Rapid Review 89: November 2014

Rapid Response Service

Hepatitis C virus (HCV) reinfection rates among people who use drugs

Question

What is the rate of reinfection with the hepatitis C virus (HCV) among people who use drugs who have been treated successfully or who have spontaneously cleared the virus?

Key Take-Home Messages

- HCV affects people differently. Some are able to spontaneously clear the virus on their own; others develop chronic HCV infection that affects their health and requires treatment.
- There appears to be no major difference in reinfection rates among people who have been treated successfully – that is, achieved a sustained viral response (SVR) (i.e. undetectable HCV RNA for at least 24 weeks after treatment is complete) – and those who clear HCV spontaneously (1-5).
- Studies report contradictory results about HCV reinfection rates among people who use drugs. The only available pooled estimate of HCV reinfection risk among people who use drugs seems to be low: 2.4 (95% CI 0.9–6.1) per 100 person-years (6). However, in communities with higher HCV prevalence, people who inject drugs and who have been treated for HCV appear to be at higher risk for reinfection (7). HCV reinfection incidence may be higher in young (<30 years) people who inject drugs (1;3;5).
- In general, people who use drugs who have been treated for HCV have only been followed for 2-5 years. Further studies on the risk of reinfection are needed to assess the long-term effectiveness of HCV treatment in this population (6).
- HCV reinfection does not always lead to persistent infection. Spontaneous clearance of HCV has been frequently recorded and data suggest that some individuals can clear HCV after one exposure more efficiently than others. Overall, clearance of the reinfection strain is relatively common, with some individuals able to spontaneously clear HCV with different genotypes from that of the initial infection (1;3-5).
- None of the identified studies investigated HCV reinfection attributed to non-drug-using behaviours.

OHTN

EVIDENCE INTO ACTION

The OHTN Rapid Response Service offers HIV/AIDS programs and services in Ontario 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 virus (HCV) re-infection rates among people who use drugs.* Toronto, ON: Ontario HIV Treatment Network; November 2014.

Prepared by:

David Gogolishvili
Jason Globerman

Program Leads / Editors:

Jason Globerman
Sean B. Rourke, PhD
Jean Bacon

Contact:

rapidresponse@ohtn.on.ca

References

1. 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.
2. Grebely J, Raffa JD, Lai C, Krajden 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.
3. 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
4. Osburn WO, Fisher BE, Dowd KA, Urban G, Liu L, Ray SC et al. Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. Gastroenterology 2010;138(1):315 -24.
5. Page K, Hahn JA, Evans J, Shiboski S, Lum P, Delwart E et al. Acute hepatitis C virus infection in young adult injection drug users: A prospective study of incident infection, resolution, and reinfection. Journal of Infectious Diseases 2009;200 (8):1216-26.
6. 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.
7. 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.
8. Public Health Agency of Canada. Epidemiology of acute hepatitis C infection in Canada: Results from the Enhanced Hepatitis Strain Surveillance System (EHSSS). 2010.
9. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. Journal of Viral Hepatitis 2006;13(1):34-41.

The Issue and Why It's Important

Injection drug use is the main risk factor for acquiring hepatitis C (HCV) – through the sharing of needles, syringes and other injection equipment. Between 70 and 80% of newly acquired HCV cases in Canada are attributed to injection drug use (8). Approximately 25% of people infected with HCV will clear the virus spontaneously (9;10); however most will develop chronic HCV. The goal of HCV treatment is to achieve a sustained virologic response (SVR), which is defined as an undetectable HCV RNA at least 24 weeks after completing treatment (6). **Note: if HCV RNA becomes detectable within 24 weeks after treatment, it is considered a relapse rather than a reinfection.**

People who use drugs respond as well to HCV treatment as those who do not use drugs (11-13), however, treatment of HCV in active drug users is controversial because of adherence concerns, side effects and risks associated with HCV reinfection (6;14;15) – particularly given the high cost of treatment. Given the fact that reinfection can occur, is the risk so substantial that treatment should be withheld from people who use drugs? We reviewed the available published literature to estimate the frequency of HCV reinfection among people who use drugs. **Note: all articles focused on people who acquired HCV infection through injection drug use; when we refer to "people who use drugs", we are referring only to people acquiring HCV or becoming reinfected through drug use**.

What We Found

Results from HCV reinfection studies in people who use drugs are contradictory (16;17), with some studies reporting high rates of reinfection while others report much lower rates.

