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

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Disclosures

- No conflicts of interest

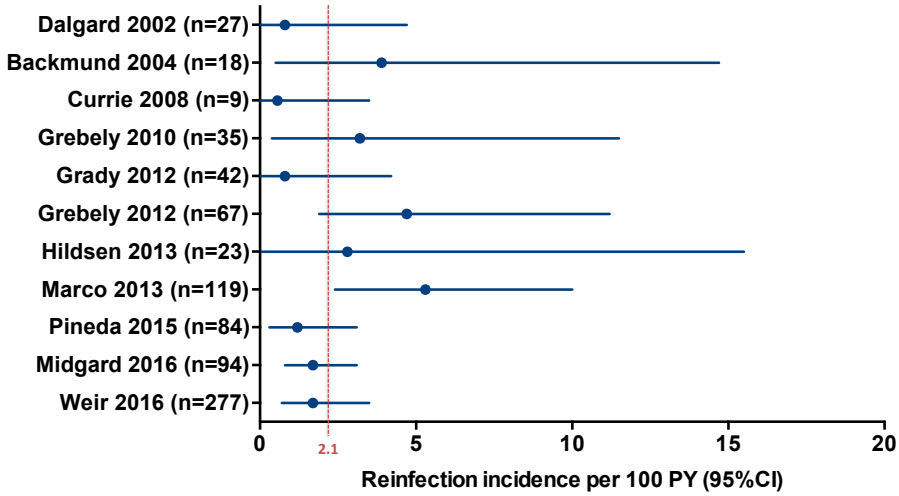
Starting point

- 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

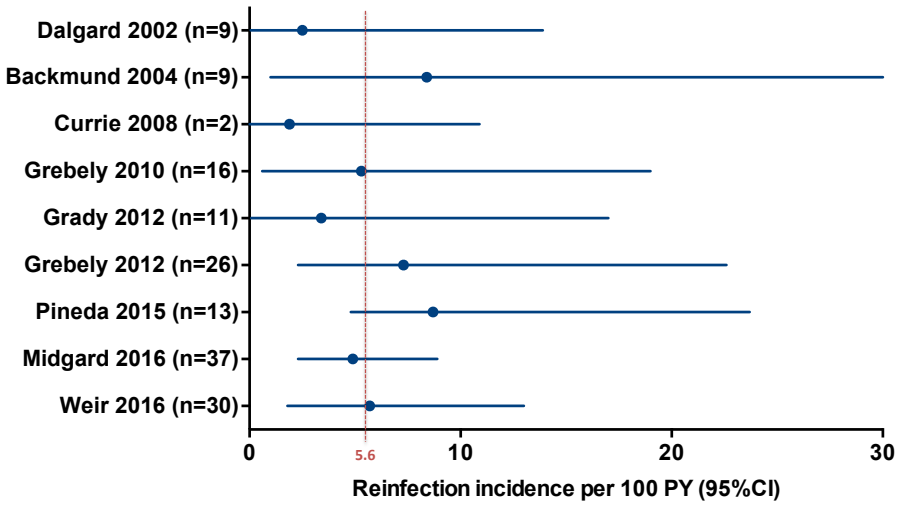
- Reinfection after interferon-based treatment
- Reinfection after DAA treatment
- Risk factors for reinfection
- Individual- and population-level implications
- Strategies to address reinfection

Reinfection estimates: IDU ever (n=795)



Modified from Midgard et al. J Hepatology 2016 (In Press)

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



Modified from Midgard et al. J Hepatology 2016 (In Press)

