Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response

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Overview

Recurrent HCV infection: some background

Systematic review of recurrence (from pre-DAA era)

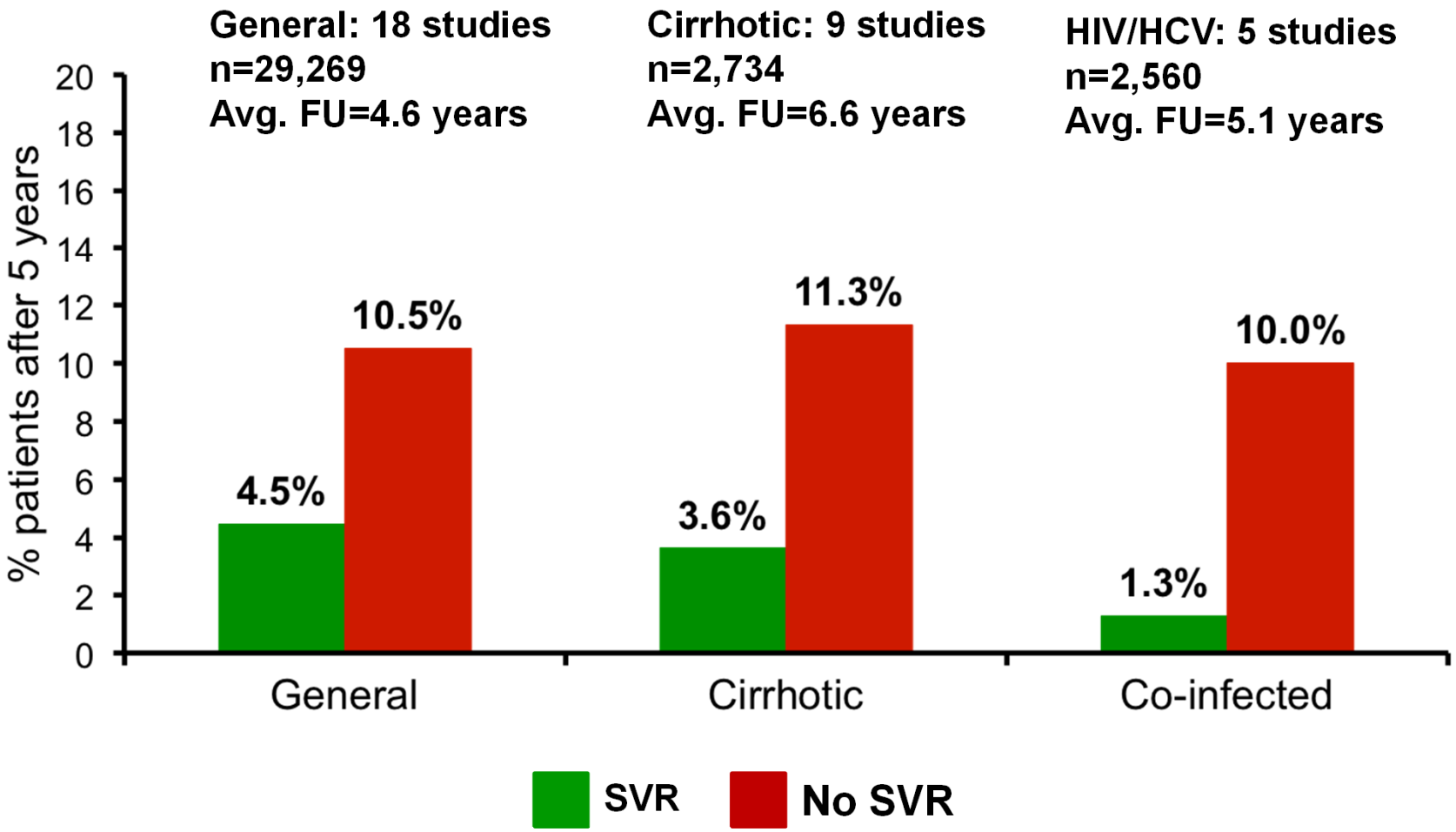
Lessons from emerging data from England in HIV cohorts

Recurrent HCV infection: why does it matter?

Challenge of control / (micro)elimination of infection

Loss of benefits of cure (SVR)

SVR associated with reduced all cause mortality



Simmons et al CID 2015

Does previous infection prevent reinfection?

Probably some increase in protective immunity following successful HCV treatment/clearance

- Lower viraemia on reinfection v primary
- Higher rates spont clearance (more female, IFNL4CC)
- Shorter duration viraema

Evidence supports the hypothesis that CD8+ T cells are key to mediating protection

Refs: Sacks-Davis JID 15 Grebely et al LID 2010

What is the incidence of recurrent HCV infection?

Clinical Infectious Diseases

MAJOR ARTICLE

Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis

Bryony Simmons,[1] Jawaad Saleem,[1] Andrew Hill,[2] Richard D. Riley,[3] and Graham S. Cooke[1]

Simmons et al CID 2016

What is the incidence of recurrent HCV infection?

Definition

HCV RNA >LLOQ after SVR (12 or 24)

Incidence of recurrent HCV infection?

