Kirby Institute

Hepatitis C virus reinfection following antiviral treatment among people who inject drugs: A systematic review and meta-analysis

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Disclosure

- No conflict of interest

Introduction

- Direct-acting antiviral (DAA) treatment has the potential to reduce the HCV disease burden, including among individuals who use drugs. *Hajarizadeh, et al. Lancet Gastro Hepatol 2018*

- Ongoing risk behaviors following successful therapy may lead to HCV reinfection and compromise treatment outcome.

- Restrictions for the reimbursement of DAA therapy for people with ongoing drug use in some states in the USA and Europe.
  Marshall et al. Lancet Gastroenterol Hepatol 2018; Barua et al. Ann Int Med 2015

- Hesitancy among some clinicians to prescribe DAA therapy for people who inject drugs
  Among clinicians attending the Liver Meeting® in 2014, 15% were willing to prescribe DAA for people who injected drugs. Reinfection and adherence to treatment were their most important concerns (Asher et al. Subst Use Misuse 2016)

Objectives

- To evaluate post-treatment HCV reinfection among overlapping populations of:
  - people with recent drug use (injecting or non-injecting),
  - people with recent injecting drug use,
  - people receiving opioid agonist therapy (OAT).

- To assess the factors explaining heterogeneity across studies.

Methods – Eligibility criteria

- Studies which met all the following criteria were included:

    a) Study population included defined populations of people with recent drug use or people receiving OAT

    a) investigated HCV reinfection following HCV treatment (Interferon-containing or DAA treatment),

    b) Reported HCV reinfection rate

Methods – Information sources

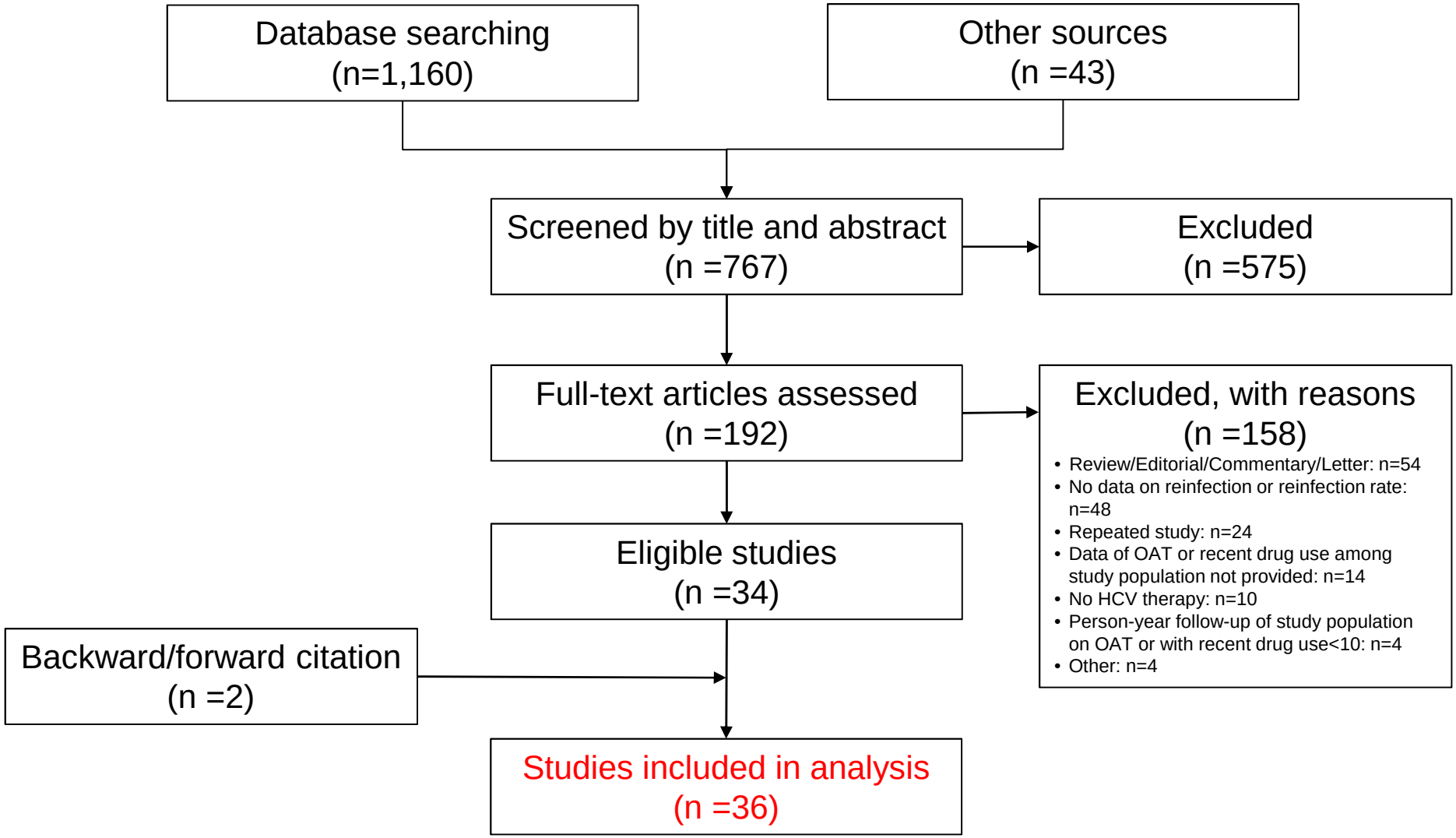
- Bibliographic databases:
  - MEDLINE (Pubmed)
  - Scopus
  - Web of Science
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - PsycINFO