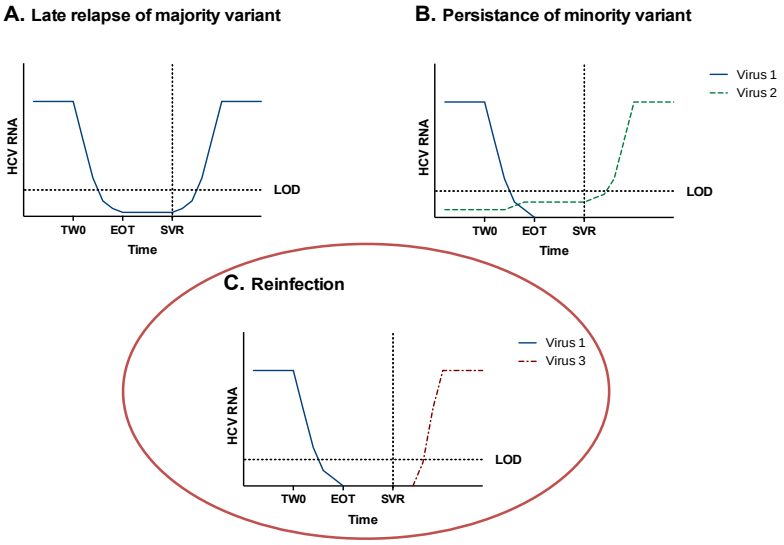
Differences in reinfection estimates reflect

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

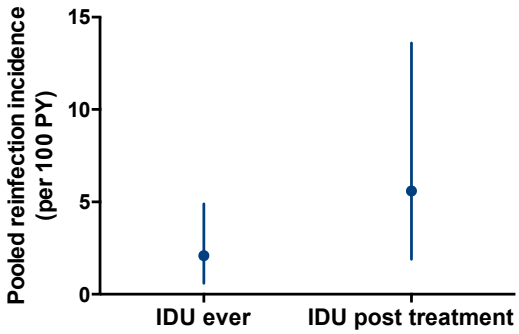
2. **Variations in study designs**
   - Prospective vs. retrospective designs
   - Small sample sizes and short longitudinal follow-up
   - Insufficient risk factor assessment

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

Scenarios for viral recurrence post-SVR



Pooled reinfection incidence from 11 studies



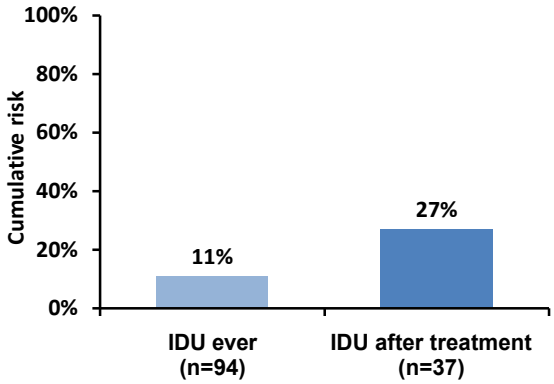
2.1/100 PY	**5.6/100 PY**
11 studies	9 studies
795 patients	153 patients
43 cases	29 cases
2082 PY	522 PY

Modified from Midgard et al. J Hepatology 2016 (In Press)

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



Time at risk after SVR (PY)	593	206
Persistent reinfections	10	10
Incidence per 100 PY	1.7	4.9
95% CI	0.8–3.1	2.3–8.9

Midgard et al. J Hepatology 2016

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)

Patient	Study	Genotype		Phylogenetic Distance
		Baseline	Post-Treatment	
1	PHOTON-2	4d	1a	Not related*
2	PHOTON-1	1a	1a	Not related*
3	PHOTON-2	1a	1a	Not related*
4	GS-US-334-0119	1b	1b	Not related*
5	FUSION	3a	3a	Not related†
6	PHOTON-2	1a	1a	Distantly related
7	FUSION	3a	3a	Distantly related
8	PHOTON-1	3a	3a	Closely related
9	VALENCE	3a	3a	Closely related
10	VALENCE	3a	3a	Closely related
11	FISSION	3a	3a	Closely related
12	PHOTON-2	3a	3a	Closely related†

*Similar results were obtained for NS3, NS5A, and NS5B when sequences were available.
†Short fragment NS5B sequencing only, due to low viral load.