Review of articles from 1.1.90 to 31.3.15

Sensitive search for studies of HCV recurrence, reinfection and relapse

All need follow up of >6/12 post SVR (either 12 or 24)

Excluded studies of spontaneous clearance and transplant recipients

Didn’t distinguish acute from chronic infection

Pooled estimates generated for recurrence /1000 PYFU and converted in to estimates of 5 year recurrence

Abstracts and Articles Screened	1191
Full text articles screen	95
Meeting inclusion criteria	68
High quality	49/68

Reported by risk group:

Monoinfected, low risk : no recognised RF for reinfection

Monoinfected, high risk : 1 or more RF for reinfection

Co-infected HIV/HCV

Results

	Studies (N)	Individuals (N)	Recurrence/ 1000 PYFU
Low risk	**43**	**7969**	**1.85** (0.71-3.35)
High risk	**14**	**771**	**22.3** (13.1-33.5)
HIV/HCV	**4**	**309**	**32.0** (0-123.5)

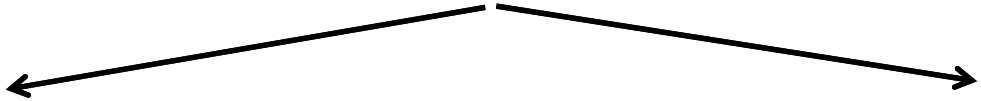
Five-year risk of recurrence

Low risk	0.95% (95%CI 0.35-1.69)
High risk	10.67% (95%CI 6.8-15.7)
HIV/HCV	15.02% (95%CI 0.00-48.3%)

Simmons et al CID 2016

Recurrent HCV infection

HCV RNA >LLOQ after SVR (12 or 24)



Relapse

Recurrence+

Same genotype/strain

(defined by genotyping

Or full sequencing)

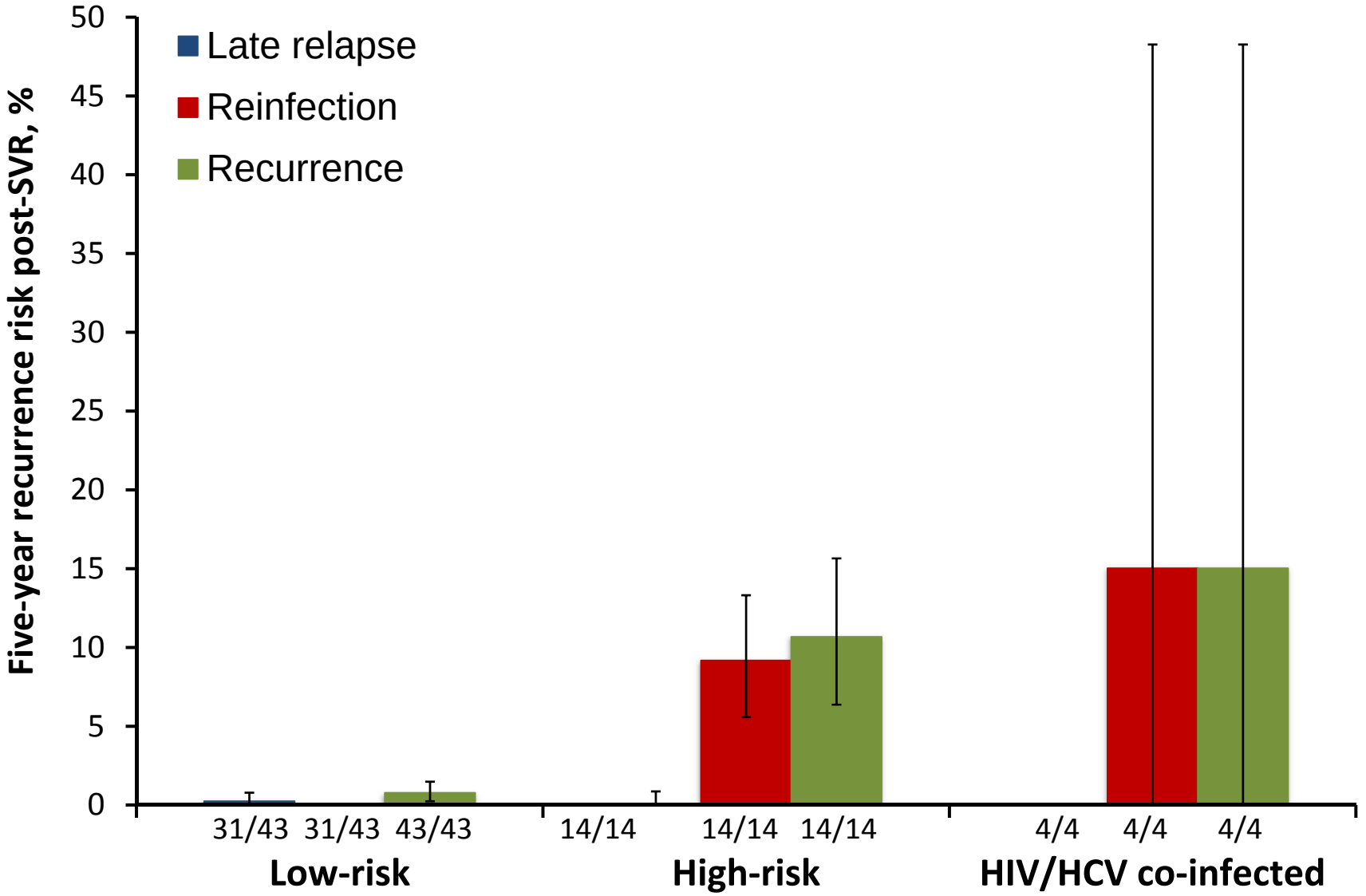
Reinfection

Recurrence+

New

strain/genotype

Five-year risk of recurrence



Simmons et al CID 2016

Key findings

High rates of apparent reinfection where identified risk factors

HIV/HCV highest rates, possibly due to overlap of high risk behaviours, but data limited

