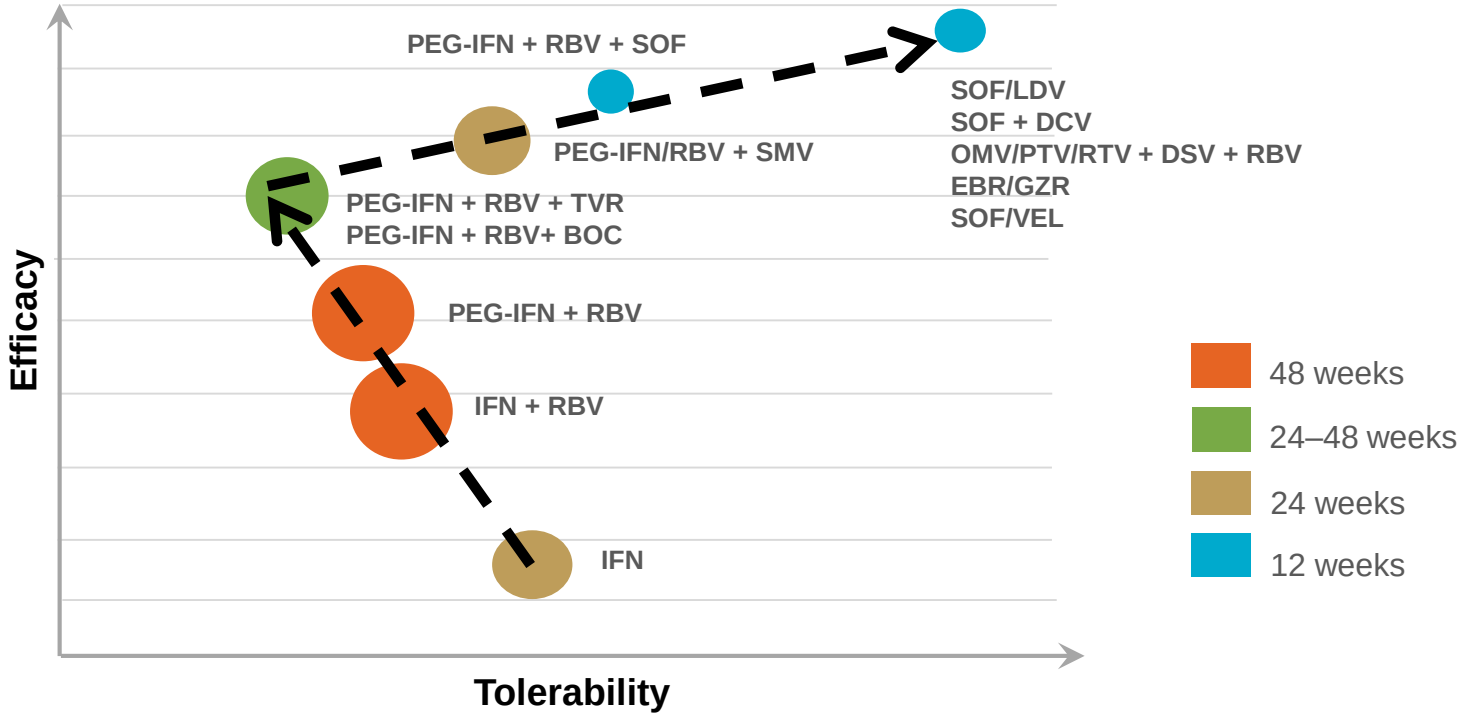
Shorter Durations and Pan-genotypic Regimens
The Final Frontier

Professor Greg Dore

Disclosures

- Funding and speaker fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences and Merck

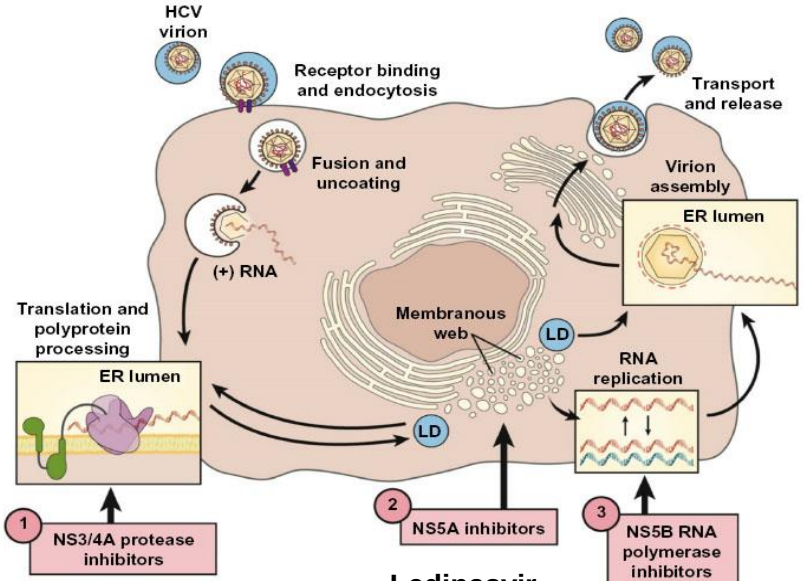
Evolution of HCV therapies



BOC: boceprevir DCV: daclatasvir; DSV: dasabuvir; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; OMV: ombitasvir;
PEG-IFN: pegylated interferon; PTV: paritaprevir; RBV: ribavirin; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir; VEL: velpatasvir

Adapted from Dore G, Feld JJ. Clin Infect Dis 2015;60:1829–36

DAA agents: licensed and in development



Simeprevir
Paritaprevir
Grazoprevir
Voxilaprevir
Glecaprevir

Ledipasvir
Daclatasvir
Ombitasvir
Elbasvir
Velpatasvir
Pibrentasvir
Ruzasvir

Sofosbuvir
Dasabuvir
Uprifosbuvir

In pursuit of *Perfectovir*

- Extremely high efficacy (>95%)
- No impact of resistance-associated substitutions
- Pan-genotypic
- Tolerance similar to placebo
- Simplified assessment and monitoring
- Ease of delivery (once daily, oral, short duration)
- Affordable!

