, which is important in light of the higher risk of HCV infection among PWID with psychiatric co morbidities.[46] Building on evidence previously established through mathematical modelling studies,[15, 47] the findings of this study show that the reinfection risk could be reduced if treatment is accompanied by opioid substitution therapy or treatment is provided with the opioid substitution therapy programmes. Additionally, other harm-reduction activities (e.g., syringe distribution and expansion of safer injection facilities) might need to be scaled up to reduce risk of HCV reinfection among injection non-opioid users and to provide broader public health benefits, as well as new access points to low-threshold health-care services for people at high risk of HCV infection or reinfection. Further research in this era of direct-acting antivirals would be helpful in understanding the changing risk behaviours.

In further analyses (Supplementary Table 5) to examine the effect of level of engagement with mental health counselling, an increase in the number of visits was not associated with a linear increase in the reduction of reinfection risk. This could be because more visits to mental health counselling might be associated with high risk factors, rather than representing individuals who are more health aware, and engaged with and using health-care services. Individuals who have to take many counselling sessions per year are probably those who have much higher risk behaviours. Thus, the relationship between mental health counselling and reinfection risk does not appear to be linear. However, because the 95% CIs of these two groups overlapped, we cannot say for sure that more than one visit is associated with less benefit, per se, than visiting once per year. This factor requires further in-depth investigation, which we are also planning to pursue.

Earlier years of HCV diagnosis were associated with a lower reinfection risk. Intuitively, we would expect that the longer an individual was in the study, the higher the number of HCV tests, and thus the higher the likelihood of being detected as a case of reinfection. Although this variable was added to the multivariable models to structurally adjust for this expectation, the findings seem to be related to changing risk behaviours. In earlier years (particularly before 1998), most HCV cases were acquired via blood transfusion or injection drug use. Over time, as people age, their drug use pattern might have changed. Earlier studies showed that older and experienced PWID were less likely to share needles compared with younger PWID.[48, 49] In our previous analysis,[50] we showed that HCV incidence was much lower in older birth cohorts compared with younger birth cohorts, which is also supported by findings from several other studies that showed a lower rate of reinfection in older populations.[16, 21, 22, 42]

In our study, HIV coinfection was associated with an increased risk of HCV reinfection, which is supported by a previous study of prisoners.[8] HIV could affect reinfection risk by affecting immune response, or could be a proxy for high-risk injection drug use or high-risk sexual behaviours among MSM.[51-53] Because of a common route of transmission, and a

greater HCV reinfection risk, HIV–HCV-coinfected individuals might benefit more from harm-reduction efforts than those with HCV infection alone.

To our knowledge, this is the largest population-based study with the longest follow-up time to examine HCV reinfections, both among those who spontaneously cleared the primary HCV infection and those who achieved an SVR. HCV testing is centralised at BCCDC Public Health Laboratory, which ensures completeness of the testing data. However, there could be missing tests because of non-linkage if identifiers were not available. Furthermore, HCV tests were not done at regular intervals which might have missed some episodes of clearance and reinfections in the intervals between testing, as suggested by mathematical modelling.[54] As a result, our estimates of reinfection might be an underestimation. Although HCV testing at regular intervals would improve the accuracy of estimating the time at reinfection, this study provides information on the real-world scenario of clinical practice with the largest sample size to date. In our main analysis, we required two negative RNA tests for HCV clearance. In clinical practice, two RNA tests are not always done for confirmation of clearance and this might have led to underestimation of reinfection incidence in the primary analysis, as supported by the analysis presented in the appendix (Supplementary Table 3). The sensitivity of different HCV PCR assays has changed over time, and might affect the classification of cases, especially the cases of spontaneous clearance and SVR. Most of the quantitative HCV PCR tests were validated by a more sensitive qualitative test up to 2007, after which quantitative PCR assays were as sensitive (RNA detection level up to 10–15 IU/mL) as the qualitative test. Between 2000 and 2006, a small proportion (2.95% of the overall cohort) of quantitative test results with a lower limit of RNA detection of 615 IU/mL (all negative) were not verified by a qualitative test.[5] However, in this analysis, eight cases of clearance (negative HCV PCR test results; HCV RNA <615 IU/mL) were not validated by a qualitative test. Although this was the test used in practice in 2000–06, and although potentially these cases could be HCV negative, the potential error rate is negligible (0.14%) even if we assume all of them had RNA concentrations between 15 and 615 IU/mL but test results were negative because of the inability of the less sensitive assays to detect them. Thus, we can safely infer that this did not affect our analysis or inference.

The concern of distinguishing between relapse and reinfection is paramount in HCV reinfection studies. However, this might not be a substantial concern in our study. First, we used two consecutive negative PCR tests 12 weeks after treatment (SVR12), at least 28 days apart. Thus, relapse soon after SVR12 could be ruled out by a second negative test at least 28 days apart, as used in previous studies.[31] Moreover, we excluded individuals with a second negative test which was noted within a 28-day timeframe. We applied a similar approach to the spontaneous clearance group. Second, the median time to reinfection (date of clearance to date of reinfection) was quite long in our study: 3 years (IQR 1.5–5.4 years). Moreover, earlier studies showed that late relapse after SVR is very rare (<1%).[42, 55] Thus, the issue of relapse might not be a serious concern in our study.

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

All prescriptions dispensed in British Columbia, both covered by public and private insurance including HCV treatments and opioid substitution therapy, are recorded in a centralised database thus capturing all dispensed opioid substitution therapy and HCV treatments. Mental health counselling is covered through a medical services plan that includes all services that are billed by health-care providers. In this case, if a service was provided without a fee for a service provider, then this information would not be captured and could lead to under-assessment of mental health counselling received. Additionally, our study was subject to the usual caveats regarding use of administrative data in defining some covariates such as injection drug use and problematic alcohol use. We selected optimal definitions based on validations done by us or other investigators;[56] however, the issue of some level of misclassification and underestimation still remains. It is expected that misclassification is non-differential, leading to underestimation of associations. Drawing causal inference on intervention effects from observational data is therefore prone to biases. We attempted to delineate this further by applying IPTW to correct for non-comparability of individuals who received and did not receive opioid substitution therapy or mental health counselling. Although this analysis yielded similar results to those from our main analysis, some unmeasured confounding might have remained. Thus, further studies with experimental design, if feasible, and appropriate analytical strategies within causal inference frameworks, are required to validate our findings. Caution should also be exercised when interpreting the stratified models in the SVR group because of small number of outcome events (i.e., 50 reinfections); however, the sensitivity analysis using single negative PCR yielded a higher sample size and more stable results (Supplementary table 6). Our use of midpoints as the date of HCV transitions, which has been standard practice in HCV literature, was shown to be robust in the sensitivity analysis using the earliest date of transition. As is the case, the difference in health-care settings with varying access to health-care services, especially to those at risk, would produce different results. We believe that our results will be similar to those from other developed countries with similar health-care settings. However, differential access to health care, especially for PWID and individuals coinfected with HIV, has been reported in developed countries (e.g., USA and Canada).[44, 45] Thus, more research from diverse health-care settings will add invaluable evidence to HCV literature.

In conclusion, the rate and risk of HCV reinfection were significantly higher in the spontaneous clearance group compared to the SVR group, those coinfected with HIV, and among PWID. Higher reinfection risk in the spontaneous clearance group calls for post-clearance follow-up of PWID, and provision of harm-reduction services to minimise HCV reinfection and transmission. Consistent with previous mathematical models,[54] the findings from our study showed that engagement opioid substitution therapy, as well as mental health counselling, is associated with a significant reduction in HCV reinfection risk among PWID. In light of this, the positive effects of scaled-up HCV treatment might be enhanced if accompanied by appropriate harm-reduction programmes to prevent reinfections among PWID, with a view to achieving WHO's goal of HCV elimination.[57]

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

## REFERENCES

1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014; **61**(1 Suppl): S45-57.

2. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144**(10): 705-14.

3. Robotin MC, Copland J, Tallis G, et al. Surveillance for newly acquired hepatitis C in Australia. *J Gastroenterol Hepatol* 2004; **19**(3): 283-8.

4. Grebely J, Prins M, Hellard M, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *Lancet Infect Dis* 2012; **12**(5): 408-14.

5. Islam N, Krajden M, Gilbert M, et al. Role of primary T-cell immunodeficiency and hepatitis B coinfection on spontaneous clearance of Hepatitis C: The BC Hepatitis Testers Cohort. *J Viral Hepat* 2016.

6. Abdel-Hakeem MS, Shoukry NH. Protective immunity against hepatitis C: many shades of gray. *Front Immunol* 2014; **5**: 274.

7. Osburn WO, Fisher BE, Dowd KA, et al. Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. *Gastroenterology* 2010; **138**(1): 315-24.

8. Marco A, Esteban JI, Sole C, et al. Hepatitis C virus reinfection among prisoners with sustained virological response after treatment for chronic hepatitis C. *J Hepatol* 2013; **59**(1): 45-51.

9. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; **365**(11): 1014-24.

10. Cunningham EB, Applegate TL, Lloyd AR, Dore GJ, Grebely J. Mixed HCV infection and reinfection in people who inject drugs--impact on therapy. *Nat Rev Gastroenterol Hepatol* 2015; **12**(4): 218-30.

11. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. *Clin Infect Dis* 2014; **58**(7): 928-36.

12. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of Hepatitis C Virus Infection Among People Who Are Actively Injecting Drugs: A Systematic Review and Meta-analysis. *Clin Infect Dis* 2013; **57**(Suppl 2): S80-S9.

13. Hellard M, Scott N. The changing landscape of hepatitis C treatment—not 'can we cure?'but 'who should we cure first?'Is this an ethical approach? *Addiction* 2015; **110**(6): 984-5.

14. Hellard M, Rolls DA, Sacks-Davis R, et al. The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. *Hepatology* 2014; **60**(6): 1861-70.

15. Martin NK, Vickerman P, Grebely J, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology* 2013; **58**(5): 1598-609.

16. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. *Clin Infect Dis* 2004; **39**(10): 1540-3.

17. Bate JP, Colman AJ, Frost PJ, Shaw DR, Harley HA. High prevalence of late relapse and reinfection in prisoners treated for chronic hepatitis C. *J Gastroenterol Hepatol* 2010; **25**(7): 1276-80.

18. Currie SL, Ryan JC, Tracy D, et al. A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. *Drug Alcohol Depend* 2008; **93**(1): 148-54.

19. Dalgard O. Follow-up studies of treatment for hepatitis C virus infection among injection drug users. *Clin Infect Dis* 2005; **40**(Suppl. 5): S336-S8.

20. Grady BP, Vanhommerig JW, Schinkel J, et al. Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam. *Eur J Gastroenterol Hepatol* 2012; **24**(11): 1302-7.

21. Grebely J, Knight E, Ngai T, et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. *J Gastroenterol Hepatol* 2010; **25**(7): 1281-4.

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

22. Grebely J, Pham ST, Matthews GV, et al. Hepatitis C virus reinfection and superinfection among treated and untreated participants with recent infection. *Hepatology* 2012; **55**(4): 1058-69.

23. Hilsden RJ, Macphail G, Grebely J, Conway B, Lee SS. Directly Observed Pegylated Interferon Plus Self-Administered Ribavirin for the Treatment of Hepatitis C Virus Infection in People Actively Using Drugs: A Randomized Controlled Trial. *Clin Infect Dis* 2013; **57**(Suppl. 2): S90-S6.

24. Dalgard O, Bjoro K, Hellum K, et al. Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up. *Eur Addict Res* 2002; **8**(1): 45-9.

25. Aitken CK, Lewis J, Tracy SL, et al. High incidence of hepatitis C virus reinfection in a cohort of injecting drug users. *Hepatology* 2008; **48**(6): 1746-52.

26. Grebely J, Conway B, Raffa JD, Lai C, Krajden M, Tyndall MW. Hepatitis C virus reinfection in injection drug users. *Hepatology* 2006; **44**(5): 1139-45.

27. Mehta SH, Cox A, Hoover DR, et al. Protection against persistence of hepatitis C. *Lancet* 2002; **359**(9316): 1478-83.

28. Micallef JM, Macdonald V, Jauncey M, et al. High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. *J Viral Hepat* 2007; **14**(6): 413-8.

29. Page K, Hahn JA, Evans J, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *J Infect Dis* 2009; **200**(8): 1216-26.

30. van de Laar TJ, Molenkamp R, van den Berg C, et al. Frequent HCV reinfection and superinfection in a cohort of injecting drug users in Amsterdam. *J Hepatol* 2009; **51**(4): 667-74.

31. Sacks-Davis R, Grebely J, Dore GJ, et al. Hepatitis C Virus Reinfection and Spontaneous Clearance of Reinfection--the InC3 Study. *J Infect Dis* 2015; **212**(9): 1407-19.

32. Midgard H, Bjoro B, Maeland A, et al. Hepatitis C reinfection after sustained virological response. *J Hepatol* 2016; **64**(5): 1020-6.

33. Treloar C, Mao L, Wilson H. Beyond equipment distribution in Needle and Syringe Programmes: an exploratory analysis of blood-borne virus risk and other measures of client need. *Harm Reduct J* 2016; **13**(1): 18.

34. Pilowsky DJ, Wu L-T, Burchett B, Blazer DG, Ling W. Depressive symptoms, substance use, and HIV-related high-risk behaviors among opioid-dependent individuals: results from the Clinical Trials Network. *Subst Use Misuse* 2011; **46**(14): 1716-25.

35. Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. *J Infect Dis* 2011; **204**(1): 74-83.

36. Janjua NZ, Kuo M, Chong M, et al. Assessing Hepatitis C Burden and Treatment Effectiveness through the British Columbia Hepatitis Testers Cohort (BC-HTC): Design and Characteristics of Linked and Unlinked Participants. *PLoS One* 2016; **11**(3): e0150176.

37. Janjua NZ, Yu A, Kuo M, et al. Twin epidemics of new and prevalent hepatitis C infections in Canada: BC Hepatitis Testers Cohort. *BMC Infect Dis* 2016; **16**(1): 334.

38. Janjua NZ, Kuo M, Yu A, et al. The Population Level Cascade of Care for Hepatitis C in British Columbia, Canada: The BC Hepatitis Testers Cohort (BC-HTC). *EBioMedicine* 2016; **12**: 189-95.

39. Pampalon R, Hamel D, Gamache P, Philibert MD, Raymond G, Simpson A. An area-based material and social deprivation index for public health in Quebec and Canada. *Can J Public Health* 2012; **103**(8 Suppl 2): S17-22.

40. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research* 2011; **46**(3): 399-424.

41. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. *Psychol Methods* 2010; **15**(3): 234-49.

42. Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. *Clin Infect Dis* 2013; **57**(suppl 2): S105-S10.

43. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. *J Hepatol* 2016.

44. Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States. *Ann Intern Med* 2015; **163**(3): 215-23.

