INCIDENCE OF HEPATITIS C REINFECTION FOLLOWING SUSTAINED VIROLOGICAL RESPONSE

SEVEN-YEAR FOLLOW-UP OF NORWEGIAN PATIENTS INFECTED THROUGH INJECTING DRUG USE

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Background

- Given the lack of protective immunity, on-going risk behaviours can lead to hepatitis C virus (HCV) reinfection after successful treatment

- Incidence of reinfection following treatment in a meta-analysis of 5 studies among people who inject drugs (PWID)[1]
  - 2.4/100 PY among patients with a history of injecting drug use (IDU)
  - 6.4/100 PY among patients with on-going IDU after treatment

- Risk of reinfection 5-years after SVR was 8% a in meta-analysis of 16 studies among PWID or prisoners[2]

- Tolerable DAAs will likely increase HCV treatment uptake among PWID and reinfection will probably emerge as an increasingly important topic

1. Aspinall E.J. et al. Clin Infect Dis 2013
2. Hill A.M. et al. AASLD 2014

Aims of the study

In a population of PWID who previously had achieved SVR following at least six months of abstinence from drug use prior to HCV treatment, we aimed to assess

1. **The long-term incidence of persistent HCV reinfection**
2. **The frequency of relapse to IDU**

Materials

North-C RCT 2004-2006 (n=428)[1]

- Mono-infected GT 2/3 patients in Norway, Sweden and Denmark
- RVR: Randomized to 14 or 24 weeks pegIFN + RBV (SVR_{24} 76%)
- 68% infected through IDU – 6 months abstinence required
- Standard of care information about risk reduction
- Patients were not followed prospectively

This follow-up study was performed in 2012-2014 at all 22 Norwegian study sites

All patients who had achieved SVR (n=161) were eligible for inclusion

1. Dalgard O. et al. Hepatology 2008

Methods

Data collection

- Patients were scheduled for a follow-up visit at local site
- Clinical, demographical and drug behavioural data were collected

Laboratory methods

- *HCV RNA*: COBAS AmpliPrep/TaqMan HCV Test v2.0
- *Genotyping:* Versant INNO-LiPA HCV 2.0
- *Viral sequencing:*
  - ~1500 bp fragment covering Core, E1, HVR1 and E2 was amplified by a nested RT-PCR using universal and subtype-specific primers[1]
  - The PCR product was sequenced using the Sanger method
  - Maximum-likelihood phylogenetic tree of the Core-E2 fragment

