HCV treatment in active PWID: Is there a concern about reinfection?

A/Professor Jason Grebely
Disclosures

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HCV treatment and reinfection among active PWID

- DAA therapy is effective in people receiving OST and PWID (former/current)
- Reinfection will occur following successful DAA therapy in active PWID
- What is the risk of reinfection following DAA therapy among active PWID?
- What happens following HCV reinfection in the setting of DAA therapy?
- What will be required to limit the impact of HCV reinfection?
DAA therapy is effective for people receiving OST, former PWID and recent PWID
Defining populations of PWID

- Former PWID
- Current PWID
- Current PWUD
- PWID in OST
People receiving OST – phase II/III trials

Former/recent PWID

<table>
<thead>
<tr>
<th>Study</th>
<th>SVR12 (%)</th>
<th>Former/recent PWID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norton 2016</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Hull 2016</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>Conway 2016</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>Bouscaillou 2017</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Powis 2017</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Read 2017</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Litwin 2017</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>Sulkowski 2017</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

Lost to follow-up post-treatment

<table>
<thead>
<tr>
<th>ITT</th>
<th>mITT</th>
<th>ITT</th>
<th>mITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>87%</td>
<td>91%</td>
<td>82%</td>
<td>91%</td>
</tr>
<tr>
<td>60</td>
<td>69</td>
<td>59</td>
<td>72</td>
</tr>
<tr>
<td>60</td>
<td>66</td>
<td>59</td>
<td>65</td>
</tr>
</tbody>
</table>

Recent PWID – The SIMPLIFY Study

- Kirby/UNSW sponsored, international open-label trial
- DAA treatment-naïve patients with GT1-6 chronic HCV infection (F0-4)
- People with recent injecting drug use (past six months)
- Electronic blister packs to monitor adherence

Week 0  Week 12  Week 24

Sofosbuvir/velpatasvir 400/100 mg od, n=103

SVR_{12}  Six-monthly follow-up for reinfection

Week 24

3 yrs
Recent PWID – The SIMPLIFY Study

- 74% injecting in past 30 days, 35% G1a, 58% G1, 9% cirrhosis, DAA-treatment naïve
- One case of reinfection

<table>
<thead>
<tr>
<th></th>
<th>Response (%)</th>
<th>ETR</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96%</td>
<td>99/103</td>
<td>97/103</td>
</tr>
<tr>
<td></td>
<td>94%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Study populations matter…

<table>
<thead>
<tr>
<th>Study name</th>
<th>HIV</th>
<th>OST</th>
<th>Recent drug use</th>
<th>Recent injecting drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christensen 2016</td>
<td>11%</td>
<td>100%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dore 2016 – CO-STAR</td>
<td>7%</td>
<td>100%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>Norton 2016</td>
<td>NA</td>
<td>78%</td>
<td>67%</td>
<td>NA</td>
</tr>
<tr>
<td>Hull 2016</td>
<td>12%</td>
<td>53%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Conway 2016</td>
<td>15%</td>
<td>40%</td>
<td>100%</td>
<td>NA</td>
</tr>
<tr>
<td>Sulkowski 2017 – CHAMPS</td>
<td>100%</td>
<td>NA</td>
<td>25%</td>
<td>NA</td>
</tr>
<tr>
<td>Litwin 2017 – PREVAIL</td>
<td>14%</td>
<td>100%</td>
<td>65%</td>
<td>NA</td>
</tr>
<tr>
<td>Powis 2017</td>
<td>NA</td>
<td>24%</td>
<td>30%</td>
<td>11%</td>
</tr>
<tr>
<td>Read 2017</td>
<td>11%</td>
<td>25%</td>
<td>NA</td>
<td>75%</td>
</tr>
<tr>
<td>Bouscaillou 2017</td>
<td>0%</td>
<td>NA</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Grebely 2017 – SIMPLIFY</td>
<td>0%</td>
<td>57%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Should we be concerned about HCV reinfection among recent PWID?
Recurrence of HCV RNA – Relapse or Reinfection?