45. Marshall AD, Saeed S, Barrett L, et al. Restrictions for reimbursement of direct-acting antiviral treatment for hepatitis C virus infection in Canada: a descriptive study. *CMAJ Open* 2016; **4**(4): E605-E14.

46. Schaefer M, Sarkar R, Diez-Quevedo C. Management of Mental Health Problems Prior to and During Treatment of Hepatitis C Virus Infection in Patients With Drug Addiction. *Clin Infect Dis* 2013; **57**(suppl 2): S111-S7.

47. Lima VD, Rozada I, Grebely J, et al. Are Interferon-Free Direct-Acting Antivirals for the Treatment of HCV Enough to Control the Epidemic among People Who Inject Drugs? *PLoS One* 2015; **10**(12): e0143836.

48. Golub ET, Strathdee SA, Bailey SL, et al. Distributive syringe sharing among young adult injection drug users in five US cities. *Drug Alcohol Depend* 2007; **91**: S30-S8.

49. Lum PJ, Sears C, Guydish J. Injection risk behavior among women syringe exchangers in San Francisco. *Subst Use Misuse* 2005; **40**(11): 1681-96.

50. Kuo M, Janjua NZ, Burchell AN, Buxton JA, Krajden M, Gilbert M. Decreasing Hepatitis C Incidence Among a Population With Repeated Tests: British Columbia, Canada, 1993–2011. *Am J Public Health* 2015; **105**(8): 1604-10.

51. Ingiliz P, Krznaric I, Stellbrink HJ, et al. Multiple hepatitis C virus (HCV) reinfections in HIV-positive men who have sex with men: no influence of HCV genotype switch or interleukin-28B genotype on spontaneous clearance. *HIV Med* 2014; **15**(6): 355-61.

52. Martin TC, Martin NK, Hickman M, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. *AIDS* 2013; **27**(16): 2551-7.

53. Butt Z, Shrestha N, Kuo M, et al. Social disparities and co-evolution of HIV/HCV infections, mental disorders and substance use: the British Columbia Hepatitis Testers Cohort. The 67th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2016. Boston, MA; 2016.

54. Vickerman P, Grebely J, Dore GJ, et al. The more you look, the more you find: effects of hepatitis C virus testing interval on reinfection incidence and clearance and implications for future vaccine study design. *J Infect Dis* 2012; **205**(9): 1342-50.

55. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 2010; **139**(5): 1593-601.

56. Kuo M, Janjua N, Yu A, et al. Assessment of Injection Drug Use Based on Diagnostic Codes in Administrative Datasets. The 25th Annual Canadian Conference on HIV/AIDS Research (CAHR 2016). Winnipeg, MB; 2016.

57. Grebely J, Dore GJ. Can hepatitis C virus infection be eradicated in people who inject drugs? *Antiviral Res* 2014; **104**: 62-72.

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**Panel 1. Research in context**

**Evidence before this study**

Hepatitis C virus (HCV) infection does not confer immunity to prevent reinfection. Thus, people infected with HCV remain at risk of reinfection even after spontaneous clearance, or treatment-induced clearance (sustained virological response [SVR]) of the virus. We searched PubMed and Google Scholar for articles published from database inception up to July 31, 2016, describing HCV reinfection using the search terms "Hepatitis C", "HCV", "reinfect", "re-infect", and "repeat infection" without any language restrictions. HCV reinfections after spontaneous clearance or SVR have been reported largely in high-risk populations, such as people who inject drugs (PWID); however, most of these studies had small sample sizes. The reported rates of HCV reinfection have been inconsistent, and they also differed between the spontaneous clearance and SVR groups. Because of their small sample sizes, most of these studies did not assess the potential risk factors for HCV reinfection comprehensively, and thus only HIV coinfection and injection drug use were reported to be the potential risk factors.

**Added value of this study**

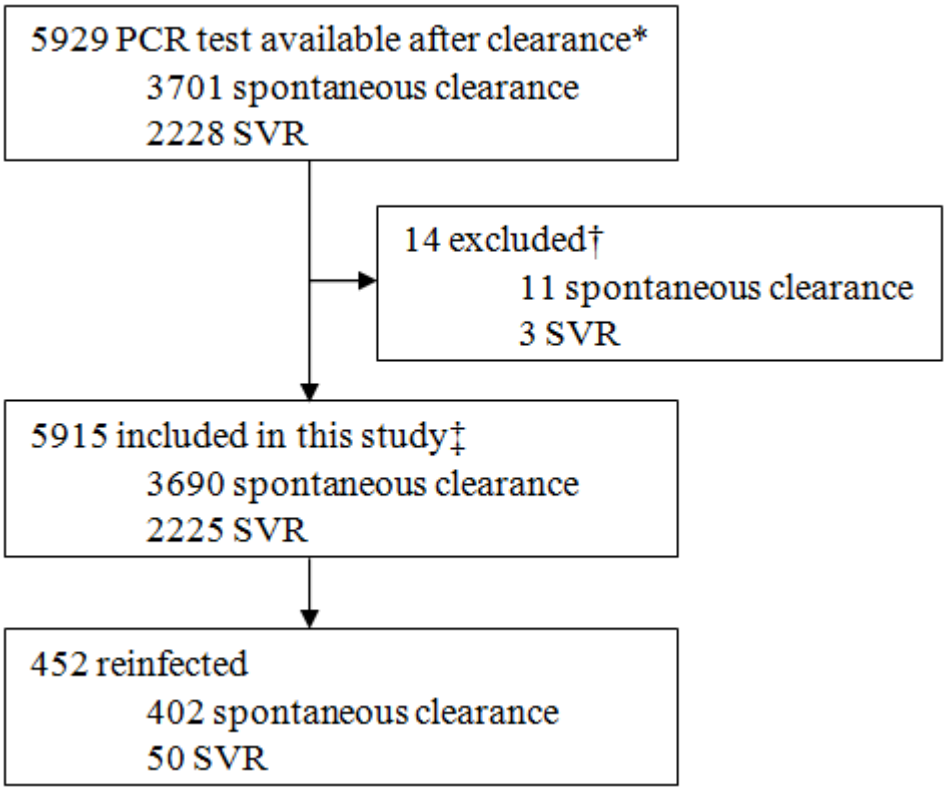
Our study was done with the largest population-based cohort (n=5915) with the largest number of HCV reinfections (n=452) so far, including both spontaneous clearance and SVR groups. Our analyses included information on patient demographic characteristics (age, sex, birth cohort, and year of HCV diagnosis), HIV coinfection, risk behaviours (injection drug use and problematic alcohol use), harm-reduction initiatives (opioid substitution therapy and mental health counselling), and socioeconomic deprivation. We noted an overall incidence rate of 1.27 per 100 person-years (95% CI 1.15–1.39), with significantly higher rates in the spontaneous clearance group than in SVR group. In an adjusted Cox proportional hazards model, the spontaneous clearance group, those coinfected with HIV, and PWID had a higher reinfection risk. Among PWID, engagement with opioid substitution therapy and mental health counselling services were associated with significantly lowered HCV reinfection risk.

**Implications of all the available evidence**

HCV reinfection remains a major public health challenge affecting decisions to treat PWID. Our results suggest that the risk of HCV reinfection among PWID could be lowered by engagement with harm-reduction initiatives such as opioid substitution therapy and mental health counselling, thus opening up opportunities for treatment of PWID and coming closer to WHO's goal of HCV elimination.