- 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

Dore et al. Ann Int Med 2016, Dalgard et al. INHSU 2016

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
2 Dore et al. Ann Int Med 2016

The "prevention benefit" hypothesis

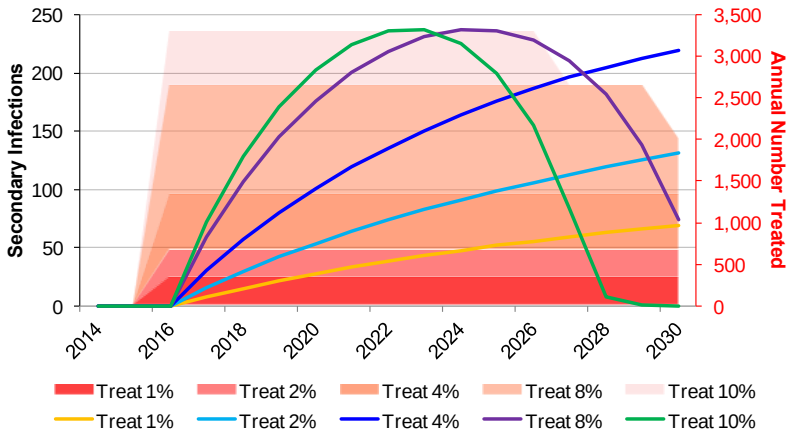
- **Good theoretical evidence from dynamic models**[1,2]
  1. Scaled-up DAA treatment + OST can reduce viremic prevalence
  2. Treating active PWID could be more cost-effective than treating those with no ongoing transmission risk
  3. More future infections and HCV-related morbidity/mortality will be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

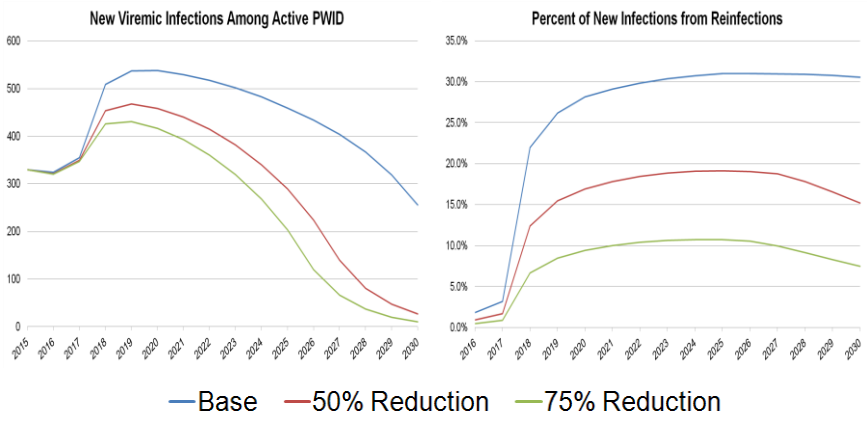
1 Martin et al. Hepatology 2013
2 Hickman et al. Curr Opin Infect Dis 2015

A slow treatment scale-up could create an increasing pool of susceptible individuals



Razavi et al. INHSU 2015

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%

Razavi-Sherarer et al. INHSU 2016

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

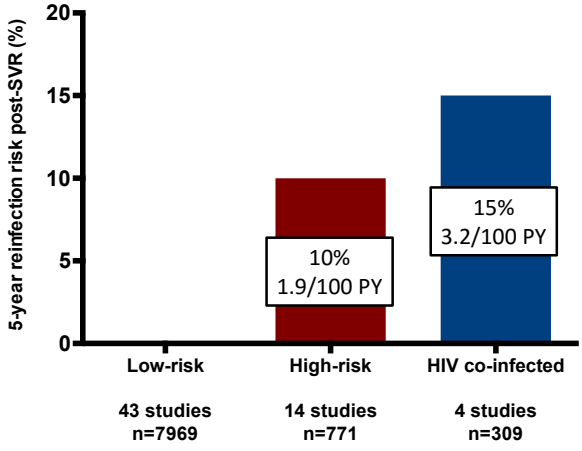
- Monitor incidence of reinfection following DAA treatment among individuals with ongoing risk behaviours
- Identify risk factors for reinfection
- Explore patient attitudes towards reinfection and risk avoidance following treatment
- Evaluate novel prevention and re-treatment strategies (post-treatment 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