Dore GJ & Feld JJ. CID 2015

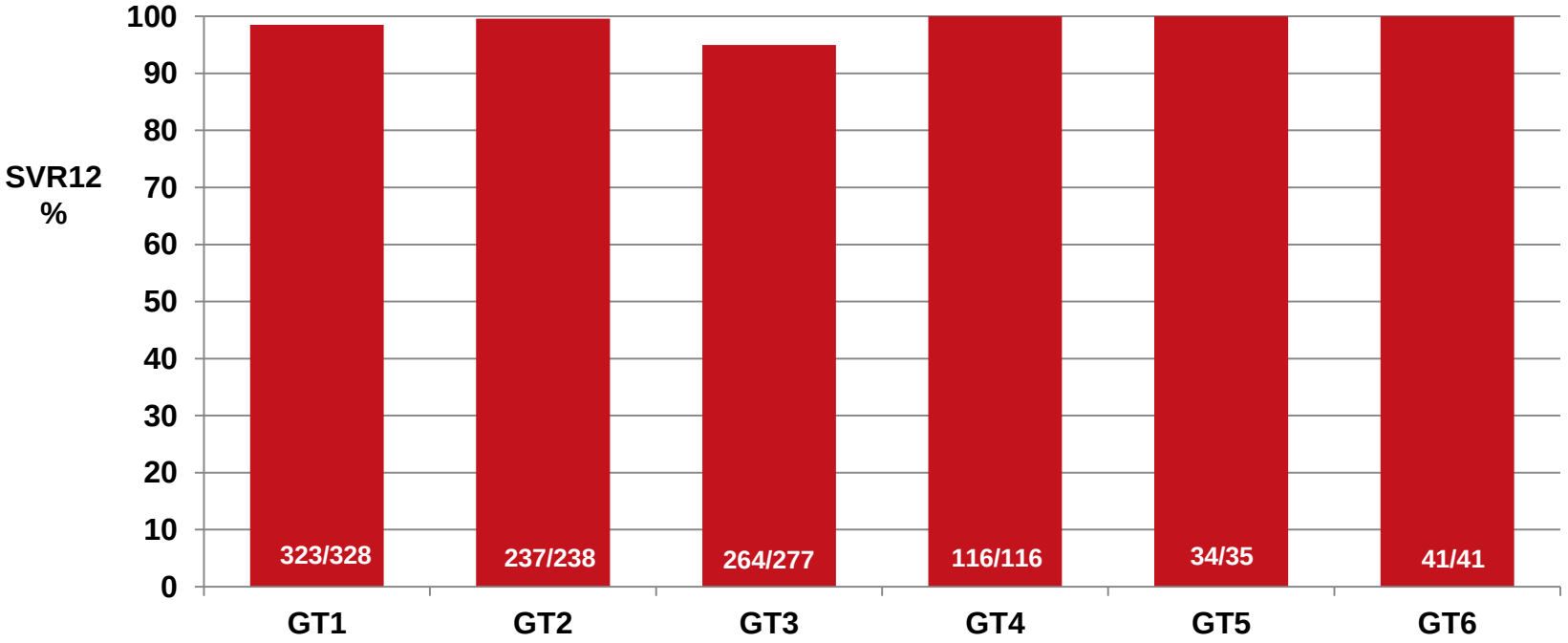
In pursuit of *Perfectovir*

- Extremely high efficacy (>95%)
- No impact of resistance-associated substitutions
- **Pan-genotypic**
- Tolerance similar to placebo
- Simplified assessment and monitoring
- Ease of delivery (once daily, oral, **short duration**)
- Affordable!

Dore GJ & Feld JJ. CID 2015

Sofosbuvir/Velpatasvir

GT1-6, treatment naïve and IFN exp. (28%), F0-4 (21% F4), 12 wks



Feld JJ, et al. NEJM 2015; Foster GR, et al. NEJM 2015

Sofosbuvir/Velpatasvir

Adverse Events >10%

Patients, n (%)	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116
Headache	296 (29)	33 (28)
Fatigue	217 (21)	23 (20)
Nausea	135 (13)	13 (11)
Insomnia	87 (8)	11 (9)
Nasopharyngitis	121 (12)	12 (10)
Cough	57 (6)	4 (3)
Irritability	49 (5)	4 (3)
Pruritus	33 (3)	5 (4)
Dyspepsia	33 (2)	4 (3)

Jacobson I et al, ILC 2016

In pursuit of *Perfectovir*

- Extremely high efficacy (>95%) ✓
- Incredibly well tolerated (similar to placebo) ✓
- Pan-genotypic ✓
- No significant impact of resistance-associated substitutions ✓
- Simplified assessment and monitoring ✓
- Ease of delivery (once daily, oral, short duration) ✓
- Affordable! ✗

Dore GJ & Feld JJ. CID 2015

Is the pursuit of shorter duration DAA therapy a major priority for Global HCV Elimination?