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**Figure 1: Selection of participants for HCV reinfection analysis in British Columbia, Canada**




HCV = Hepatitis C virus; PCR = Polymerase Chain Reaction

*Clearance was defined as two consecutive negative PCR tests after HCV diagnosis without treatment (spontaneous clearance group), or ≥12 weeks post-treatment (for the sustained virological response group), as applicable. †Excluded because the difference between the two negative PCR tests was <28 days. ‡Participants with two consecutive negative PCR tests ≥28 days apart who had ≥1 valid PCR after clearance.

*Author's accepted version* DOI: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

**Table 1: Characteristics of participants for the analysis of Hepatitis C reinfection in British Columbia, Canada (n=5,915)**

| | Spontaneous clearance* | | SVR* | | Total | |
|---|---|---|---|---|---|---|
| | Overall | Reinfection | Overall | Reinfection | Overall | Reinfection |
| **Age at clearance (years)** | | | | | | |
| < 35 | 1216 (33) | 180 (44.8) | 248 (11.1) | 9 (18) | 1464 (24.8) | 189 (41.8) |
| 35-44 | 1224 (33.2) | 151 (37.6) | 443 (19.9) | 16 (32) | 1667 (28.2) | 167 (37) |
| ≥ 45 | 1250 (33.9) | 71 (17.7) | 1534 (68.9) | 25 (50) | 2784 (47.1) | 96 (21.2) |
| Median (IQR) | 40 (32-47) | 36 (28-42) | 50 (42-55) | 45 (36-53) | 43 (35-51) | 37 (30-43) |
| **Birth cohort** | | | | | | |
| < 1965 | 1992 (54) | 157 (39.1) | 1719 (77.3) | 32 (64) | 3711 (62.7) | 189 (41.8) |
| 1965-1974 | 998 (27) | 140 (34.8) | 333 (15) | 15 (30) | 1331 (22.5) | 155 (34.3) |
| ≥ 1975 | 700 (19) | 105 (26.1) | 173 (7.8) | 3 (6) | 873 (14.8) | 108 (23.9) |
| **Sex** | | | | | | |
| Female | 1622 (44) | 154 (38.3) | 822 (36.9) | 10 (20) | 2444 (41.3) | 164 (36.3) |
| Male | 2068 (56) | 248 (61.7) | 1403 (63.1) | 40 (80) | 3471 (58.7) | 288 (63.7) |
| **Year of HCV diagnosis** | | | | | | |
| 1990-97 | 1213 (32.9) | 137 (34.1) | 654 (29.4) | 15 (30) | 1867 (31.6) | 152 (33.6) |
| 1998-04 | 1552 (42.1) | 180 (44.8) | 1131 (50.8) | 30 (60) | 2683(45.4) | 210 (46.5) |
| 2005-13 | 925 (25.1) | 85 (21.1) | 440 (19.8) | 5 (10) | 1365 (23.1) | 90 (19.9) |
| **HIV co-infection**** | | | | | | |
| Yes | 407 (11) | 79 (19.7) | 126 (5.7) | 12 (24) | 533 (9) | 91 (20.1) |
| No | 3283 (89) | 323 (80.4) | 2099 (94.3) | 38 (76) | 5382 (91) | 361 (79.9) |
| **At least one mental health** | | | | | | |
| Yes | 1168 (31.7) | 119 (29.6) | 414 (18.6) | 16 (32) | 1582 (26.7) | 135 (29.9) |
| No | 2522 (68.3) | 283 (70.4) | 1811 (81.4) | 34 (68) | 4333 (73.3) | 317 (70.1) |
| **Injection drug use‡** | | | | | | |
| Yes | 1928 (52.2) | 268 (66.7) | 565 (25.4) | 30 (60) | 2493 (42.1) | 298 (65.9) |
| No | 1762 (47.8) | 134 (33.3) | 1660 (74.6) | 20 (40) | 3422 (57.9) | 154 (34.1) |
| **Problematic alcohol use‡** | | | | | | |
| Yes | 1615 (43.8) | 210 (52.2) | 586 (26.3) | 19 (38) | 2201 (37.2) | 229 (50.7) |
| No | 2075 (56.2) | 192 (47.8) | 1639 (73.7) | 31 (62) | 3714 (62.8) | 223 (49.3) |
| **Material deprivation** | | | | | | |
| Q1 (most privileged) | 492 (13.3) | 42 (10.5) | 321 (14.4) | 11 (22) | 813 (13.7) | 53 (11.7) |
| Q2 | 500 (13.6) | 62 (15.4) | 373 (16.8) | 7 (14) | 873 (14.8) | 69 (15.3) |
| Q3 | 580 (15.7) | 67 (16.7) | 453 (20.4) | 7 (14) | 1033 (17.5) | 74 (16.4) |
| Q4 | 804 (21.8) | 82 (20.4) | 484 (21.8) | 12 (24) | 1288 (21.8) | 94 (20.8) |
| Q5 (most deprived) | 1183 (32.1) | 132 (32.8) | 577 (25.9) | 13 (26) | 1760 (29.8) | 145 (32.1) |
| Unknown | 131 (3.6) | 17 (4.2) | 0 | 0 | 148 (2.5) | 17 (3.8) |
| **Social deprivation quintile†** | | | | | | |
| Q1 (most privileged) | 359 (9.7) | 27 (6.7) | 384 (17.3) | 6 (12) | 743 (12.6) | 33 (7.3) |
| Q2 | 418 (11.3) | 39 (9.7) | 348 (15.6) | 5 (10) | 766 (13) | 44 (9.7) |
| Q3 | 586 (15.9) | 72 (17.9) | 377 (16.9) | 10 (20) | 963 (16.3) | 82 (18.1) |
| Q4 | 748 (20.3) | 89 (22.1) | 431 (19.4) | 11 (22) | 1179 (19.9) | 100 (22.1) |
| Q5 (most deprived) | 1448 (39.2) | 158 (39.3) | 668 (30) | 18 (36) | 2116 (35.8) | 176 (38.9) |
| Unknown | 131 (3.6) | 17 (4.2) | 0 | 0 | 148 (2.5) | 17 (3.8) |

Data are n (%). * Clearance type of first HCV diagnosis; ** HIV diagnosis before the end of the study; *** reported between the date on HCV clearance and the last day of follow-up; ‡ ever reported in the cohort; † at the time of HCV clearance.
SVR: Sustained virological response; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus

*Author's accepted version* DOI: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