1. Jacka B. et al. Hepatology 2014

Study definitions of HCV reinfection

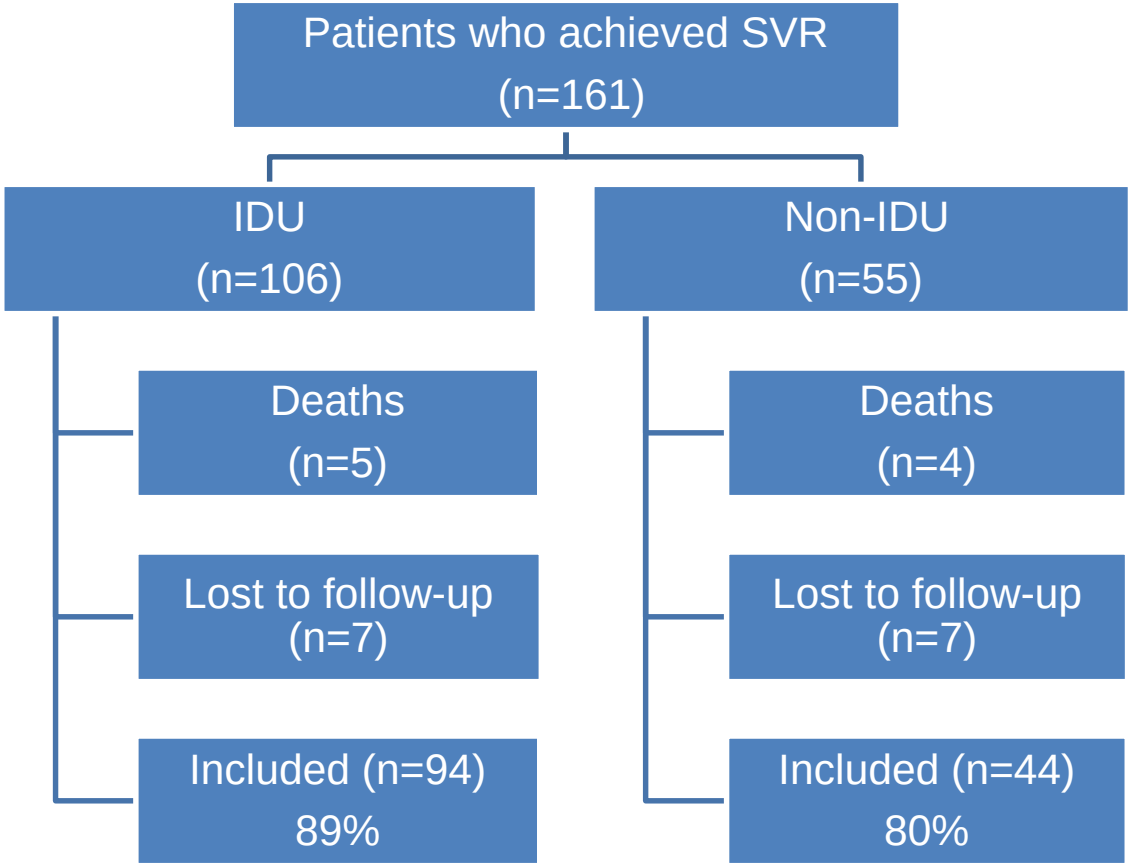
Confirmed reinfection

- Recurrence of HCV RNA post SVR with a viral strain different from strain(s) detected in the baseline sample prior to treatment

Probable reinfection

- Recurrence of HCV RNA post SVR with lacking sequence data, but occurring in a patient who relapsed to IDU after treatment

Overview of the study population



Patient characteristics (n=138)

	IDU (n=94)	Non-IDU (n=44)
Age at treatment (years), median (IQR)	36 (12)	39 (14)
Male gender, n (%)	57 (61)	25 (57)
Low education level, n (%) (secondary school or lower)	45 (48)	13 (31)
Unemployed or welfare benefits, n (%)	36 (38)	17 (39)
Short treatment (14 weeks)	35 (37)	17 (39)
IDU before treatment, n (%) < 100 lifetime injections ≥ 100 lifetime injections	 19 (20) 75 (80)	 NA
Follow-up time (years), median	7.1	7.5

