Hepatitis C virus reinfection after successful treatment among PWID: Clinical and Public Health Implications

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Disclosures

• No conflicts of interest
Starting point

• New DAA treatment provides unique opportunities for prevention of liver disease burden, epidemic control and HCV elimination

• Ongoing injecting risk behaviours can lead to reinfection after successful treatment

• High levels of reinfection might challenge
  – Individual- and population-level treatment benefits
  – Cost-benefit of expensive DAAs
  – Existing HCV prevention strategies

Overview

• Reinfection after interferon-based treatment

• Reinfection after DAA treatment

• Risk factors for reinfection

• Individual- and population-level implications

• Strategies to address reinfection
Reinfection estimates: IDU ever (n=795)

- Dalgard 2002 (n=27)
- Backmund 2004 (n=18)
- Currie 2008 (n=9)
- Grebely 2010 (n=35)
- Grady 2012 (n=42)
- Grebely 2012 (n=67)
- Hildsen 2013 (n=23)
- Marco 2013 (n=119)
- Pineda 2015 (n=84)
- Midgard 2016 (n=94)
- Weir 2016 (n=277)

Reinfection incidence per 100 PY (95%CI)


Reinfection estimates: IDU post-treatment (n=153)

- Dalgard 2002 (n=9)
- Backmund 2004 (n=9)
- Currie 2008 (n=2)
- Grebely 2010 (n=16)
- Grady 2012 (n=11)
- Grebely 2012 (n=26)
- Pineda 2015 (n=13)
- Midgard 2016 (n=37)
- Weir 2016 (n=30)

Reinfection incidence per 100 PY (95%CI)

Differences in reinfection estimates reflect

1. **Heterogeneity in study populations**
   - Risk behaviours (former vs. recent PWID, acute vs. chronic HCV)
   - Harm reduction coverage
   - Background viremic prevalence

2. **Variations in study designs**
   - Prospective vs. retrospective designs
   - Small sample sizes and short longitudinal follow-up
   - Insufficient risk factor assessment

3. **Virological methods**
   - Testing intervals: “The more often you look”
   - Sequencing methods: “The closer you look”

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**Scenarios for viral recurrence post-SVR**

A. Late relapse of majority variant

B. Persistence of minority variant

C. Reinfection
Pooled reinfection incidence from 11 studies

![Graph showing pooled reinfection incidence](image)

Long-term reinfection risk: Little is known

- Existing reinfection estimates are
  - mainly based on small studies with short follow-up time
  - including cases with spontaneous clearance
  - probably lower than reported rates of primary infection

- Even low rates could be a concern over time
  - Particularly if constant rates, no re-treatment, no scale-up
  - Rates may be declining due to a “saturation effect”

- Projected 5-year risk ("worst case scenario")
  - IDU ever: 10.5%
  - IDU post-treatment: 28%

Long-term reinfection risk: 7-year follow-up

Reinfection risk after DAA treatment

- Are current estimates generalizable for the DAA era?
- Increased treatment uptake among people with ongoing risk behaviours
- Less fear of treatment adverse effects
- Less interaction with health care providers

- Less potential for behavioural change?
- Increasing reinfection rates?
Reinfections in SOF Phase 3 trials (n=3004)

- 7 reinfections after 3 months (SVR12 - SVR24)
- 750 person-years of follow-up
- **Reinfection incidence 0.9/100 PY**

Sarrazin et al. EASL 2015

C-EDGE CO-STAR: Reinfection incidence

- Grazoprevir/elbasvir for patients on stable OST (n=301)
- High SVR rates and high adherence
- High proportion with positive urine drug screen

Immediate and deferred treatment groups (EOT - FW24)

- 6 reinfections out of 296 total patients
- 130.6 person-years of follow-up
- **4.6 reinfections per 100 person years**
- 5 of 6 cases tested positive for opioids other than OST
- 3 of 6 cases cleared spontaneously

Risk factors for reinfection

- Identifying those at highest risk for reinfection could aid post-treatment HCV care ("secondary prevention")

- Predictors for reinfection have not been clearly identified
  - Low statistical power
  - Lack of behavioural data

- Factors associated with reinfection/superinfection\(^1\)
  - Poorer social functioning at enrolment (AOR 5.85)
  - Methamphetamine injecting during follow-up (AOR 7.29)

- OST protective against reinfection\(^2\)

1 Grebely et al. Hepatology 2012
2 Bruneau et al. INHSU 2016

Implications at the individual level

- Reinfections after spontaneous clearance have a benign course\(^1\)
  - Lower viral loads than in primary infection
  - High rates of spontaneous clearance (30-100%)
  - Evidence of a partial protective immunity against persistent reinfection with the same viral strain

- Spontaneous clearance of reinfections after treatment can occur\(^2\)

- Early reinfections may be easy to treat (acute, no virological failure)

- Reinfection in a cirrhotic patient is more concerning than in a non-cirrhotic patient

1 Grebely et al. Lancet Infect Dis 2012
The “prevention benefit” hypothesis

- **Good theoretical evidence from dynamic models**\(^1,2\)
  1. Scaled-up DAA treatment + OST can reduce viremic prevalence
  2. Treating active PWID could be more cost-effective than treating those with no ongoing transmission risk
  3. More future infections and HCV-related morbidity/mortality will be averted than lost through reinfections

- No empirical evidence (yet) showing that HCV treatment for PWID reduces HCV transmission

- Little empirical evidence showing that achieving SVR could result in behavioural change
  - Models assume reinfection risk = primary infection risk
  - Alternation between high/low risk states

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1 Martin et al. Hepatology 2013
2 Hickman et al. Curr Opin Infect Dis 2015

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A slow treatment scale-up could create an increasing pool of susceptible individuals
Reduction of reinfection probability could increase impact of scale-up

Model inputs, aggressive treatment strategy in Norway: HCV RNA prevalence 48%, harm reduction 87%, PWID mortality 2%

Addressing reinfection: Potential strategies

1. Acknowledgement without stigma and discrimination
2. Education and counselling including peer support
3. Harm reduction optimization
4. Post-treatment surveillance and rapid re-treatment

1. Scaled-up DAA treatment among PWID
2. Targeted treatment of high-risk transmitters and injecting networks ("bring your friends" strategy)\(^1\)

\(^1\) Hellard et al. Int J Drug Policy 2015
Future research priorities

• Monitor incidence of reinfection following DAA treatment among individuals with ongoing risk behaviours

• Identify risk factors for reinfection

• Explore patient attitudes towards reinfection and risk avoidance following treatment

• Evaluate novel prevention and re-treatment strategies (post-treatment HCV care)

Conclusions

• Pooled incidence from 11 studies of reinfection following interferon-based treatment among PWID
  – 2.1/100 PY among those with IDU ever
  – 5.6/100 PY among those with post-treatment IDU

• Strategies to address reinfection
  – Acknowledgement, education, counselling, peer support
  – Harm reduction optimization
  – Post-treatment surveillance and re-treatment
  – Scaled-up DAA treatment
  – Targeted treatment of high-risk transmitters and injecting networks

• Novel prevention and re-treatment strategies should be evaluated
Backup slides

Meta-analysis: Projected 5-year risk

Narrow intervals: All episodes are captured

Wide intervals: Persistent cases are captured
C-EDGE CO-STAR: Urine drug screening

ACTIVATE: Risk behaviours during and following IFN-based treatment
Simulation of HCV incidence by number of network partners and injecting frequency

Impact of network-based strategies

Rolls et al. Journal of Theoretical Biology 2012