Potential Pros and Cons of Shorter Duration

	SOF/VEL (12 weeks)	Shorter Duration (4-8 weeks)

Potential Pros and Cons of Shorter Duration

	SOF/VEL (12 weeks)	Shorter Duration (4-8 weeks)
Covers all major sub-populations	YES	Unlikely

Potential Pros and Cons of Shorter Duration

	SOF/VEL (12 weeks)	Shorter Duration (4-8 weeks)
Covers all major sub-populations	YES	Unlikely
Simplicity	HIGH	Lower

Potential Pros and Cons of Shorter Duration

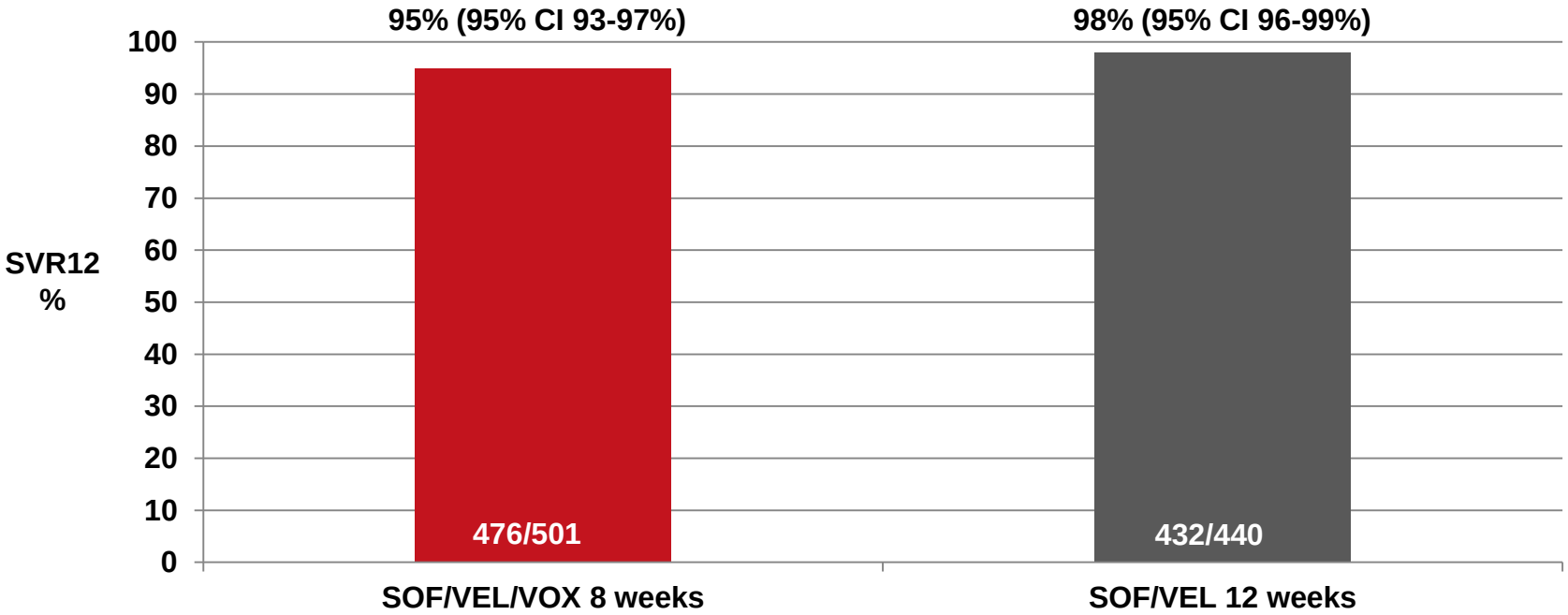
	SOF/VEL (12 weeks)	Shorter Duration (4-8 weeks)
Covers all major sub-populations	YES	Unlikely
Simplicity	HIGH	Lower
Toxicity	MINIMAL	May be increased or decreased

Potential Pros and Cons of Shorter Duration

	SOF/VEL (12 weeks)	Shorter Duration (4-8 weeks)
Covers all major sub-populations	YES	Unlikely
Simplicity	HIGH	Lower
Toxicity	MINIMAL	May be increased or decreased
Non-adherence “Forgiveness”	Probably HIGH	May be lower

Sofosbuvir/Velpatasvir/Voxilaprevir

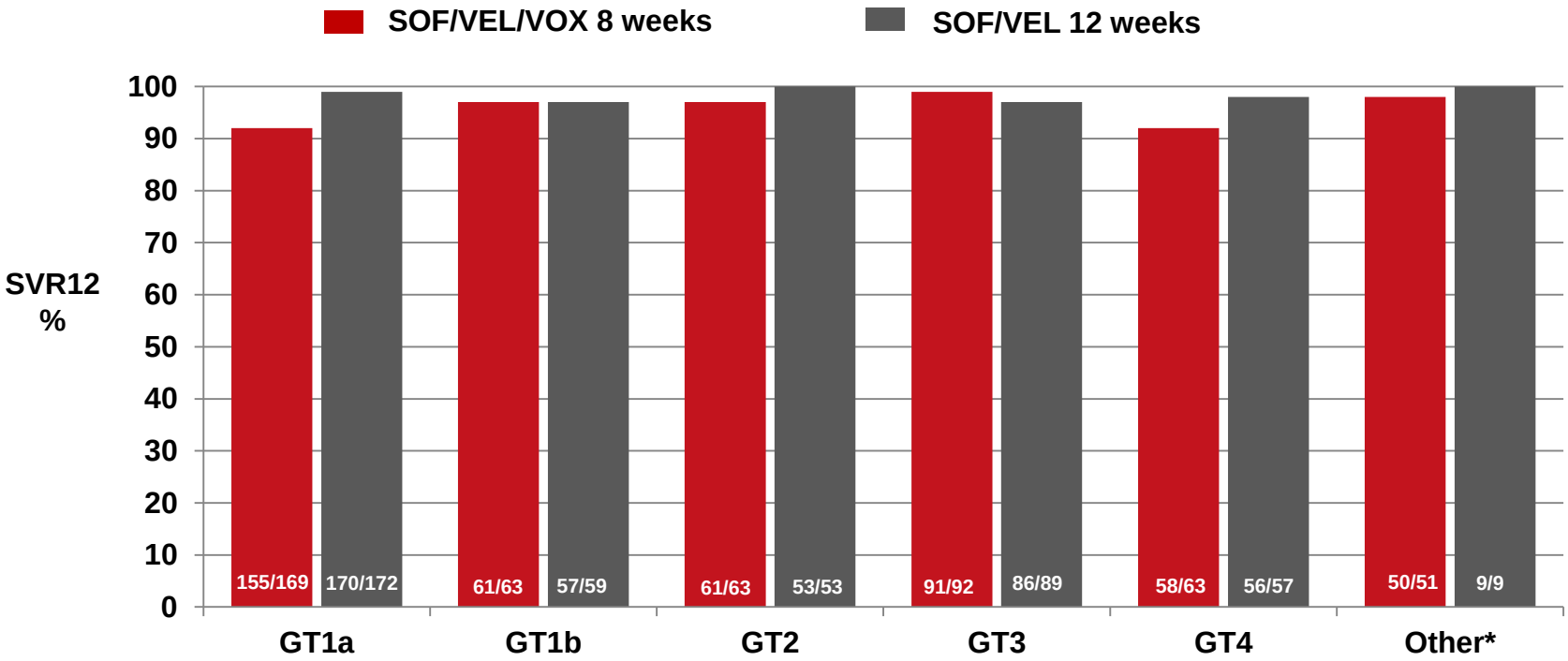
POLARIS 2: GT1-6, DAA naive, F0-4 (18% F4, 0% GT3), 8 weeks