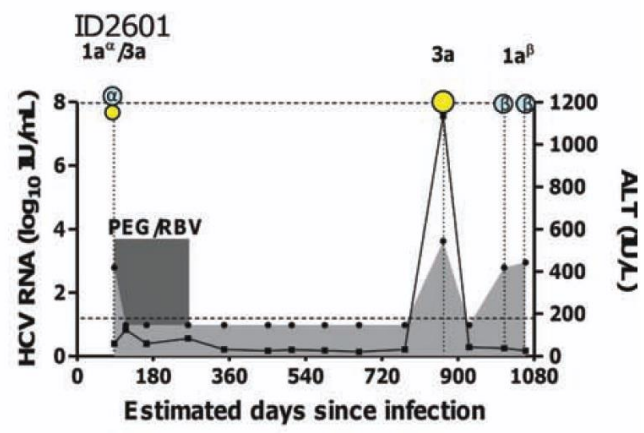
Backup slides

Meta-analysis: Projected 5-year risk



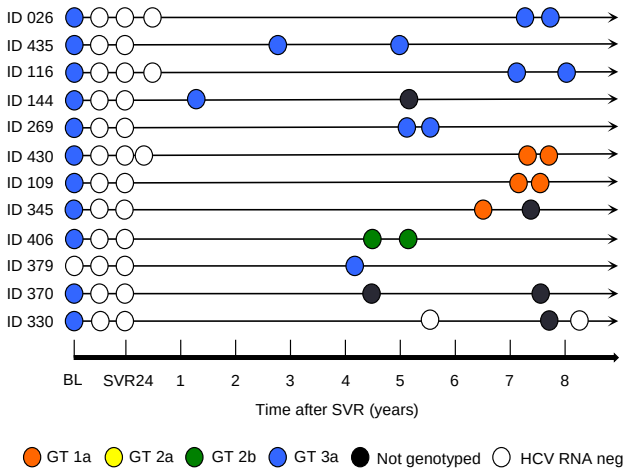
Modified from Simmons et al. Clin Infect Dis 2016

