



# Hepatitis C reinfection after successful treatment

## Question

- What is the risk of hepatitis C reinfection after successful treatment?

## Key Take-Home Messages

- HCV reinfection rates vary widely. Reinfection depends on the extent to which an individual engages in high risk activities after having achieved sustained virologic response through treatment.
- The risk of HCV reinfection among patients who do not engage in higher-risk activities appears to be negligible (1).
- Some studies suggest that the risk of HCV reinfection among people who inject drugs is low but the quality of this evidence has been assessed as very low (2;3). Conversely, a recent systematic review and meta-analysis estimated that, among patients that engage in “high-risk” behaviour (e.g. people who inject drugs), the likelihood of being reinfected over a five-year period was 11% (1).
- The risk of HCV reinfection through sexual contact among men who have sex with men appears to be high (4-6).
- The risk of HCV reinfection among HIV co-infected patients is high (1).

## The Issue and Why It's Important

Hepatitis C virus (HCV) is a major public health problem: approximately 185 million people worldwide are infected (7). In Canada, the overall prevalence of chronic HCV infection in 2011 was 0.6% or 220,697 people (8).

Traditionally, HCV treatment has consisted of pegylated-interferon and ribavirin (9). However, this therapy was associated with poor sustained virologic response (SVR) rates – a surrogate marker for cure – which is defined as undetectable HCV RNA 24 weeks after the completion of therapy (10). Early therapeutic approaches were

## References

1. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: A systematic review and meta-analysis. *Clinical Infectious Diseases* 2016;62(6):683-94.
2. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. *Clinical Infectious Diseases* 2013;57(Suppl 2):S80-S89.
3. Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. *Clinical Infectious Diseases* 2013;57(Suppl 2):S105-S110.
4. Ingiliz P, Krznaric I, Stellbrink HJ, Knecht G, Lutz T, Noah C, 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 Medicine* 2014;15(6):355-61.

followed by protease inhibitors boceprevir and telaprevir combined with pegylated interferon and ribavirin – a change that improved overall rates of sustained virologic response (9). Most recently, highly efficacious interferon-free regimens of direct acting antiviral agents (DAAs) (including sofosbuvir, ledipasvir and others) have fundamentally transformed the treatment landscape (9). The high sustained virologic response rate with the newer medications has been found in populations typically considered difficult-to-treat, such as those with advanced fibrosis or co-infection with HIV (10-12).

Despite these recent successes in HCV treatment, clinicians and health systems continue to be concerned about the risk of HCV recurrence – either due to reinfection following treatment or to late relapse after having had a sustained virological response for 24 weeks (1). HCV reinfection is a particular concern in patients, including people with HIV/HCV co-infection, who continue to engage in high-risk behaviours such as injection drug use. (1).

## What We Found

### Studies of HCV reinfection among people who inject drugs

Since intravenous drug use remains the leading cause of HCV infection and reinfection, several studies have addressed HCV reinfection following treatment-induced clearance among people who inject drugs (3).

Evidence suggests that the incidence of HCV reinfection among people who inject drugs is low. However, the studies in question are limited by small sample sizes and by few cases of reinfection (3). A systematic review (3) identified seven such studies with a prospective design including data from Germany (13), Norway (14), the United States (15), Canada (16), the Netherlands (17) and Australia (18;19). Sample sizes within the studies varied between nine and 88 persons, and data on injection drug use before and during treatment was available in only three studies. All seven studies detected at least one case of reinfection with a total of 17 reinfections across the studies. Among the six studies providing data on person-years of follow-up, the reinfection rate varied from 0.8 to 4.7 per 100 person years.

According to the authors of the systematic review, reinfection can occur after successful HCV treatment but the rate is low even among persons who continue to inject drugs during and after treatment (3). The authors did note that the risk of reinfection may vary depending on the local HCV epidemic among people who inject drugs and be higher in communities with higher prevalence. For example, in Vancouver, the incidence of first HCV infection was 7.3 cases per 100 person years (20) and the risk of reinfection after HCV treatment was 3.2 cases per 100 person years (16). In Amsterdam, the

5. Lambers FA, Prins M, Thomas X, Molenkamp R, Kwa D, Brinkman K, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. *AIDS* 2011;25(17):F21-F27.
6. Martin TC, Martin NK, Hickman M, Vickerman P, Page EE, Everett R, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. *AIDS* 2013;27(16):2551-7.
7. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013;57(4):1333-42.
8. Trubnikov M, Yan P, Archibald C. Estimated prevalence of Hepatitis C Virus infection in Canada, 2011. *Canada Communicable Disease Report* 2014;40(19):429.
9. Elbaz T, El-Kassas M, Esmat G. New era for management of chronic hepatitis C virus using direct antiviral agents: A review. *Journal of advanced research* 2015;6(3):301-10.
10. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-term treatment outcomes of patients infected with hepatitis C virus: A systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. *Clinical Infectious Diseases* 2015;61(5):730-40.
11. Puoti M, Panzeri C, Rossotti R, Baiguera C. Efficacy of sofosbuvir-based therapies in HIV/HCV infected patients and persons who inject drugs. *Digestive and Liver Disease* 2014;46:S206-S211.

local incidence of first HCV infection of 0.35 cases per 100 person years (17) – significantly lower than in Vancouver – and the risk of reinfection after HCV treatment was 0.76 cases per 100 person years.

