Efficacy of response-guided pegylated interferon and ribavirin therapy for people who inject drugs with HCV genotype 2/3 infection: the ACTIVATE study

Jason Grebely[1], Olav Dalgard[2], Brian Conway[3], Graham Foster[4], Philip Bruggmann[5], Markus Backmund[6], Geert Robaeys[7, 8, 9], Tracy Swan[10], Behzad Hajarizadeh[1], Evan Cunningham[1], Janaki Amin[1], Phillipa Marks[1], Sophie Quiene[1], Martin Weltman[11], David Shaw[12], Adrian Dunlop[13], Margaret Hellard[14], Julie Bruneau[15], Stefan Bourgeois[16], Christine Thurnheer[17], and Gregory J. Dore[1] on behalf of the ACTIVATE Study Group

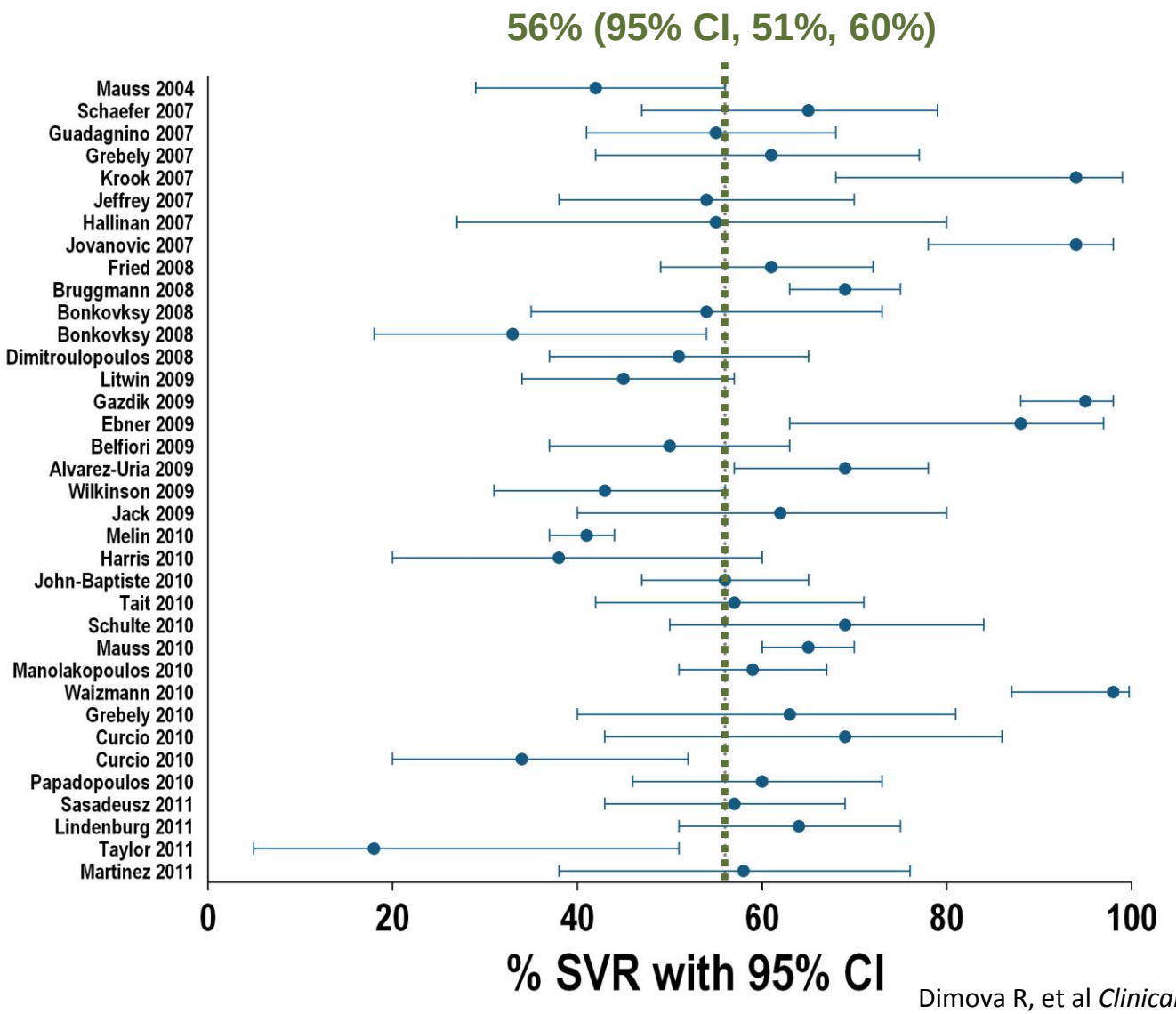
[1]The Kirby Institute, UNSW Australia, Sydney, Australia, [2]Akershus University Hospital, Oslo, Norway, [3]Vancouver Infectious Diseases Center, Vancouver, Canada, [4]The Liver Unit, Queen Marys University of London, London, United Kingdom, [5]Arud Centres for Addiction Medicine, Zurich, Switzerland, [6]Ludwig-Maximilians-University Munich , Munich, Germany, [7]Department of Gastroenterology and Hepatology, Ziekenhuis Oost Limburg, Genk, [8]Department of Hepatology, UZLeuven, Leuven, [9]UHasselt, Hasselt, Belgium, [10]Treatment Action Group, New York, United States, [11]Nepean Hospital, Sydney, [12]Royal Adelaide Hospital, Adelaide, [13]School of Medicine and Public Health, University of Newcastle, Newcastle, 14Burnet Institute, Melbourne, Australia, [15]Universite de Montreal, Montreal, Canada, [16]Stuivenberg ZNA, Antwerp, Belgium, [17]Division of Infectious Diseases, University Hospital and University of Bern, Bern, Switzerland