Studies reporting low rates of reinfection

Out of four systematic reviews discussing HCV reinfection rates among people who use drugs who have been successfully treated for HCV or spontaneously cleared the virus (6;7;16;17), only one included a meta-analysis to derive pooled estimates of HCV reinfection (6). Across the five prospective cohort studies in this meta-analysis (18-22):

- The pooled risk was low: 2.4% (95% CI 0.9–6.1) per 100 person-years.
- Three recruited drug users who were receiving harm reduction services when they started HCV treatment (18;19;21). Two recruited current as well as former drug users who were not necessarily receiving harm reduction services (20;22).
- One reported 54% of participants having injected drugs in the six months prior to HCV treatment (19).
- Populations (n=131 combined) comprised current and former people who use drugs. The proportion who were injecting at the start of treatment was unknown; however all five studies reported the proportion who injected drugs after achieving sustained virologic response (SVR) – which ranged from 21% to 50%.

In all studies, a positive HCV RNA within six months of completing treatment was considered a relapse rather than a reinfection, and was excluded. SVR was defined as the proportion of individuals who had undetectable HCV RNA at least 24 weeks after completing HCV treatment.

Individuals treated for HCV who reported injecting drugs post-SVR had more than six times the risk of HCV reinfection (95% CI 2.5–16.7) than those who did not inject drugs post-SVR (6). However, using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology, the quality of evidence

for reinfection was assessed as very low (23). This was due to the observational design of the studies as well as concerns about:

- the study populations including former drug users, whose risk of relapse may be lower
- the incorporation of harm reduction programs into some studies, which may have reduced the observed risk of HCV reinfection (6).

A recent qualitative review of data on HCV reinfection (7) from the five studies above, plus two other studies (24;25) attempted to estimate how frequently reinfection occurs. Despite the limited numbers of cases and follow-up years, the incidence of reinfection after successful HCV treatment appears to be low (7). According to the authors, when comparing incidence rates of new HCV infections and reinfections it is important to consider:

- Local HCV epidemics among people who use drugs. In communities with higher HCV prevalence, people who use drugs appear to have higher rates of reinfection. In Vancouver, the risk of reinfection after HCV treatment was 3.2 cases per 100 person-years (19) while the risk of first HCV infection was 7.3 cases per 100 person-years (2). In Amsterdam, the risk of reinfection after HCV treatment was 0.76 cases per 100 person-years compared to an incidence of first HCV infection of 0.35 cases per 100 person-years (18).
- Implementation of or access to a needle exchange programs, which may reduce the risk of reinfection (7).

Two other systematic reviews (16;17) assessed data from studies of HCV reinfection after spontaneous clearance, however the studies included in these reviews had contradictory results. Some studies, including a Baltimore cohort (26) and a large Vancouver inner-city cohort (27), found low reinfection rates: individuals with previous HCV clearance were two to four times less likely to be infected during follow-up as those who had not been infected before. In both these studies, the median time between HCV RNA testing was long.

An initial 2009 publication providing data about a San Francisco cohort reported a high incidence of HCV reinfection (5) but, in a 2013 article, the same authors revised the results to include a lower incidence (28): Their new estimate of incidence of first reinfection was 5.4 per 100 person-years (95% CI, 2.0–14.5) compared to 25% in the earlier estimates. The authors noted that misclassification of reinfection as a result of lack of viral sequencing and limited follow-up could have led to significant overestimation of reinfection rates (28). In an earlier San Francisco cohort of injection drug users (20), only one reinfection occurred in the resolvers, for a reinfection rate of 0.47 cases/100 person-years of follow-up. The single reinfection, which occurred in a person who continued to inject drugs, represents a reinfection rate of 1.75 cases/100 person-years of injection drug use. Further studies from the UK (29), Germany (21) and Norway (22) all demonstrated comparable low rates of HCV-reinfection among people who use drugs.

It should be noted that reinfection does not always lead to persistent infection. Spontaneous clearance of HCV reinfection has been recorded frequently. Some individuals clear HCV after one exposure more efficiently than others. Clearance of the reinfection strain is relatively common, with some people able to spontaneously clear HCV with different genotypes from that of the initial infection (1;3-5).