- Conference presentations:
  - International Liver Congress™
  - The Liver Meeting®
  - Annual Conference on Retroviruses and Opportunistic Infections (CROI)
  - International Symposium on Hepatitis Care in Substance Users (INHSU)

- ClinicalTrials.gov was searched for registered clinical trials, including ongoing studies.

- Searches were performed in Oct 2018, and updated in June 2019.

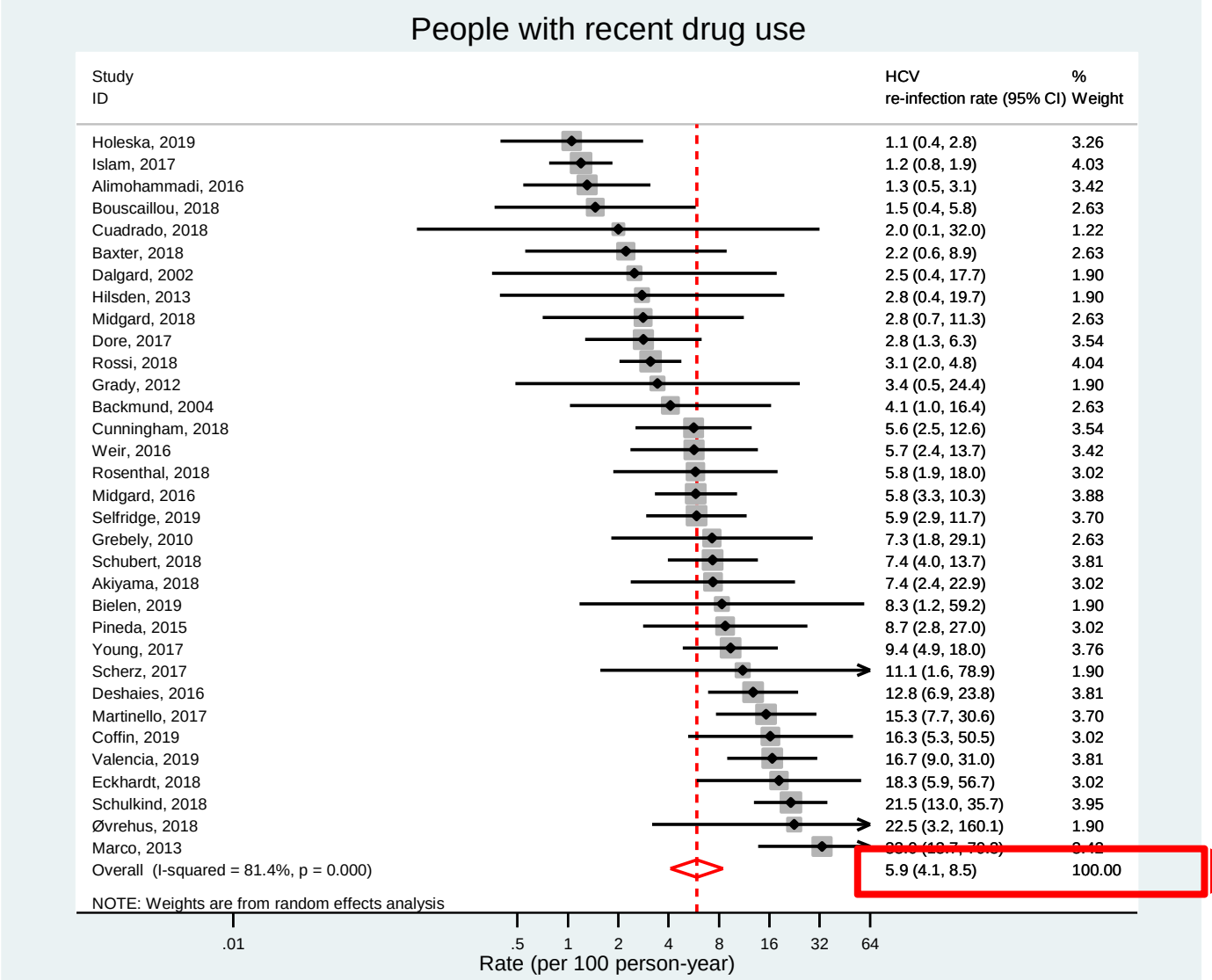
Results


Database searching
(n=1,160)
Other sources
(n =43)
Screened by title and abstract
(n =767)
Excluded
(n =575)
Full-text articles assessed
(n =192)
Excluded, with reasons
(n =158)
• Review/Editorial/Commentary/Letter: n=54
• No data on reinfection or reinfection rate: n=48
• Repeated study: n=24
• Data of OAT or recent drug use among study population not provided: n=14
• No HCV therapy: n=10
• Person-year follow-up of study population on OAT or with recent drug use<10: n=4
• Other: n=4
Eligible studies
(n =34)
Backward/forward citation
(n =2)
Studies included in analysis
(n =36)

Results

	Study n (%)
Study design	
Prospective	26 (73)
Retrospective	10 (27)
Study setting	
Drug treatment service	13 (36)
Community clinic / Primary care	8 (22)
Tertiary care	3 (8)
Prison	2 (6)
Mixed setting	10 (28)
Definition of "recent drug use"	
During HCV treatment or post-treatment follow-up	19 (53)
During the 1-6 month before HCV treatment initiations	14 (39)
Other or not reported	3 (9)
HCV treatment	
Interferon-containing treatment	17 (47)
Direct-acting antiviral treatment	19 (53)
Start point for reinfection assessment	
End of treatment	14 (39)
12-24 weeks post-treatment (SVR12/24)	21 (59)
Other	1 (3)
HCV re-infection diagnosis method	
Recurrent viremia following SVR	14 (39)
Detection of different HCV strain using sequencing	10 (28)
HCV genotype change	4 (11)
Mixed of above methods	6 (17)
Not reported	2 (6)