Limitations

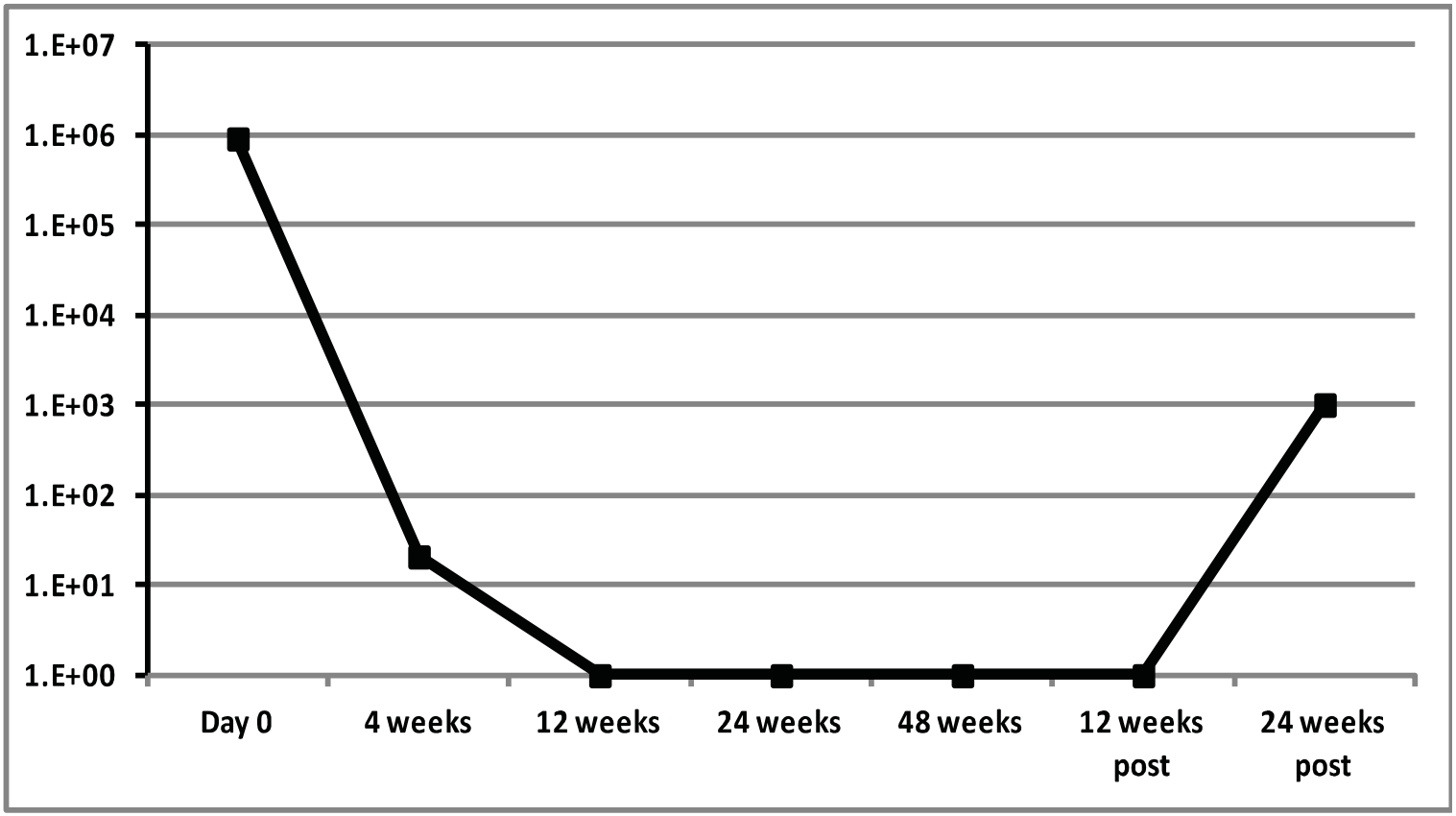
Often nature of recurrence not well defined in studies

Many studies use known patient risk factors to define relapse/reinfection – circularity