- HCV RNA testing
  - HCV RNA+ following SVR24 is likely to be reinfection (low relapse in DAA era)

- HCV genotyping
  - Genotype switch is indicative of reinfection

- HCV sequencing (Sanger or Next Generation Sequencing)
  - Nucleotide divergence/phylogenetic analysis
  - Depends on the region sequenced
What is the risk of HCV reinfection following therapy?
Type of injecting drug use/drug use frequency matters

Young J, et al. Clinical Infectious Diseases 2017
HCV reinfection following DAA therapy: C-EDGE CO-STAR

Through FW12
- 5 reinfections

Through FW24
- 1 reinfection

Through 6 months follow-up
- 2 reinfections

= 8 reinfections
- 4.0 reinfections per 100 person years

From ETR Through Long-term follow-up visit 1
- 8 reinfections
- 197.5 person years
- 4.0 per 100 p-yrs (95% CI: 1.7, 8.0)

From ETR Through Long-term follow-up visit 1 (persistence only)
- 5 reinfections
- 199.0 person years
- 2.5 per 100 p-yrs (95% CI: 0.8, 5.9)

Clearance of reinfection was observed in 3/8 (38%) reinfection cases

Dore GJ, et al. AASLD 2016, Boston, United States
Spontaneous clearance of reinfection post-DAA therapy

Dore GJ, et al. AASLD 2016, Boston, United States
The more you look, the more you find….

<table>
<thead>
<tr>
<th>Frequency of HCV RNA testing</th>
<th>Number of viremic events detected (%) of total</th>
<th>Apparent Clearance or Persistence of Reinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>5/5 (100%)</td>
<td>Clearance</td>
</tr>
<tr>
<td>12</td>
<td>3/5 (60%)</td>
<td>Clearance</td>
</tr>
<tr>
<td>24</td>
<td>1/5 (20%)</td>
<td>Clearance</td>
</tr>
<tr>
<td>48</td>
<td>1/5 (20%)</td>
<td>Persistence</td>
</tr>
</tbody>
</table>

What will be required to limit the impact of HCV reinfection at a population level?
Strategies to prevent primary HCV infection

- Meta-analysis of the effects of risk-reduction interventions on HCV seroconversion - 26 eligible studies
- Behavioral interventions, substance-use treatment, syringe access, syringe disinfection and multicomponent interventions
- No impact of any single component interventions

Combined OST/NSP to prevent primary HCV infection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High NSP coverage</strong></td>
<td></td>
</tr>
<tr>
<td>Hope, 2011</td>
<td>0.17 (0.02, 1.54)</td>
</tr>
<tr>
<td>Bruneau, 2015</td>
<td>0.63 (0.37, 1.07)</td>
</tr>
<tr>
<td>Van Den Berg, 2007</td>
<td>0.15 (0.06, 0.40)</td>
</tr>
<tr>
<td>Palmateer, 2014</td>
<td>0.24 (0.10, 0.59)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 64.4%, p = 0.038)</td>
<td><strong>0.29 (0.13, 0.65)</strong></td>
</tr>
<tr>
<td><strong>Low NSP coverage</strong></td>
<td></td>
</tr>
<tr>
<td>Hope, 2011</td>
<td>1.08 (0.31, 3.82)</td>
</tr>
<tr>
<td>Van Den Berg, 2007</td>
<td>1.04 (0.53, 2.05)</td>
</tr>
<tr>
<td>Palmateer, 2014</td>
<td>0.48 (0.24, 0.95)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 29.6%, p = 0.242)</td>
<td>0.76 (0.44, 1.33)</td>
</tr>
<tr>
<td>Overall (I-squared = 62.2%, p = 0.014)</td>
<td><strong>0.47 (0.27, 0.80)</strong></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Platt L, et al. Cochrane Database of Systematic Reviews 2017
Optimization of OST and high-coverage NSP services

40% baseline chronic prevalence

Annual treatments per 1000 PWID

Coverage of OST and HCNSP (%)
Rapid DAA scale-up is required to limit reinfection

Strategies addressing individual-level risk: Bring a friend

“Bring your friends” strategy performed better than the random strategy

Plausible real-world treatment strategy as most people will know their injecting partners
Re-treatment of reinfection is critical

- Retreatment should be offered without stigma or discrimination
- Treatment should also be offered to injecting partner(s)
- People with reinfection are by the nature of their reinfection “high-risk”
- Opportunity to reduce the duration of reinfection viremia
Involvement of the community is crucial
HCV treatment and reinfection among active PWID

- DAA therapy is effective in people receiving OST and PWID (former/current)
- Reinfection will occur following successful DAA therapy in active PWID
- HCV reinfection risk is low among PWID, but not negligible
- Need further data on long-term reinfection outcomes, particularly active injectors
- Spontaneous clearance post-DAA therapy requires further study
- Rapid DAA scale-up and high-coverage OST/NSP crucial
- Need to evaluate interventions to address reinfection, including retreatment
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Dr. Natasha Martin (USA)
Prof. Olav Dalgard (Norway)
Prof. Julie Bruneau (Canada)
Dr. Jordan Feld (Canada)
Dr. Brian Conway (Canada)
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