**Table 2: Incidence rates of HCV reinfection among those who cleared primary infections in British Columbia, Canada**

| Characteristics | Number of reinfection | Incidence rate (95% CI); per 100 person-years |
|---|---|---|
| **Overall** | 452 | 1.27 (1.15-1.39) |
| **Clearance type*** | | |
| Spontaneous clearance | | |
| Total | 402 | 1.59 (1.44-1.76) |
| PWID | 268 | 1.88 (1.66-2.12) |
| SVR | | |
| Total | 50 | 0.48 (0.36-0.63) |
| PWID | 30 | 1.14 (0.77-1.63) |
| **Age at clearance (years)** | | |
| < 35 | 189 | 1.99 (1.71-2.29) |
| 35-44 | 167 | 1.49 (1.27-1.73) |
| ≥ 45 | 96 | 0.64 (0.52-0.79) |
| **Birth cohort** | | |
| < 1965 | 189 | 0.82 (0.71-0.95) |
| 1965-1974 | 155 | 1.88 (1.60-2.20) |
| ≥1975 | 108 | 2.43 (2.00-2.94) |
| **Sex** | | |
| Female | 164 | 1.03 (0.88-1.20) |
| Male | 288 | 1.46 (1.30-1.64) |
| **Year of HCV diagnosis** | | |
| 1990-97 | 152 | 1.03 (0.87-1.20) |
| 1998-04 | 210 | 1.28 (1.11-1.47) |
| 2005-13 | 90 | 2.01 (1.62-2.47) |
| **HIV co-infection**** | | |
| Yes | 91 | 2.56 (2.06-3.14) |
| No | 361 | 1.12 (1.01-1.25) |
| **At least one mental health counseling visit***** | | |
| Yes | 135 | 1.16 (0.97-1.37) |
| No | 317 | 1.32 (1.18-1.47) |
| **Injection drug use‡** | | |
| Yes | 298 | 1.77 (1.57-1.98) |
| No | 154 | 0.82 (0.69-0.96) |
| **Problematic alcohol use‡** | | |
| Yes | 229 | 1.53 (1.34-1.74) |
| No | 223 | 1.08 (0.94-1.23) |
| **Material deprivation quintile†** | | |
| Q1 (most privileged) | 53 | 1.14 (0.85-1.49) |
| Q2 | 69 | 1.30 (1.01-1.64) |
| Q3 | 74 | 1.23 (0.97-1.54) |
| Q4 | 94 | 1.19 (0.96-1.45) |
| Q5 (most deprived) | 145 | 1.31 (1.11-1.54) |
| Unknown | 17 | 2.37 (1.38-3.79) |
| **Social deprivation quintile†** | | |

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

| | | |
|---|---|---|
| Q1 (most privileged) | 33 | 0.79 (0.55-1.11) |
| Q2 | 44 | 0.98 (0.72-1.32) |
| Q3 | 82 | 1.37 (1.09-1.70) |
| Q4 | 100 | 1.43 (1.16-1.74) |
| Q5 (most deprived) | 176 | 1.32 (1.13-1.53) |
| Unknown | 17 | 2.37 (1.38-3.79) |

* Clearance type of first HCV diagnosis; ** HIV diagnosis before the end of the study; *** reported between the date on HCV clearance and the last day of follow-up; ‡ ever reported in the cohort; † at the time of HCV clearance.
CI: Confidence interval; SVR: Sustained virological response; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**Table 3: Unadjusted and adjusted hazard ratio from Cox proportional hazards model for time to HCV reinfection in British Columbia, Canada**

| Characteristics | Unadjusted HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
|---|---|---|---|---|
| **Age at clearance (years)** | | <0.0001 | | |
| < 35 | 3.18 (2.49-4.07) | | | |
| 35-44 | 2.39 (1.86-3.08) | | | |
| ≥ 45 | *Ref* | | | |
| **Birth cohort** | | <0.0001 | | <0.0001 |
| < 1965 | 0.35 (0.27-0.44) | | 0.48 (0.37-0.63) | |
| 1965-1974 | 0.79 (0.62-1.01) | | 0.87 (0.68-1.13) | |
| ≥1975 | *Ref* | | *Ref* | |
| **Female** | 0.71 (0.59-0.86) | 0.0006 | 0.57 (0.47-0.70) | <0.0001 |
| **Year of HCV diagnosis** | | <0.0001 | | 0.002 |
| 1990-97 | 0.54 (0.41-0.71) | | 0.60 (0.44-0.80) | |
| 1998-04 | 0.66 (0.51-0.85) | | 0.74 (0.57-0.96) | |
| 2005-13 | *Ref* | | *Ref* | |
| **Spontaneous clearance*** | 3.63 (2.7-4.89) | <0.0001 | 2.71 (2.00-3.68) | <0.0001 |
| **HIV co-infection**** | 2.77 (2.20-3.49) | <0.0001 | 2.25 (1.78-2.85) | <0.0001 |
| **At least one mental health counseling visit***** | 0.90 (0.74-1.10) | 0.315 | | |
| **Injection drug use‡** | 2.21 (1.82-2.69) | <0.0001 | 1.53 (1.21-1.92) | <0.001 |
| **Problematic alcohol use‡** | 1.45 (1.21-1.75) | <0.0001 | 1.04 (0.84-1.28) | 0.726 |
| **Material deprivation quintile†** | | 0.164 | | |
| Q1 (most privileged) | *Ref* | | | |
| Q2 | 1.15 (0.80-1.64) | | | |
| Q3 | 1.08 (0.76-1.53) | | | |
| Q4 | 1.05 (0.75-1.47) | | | |
| Q5 (most deprived) | 1.16 (0.85-1.59) | | | |
| Unknown | 2.08 (1.20-3.58) | | | |
| **Social deprivation quintile†** | | 0.002 | | 0.121 |
| Q1 (most privileged) | *Ref* | | | |
| Q2 | 1.25 (0.80-1.96) | | 1.16 (0.74-1.82) | |
| Q3 | 1.75 (1.17-2.63) | | 1.45 (0.97-2.18) | |
| Q4 | 1.82 (1.23-2.70) | | 1.39 (0.93-2.06) | |
| Q5 (most deprived) | 1.69 (1.16-2.45) | | 1.20 (0.82-1.75) | |
| Unknown | 3.00 (1.67-5.39) | | 2.04 (1.13-3.68) | |

* Clearance type of first HCV diagnosis (reference group: SVR); ** used as a time-varying covariate; *** reported between the date on HCV clearance and the last day of follow-up; ‡ ever reported in the cohort; † at the time of HCV clearance.
HR: Hazard ratio; CI: Confidence interval; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus; SVR: Sustained virological response

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**Table 4: Adjusted hazard ratio from Cox proportional hazards model for time to HCV reinfection, stratified by clearance type, in British Columbia, Canada.**

| | Spontaneous clearance* | | Sustained Virological Response* | |
|---|---|---|---|---|
| **Characteristics** | **Adjusted HR (95% CI)** | **p-value** | **Adjusted HR (95% CI)** | **p-value** |
| **Birth cohort** | | <0.0001 | | 0.546 |
| < 1965 | 0.45 (0.35-0.60) | | 1.32 (0.39-4.50) | |
| 1965-1974 | 0.84 (0.64-1.09) | | 1.78 (0.50-6.29) | |
| ≥1975 | *Ref* | | *Ref* | |
| **Female** | 0.60 (0.48-0.73) | <0.0001 | 0.47 (0.23-0.96) | 0.037 |
| **Year of HCV diagnosis** | | 0.003 | | 0.598 |
| 1990-97 | 0.58 (0.43-0.79) | | 0.78 (0.27-2.25) | |
| 1998-04 | 0.71 (0.54-0.94) | | 1.08 (0.41-2.88) | |
| 2005-13 | *Ref* | | *Ref* | |
| **HIV co-infection**** | 2.14 (1.66-2.75) | <0.0001 | 3.37 (1.68-6.76) | <0.001 |
| **Injection drug use‡** | 1.34 (1.05-1.70) | 0.019 | 3.94 (2.00-7.76) | <0.0001 |
| **Problematic alcohol use‡** | 1.07 (0.86-1.34) | 0.536 | 0.86 (0.46-1.61) | 0.631 |
| **Social deprivation quintile†** | | 0.152 | | 0.956 |
| Q1 (most privileged) | *Ref* | | *Ref* | |
| Q2 | 1.22 (0.74-1.99) | | 0.68 (0.20-2.25) | |
| Q3 | 1.45 (0.93-2.26) | | 1.17 (0.42-3.28) | |
| Q4 | 1.40 (0.91-2.15) | | 0.91 (0.32-2.56) | |
| Q5 (most deprived) | 1.20 (0.80-1.81) | | 0.90 (0.34-2.36) | |
| Unknown | 2.09 (1.14-3.85) | | - | |

* Clearance type of first HCV diagnosis (reference group: SVR); ** used as a time-varying covariate; ‡ ever reported in the cohort; † at the time of HCV clearance.