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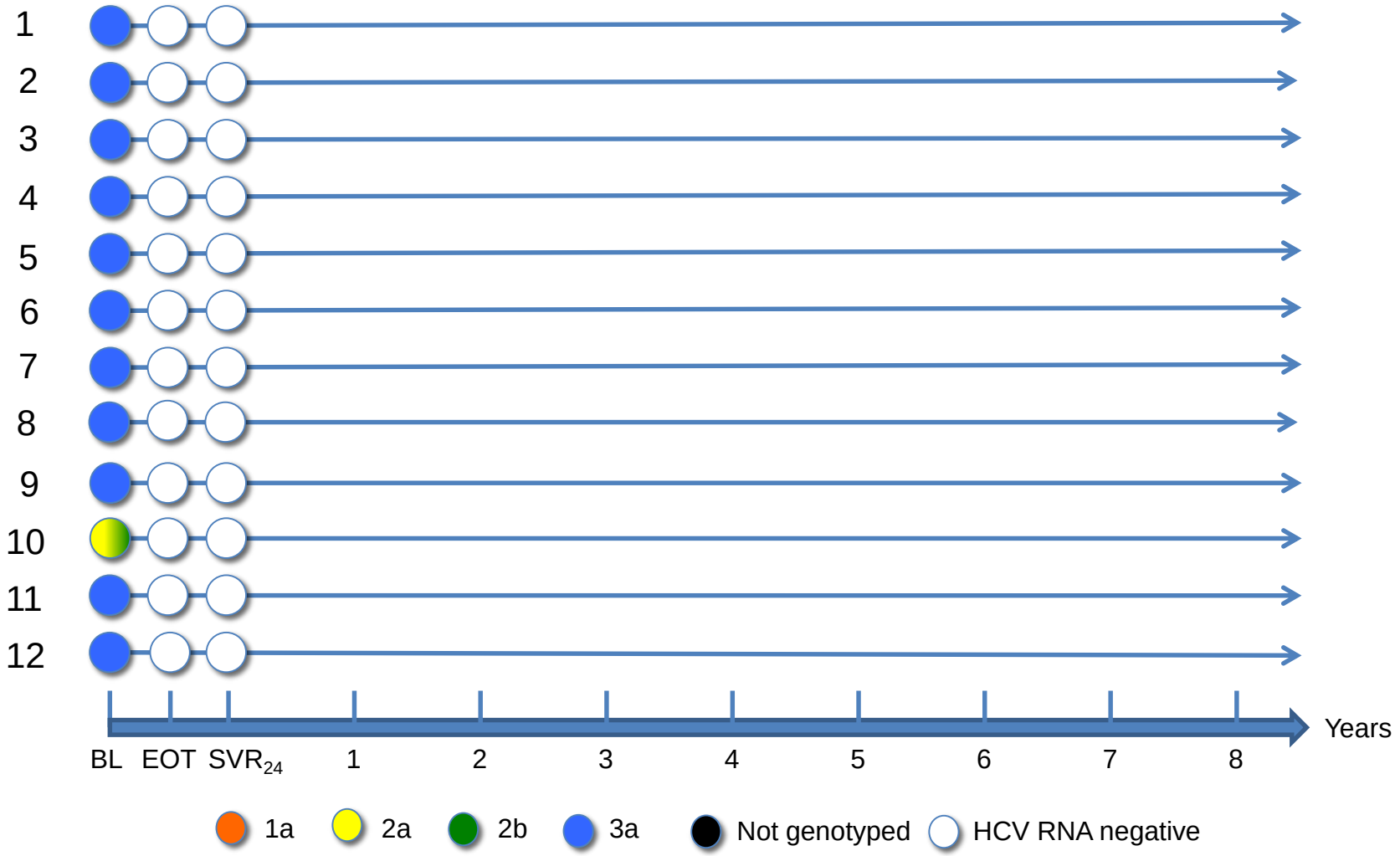
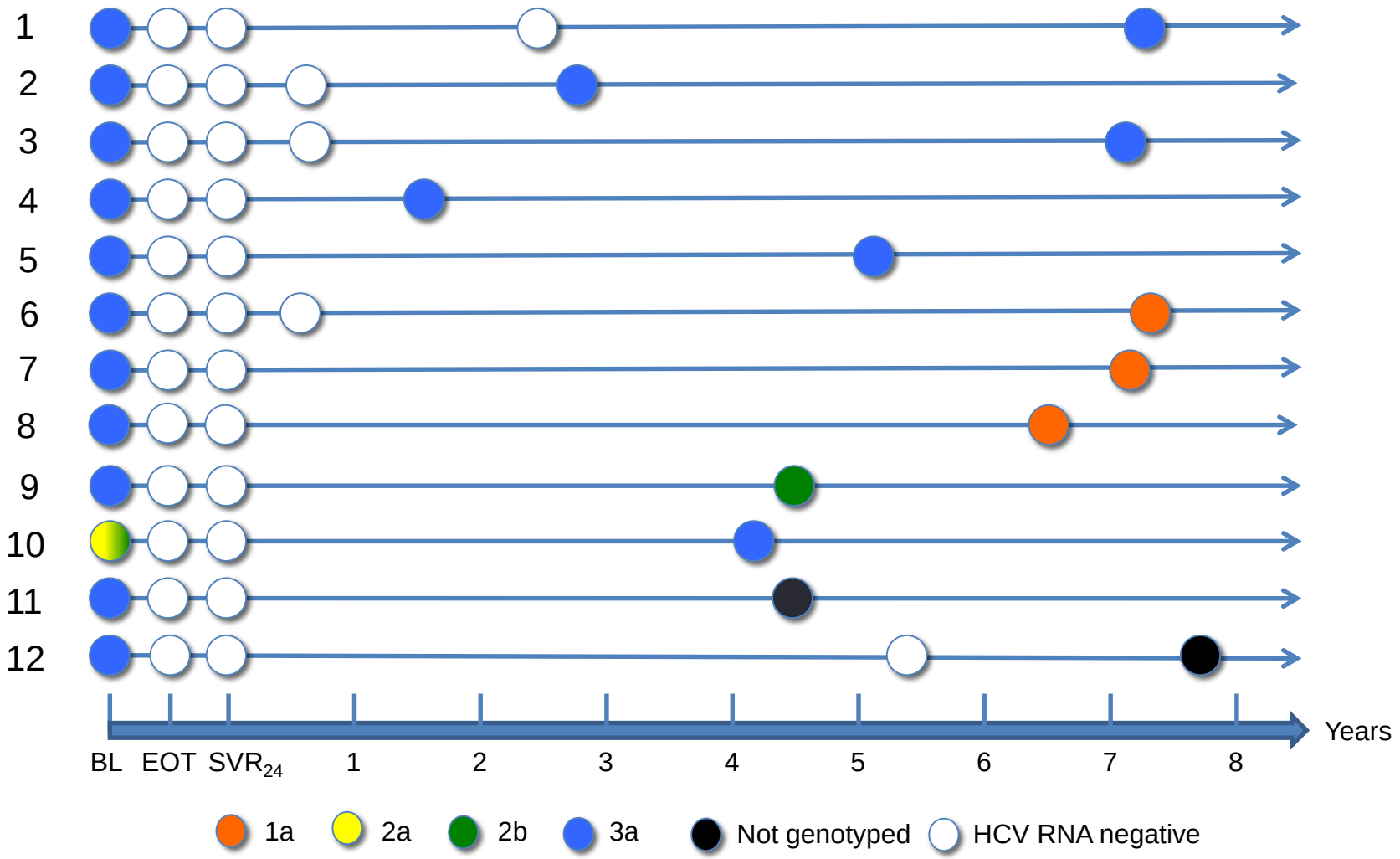
Recurrence of HCV RNA, n (%)	**12 (13)**	**0**