Injecting behaviour after treatment, as well as the implementation of needle exchange programs, influence the risk of HCV reinfection among people who inject drugs (3). Aspinall et al. (2) performed a meta-analysis on the incidence of reinfection after successful treatment using five of the seven studies mentioned above and estimated that reinfection among all study participants was 2.36 (95% CI 0.91–6.12) per 100 person years. When the analysis was stratified to those who reported injection drug use after treatment, the pooled estimate of HCV reinfection was 6.44 (95% CI, 2.49–16.69) per 100 person years. In comparison, the incidence of new HCV infection outside the treatment setting was 6.1–27.2 per 100 person years (21).

These data suggest a relatively low risk of reinfection following successful treatment. However, the total number of person years of observation across the five studies was very low, creating considerable uncertainty about this estimate. There was also uncertainty related to the number of participants lost to follow-up, which was only mentioned by one study in the review (20). In addition, the inclusion of former drug users in the study population and the fact that some studies incorporated harm reduction programs may have reduced the observed risk of HCV reinfection (2).

In other studies that were not part of the systematic review, there is considerable evidence that HCV reinfection rates among people who inject drugs is high. For example:

- In a prospective Australian cohort study of people who inject drugs, the incidence rate of HCV infection was high in patients who had previously cleared HCV, even surpassing the rate seen in previously HCV-uninfected individuals (22).
- In another Australian study, incidence of potential HCV reinfection among participants with HCV clearance with 42 per 100 person years (95% CI, 25–61/100 PY) was comparable to the incidence of initial HCV infection among HCV negative participants (23).
- A study from Spain followed 118 prisoners (81% injection drug users) treated for HCV who had achieved a sustained virologic response between 2003 and 2009 (24) and found that the incidence of reinfection was high, especially among those who reported ongoing injection drug use (24). At follow-up, HCV reinfection was identified in nine former injection drug users – seven with an HCV genotype switch – for an overall reinfection rate of 5.27 cases

12. Yau AHL, Yoshida EM. Hepatitis C drugs: The end of the pegylated interferon era and the emergence of all-oral, interferon-free antiviral regimens: A concise review. *Canadian Journal of Gastroenterology and Hepatology* 2014;28(8):445-51.

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

14. Dalgard O, Bjoro K, Hellum K, Myrvang B, Skaug K, Gutigard B, et al. Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up. *European Addiction Research* 2002;8(1):45-9.

15. Currie SL, Ryan JC, Tracy D, Wright TL, George S, McQuaid R, et al. A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. *Drug and Alcohol Dependence* 2008;93(1-2):148-54.

16. Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M, et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. *Journal of Gastrointestinal and Hepatology* 2010;25(7):1281-4.

17. Grady BP, Vanhommerig JW, Schinkel J, Weegink CJ, Bruisten SM, Lindenburg CE, et al. Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam. *European Journal of Gastroenterology & Hepatology* 2012;24(11):1302-7.

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

per 100 person years. The incidence of reinfection was significantly higher among people who were actively using drugs (hazard ratio HR = 12.47; 95% CI: 2.90–53.71), people who were HIV co-infected (HR = 9.95; 95% CI: 1.73–57.34) and those engaging in more than one risk behaviour after treatment (HR = 7.47; 95% CI: 1.19–46.89).

## HCV reinfection among men who have sex with men

Men who have sex with men – in particular HIV-positive men who have sex with men – demonstrate a different dynamic of HCV infection and reinfection risk:

- Researchers in London UK analyzed retrospectively reinfection rates among 145 HIV-HCV co-infected men who have sex with men with sexually acquired HCV who subsequently spontaneously cleared or underwent successful HCV treatment between 2004 and 2012 (6). Among individuals successfully treated for a primary infection, as many as 25% were re-infected within two years.
- Another retrospective study – this time in the Netherlands – found comparably high rates of HCV reinfection rate following treatment of 96. Per 100 person year among men who have sex with men of 9.6/100 person years (95% CI 6.6–14.1) (5) and higher rates of 15.2 per 100 person years among HIV-positive men who have sex with men (95% CI 8.0–26.5) (5).
- In a German study that examined 402 HIV-positive patients attending four HIV and hepatitis care centres between 2001 and 2013, about 75% of those with acute HCV infection (302 patients) were cured and therefore at risk for reinfection. Over the 12 year observation period, 48 of the 302 had at least one further HCV episode for a reinfection rate of 16% (4).