Studies reporting high rates of reinfection

All the above described results are at odds with data presented in other studies that have observed a higher incidence of reinfection among people who use

10. Grebely J, Raffa JD, Lai C, Krajden M, Conway B, Tyndall MW. Factors associated with spontaneous clearance of hepatitis C virus among illicit drug users. Canadian Journal of Gastroenterology 2007;21 (7):447.
11. Grebely J, Matthews GV, Hellard M, Shaw D, van Beek I, Petoumenos K et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. Journal of Hepatology 2011;55(1):76-85.
12. Lindenburg CE, Lambers FA, Urbanus AT, Schinkel J, Jansen PL, Krol A et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. European Journal of Gastroenterology & Hepatology 2011;23(1):23-31.
13. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clinical Infectious Diseases 2009;49(4):561-73.
14. Edlin BR. Prevention and treatment of hepatitis C in injection drug users. Hepatology 2002;36 (5B):s210-s219.
15. Grebely J, Genoway KA, Raffa JD, Dhadwal G, Rajan T, Showler G et al. Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. Drug and alcohol dependence 2008;93 (1):141-7.
16. Corson S, Greenhalgh D, Palmateer N, Weir A, Hutchinson S. Risk of Hepatitis C virus re-infection following spontaneous viral clearance in injecting drug users: a systematic review. Int J Drug Policy 2011 March;22(2):102-8.
17. 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;12 (5):408-14.

18. 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 (11):1302-7.

19. 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 Gastroenterology & Hepatology 2010;25(7):1281-4.

20. 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 & Alcohol Dependence 2008;93(1-2):148-54.

21. 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.

22. 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.

23. GRADE Working Group. Grading quality of evidence and strength of recommendations. Bmj 2004;328 (19):1490-4.

24. 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 Gastroenterology & Hepatology 2010;25(7):1276-80.

25. 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.

26. Mehta SH, Cox A, Hoover DR, Wang XH, Mao Q, Ray S et al. Protection against persistence of hepatitis C. Lancet 2002;359(9316):1478-83.

drugs who have been successfully treated or who have spontaneously cleared the virus.

The systematic reviews mentioned above also include studies from other cohorts suggesting that previous spontaneous clearance of HCV infection may not reduce the risk of new infections (1;3-5;30). For example, a retrospective cohort of young, high-risk injection drug users from Sydney, Australia (3), which had more frequent testing than the other studies (26;27), a study of young drug users in Baltimore (4), and a cohort in the Netherlands (30) showed no differences between incidence of HCV infection in individuals with no previous infection compared to those with previous HCV clearance. In a Netherlands-based study (30) HCV reinfection and superinfection were common among active injection drug users. Forty-two per cent of previously exposed drug users experienced HCV reinfection. Incidence of HCV reinfection was at least similar to the incidence of naive HCV infection. Interestingly, the incidence of HCV reinfection declined from 20.4/100 person-years in the period between 1985 and 1995 to 4.17/100 person-years in the period between 1995 and 2005.

Similarly, three Australian studies also reported higher rates of HCV reinfection (1;24;31). According to these studies, injection drug users who had previously cleared HCV infection were 2-2.5 times more likely to become infected than those who had not been previously infected. The reinfection rate seems to be especially high in young (<30 years) active injection drug users. The incidence of HCV reinfection in these cohorts was similar (3) or even higher (1;5) than the incidence of initial infection, resulting in reinfection in 46–50% of young drug users who had previously cleared the virus. HCV reinfection among prisoners after successful treatment has also been shown to be high, especially among those who are actively injecting drugs. Studies have reported prevalence of late recurrence of viremia between 8% and 17% (24;32) - likely a reflection of reinfection due to ongoing risk behaviours.

Factors That May Affect Local Applicability

The literature discussed dealt exclusively with high-income countries (US, Western Europe, Australia, Canada). While these findings may be relevant in Canada, jurisdictions cited have different HCV rates and populations, therefore findings should be interpreted with caution as they may not be generalizable in all settings.

What we did

We searched Medline using Hepatitis C (text term OR MESH term) in combination with Reinfection AND Drug Use* (text terms). The search was conducted on 11 July 2014 and articles were limited to those published since 1996 in English. We only included studies from high-income countries. Reference lists of identified studies were also reviewed.

Suggested citation

Rapid Response Service. *Hepatitis C virus (HCV) re-infection rates among people who use drugs.* Toronto, Canada: Ontario HIV Treatment Network; November 2014.

27. 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.

28. Page K, Osburn W, Evans J, Hahn JA, Lum P, Asher A et al. Frequent longitudinal sampling of hepatitis C virus infection in injection drug users reveals intermittently detectable viremia and reinfection. Clinical Infectious Diseases 2013;56(3):405-13.

29. McDonald SA, Hutchinson SJ, Cameron SO, Innes HA, McLeod A, Goldberg DJ. Examination of the risk of reinfection with hepatitis C among injecting drug users who have been tested in Glasgow. International Journal of Drug Policy 2012;23(5):353-7.

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

31. Sacks-Davis R, Aitken CK, Higgs P, Spelman T, Pedrana AE, Bowden S et al. High rates of hepatitis C virus reinfection and spontaneous clearance of reinfection in people who inject drugs: A prospective cohort study. PloS One 2013;8(11):e80216.

32. 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