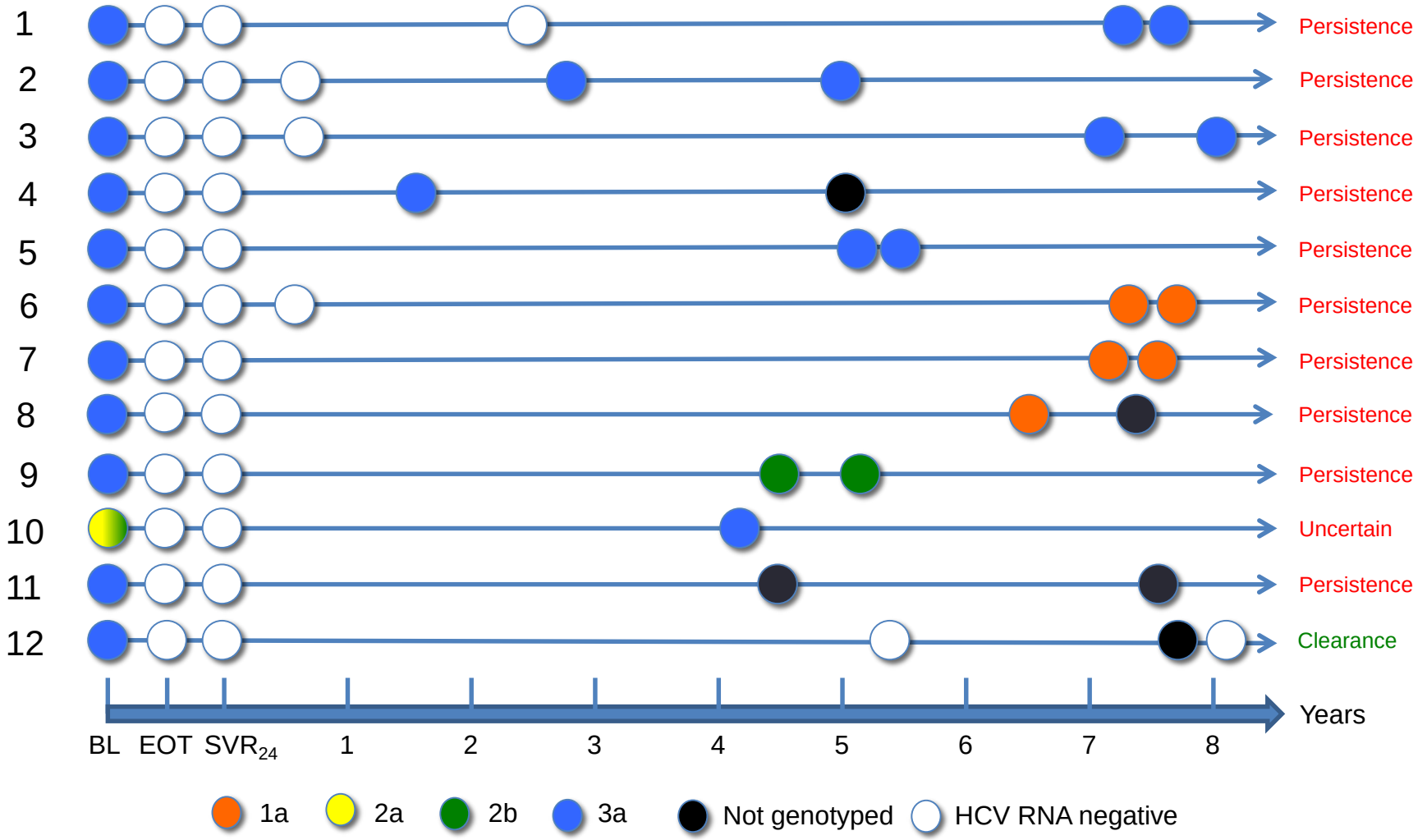
Timelines for 12 recurrent cases: **baseline**