HCV therapeutic evaluation among PWID

Issues

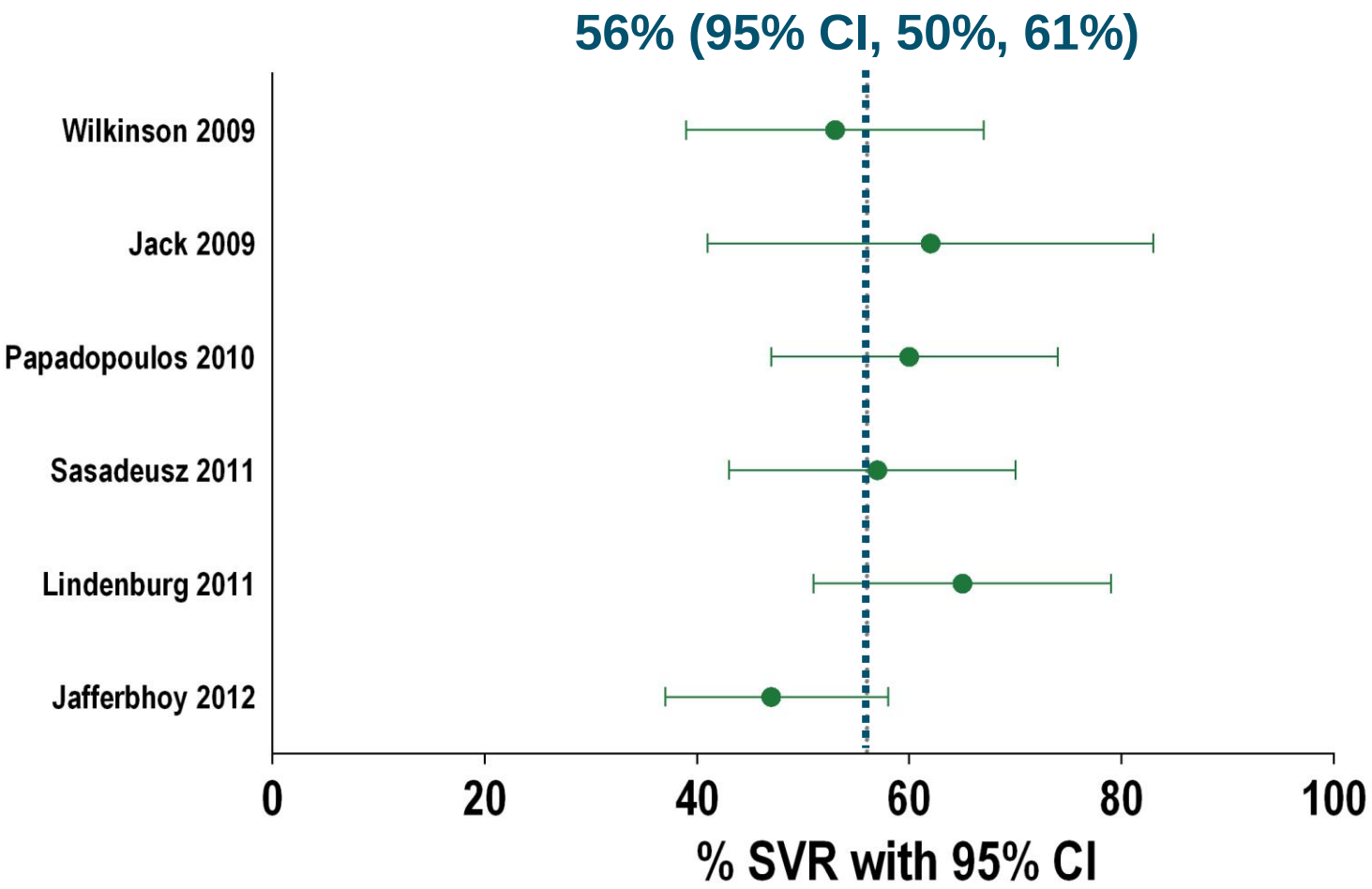
- PWID initially excluded from HCV treatment guidelines
- Ongoing concern from some HCV clinicians, re safety, efficacy (including re-infection), and competing morbidity
- Increasing evidence of favorable HCV treatment outcomes, from observational studies, although heterogeneous and small
- Exclusion of PWID from HCV phase II/III protocols
- Need for PWID-specific HCV therapeutic evaluation