Same genotype may be reinfection, especially in small transmitting populations

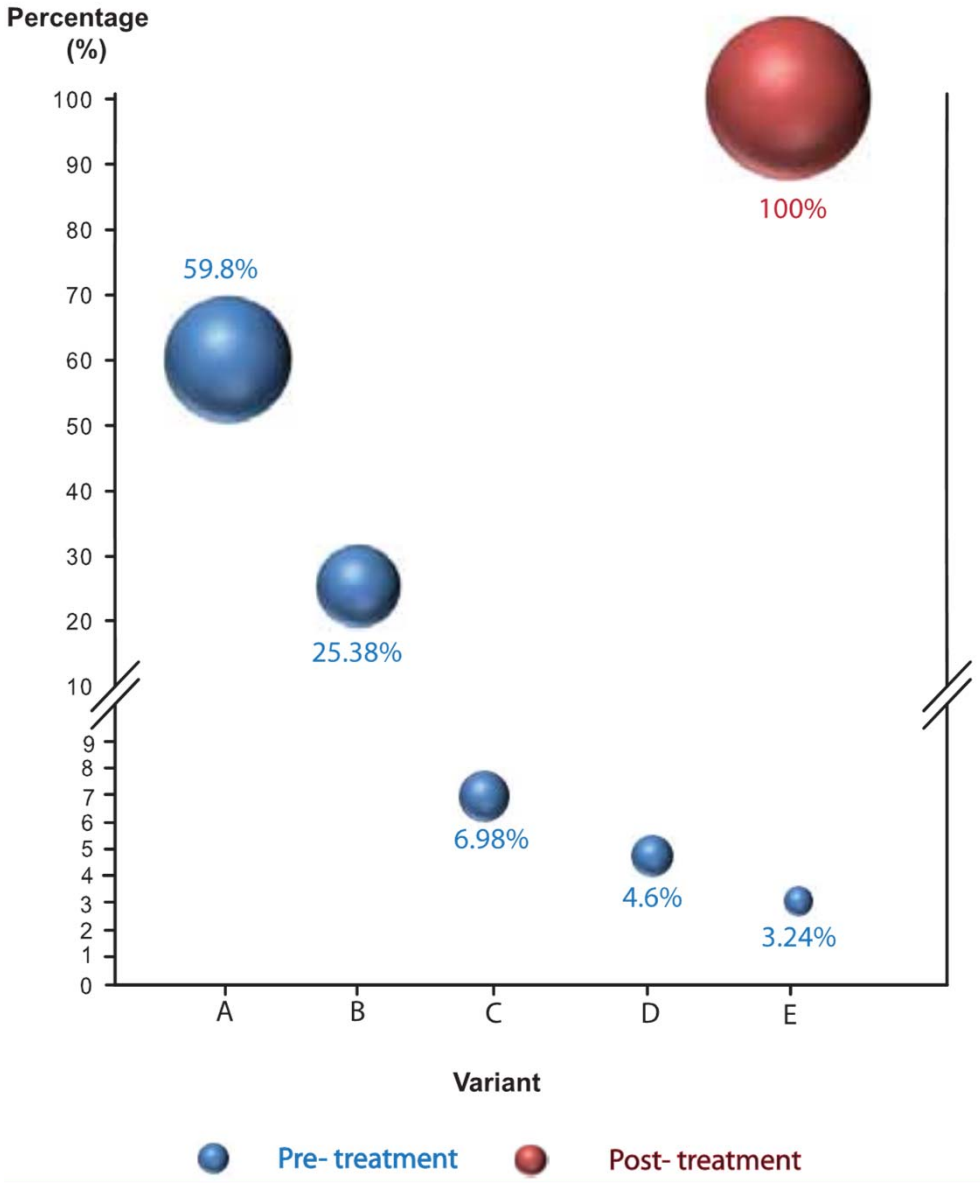
Genotype switching might not be due to reinfection