Jacobson IM, et al. Gastroenterology 2017

Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS 2: GT1-6, DAA naive, F0-4 (18% F4, 0% GT3), 8 weeks



* 2 Other GT1, 18 GT5, 39 GT6 (9/9 SOF/VEL)

Jacobson IM, et al. Gastroenterology 2017

Sofosbuvir/Velpatasvir/Voxilaprevir

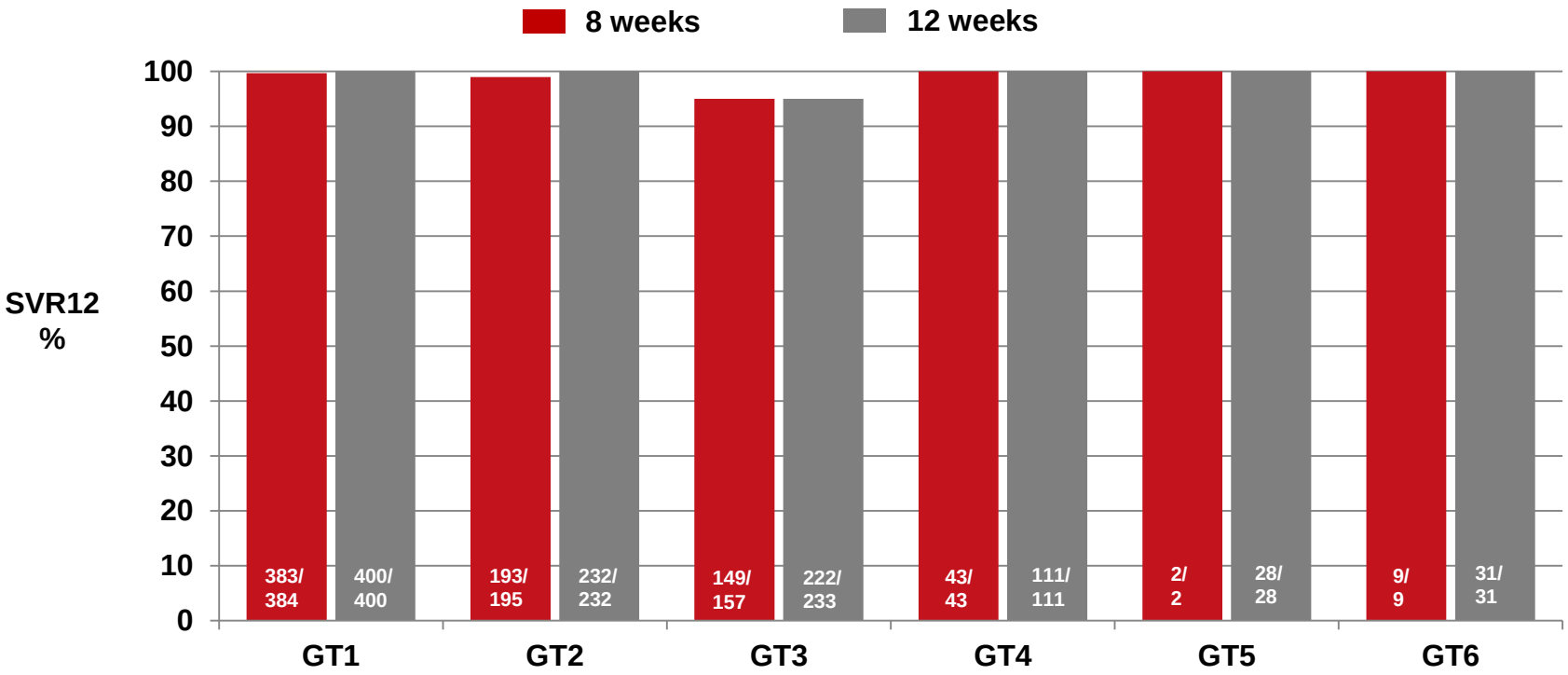
POLARIS 2: Adverse Events >10%

Patients, n (%)	SOF/VEL/VOX 8 Week N=501	SOF/VEL 12 Week N=440
Headache	134 (27)	99 (23)
Fatigue	106 (21)	90 (20)
Diarrhea	**88 (18)**	**32 (7)**
Nausea	**80 (16)**	**40 (9)**
Any Adverse Event	361 (72)	303 (69)
Serious Adverse Events	15 (3)	7 (2)