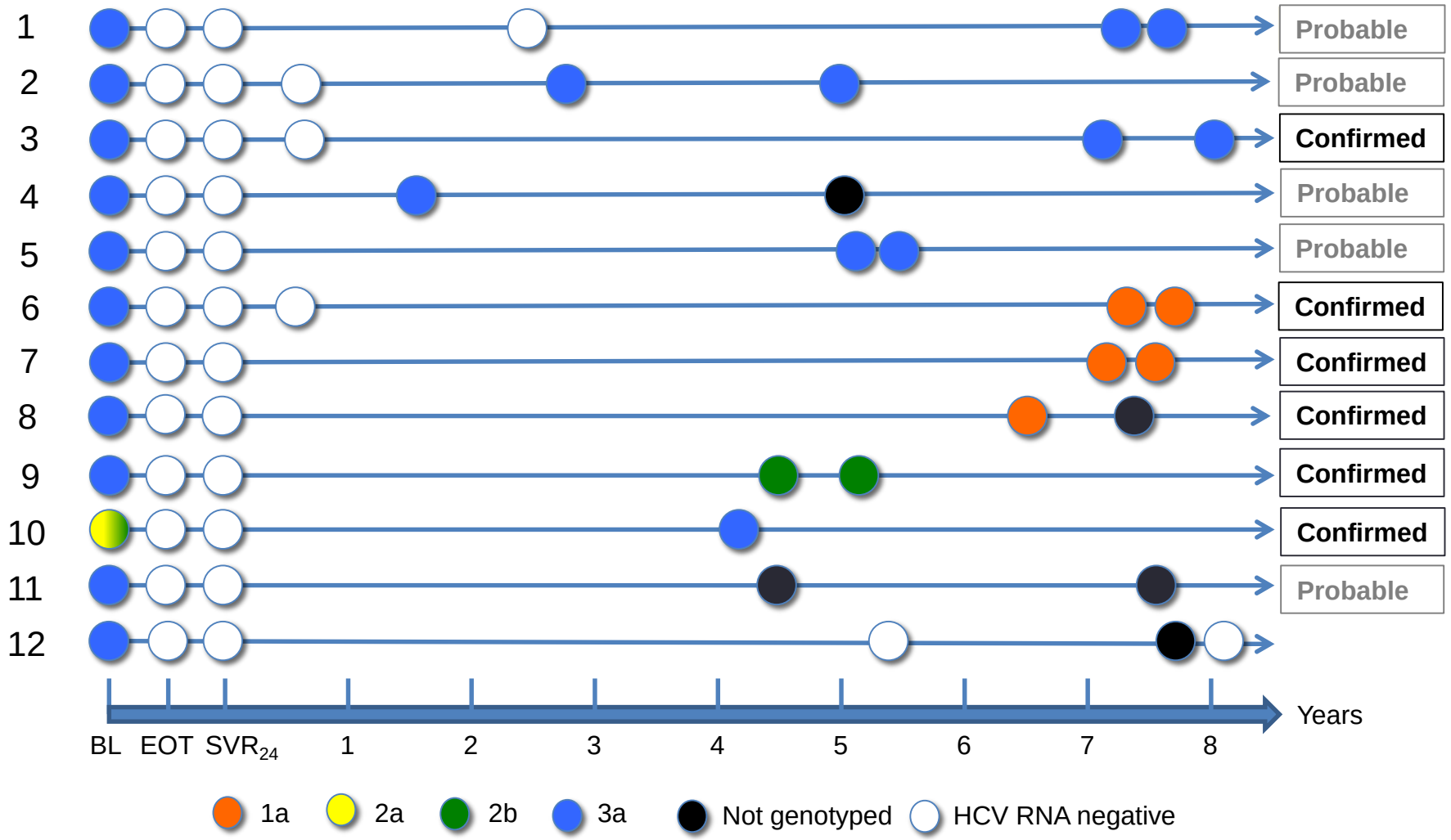
Timelines for 12 recurrent cases: **follow-up**