P 101



Abdelrahman Hepatology 2015

Change in dominant variant might not be reinfection



Abdelrahman Hepatology 2015

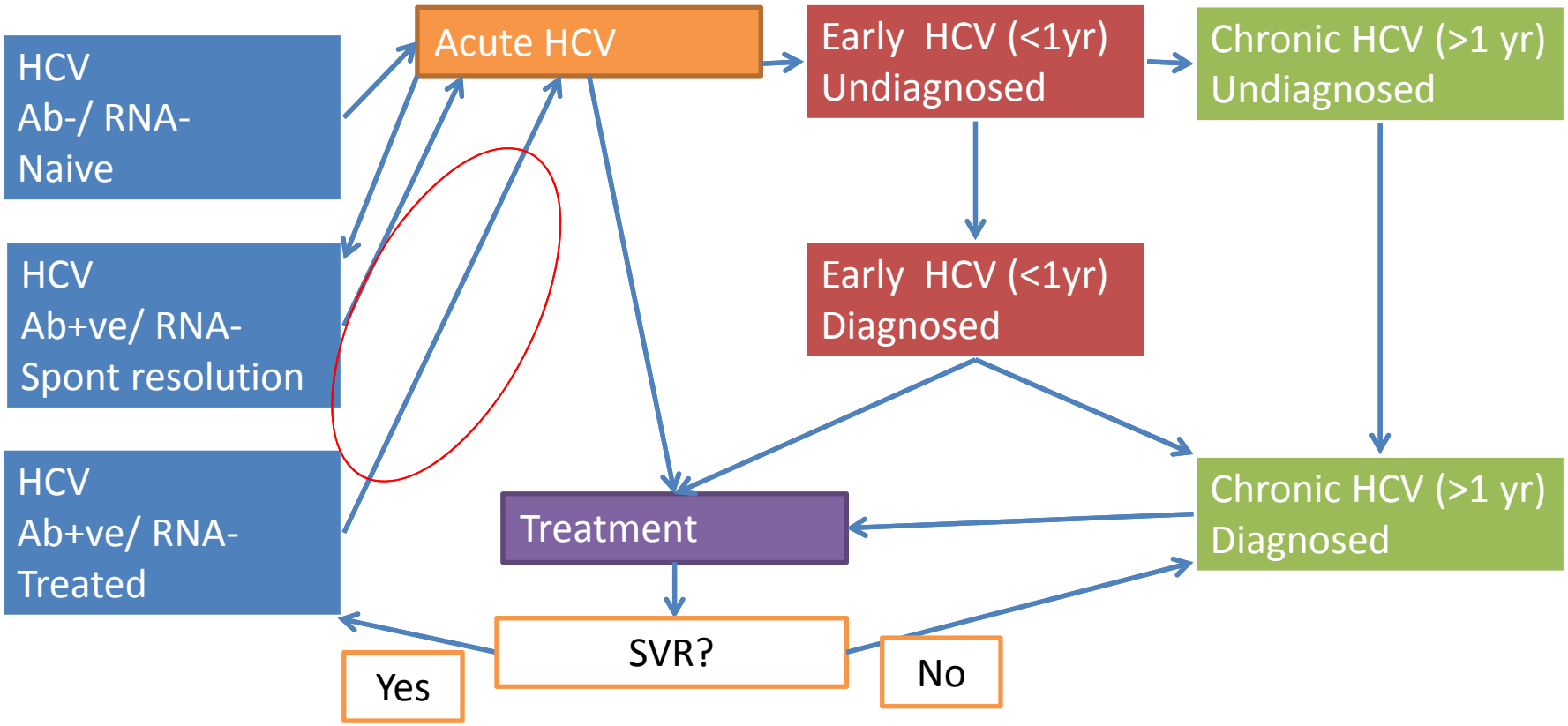
Impact of widespread access to DAAs

Do recurrence/reinfection rates differ with DAAs?

Suggestions that immune restoration post treatment may differ with IFN/non-IFN based therapies

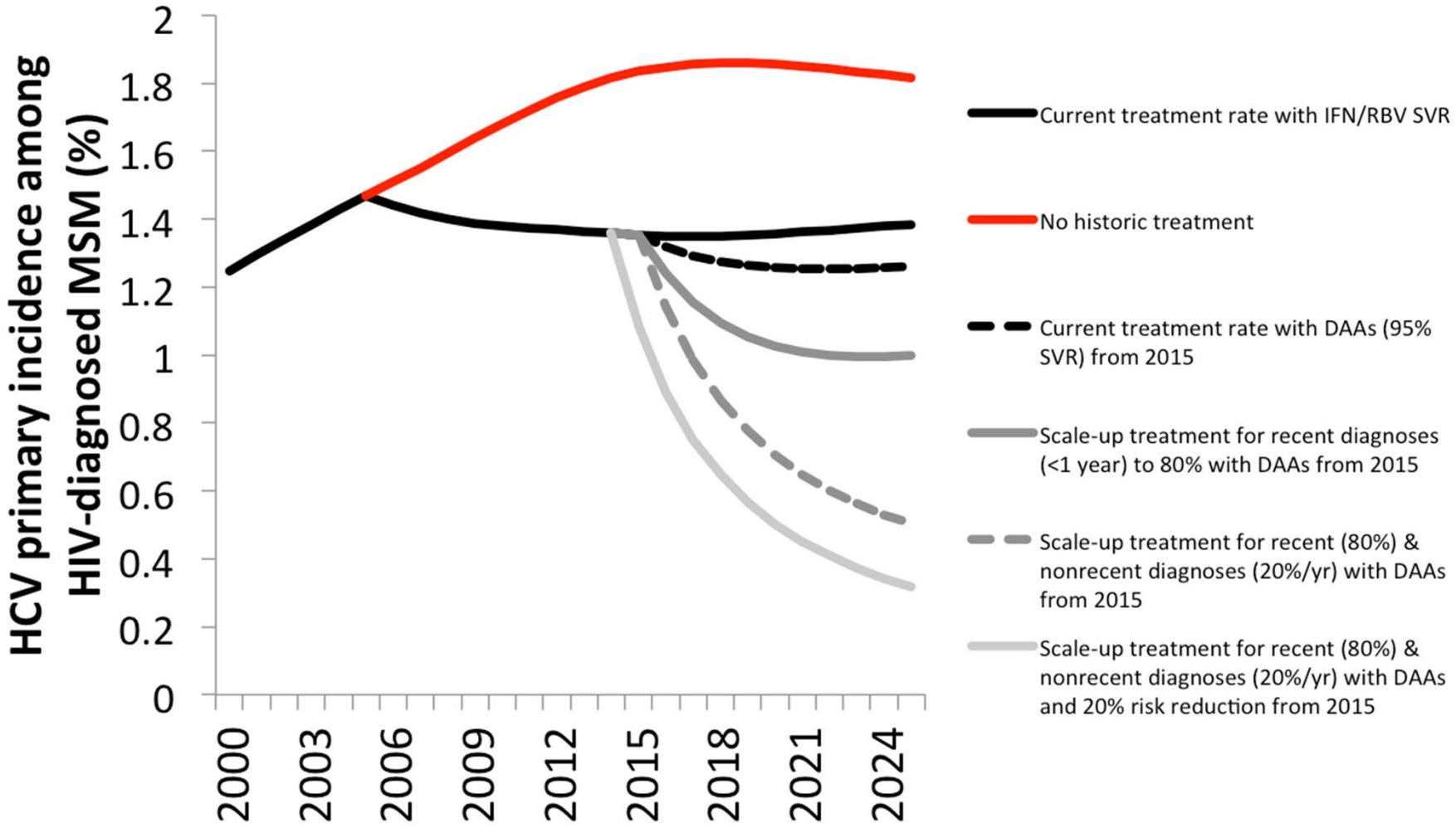
Potential that individual's motivation to prevent reinfection will be reduced if better AE profile and that ongoing risk may change over time