Jacobson IM, et al. Gastroenterology 2017

Glecaprevir/Pibrentasvir

GT1-6, treatment naïve, F0-3, 8 and 12 weeks in Phase II/III trials



Kwo P, J Hepatology 2017; Zeuzem S, AASLD 2016; Kowdley K, AASLD 2016; Asselah T, AASLD 2016; Gane E, AASLD 2016; Foster G, ILC 2017

Glecaprevir/Pibrentasvir

ENDURANCE 2: Adverse Events

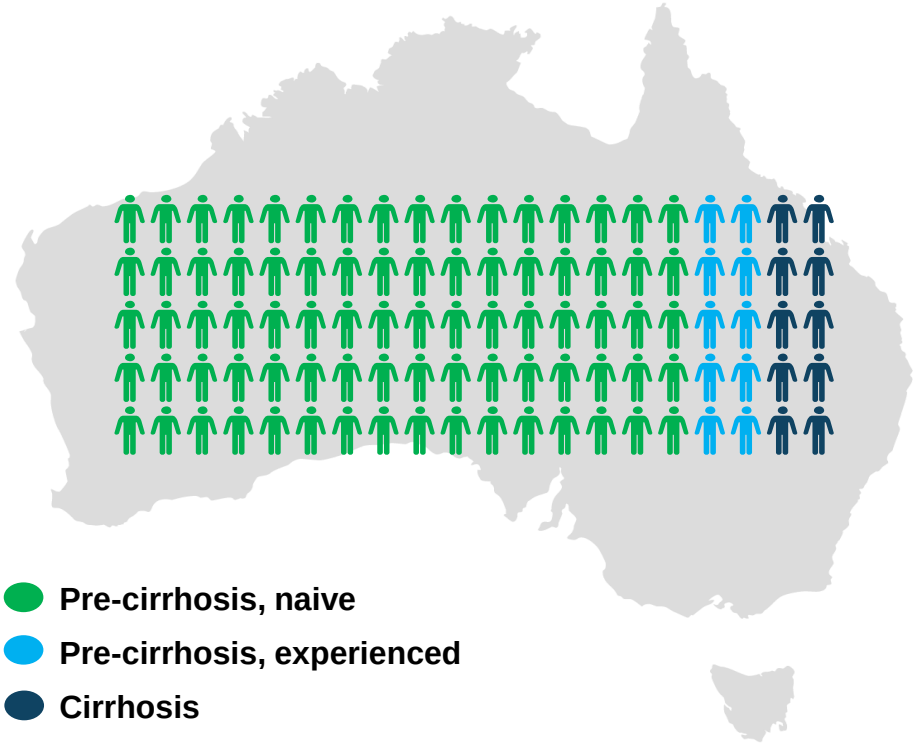
Patients, n (%)	GLE/PIB 12 Week N=202	Placebo 12 Week N=100
Headache	24 (12)	12 (12)
Fatigue	23 (11)	10 (10)
Any Adverse Event	131 (65)	58 (58)
Serious Adverse Events	3 (1)	1 (1)
ALT (>3xULN)	1 (0.5)	8 (8)
Bilirubin (3-10xULN)	1 (0.5)	0 (0)

Kowdley KV, et al. AASLD 2016

HCV care cascade in Australia: end 2015

230,000

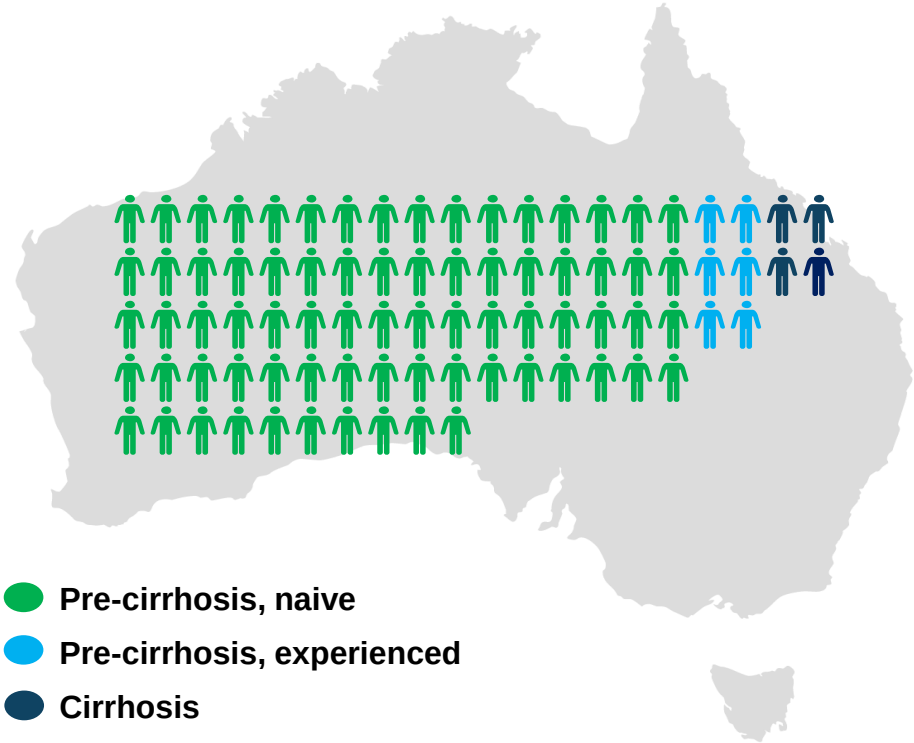
Australians live with chronic HCV infection