## Comparison of reinfection rates between groups

The latest and most comprehensive systematic review and meta-analysis of long-term treatment outcomes of patients infected with HCV evaluated the risk of post-treatment reinfection among three populations: (a) mono-HCV infected patients with no recognized risk factors for reinfection; (b) mono-HCV infected patients engaging in activities that are higher risk (i.e. people who inject drugs, prisoners or men who have sex with men); (c) HIV/HCV co-infected patients (1). The findings were as follows:

- In HCV mono-infected patients with no recognized risk factors, the pooled estimate of reinfection rate and

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

20. Grebely J, Raffa JD, Lai C, Kraiden M, Kerr T, Fischer B, et al. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. *Journal of Viral Hepatitis* 2009;16(5):352-8.

21. Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, Lauer G, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: Towards a vaccine. *The Lancet Infectious Diseases* 2012 May;12(5):408-14.

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

23. Micallef JM, Macdonald V, Jauncey M, Amin J, Rawlinson W, van B, I, et al. High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. *Journal of Viral Hepatitis* 2007;14(6):413-8.

24. Marco A, Esteban JI, Sole C, da SA, Ortiz J, Roget M, et al. Hepatitis C virus reinfection among prisoners with sustained virological response after treatment for chronic hepatitis C. *Journal of Hepatology* 2013;59(1):45-51.

summary 5-year reinfection risk were zero.

- In HCV mono-infected patients engaging in activities that are higher risk, the pooled reinfection rate was 19.06/1000 person years (95% CI, 11.42–28.16) leading to a summary five-year risk of 10.67% (95% CI, 6.38%–15.66%).
- In HIV/HCV co-infected patients, the pooled reinfection rate was 32.02/1000 person years (95% CI, 0.00–123.49) leading to a summary five-year risk of 15.02% (95% CI, 0.00%–48.26%).

The review concluded that most patients continue to have a sustained virologic response (i.e. no reinfection) five years post-treatment (1). In the authors' view, the greater reinfection risk among people engaging in higher risk activities and among people with HIV-HCV co-infection highlight the need for prevention campaigns specifically targeted at these groups (1).

It should be noted that the majority of included studies analyzed reinfection after treatment with interferon-based therapies – which have now been replaced with interferon-free regimens. Although there is no evidence that reinfection rates may differ with new the treatments, it is possible that this will be the case, particularly if the consequences of reinfection are perceived to be lower than with the old regimens (1).

To minimize the risk and rate of reinfection among individuals who engage in higher risk activities or who are at higher risk because of the presence of HIV (e.g. people who inject drugs, HIV-positive men who have sex with men, people with HIV/HCV co-infection), health systems should develop intensive targeted harm reduction and sexual education programs for and with these groups.

## Factors That May Impact Local Applicability

All studies cited in this review were conducted in high income countries in Western Europe (U.K., Germany, The Netherlands, Spain, Norway) as

well as in the U.S., Canada and Australia. Because of similar HIV and HCV epidemics among people who inject drugs and among men who have sex with men across these countries, the findings in this review are highly relevant and transferable to the Canadian context.

## What We Did

We searched Medline using a combination of [Hepatitis C or HCV (text terms) or Hepatitis C or Hepatitis C, Chronic (MeSH terms)] AND [reinfection or re-infection or HIV or Sexually Transmitted Disease\* or Sexually Transmitted Infection\* or Sexually Transmitted or STD\* (text terms) or Sexually Transmitted Diseases or Sexually transmitted Infections (MeSH terms)]. Reference lists of identified literature reviews and systematic reviews were also searched. All searches were conducted on February 2, 2016 and results limited to English articles published from 2005 to present in high income countries. The search yielded 486 references from which 24 studies were included. Sample sizes of primary studies ranged from nine to 402.

### Rapid Response: Evidence into Action

The OHTN Rapid Response Service offers quick access to research evidence to help inform decision making, service delivery and advocacy. In response to a question from the field, the Rapid Response Team reviews the scientific and grey literature, consults with experts, and prepares a brief fact sheet summarizing the current evidence and its implications for policy and practice.

#### Suggested Citation

Rapid Response Service. Hepatitis C reinfection after successful treatment. Toronto, ON: Ontario HIV Treatment Network; May 2016.

#### Prepared by

David Gogolishvili  
Jason Globerman

#### Program Leads / Editors

Jason Globerman  
Jean Bacon  
Sean B. Rourke

#### Contact

rapidresponse@ohtn.on.ca

#### For more information visit

[www.ohtn.on.ca/rapid-response-service](http://www.ohtn.on.ca/rapid-response-service)



THE ONTARIO HIV  
TREATMENT NETWORK

The Ontario HIV Treatment Network  
1300 Yonge Street, Suite 600  
Toronto ON M4T 1X3

[www.ohtn.on.ca](http://www.ohtn.on.ca)