HR: Hazard ratio; CI: Confidence interval; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**Table 5: Unadjusted and adjusted hazard ratio from Cox proportional hazards model for time to HCV reinfection among current injection drug users in British Columbia, Canada**

| Characteristics | Unadjusted HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
|---|---|---|---|---|
| **Age at clearance (years)** | | <0.001 | | |
| < 35 | 2.47 (1.58-3.86) | | | |
| 35-44 | 1.80 (1.13-2.87) | | | |
| ≥ 45 | *Ref* | | | |
| **Birth cohort** | | <0.0001 | | <0.0001 |
| < 1965 | 0.39 (0.28-0.55) | | 0.47 (0.33-0.69) | |
| 1965-1974 | 0.71 (0.52-0.98) | | 0.89 (0.63-1.25) | |
| 1975+ | *Ref* | | *Ref* | |
| **Female** | 0.82 (0.63-1.07) | 0.143 | 0.71 (0.54-0.93) | 0.013 |
| **Year of HCV diagnosis** | | <0.0001 | | <0.0001 |
| 1990-97 | 0.24 (0.16-0.36) | | 0.27 (0.17-0.42) | |
| 1998-04 | 0.46 (0.32-0.67) | | 0.47 (0.32-0.69) | |
| 2005-13 | *Ref* | | *Ref* | |
| **Spontaneous clearance*** | 1.52 (0.90-2.58) | 0.119 | | |
| **HIV co-infection**** | 2.11 (1.59-2.81) | <0.0001 | 2.39 (1.79-3.19) | <0.0001 |
| **At least one mental health counseling visit***** | 0.72 (0.55-0.94) | 0.014 | 0.71 (0.54-0.92) | 0.011 |
| **Problematic alcohol use‡** | 0.92 (0.69-1.22) | 0.548 | | |
| **Opioid substitution therapy**** | 0.74 (0.55-1.00) | 0.05 | 0.73 (0.54-0.98) | 0.038 |
| **Material deprivation quintile†** | | 0.677 | | |
| Q1 (most privileged) | *Ref* | | | |
| Q2 | 1.45 (0.82-2.56) | | | |
| Q3 | 1.62 (0.93-2.82) | | | |
| Q4 | 1.37 (0.81-2.32) | | | |
| Q5 (most deprived) | 1.32 (0.80-2.18) | | | |
| Unknown | 1.40 (0.41-4.72) | | | |
| **Social deprivation quintile†** | | 0.186 | | |
| Q1 (most privileged) | *Ref* | | | |
| Q2 | 1.46 (0.73-2.93) | | | |
| Q3 | 1.76 (0.95-3.26) | | | |
| Q4 | 1.49 (0.81-2.77) | | | |
| Q5 (most deprived) | 1.14 (0.64-2.04) | | | |
| Unknown | 1.37 (0.39-4.80) | | | |

* Clearance type of first HCV diagnosis (reference group: SVR); ** used as a time-varying covariate; *** reported between the date on HCV clearance and the last day of follow-up; ‡ ever reported in the cohort; † at the time of HCV clearance.

HR: Hazard ratio; CI: Confidence interval; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus; SVR: Sustained virological response.

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

## APPENDICES

### Supplementary Table 1: Criteria and Data Sources for the BC Hepatitis Testers Cohort (BC-HTC)

| | |
|---|---|
| **Criteria for Inclusion in BC-HTC** | |
| All individuals: | |
| • tested at the centralized provincial laboratory for HCV or HIV OR | |
| • reported by BC public health as a confirmed case of HCV OR | |
| • reported in BC enhanced surveillance system as a confirmed case of HIV or AIDS (all reports) OR | |
| • reported by BC public health as a confirmed case of HBV OR | |
| • included in BC Enhanced Strain Surveillance System (EHSSS) as an acute HBV or HCV case | |
| • All individuals meeting at least one the above criteria were linked internally across all their tests and case reports. Those with a valid personal health number (PHN) were then sent for deterministic linkage with province-wide Cancer and Ministry of Health (MoH) datasets | |
| **Provincial Communicable Disease Data Sources:** | **Data Date Ranges:** |
| BC-PHMRL HIV laboratory testing datasets (tests: ELISA, Western blot, NAAT, p24, culture) | 1988–2013 |
| BC-PHMRL HCV laboratory tests datasets (tests: antibody, HCV RNA, genotyping) | 1992–2013 |
| HIV/AIDS Information System (HAISYS) (public health HIV/AIDS case reports) | 1980–2013 |
| Integrated Public Health information System (iPHIS) (public health case reports of HCV, HBV, and TB) | 1990–2013 |
| Enhanced Strain Surveillance System (EHSSS) (risk factor data on a subset of acute HCV and acute HBV cases) | 2000–2013 |
| **Cancer and MoH Administrative Data Sources:** | |
| BC Cancer Registry (BCCR) (primary tumour registry, excludes metastatic cancers) | 1970–2012 |
| Discharge Abstracts Dataset (DAD) (hospitalization records)[S1] | 1985–2013Q1 |
| Medical Services Plan (MSP) (physician diagnostic and billing data)[S2] | 1990–2012 |
| PharmaCare/PharmaNet (Pharma) (prescription drug dispensations)[S3, S4] | 1985–2012 |
| BC Vital Statistics (VS) (deaths registry)[S5] | 1985–2013 |
| The final BC-HTC comprises all individuals successfully linked on PHN to the MoH Client Roster[S6] (a registry of all BC residents enrolled in the publicly-funded universal healthcare system) | |

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; BC-PHMRL: BC Public Health Microbiology and Reference Laboratory: RNA: Ribonucleic Acid; PCR: Polymerase Chain Reaction.

**Supplementary References**:

S1. British Columbia Ministry of Health [creator]. Discharge Abstract Database (Hospital Separations). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2014. http://www.health.gov.bc.ca/data

S2. British Columbia Ministry of Health [creator]. Medical Services Plan (MSP) Payment Information File. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2014. http://www.health.gov.bc.ca/data

S3. British Columbia Ministry of Health [creator]. PharmaCare. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2014. http://www.health.gov.bc.ca/data

S4. British Columbia Ministry of Health [creator]. PharmaNet. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2014. http://www.health.gov.bc.ca/data

S5. BC Vital Statistics Agency [creator]. Vital Statistics Deaths. BC Vital Statistics Agency [publisher]. Data Extract. BC Vital Statistics Agency (2014). 2014.