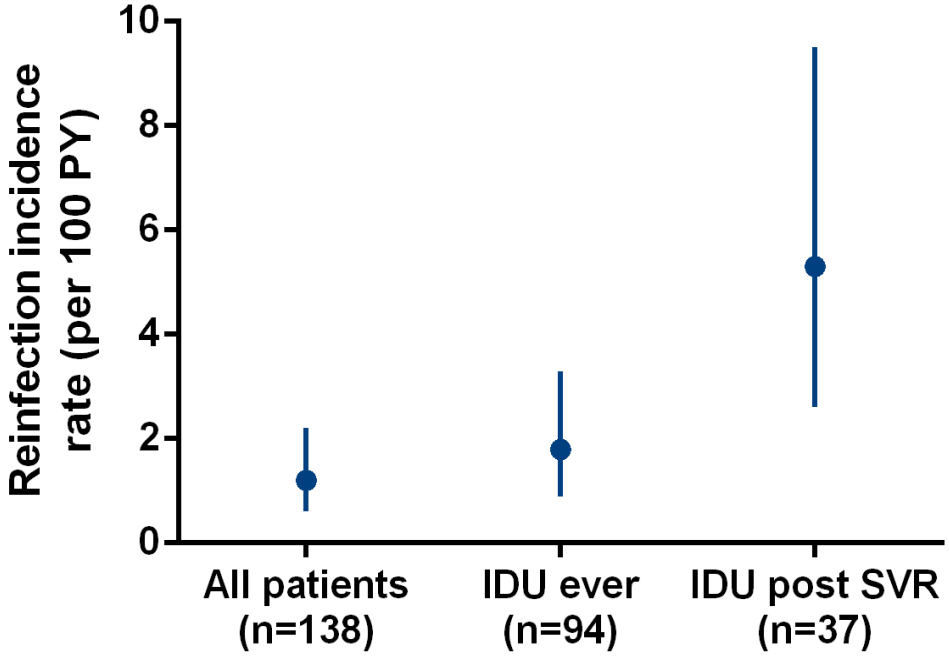
Timelines for 12 recurrent cases: **outcome**