HCV care cascade in Australia: end 2016

200,000

Australians live with chronic HCV infection

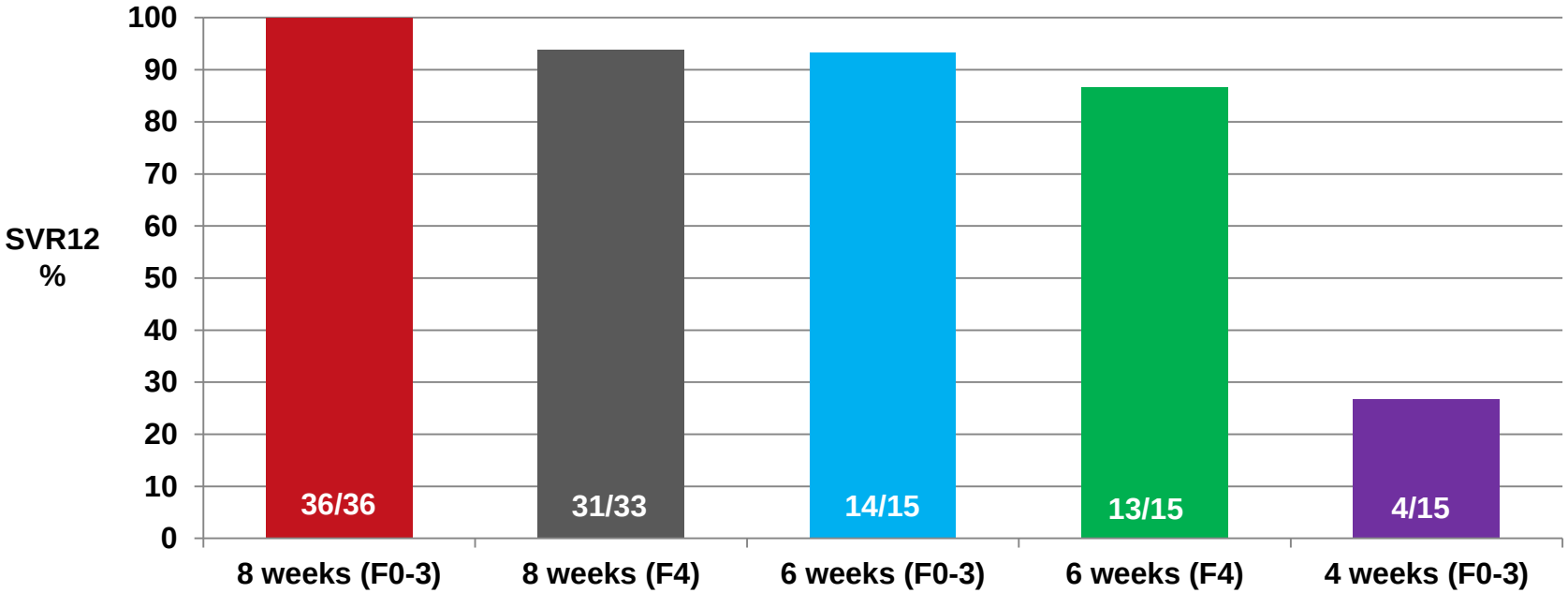


Where would shorter durations (4-6 weeks) help?

- Prisons, particularly remand and medium security settings
- Inpatient HCV treatment (e.g. PWID with infectious complications of injecting)
- Needle Syringe Program – based treatment for PWID
- Acute HCV, including treatment of HCV reinfection
- When cost-effectiveness significantly enhanced (including generic LMIC settings)