S6. British Columbia Ministry of Health [creator]. Client Roster (Client Registry System/Enterprise Master Patient Index). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2014. http://www.health.gov.bc.ca/data

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**Supplementary Table 2: Definitions for comorbid conditions for the BC Hepatitis Testers Cohort (BC-HTC) and current analysis**

| |
|---|
| **Mental health counseling**<br>Mental health counseling and rehabilitation was defined at the first occurrence of 1 medical services plan (MSP) fee item code for consultations and psychotherapy sessions related to mental health problems within the study period.<br>**MSP fee item code:** 600-699, 60607-45 |
| **Injection Drug Use**<br>Illicit Drug Use was defined at the first occurrence of 2 MSP or 1 hospitalization diagnostic codes or 1 PharmeNet code for major drug-related diagnoses involving addiction, dependence, and drug-induced mental disorders; illicit drug use most likely to be injectables (e.g. excluding cannabis), or illicit use of prescribed drugs including: hallucinogens, barbituates/tranquillizers, sedatives, hypnotics, anxiolytics, opioids, cocaine, amphetamine, volatile solvents; or discharge to drug rehabilitation, counselling, or surveillance.<br>**Physician Billing Data**: MSP ICD-9 diagnostic codes: starting with 292, 3040, 3042, 3044, 3046-9, 3054-7, 3059, 6483, 9650, 9697, 970, E8500, or exact codes V6542<br>**Hospitalization Data**: **DAD1/ICD-9-CM**: starting with 292, 3040, 3042, 3044, 3046-9, 3054-7, 3059, 6483, 9650, 9697, 970, E8500; **DAD2/ICD-10-CA**: starting with F11, F13-5, F18, F19, T42, or exact codes T401, T402, T404-6, T436, T438, T439, T507. |
| **Problematic Alcohol Use**<br>Problematic alcohol use was defined at the first occurrence of 2 MSP or 1 hospitalization codes for major alcohol-related diagnoses including alcoholic mental disorders and dependence/abuse syndromes; alcoholic polyneuropathy, myopathy, cardiomyopathy; pseudo Cushing's syndrome; or discharge to alcohol rehabilitation, counselling, or surveillance<br>**Physician Billing Data:** MSP ICD-9 diagnostic codes: starting with 291, 303, 3050, 3575, 4255<br>**Hospitalization Data:** DAD1/ICD-9-CM: starting with 291, 303, 3050,3575, 4255; DAD2/ICD-10-CA: starting with F10, E244, G312, G621, G721, I426, Z502, Z714 |
| **Opioid substitution therapy**<br>Opioid substitution therapy was defined at the first occurrence of 2 MSP or 1 PharmeNet DIN/PIN code for methadone/buprenorphine substitution treatment.<br>**Physician Billing Data:** MSP ICD-9: fee item = 39<br>**PharmeNet DIN/PIN**: 2242963, 2242964, 99792, 66999990-3, 66999997, 66999999, 67000000, 2295695, 2295709.<br><br>*DIN = Drug Identification Number, PIN = Product Identification Numbers |

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

**Supplementary Table 3: Incidence rates of HCV reinfection among those who cleared primary infections (defined as a single negative PCR) in British Columbia, Canada (N=10,408)**

| Characteristics | Number of reinfection | Incidence Rate (95% CI) per 100 person-years |
|---|---|---|
| **Overall** | **1231** | **2.42 (2.29-2.56)** |
| Injection drug use | | |
| Yes | 858 | 3.34 (3.12-3.56) |
| No | 373 | 1.48 (1.33-1.63) |
| Clearance type of first infection | | |
| Spontaneous clearance | 1106 | 2.88 (2.71-3.05) |
| Injection drug use | | |
| Yes | 784 | 3.53 (3.29-3.79) |
| No | 322 | 1.99 (1.78-2.22) |
| Sustained Virological Response | 125 | 1.00 (0.83-1.18) |
| Injection drug use | | |
| Yes | 74 | 2.11 (1.66-2.65) |
| No | 51 | 0.57 (0.42-0.75) |
| HIV | | |
| Yes | 122 | 4.17 (3.43-4.91) |
| No | 1109 | 2.31 (2.18-2.45) |

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**Supplementary Table 4: Adjusted hazard ratio from Cox proportional hazards models for time to HCV reinfection among current injection drug users in British Columbia, Canada (**analysis checking the interaction between opioid substitution therapy and mental health counselling**)**

| **Characteristics** | **Adjusted hazard ratio (95% CI)** | **p-value** |
|---|---|---|
| **Mental health counselling ever reported during the follow-up time** | | |
| ≥ 1 mental health counseling visit*** | 0.77 (0.56-1.06) | 0.104 |
| Opioid substitution therapy (OST)** | 0.84 (0.56-1.25) | 0.389 |
| OST and mental health counselling interaction | 0.74 (0.41-1.35) | 0.326 |
| **Mental health counselling; number of visits per year** | | |
| Mental health counseling visit per year*** | | 0.0001 |
| 0 | *Ref* | |
| 1 | 0.33 (0.19-0.58) | |
| ≥ 2 | 0.65 (0.45-0.95) | |
| Opioid substitution therapy (OST)** | 0.72 (0.50-1.02) | 0.062 |
| OST and mental health counselling interaction | | 0.885 |
| OST and no mental health counselling visit | *Ref* | |
| OST and 1 mental health counselling visit | 0.82 (0.28-2.39) | |
| OST and ≥ 2 mental health counselling visit | 1.11 (0.53-2.33) | |

** used as a time-varying covariate; *** reported between the date on HCV clearance and the last day of follow-up.

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

**Supplementary Table 5: Unadjusted and adjusted hazard ratio from Cox proportional hazards model for time to HCV reinfection among current injection drug users in British Columbia, Canada (Sensitivity analysis using mental health counseling as number of visits per year)**

| Characteristics | Unadjusted HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
|---|---|---|---|---|
| Age at clearance (years) | | <0.001 | | |
| < 35 | 2.47 (1.58-3.86) | | | |
| 35-44 | 1.80 (1.13-2.87) | | | |
| ≥ 45 | *Ref* | | | |
| Birth cohort | | <0.0001 | | <0.0001 |
| < 1965 | 0.39 (0.28-0.55) | | 0.46 (0.32-0.67) | |
| 1965-1974 | 0.71 (0.52-0.98) | | 0.86 (0.61-1.21) | |
| ≥1975 | *Ref* | | *Ref* | |
| Female | 0.82 (0.63-1.07) | 0.143 | 0.72 (0.55-0.95) | 0.012 |
| Year of HCV diagnosis | | <0.0001 | | <0.0001 |
| 1990-97 | 0.24 (0.16-0.36) | | 0.28 (0.18-0.43) | |
| 1998-04 | 0.46 (0.32-0.67) | | 0.48 (0.33-0.71) | |
| 2005-13 | *Ref* | | *Ref* | |
| Spontaneous clearance* | 1.52 (0.90-2.58) | 0.119 | | |
| HIV co-infection** | 2.11 (1.59-2.81) | <0.0001 | 2.47 (1.85-3.30) | <0.0001 |
| Problematic alcohol use‡ | 0.92 (0.69-1.22) | 0.548 | | |
| Mental health counseling visit per year*** | | <0.0001 | | <0.0001 |
| 0 | *Ref* | | | |
| 1 | 0.32 (0.20-0.51) | | 0.32 (0.20-0.51) | |
| ≥ 2 | 0.71 (0.51-0.98) | | 0.67 (0.48-0.93) | |
| Opioid substitution therapy** | 0.74 (0.55-1.00) | 0.05 | 0.72 (0.53-0.97) | 0.028 |
| Material deprivation quintile† | | 0.677 | | |
| Q1 (most privileged) | *Ref* | | | |
| Q2 | 1.45 (0.82-2.56) | | | |
| Q3 | 1.62 (0.93-2.82) | | | |
| Q4 | 1.37 (0.81-2.32) | | | |
| Q5 (most deprived) | 1.32 (0.80-2.18) | | | |
| Unknown | 1.40 (0.41-4.72) | | | |
| Social deprivation quintile† | | 0.186 | | |
| Q1 (most privileged) | *Ref* | | | |
| Q2 | 1.46 (0.73-2.93) | | | |
| Q3 | 1.76 (0.95-3.26) | | | |
| Q4 | 1.49 (0.81-2.77) | | | |
| Q5 (most deprived) | 1.14 (0.64-2.04) | | | |
| Unknown | 1.37 (0.39-4.80) | | | |

* Clearance type of first HCV diagnosis (reference group: SVR); ** used as a time-varying covariate; *** reported between the date on HCV clearance and the last day of follow-up; ‡ ever reported in the cohort; † at the time of HCV clearance.