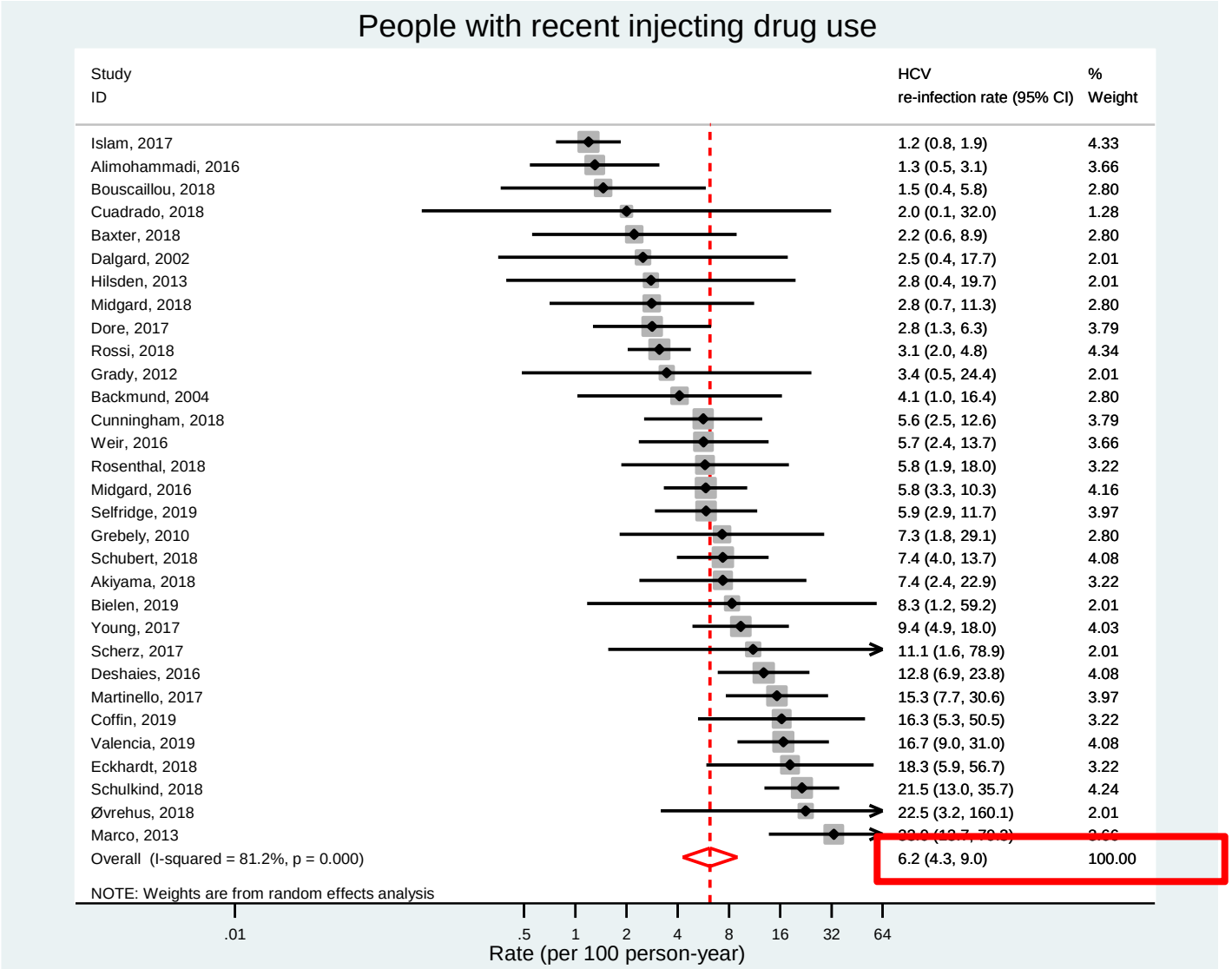
Results – Reinfection rate, individuals with recent drug use