Treatment outcomes: History of injecting - PEG-IFN/RBV



Dimova R, et al *Clinical Infectious Diseases* 2013

Treatment outcomes: Active injecting - PEG-IFN/RBV



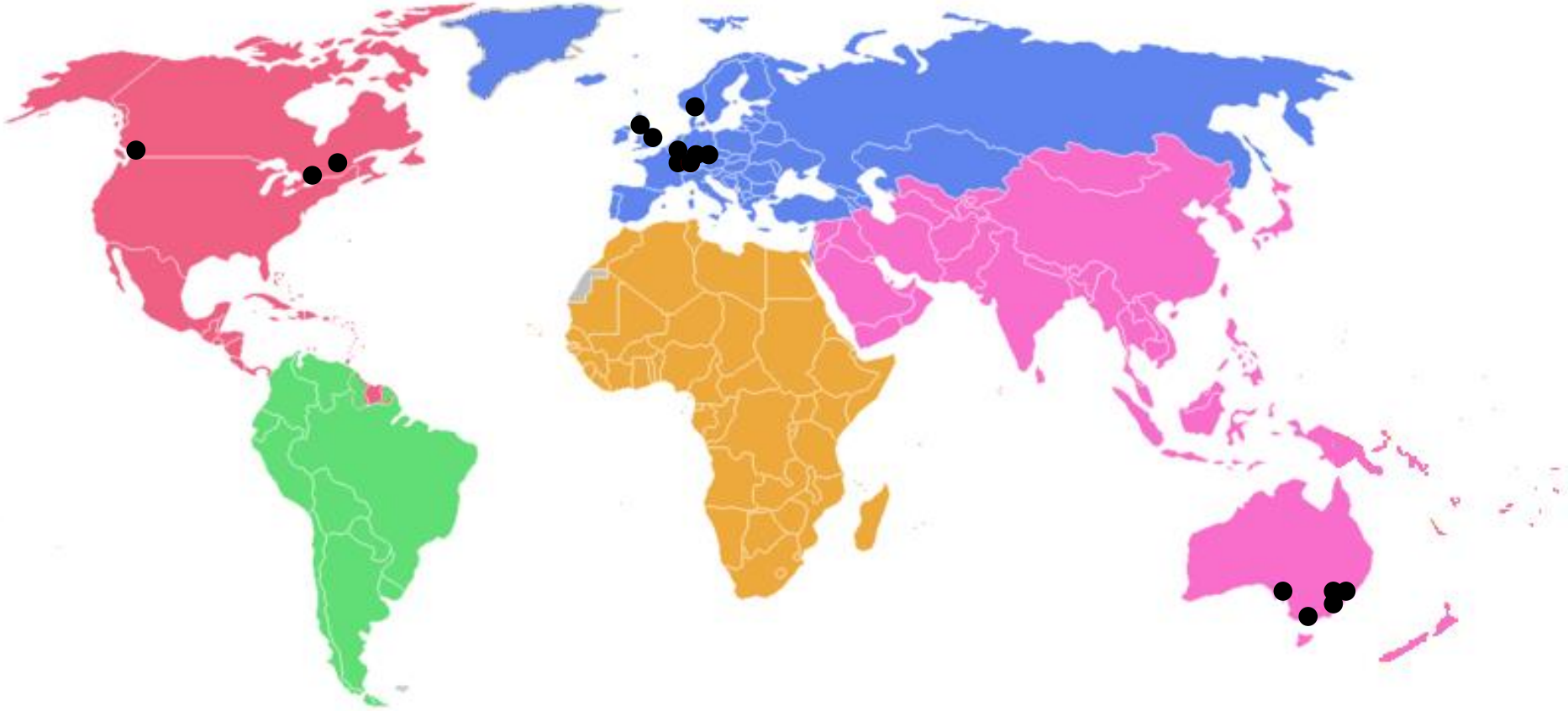
Aspinall E, et al *Clinical Infectious Diseases* 2013

ACTIVATE study: Aims

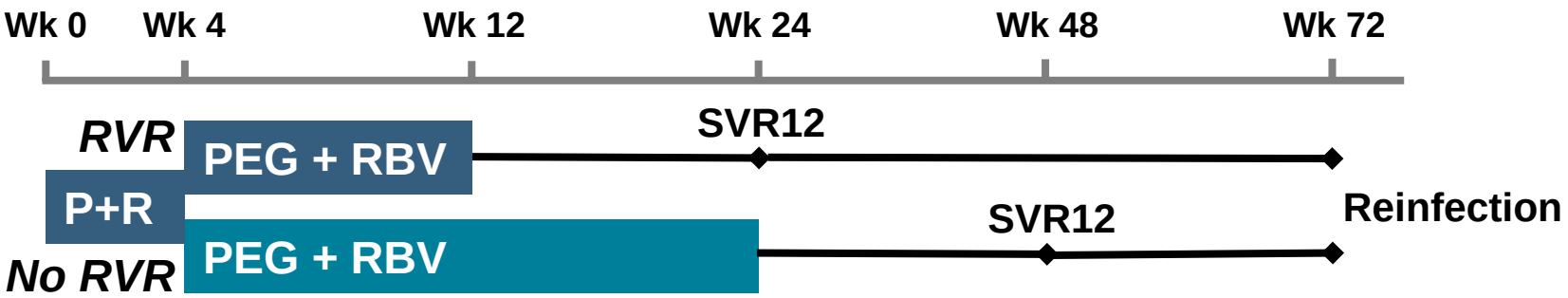
- To establish an international network to evaluate HCV therapy among PWID
- To evaluate safety and efficacy of PEG-IFN-alfa2b and RBV for treatment of chronic HCV genotype 2/3 among active PWID and those receiving opioid substitution therapy
- To evaluate shortened therapy (12 weeks) for individuals with a rapid virological response