Sofosbuvir/Velpatasvir/Voxilaprevir

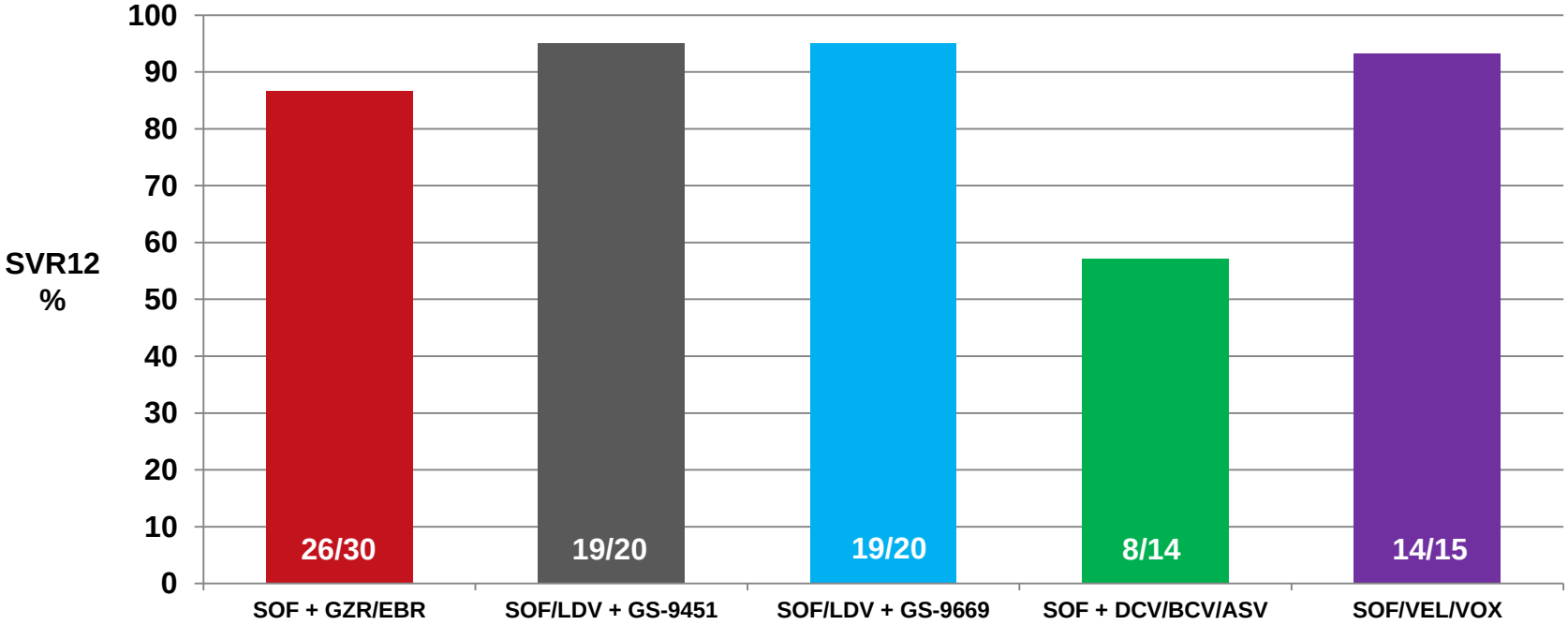
GT1, treatment naïve, F0-4, 4-8 weeks



Gane E, et al. Gastroenterology 2016

DAA regimens for 6 weeks

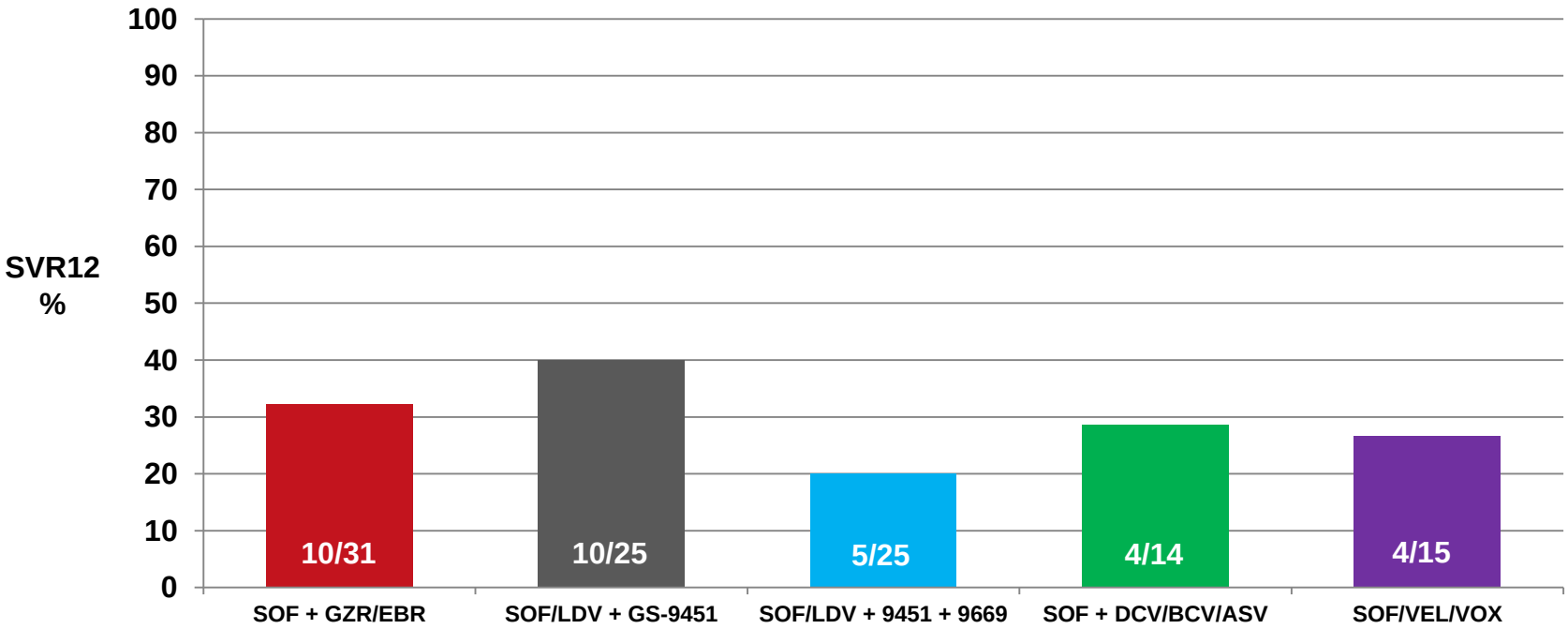
GT1, treatment naïve, F0-3



Lawitz E, et al. Hepatology 2017; Kohli A, et al. AIM 2015; Sulkowski M,et al. Liver Inter 2016; Gane E, et al. Gastroenterology 2016