Study n = 33
Pt. n = 5,061

5.9 / 100 PY

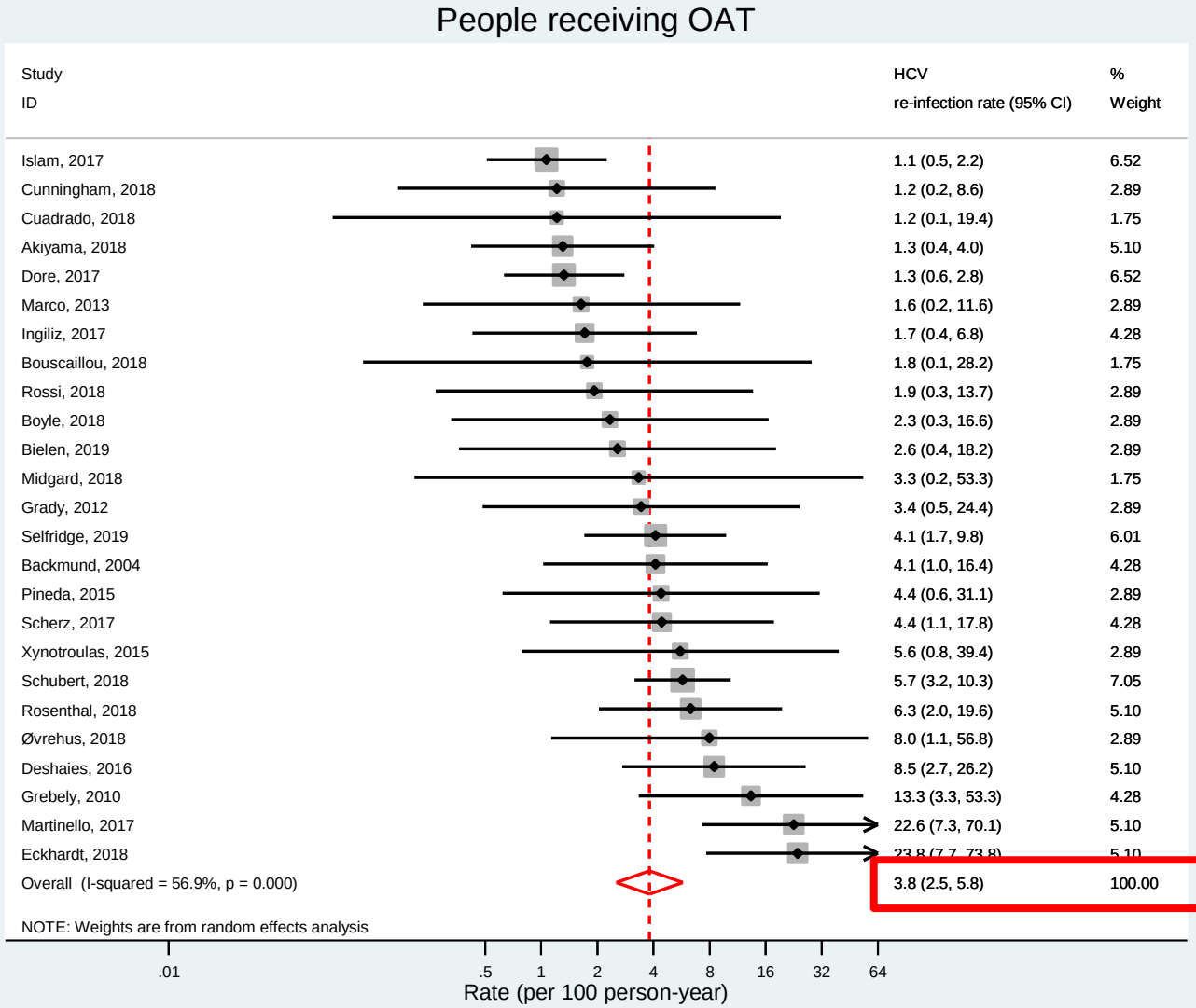
Results – Reinfection rate, individuals with recent IDU