ACTIVATE study: Participants

- 17 sites, 7 countries
- Participants recruited between May 2012 and Sept 2014



ACTIVATE study: Design



Inclusion criteria

- Chronic GT 2/3 HCV treatment naïve patients
- Active injection drug use (defined as injection drug use within the 24 weeks prior to consent) OR currently receiving opioid substitution therapy
- Compensated liver disease (Child-Pugh class A)
- 93 participants initiated therapy

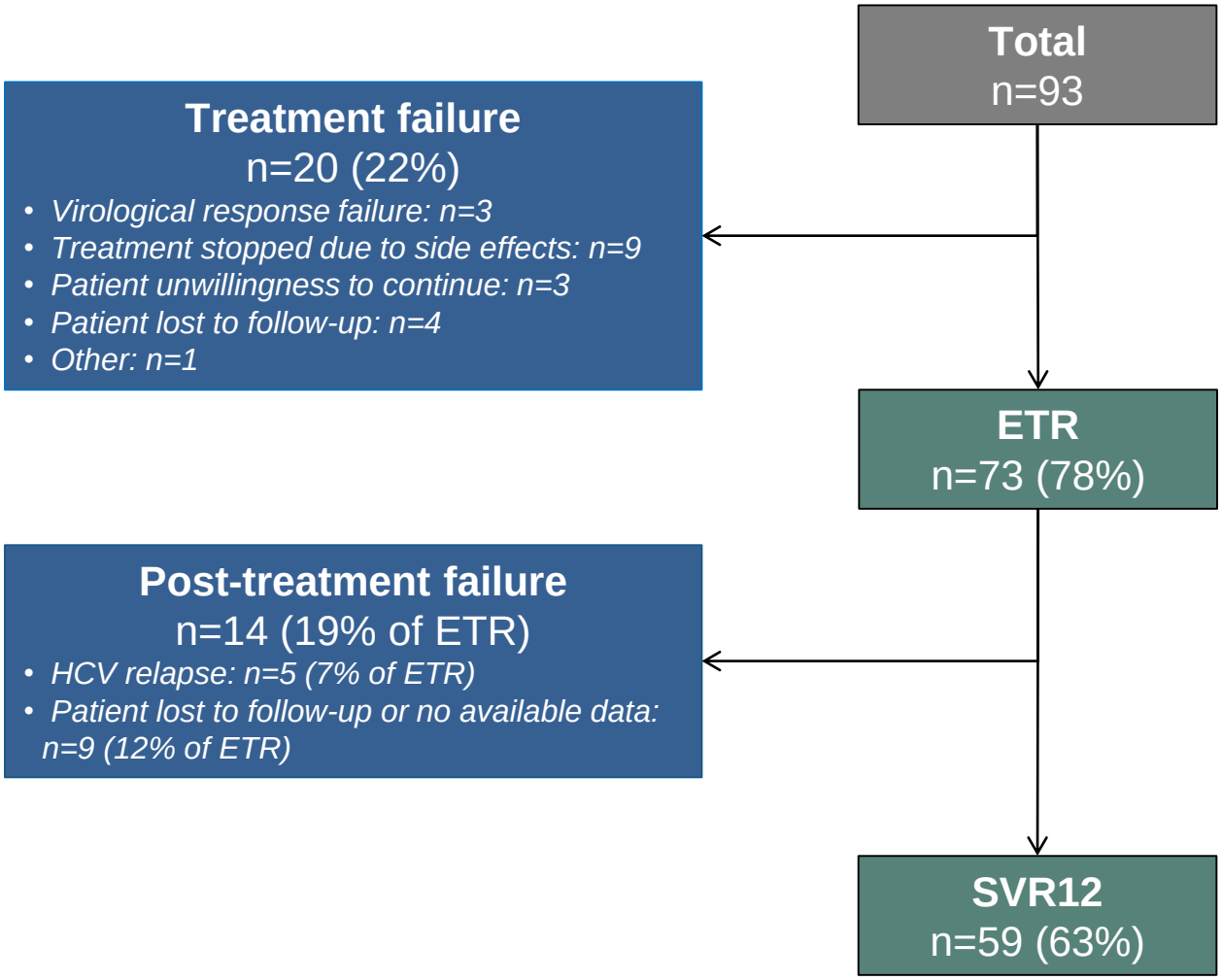
ACTIVATE study: Endpoints and Analysis

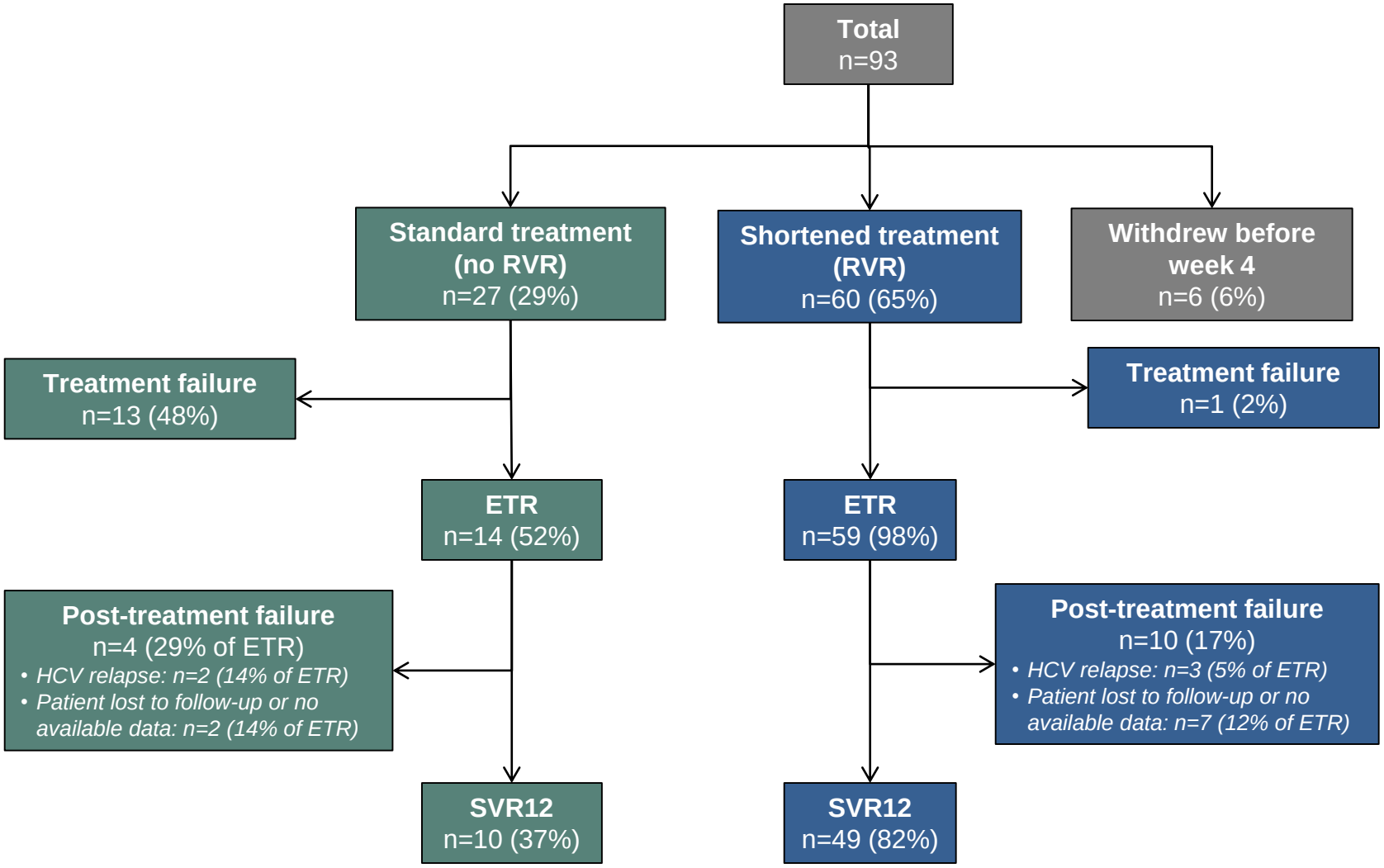
- SVR was the primary efficacy endpoint (intent-to-treat)
  - HCV RNA undetectable at post-treatment week 12
- Questionnaires were administered to obtain information on injecting drug use risk behaviours
- Detailed information on adverse events
- Logistic regression analyses used to identify predictors of SVR

