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.
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

References

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

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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.