HR: Hazard ratio; CI: Confidence interval; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus; SVR: Sustained virological response.

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

**Supplementary Table 6: Adjusted hazard ratio from Cox proportional hazards models (sensitivity analysis using single negative PCR for clearance) for time to HCV reinfection in British Columbia, Canada**

| Characteristics | Full cohort (n=10,408) | Spontaneous clearance* (n=6874) | SVR* (n=3534) | PWID (n=4626) |
|---|---|---|---|---|
| Birth cohort | | | | |
| < 1965 | 0.54 (0.46-0.63) | 0.52 (0.44-0.61) | 0.99 (0.49-1.98) | 0.50 (0.42-0.61) |
| 1965-1974 | 0.77 (0.66-0.90) | 0.73 (0.62-0.86) | 1.58 (0.78-3.20) | 0.89 (0.75-1.05) |
| ≥1975 | *Ref* | *Ref* | *Ref* | *Ref* |
| Female | 0.77 (0.68-0.86) | 0.78 (0.69-0.88) | 0.71 (0.48-1.06) | 0.83 (0.73-0.96) |
| Year of HCV diagnosis | | | | |
| 1990-97 | 0.70 (0.59-0.83) | 0.68 (0.57-0.82) | 0.89 (0.48-1.65) | 0.39 (0.32-0.48) |
| 1998-04 | 0.77 (0.66-0.90) | 0.75 (0.64-0.87) | 1.08 (0.62-1.89) | 0.56 (0.47-0.67) |
| 2005-13 | *Ref* | *Ref* | *Ref* | *Ref* |
| Spontaneous clearance* | 2.62 (2.16-3.17) | - | - | - |
| HIV co-infection** | 2.03 (1.74-2.38) | 1.96 (1.66-2.32) | 2.63 (1.62-4.25) | 1.89 (1.60-2.23) |
| Injection drug use‡ | 1.72 (1.49-1.98) | 1.59 (1.37-1.85) | 2.94 (1.92-4.50) | - |
| Problematic alcohol use‡ | 1.01 (0.89-1.14) | 1.01 (0.88-1.14) | 1.03 (0.69-1.53) | - |
| ≥ 1 mental health counseling visit*** | - | - | - | 0.61 (0.53-0.71) |
| Opioid substitution therapy** | - | - | - | 0.80 (0.69-0.94) |
| Social deprivation quintile† | | | | |
| Q1 (most privileged) | *Ref* | | *Ref* | - |
| Q2 | 1.03 (0.80-1.33) | 1.08 (0.83-1.42) | 0.68 (0.33-1.40) | - |
| Q3 | 1.05 (0.83-1.32) | 1.09 (0.85-1.39) | 0.70 (0.35-1.39) | - |
| Q4 | 1.08 (0.87-1.35) | 1.08 (0.85-1.37) | 1.00 (0.55-1.81) | - |
| Q5 (most deprived) | 0.98 (0.79-1.20) | 0.97 (0.78-1.21) | 0.96 (0.55-1.67) | - |
| Unknown | 1.44 (0.97-2.12) | 1.44 (0.97-2.16) | 1.43 (0.19-10.77) | - |

* Clearance type of first HCV diagnosis (reference group: SVR); ** used as a time-varying covariate; ‡ ever reported in the cohort; † at the time of HCV clearance.

HR: Hazard ratio; CI: Confidence interval; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus; PWID: People who inject drugs; SVR = Sustained virological response.

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

**Supplementary Table 7: Unadjusted and adjusted hazard ratio from Cox proportional hazards model for time to HCV reinfection in British Columbia, Canada (using the earliest date of HCV transitions, instead of the mid-points as used in the main analysis)**

| Characteristics | Unadjusted HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
|---|---|---|---|---|
| Age at clearance (years) | | <0.0001 | | |
| < 35 | 3.22 (2.52-4.12) | | | |
| 35-44 | 2.43 (1.89-3.13) | | | |
| ≥ 45 | *Ref* | | | |
| Birth cohort | | <0.0001 | | <0.0001 |
| < 1965 | 0.35 (0.28-0.45) | | 0.49 (0.38-0.63) | |
| 1965-1974 | 0.81 (0.63-1.03) | | 0.87 (0.68-1.13) | |
| ≥1975 | *Ref* | | *Ref* | |
| Female | 0.72 (0.59-0.87) | 0.0008 | 0.58 (0.47-0.70) | <0.0001 |
| Year of HCV diagnosis | | 0.0004 | | 0.01 |
| 1990-97 | 0.58 (0.44-0.77) | | 0.64 (0.48-0.85) | |
| 1998-04 | 0.67 (0.52-0.87) | | 0.75 (0.58-0.98) | |
| 2005-13 | *Ref* | | *Ref* | |
| Spontaneous clearance* | 3.73 (2.77-5.01) | <0.0001 | 2.75 (2.03-3.74) | <0.0001 |
| HIV co-infection** | 2.74 (2.19-3.44) | <0.0001 | 2.22 (1.76-2.80) | <0.0001 |
| Injection drug use‡ | 2.24 (1.85-2.73) | <0.0001 | 1.52 (1.21-1.92) | 0.0003 |
| Problematic alcohol use‡ | 1.48 (1.23-1.78) | <0.0001 | 1.05 (0.85-1.29) | 0.665 |
| ≥ 1 mental health counseling visit*** | 0.91 (0.75-1.12) | 0.372 | | |
| Material deprivation quintile† | 1.45 (1.21-1.75) | <0.0001 | | |
| Q1 (most privileged) | *Ref* | 0.17 | | |
| Q2 | 1.15 (0.81-1.65) | | | |
| Q3 | 1.08 (0.76-1.54) | | | |
| Q4 | 1.05 (0.75-1.48) | | | |
| Q5 (most deprived) | 1.17 (0.86-1.61) | | | |
| Unknown | 2.06 (1.19-3.56) | | | |
| Social deprivation quintile† | | | | 0.119 |
| Q1 (most privileged) | *Ref* | 0.002 | | |
| Q2 | 1.25 (0.80-1.96) | | 1.16 (0.74-1.83) | |
| Q3 | 1.76 (1.17-2.63) | | 1.45 (0.97-2.18) | |
| Q4 | 1.82 (1.23-2.70) | | 1.38 (0.93-2.06) | |
| Q5 (most deprived) | 1.69 (1.17-2.46) | | 1.19 (0.82-1.73) | |
| Unknown | 2.97 (1.65-5.33) | | 2.02 (1.12-3.64) | |

* Clearance type of first HCV diagnosis (reference group: SVR); ** used as a time-varying covariate; *** reported between the date on HCV clearance and the last day of follow-up; ‡ ever reported in the cohort; † at the time of HCV clearance.

HR: Hazard ratio; CI: Confidence interval; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus; SVR: Sustained virological response.

Lancet Gastroenterol Hepatol. 2017:2(3);200-210

*Author's accepted version* DOI: **http://dx.doi.org/10.1016/S2468-1253(16)30182-0**

**The British Columbia Hepatitis Testers Cohort (BC-HTC) team**

Maria Alvarez, Zahid Butt, Mei Chong, Margot Kuo, Hasina Samji, Nabin Shrestha, Amanda Yu (British Columbia Centre for Disease Control, Vancouver, BC, Canada), and Seyed Ali Mussavi Rizi (Performance Measurement & Reporting, Provincial Health Services Authority, Vancouver, BC, Canada).