Persistent reinfections: **Confirmed or probable**

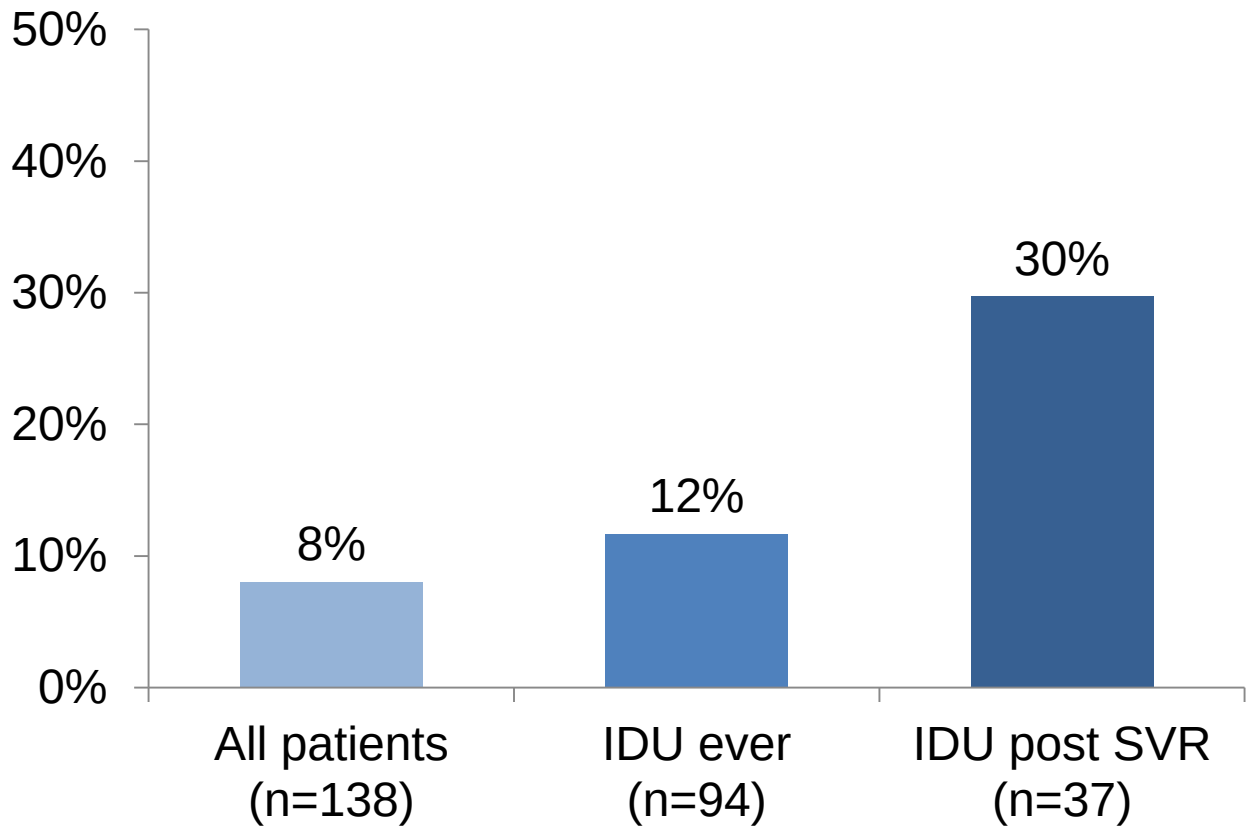


Incidence of persistent HCV reinfection



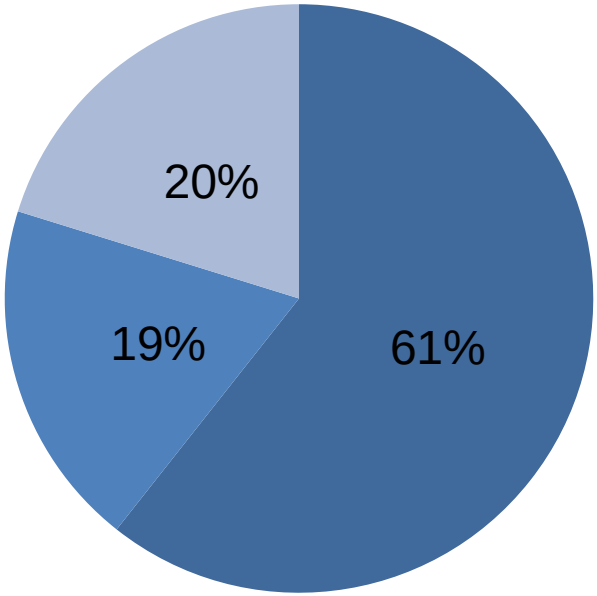
Time at risk after SVR (PY)	**908**	**595**	**208**
Persistent reinfections	**11**	**11**	**11**
Incidence per 100 PY	**1.2**	**1.8**	**5.3**
95% CI	**0.6–2.2**	**0.9–3.3**	**2.6–9.5**

7-year risk of persistent HCV reinfection



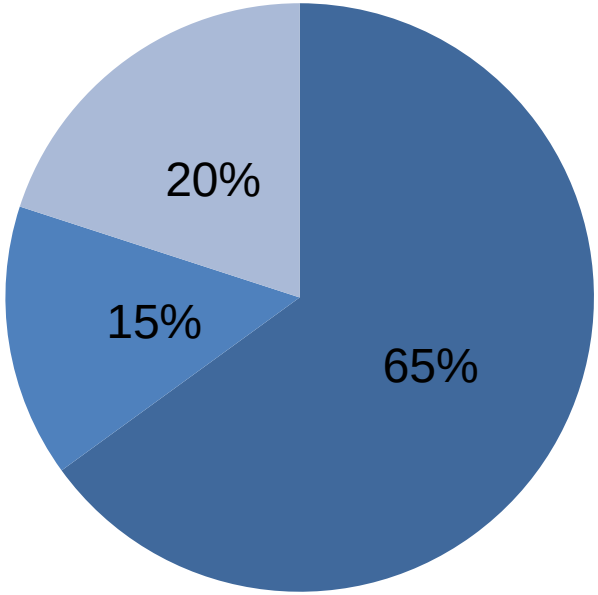
Injecting risk behaviours post SVR

Relapse to IDU*



- No IDU
- Short term/sporadic (<100 injections)
- Dependent/frequent (>100 injections)

Sharing of drug equipment§



- No sharing
- Needles or syringes
- Water, cookers or cotton

*Among 94 patients with a history of IDU prior to treatment
§Among 20 patients who responded completely to the behavioural survey

Predictors of reinfection and relapse to IDU

- All cases of reinfection occurred among those who had relapsed to IDU after treatment

- Reinfection was not associated with any baseline variables and was not associated with post treatment injecting risk behaviours

- Relapse to IDU was associated with
  - **Low age at treatment:** aOR 0.89 per year (95% CI 0.83-0.95)
  - **Low education level**: aOR 4.10 (95% CI 1.56-10.8)