Context of risk will change as treatment access improves and infecting population declines



Adapted from Martin et al CID 2016

Impact on recurrence/reinfection?



Martin et al CID 2016

Fall in HCV incidence in HIV+ MSM in London following expansion of access to DAA therapy

Garvey et al CROI 2019

BHIVA British HIV Association
Imperial College London
NIHR National Institute for Health Research
NHS Imperial College Healthcare NHS Trust
NHS Central and North West London NHS Foundation Trust
NHS Royal Free London NHS Foundation Trust

Aims and Setting

- Use real world experience to examine trends in incidence of acute HCV in HIV+ MSM between 2013-2018 (pre and post DAAs)
- 3 central London HIV clinics which provide care for over 6000 HIV+ MSM

Royal Free NHS Trust

Imperial College Healthcare NHS Trust

Mortimer Market Centre

Methods

Period of study:

- July 2013- June 2018; data reported by 6-month interval

Data collected:

- Number of acute HCV episodes: first and subsequent (reinfections)
- Number of HIV+MSM under active FU (denominator)
- Type of HCV treatment selected
- Timing of treatment initiation relative to acute HCV diagnosis

[1] *European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel AIDS. 2011 Feb 20;25(4):399-409.*

[2] *EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018 Aug;69(2):461-511*

Methods

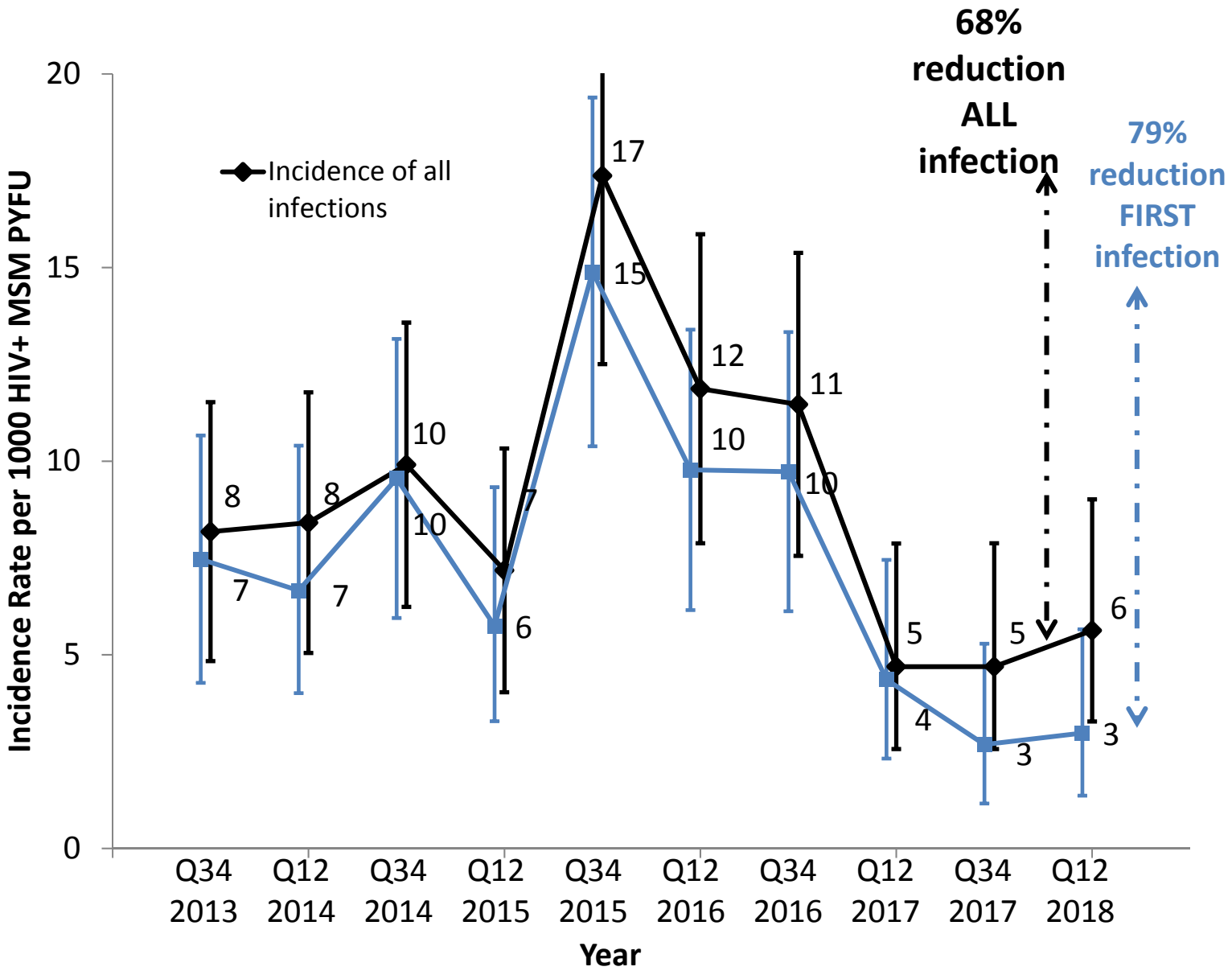
Definitions[1,2]:

- **Acute HCV:** positive HCV RNA test plus a negative anti-HCV test within 12 months; or positive HCV RNA test with an acute ALT rise and no other identifiable cause
- **Acute HCV reinfection:** positive HCV RNA test with prior confirmed spontaneous clearance, SVR following HCV treatment or with evidence of genotype switch (not deep sequencing)

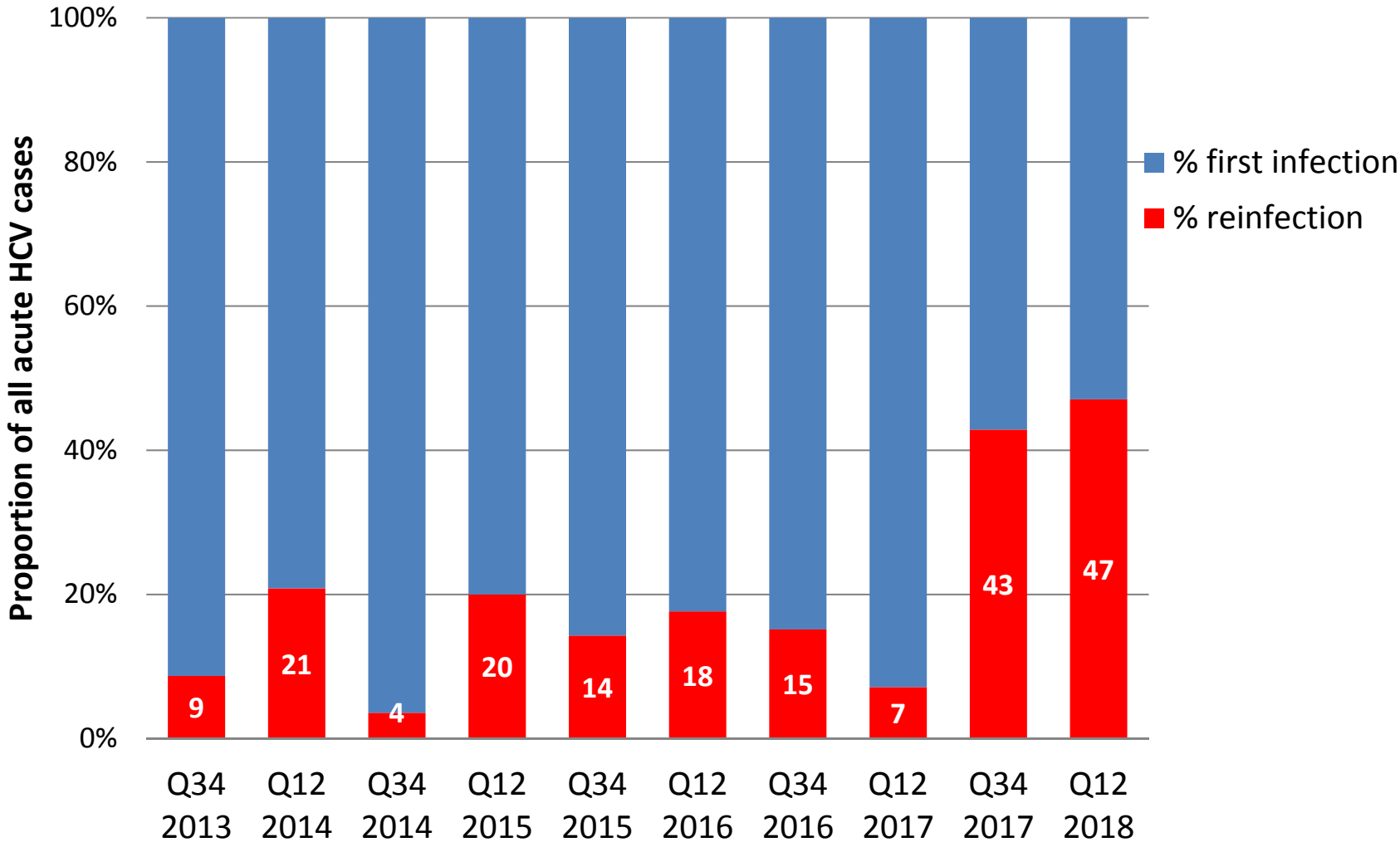
[1] *European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel AIDS. 2011 Feb 20;25(4):399-409.*

[2] *EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018 Aug;69(2):461-511*