Study n = 31
Pt. n = 4,648

6.2 / 100 PY

Results – Reinfection rate, individuals on OAT



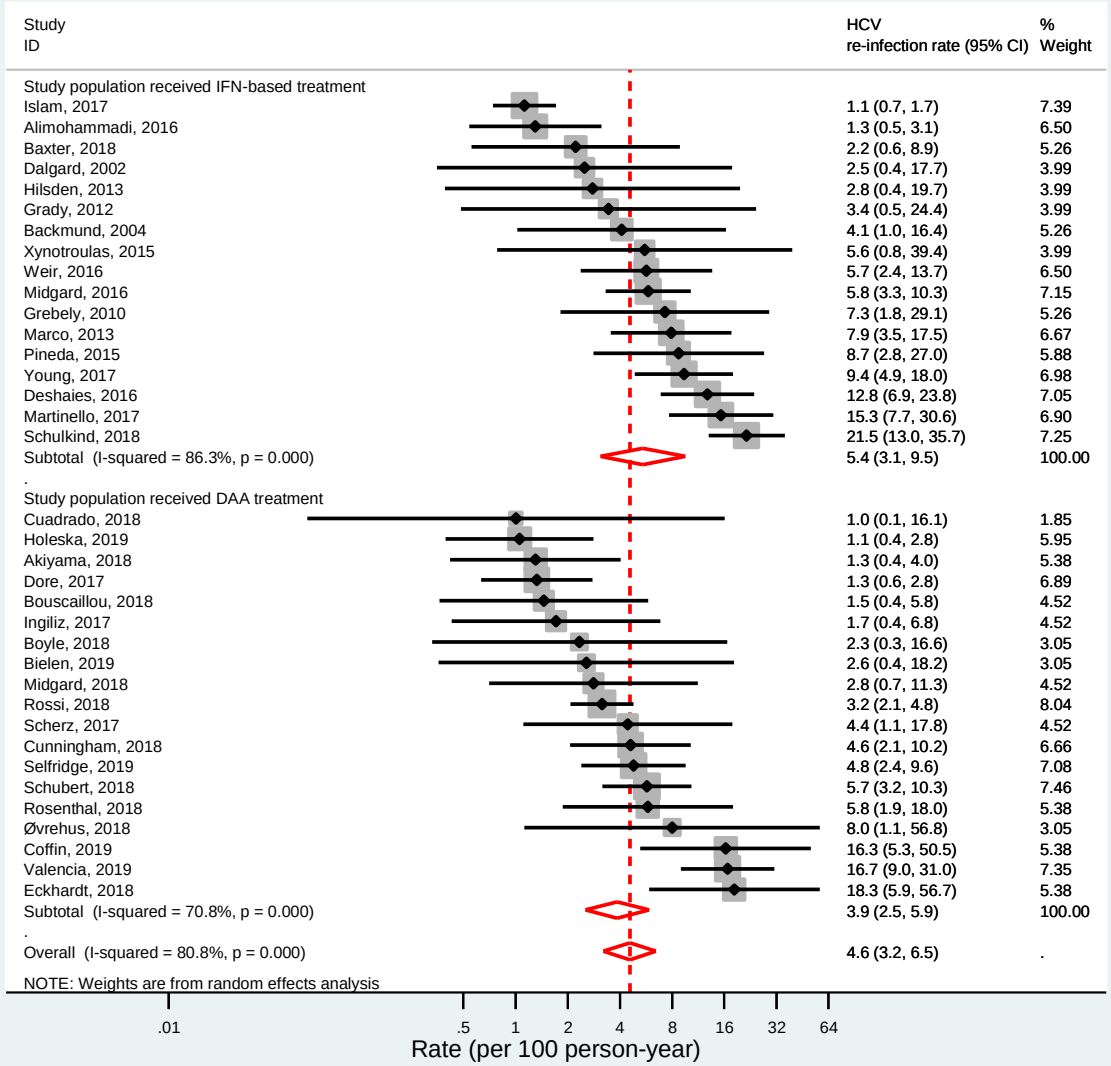