Conclusions and implications

- The incidence of HCV reinfection after SVR among PWID was moderate, but lower than reported rates of primary infection
- At the individual level, reinfection might compromise long-term benefits of treatment for patients with on-going risk behaviours
- At the population level, treating patients at high risk of reinfection may have great prevention potential as these patients are being “kept out of the pool” for a period and prevented from transmitting the virus
- Strategies to prevent reinfection should be addressed and evaluated in future studies

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Study participants

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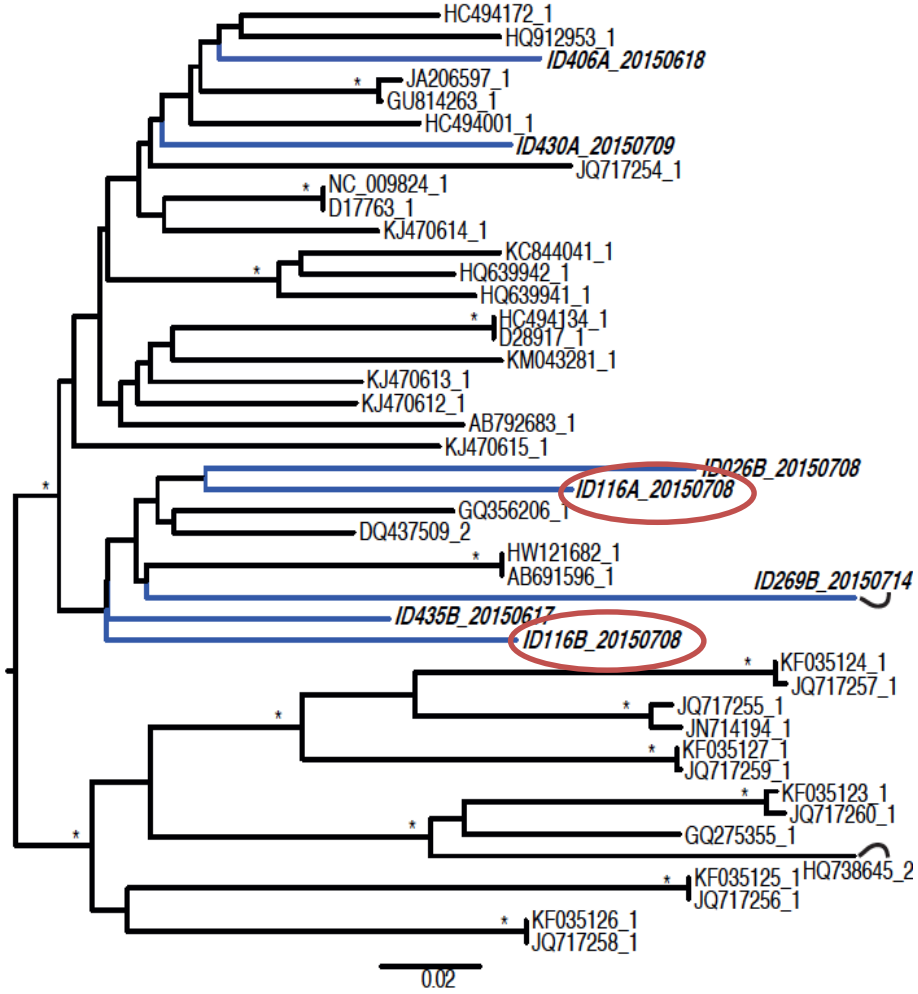
Backup slides

Viral sequencing of the core-E2 region

- 18/24 samples were available for sequencing
- Adequate sequences were obtained in 10/18 samples
  - Old samples
  - Suboptimal storage
  - Low viral load
  - Primer mismatch
- Results also depend on line probe assays



Limitations of the study

1. Lengthy follow-up intervals – spontaneously cleared reinfections may be missed
   - Persistent reinfections are the most clinically significant endpoint

1. Incomplete HIV status at follow-up
   - HIV infection is infrequent in the Norwegian IDU-population (1%)[1]

2. Suboptimal methods/conditions for viral sequencing
   - Late viral relapse of coexisting unresponsive strains?
   - Late viral relapse in patients with recurrence of the same genotype?

- However,
  - All viral recurrences occurred in patients with IDU post SVR
  - Late relapse post SVR_{24} is a very rare event (< 1%)[2]

1. Dalgard O. et al. Tidsskr Nor Laegeforen 2009
2. Pearlman B.L. et al. Clin Infect Dis. 2011