Results: Incidence Rate Reduction

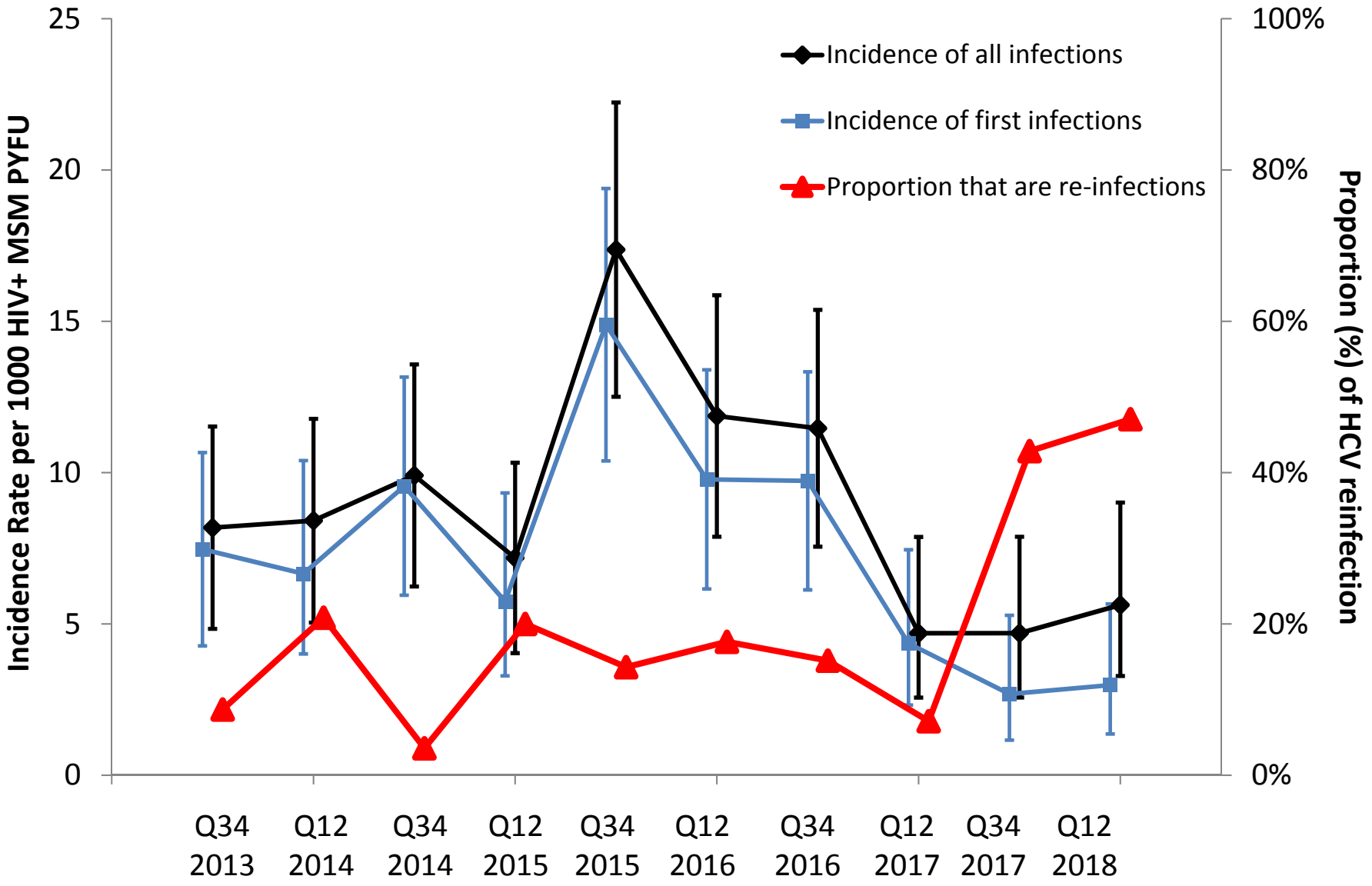


Results: Reinfection proportion of acute HCV



	Q34 2013	Q12 2014	Q34 2014	Q12 2015	Q34 2015	Q12 2016	Q34 2016	Q12 2017	Q34 2017	Q12 2018
Reinfection (n)	2	5	1	4	7	6	5	1	6	8
First infection (n)	21	19	27	16	42	28	28	13	8	9

Results: Incidence and proportion reinfection



Implications

- Declines in first infection close to the more optimistic of those predicted by modelling – microelimination is credible
- We can set targets for elimination based on incidence (comparable to other well studied cohorts e.g. Amsterdam) – we will likely aim for 10% of 2015 high water
- Reinfection increasing as proportion of acute infection and we need access to retreatment (currently possible in Scotland but not England)

Limitations

- Data collected retrospective and not part of a formal study process
- HIV+MSM in one city therefore findings may not be replicated in other settings (though we have now added two centres)
  - *HCV clinical trials available in all centres which may not be representative*
- HCV transmission dynamics in national/international networks and HCV in HIV-neg MSM on PreP in London not evaluated
- All such studies are highly context specific

Final thoughts for discussion

- Definitions reasonably consistent, need to balance precision against pragmatism
- Bear in mind that many settings don’t have access to PCR (antigen may be as good)
- Recurrent infection can be viewed as a positive signal that high risk groups are accessing treatment (at least early on in response)
- Access to retreatment crucial alongside other public health measures if progress to be sustained

Thank you

Thank you

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Questions