Study n = 25
Pt. n = 2,507

3.8 / 100 PY

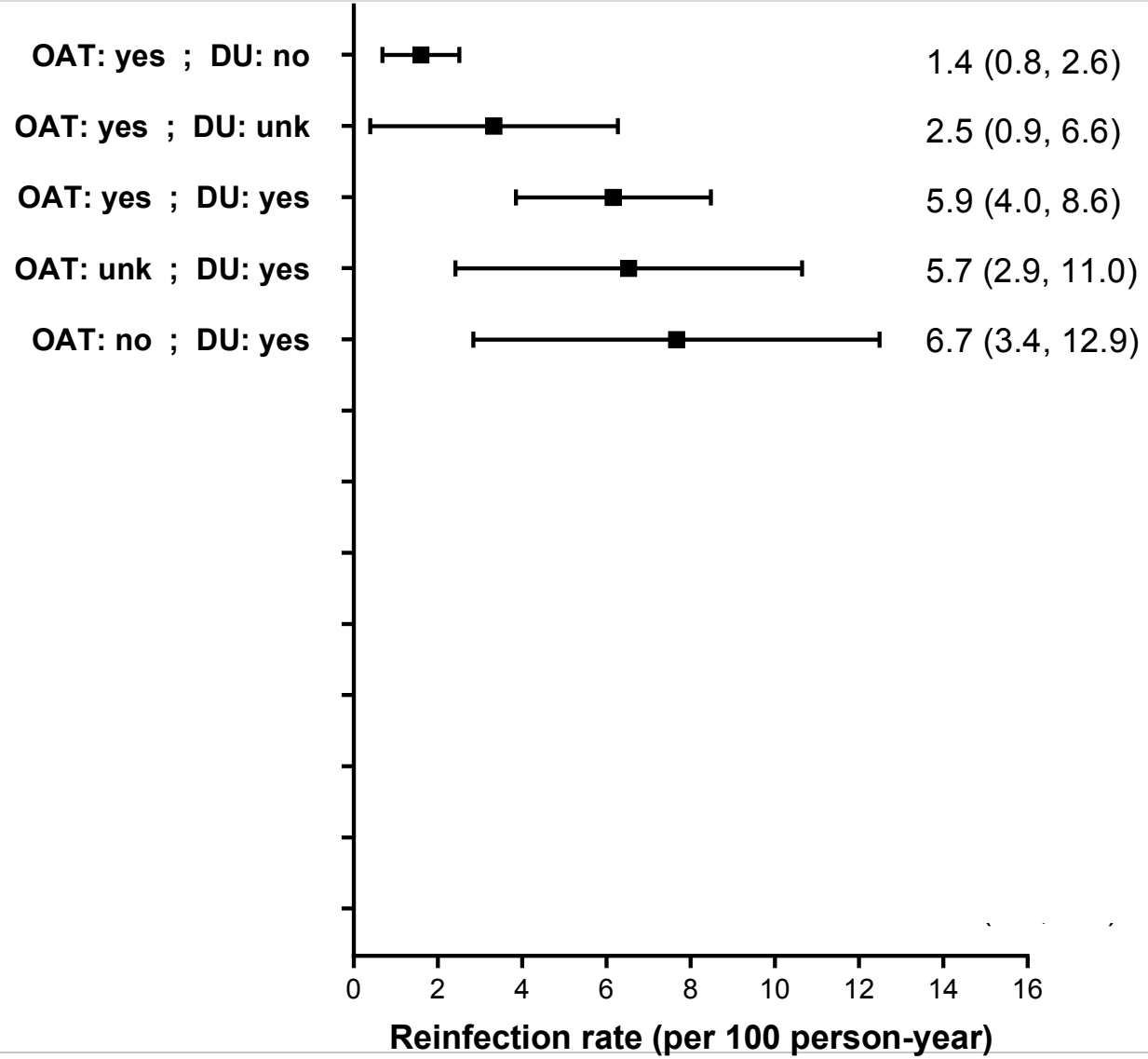
Results – Reinfection rate, by HCV treatment regimen