ACTIVATE study: Baseline characteristics

	PEG-IFN/RBV N=93
Mean age, year ± SD	42 ± 9
Male, n (%)	77 (83)
Caucasian ethnicity, n (%)	84 (90)
Privately owned or rented accommodation, n (%)	71 (74)
Opioid Substitution Therapy (OST)	
OST with no injecting in the previous 12 weeks	23 (25)
OST with injecting in the previous 12	16 (17)
No OST	54 (58)
Recent injecting	
Injecting in the previous month (4 weeks)	57 (61)
Injecting in the previous 4-12 weeks	13 (14)
No injecting in the previous 12 weeks	23 (25)
HCV genotype at screening	
Genotype 2	11 (12)
Genotype 3	82 (88)
HCV RNA levels at screening, log IU/mL, median (IQR)	6.0 (5.3, 6.7)

ACTIVATE study: Disposition and Outcomes




Total
n=93
Standard treatment (no RVR)
n=27 (29%)
Shortened treatment (RVR)
n=60 (65%)
Withdrew before week 4
n=6 (6%)
Treatment failure
n=13 (48%)
Treatment failure
n=1 (2%)
ETR
n=14 (52%)
ETR
n=59 (98%)
Post-treatment failure
n=4 (29% of ETR)
• HCV relapse: n=2 (14% of ETR)
• Patient lost to follow-up or no available data: n=2 (14% of ETR)
Post-treatment failure
n=10 (17%)
• HCV relapse: n=3 (5% of ETR)
• Patient lost to follow-up or no available data: n=7 (12% of ETR)
SVR12
n=10 (37%)
SVR12
n=49 (82%)

Predictors of SVR in those reaching W4 (n=87)

	Number with SVR12 (%)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age, year	-	0.98 (0.93, 1.03)	0.41	-	-
Gender				-	-
Female	11 (73)	1.00	-		
Male	48 (67)	0.73 (0.21, 2.52)	0.62		
OST and recent injecting					
OST	23 (68)	1.00	-	-	-
No OST, injecting in the past 4-12 weeks	6 (86)	2.87 (0.31, 26.84)	0.35	-	
No OST, injecting in the past month	30 (65)	0.90 (0.35, 2.30)	0.82	-	
HCV genotype at screening				-	-
Genotype 2	6 (75)	1.00	-		
Genotype 3	53 (67)	0.68 (0.12, 3.60)	0.65		
HCV RNA levels at screening, log IU/mL	-	0.82 (0.53, 1.26)	0.36	-	-
Rapid Virologic Response (RVR)					
No RVR (Standard treatment)	10 (37)	1.00	-	1.00	-
RVR (Shortened treatment)	49 (82)	7.57 (2.73, 20.97)	<0.01	9.02 (2.94, 27.70)	<0.01

Conclusions

- Among PWID with chronic HCV genotypes 2/3, SVR12 was 63%
  - SVR12 was 82% in those with an RVR and 37% in those who did not achieve an RVR

- On-treatment RVR was a strong predictor of SVR in patients receiving a 12 week course of PEG-IFN/RBV therapy

- The response to therapy was similar among people receiving OST and those with active injecting drug use

- Support for HCV treatment in active PWID and the use of innovative shorter therapies in this context