Narrow intervals: All episodes are captured



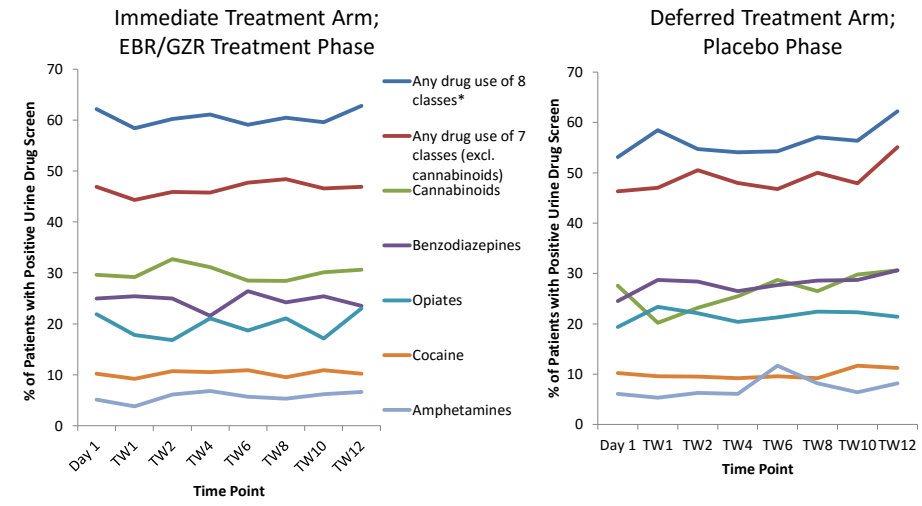
Grebely et al. Hepatology 2012

Wide intervals: Persistent cases are captured



Midgard et al. J Hepatol 2016

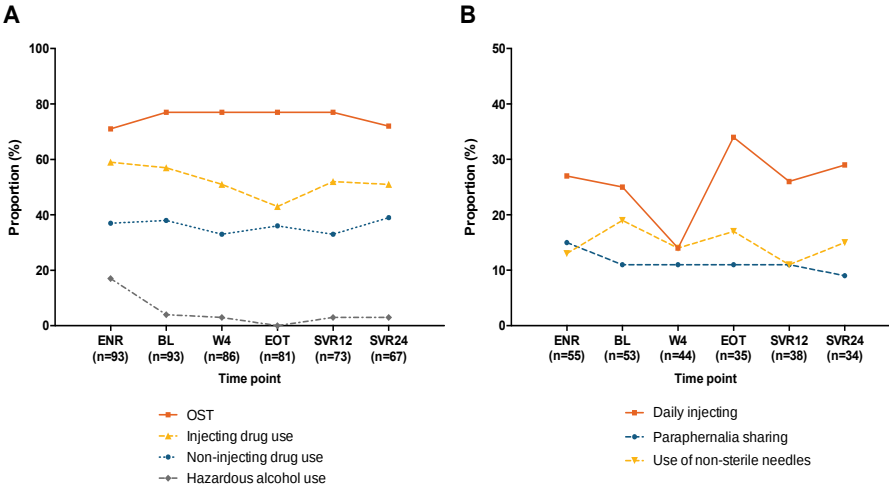
C-EDGE CO-STAR: Urine drug screening



* 8 drug classes: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, propoxyphene

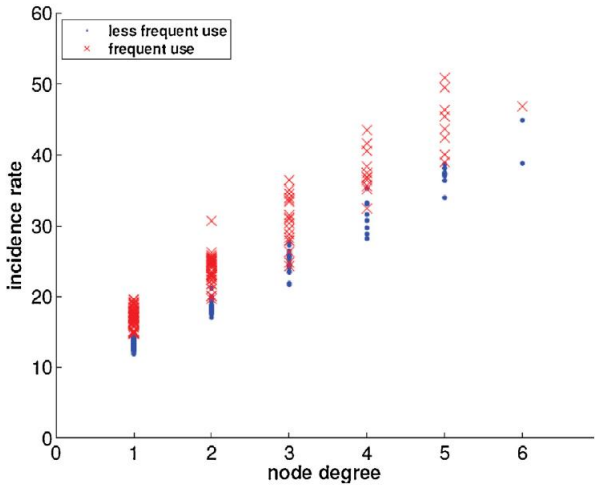
Dore et al. Ann Int Med 2016

ACTIVATE: Risk behaviours during and following IFN-based treatment



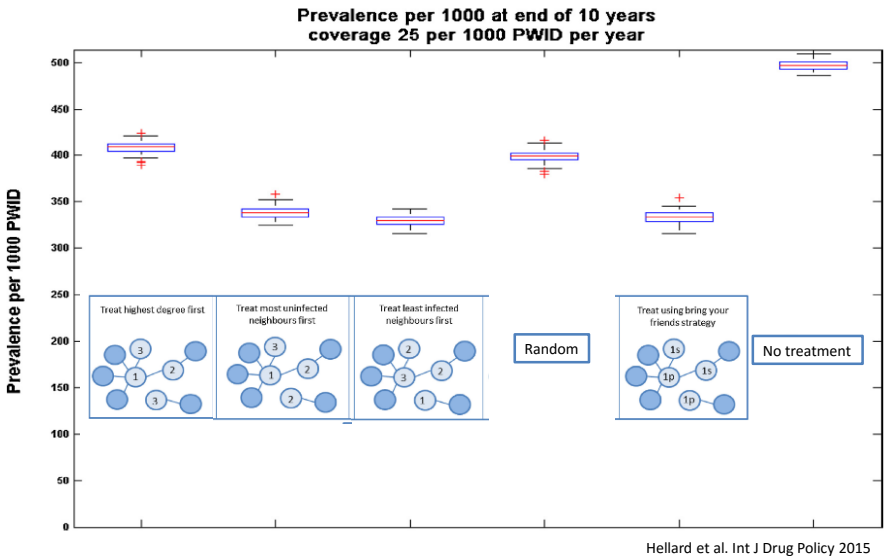
Midgard et al. INHSU 2016

Simulation of HCV incidence by number of network partners and injecting frequency



Rolls et al. Journal of Theoretical Biology 2012

Impact of network-based strategies



Hellard et al. Int J Drug Policy 2015