IFN therapy

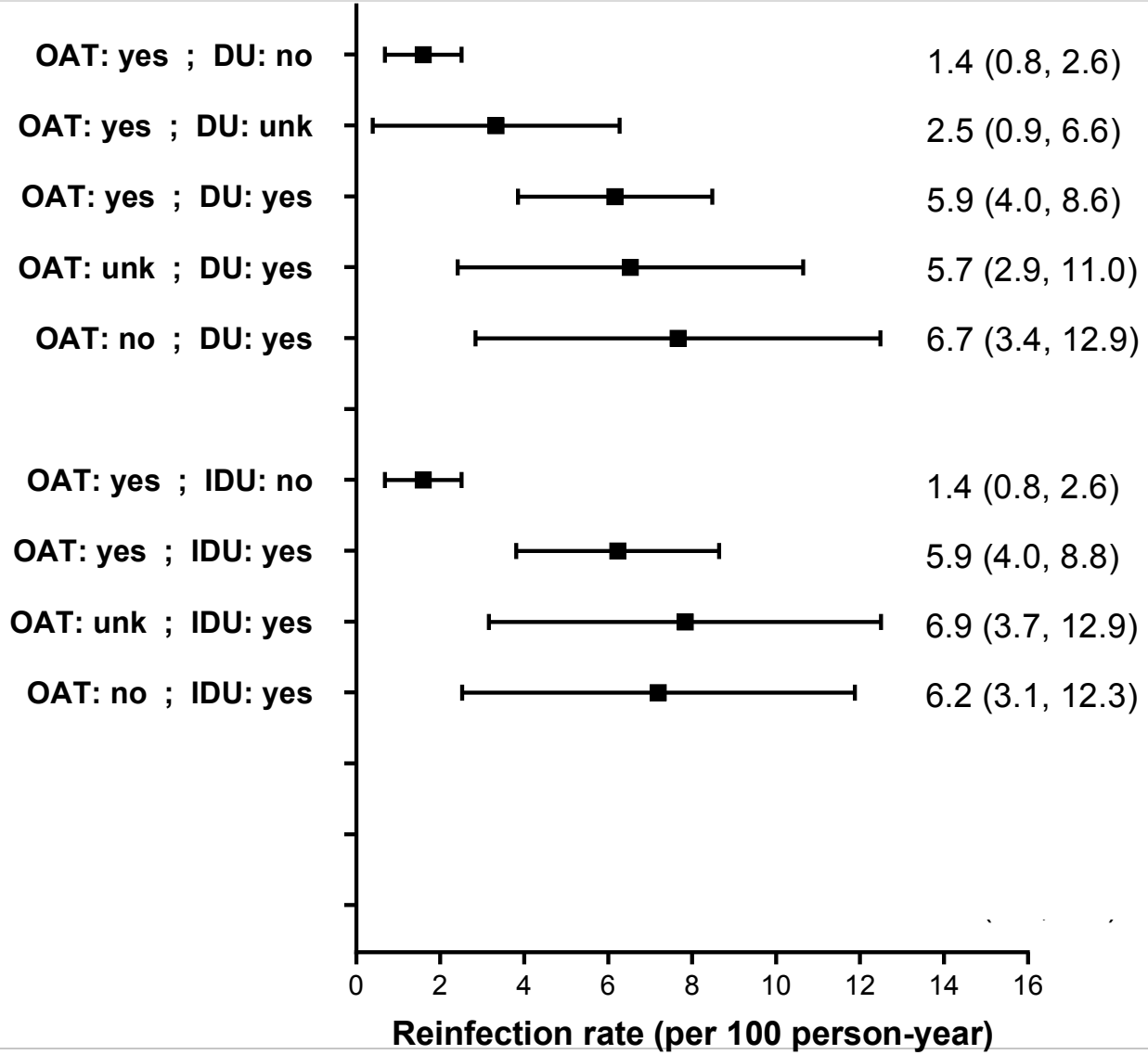
DAA therapy



Results – Reinfection rate by OAT and DU status



Results – Reinfection rate by OAT and DU status



Results – Meta-regression

		Unadjusted models	
		Rate Ratio (95% CI)	P
Proportion of men, per 10% increase		1.08 (0.84, 1.39)	0.524
Median/mean age, per year increase		0.95 (0.91, 0.98)	0.002
Proportion with HIV, per 10% increase		1.04 (0.93, 1.17)	0.465
Study design	Observational, retrospective	1.00	
	Observational, prospective	2.62 (1.38, 4.99)	0.004
	Clinical trial	2.02 (1.06, 3.88)	0.034
Study setting	Tertiary, primary or community clinic	1.00	
	Drug treatment service	1.74 (0.84, 3.63)	0.136
	Prison	1.74 (0.48, 6.29)	0.392
	Mixed setting	0.82 (0.39, 1.70)	0.584
HCV treatment	IFN-based therapy	1.00	
	DAA therapy	0.79 (0.44, 1.42)	0.426
Study population			
	OAT: yes, DU: no	1.00	
	OAT: yes, DU: unknown	1.80 (0.37, 8.82)	0.463
	OAT: yes, DU: yes	4.00 (1.58, 10.15)	0.004
	OAT: unknown, DU: yes	3.96 (1.47, 10.66)	0.007
	OAT: no DU: yes	4.53 (1.72, 11.97)	0.003
Median/mean follow-up, per year increase		0.87 (0.76, 0.99)	0.031
Start point for reinfection assessment			
	SVR12 or later	1.00	