ACTIVATE network: Future directions

- **SIMPLIFY (Gilead) :** Phase IV study of SOF/VEL in PWID
  - n=100; pangenotypic; treatment naive
  - on OST +/- active injecting drug use
  - 21 sites

- **D3FEAT (Abbvie):** Phase IV study of PTV/OBV/DBV/RBV in PWID
  - n=100; genotype 1; treatment naïve
  - on OST +/- active injecting drug use
  - 20 sites

Acknowledgements

Project Steering Committee

- **Professor Greg Dore :** Kirby Institute, UNSW Australia
- **A/Professor Jason Grebely :** Kirby Institute, UNSW Australia
- **Ms Pip Marks :** Kirby Institute, UNSW Australia
- **Professor Olav Dalgard :** Akershus University, Oslo Norway
- **Dr Philip Bruggmann :** ARUD, Zurich Switzerland
- **Dr Geert Robaeys :** MSOC, Genk Belgium
- **Ms Tracy Swan :** Treatment Action Group, USA
- **Dr Markus Backmund :** Praxiszentrum im Tal, Munich Germany
- **Professor Brian Conway :** VIDC, Vancouver Canada
- **Professor Graham Foster :** East London NHS Trust, London UK
- **Ms Sophie Quiene :** Kirby Institute, UNSW Australia

Acknowledgements

Site Principle Investigators

- **Professor Olav Dalgard :** Akershus University Hospital, Oslo
- **Professor Greg Dore :** St Vincent's Hospital, Sydney
- **Professor Margaret Hellard :** The Alfred Hospital, Melbourne
- **A/Professor Adrian Dunlop :** Hunter Pharmacotherapy, Newcastle
- **Professor Graham Foster :** The Blizard Institute, London
- **A/Professor David Shaw :** Royal Adelaide Hospital, Adelaide
- **Professor Julie Bruneau :** CHUM, Montreal
- **Dr Jeff Powis :** South Riverdale Community Health Centre, Toronto
- **Professor Martin Weltman :** Nepean Hospital, Nepean
- **Dr Maria Christine Thurnheer & Dr Cornelia Staehelin :** Inselspital, Bern
- **Dr Geert Robaeys :** Ziekenhuis Oost Limburg, Genk
- **Dr Markus Backmund :** PIT, Munich
- **Professor Brian Conway :** VIDC, Vancouver Canada
- **Dr Philip Bruggmann :** ARUD, Zurich
- **Dr Stephen Ryder :** Queen's Medical Centre Campus, Nottingham
- **Dr Stefan Bourgeois :** Stuievenberg, Antwerp
- **Dr Claude Sheidegger :** Zentrum for Suchtmedizin, Basel

Acknowledgements

Site Study Coordinators

- **Ms Jessica Andreassen :** Akershus University Hospital, Oslo
- **Ms Alison Sevehon :** St Vincent's Hospital, Sydney
- **Ms Sally von Bibra :** The Alfred Hospital, Melbourne
- **Ms Susan Hazelwood :** Hunter Pharmacotherapy, Newcastle
- **Mr David Axten :** The Blizard Institute, London
- **Ms Catherine Ferguson :** Royal Adelaide Hospital, Adelaide
- **Ms Barbara Kostoros :** CHUM, Montreal
- **Ms Kate Mason :** South Riverdale Community Health Centre, Toronto
- **Mr Vincenzo Fragomelli :** Nepean Hospital, Nepean
- **Ms Melanie Lacalamita :** Inselspital, Bern
- **Ms Anita Eevers :** Ziekenhuis Oost Limburg, Genk
- **Ms Nicole Widder :** PIT, Munich
- **Mr Shawn Sharma :** VIDC, Vancouver Canada
- **Ms Tina Horschik:** ARUD, Zurich
- **Ms Kate Jack :** Queen's Medical Centre Campus, Nottingham
- **Mr Kristof Lesneuck:** Stuievenberg, Antwerp
- **Ms Christine Huber :** Zentrum for Suchtmedizin, Basel