	End of treatment	1.39 (0.78, 2.51)	0.260

Results – Meta-regression

		Adjusted models	
		Rate Ratio (95% CI)	P
Median/mean age, per year increase		0.94 (0.91, 0.97)	<0.001
Study design	Observational, retrospective	1.00	
	Observational, prospective	1.36 (0.77, 2.43)	0.287
	Clinical trial	1.29 (0.74, 2.25)	0.358
Study population			
	OAT: yes, DU: no	1.00	
	OAT: yes, DU: unknown	1.15 (0.27, 4.88)	0.846
	OAT: yes, DU: yes	3.47 (1.61, 7.45)	0.002
	OAT: unknown, DU: yes	5.65 (2.52, 12.69)	<0.001
	OAT: no DU: yes	3.95 (1.82, 8.58)	0.001
Median/mean follow-up, per year increase		0.77 (0.69, 0.86)	<0.001

Residual I-square = 20.6%

Conclusion

- Post-treatment HCV reinfection rate was associated with recent drug use/OAT status, with the highest rate identified among people with recent drug use, not receiving OAT.
- Lower rate in studies with longer follow-up suggested higher risk of reinfection early post-treatment (or cohort effect?).
- Harm reduction services are required to reduce the reinfection risk while regular post-treatment HCV assessment is required to detect and treat reinfection early.

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