DAA regimens for 4 weeks

GT1, treatment naïve, F0-3



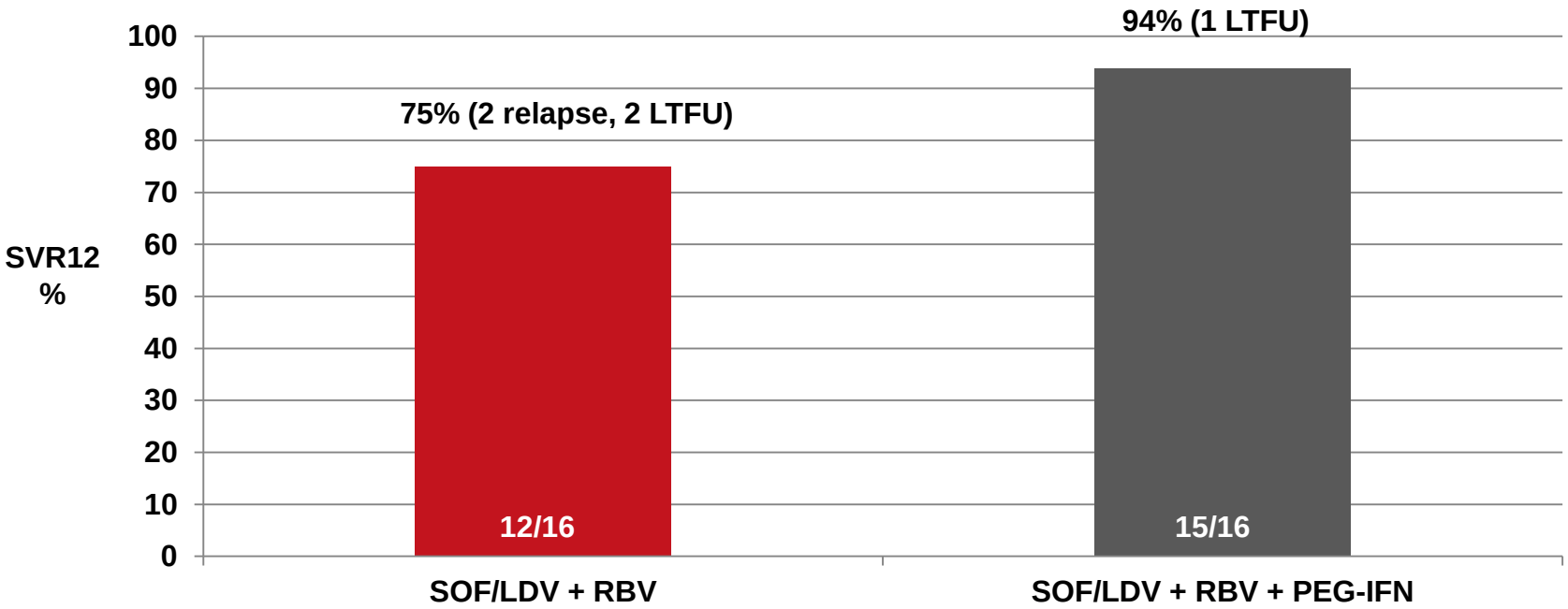
Lawitz E, et al. Hepatology 2017; Kohli A, et al. AIM 2015; Sulkowski M,et al. Liver Inter 2016; Gane E, et al. Gastroenterology 2016

Future short duration studies

- Favourable sub-populations (F0-2, younger age, genotype/subtype): current DAA regimens
- Strategy studies: response-guided
- Acute/recent HCV
- New DAA combinations: SOF + GLE/PIB
- DAA + other classes: DAAs + long-acting non-oral agent

DAA regimens for 4 weeks

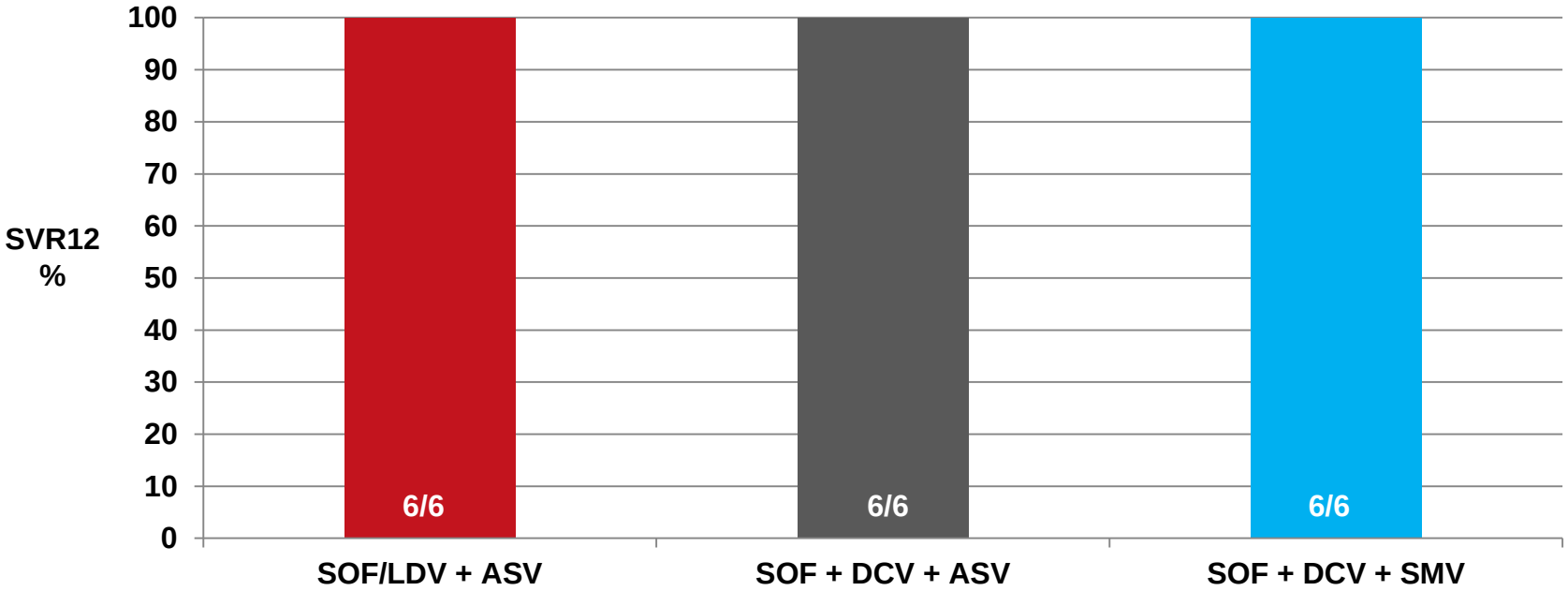
GT1-3, treatment naive, F0-1, RNA <2 million, <50 years (mean, 39 years), PWUD



Karup, et al. ILC 2017

Ultra-short DAA therapy: response-guided 3 weeks

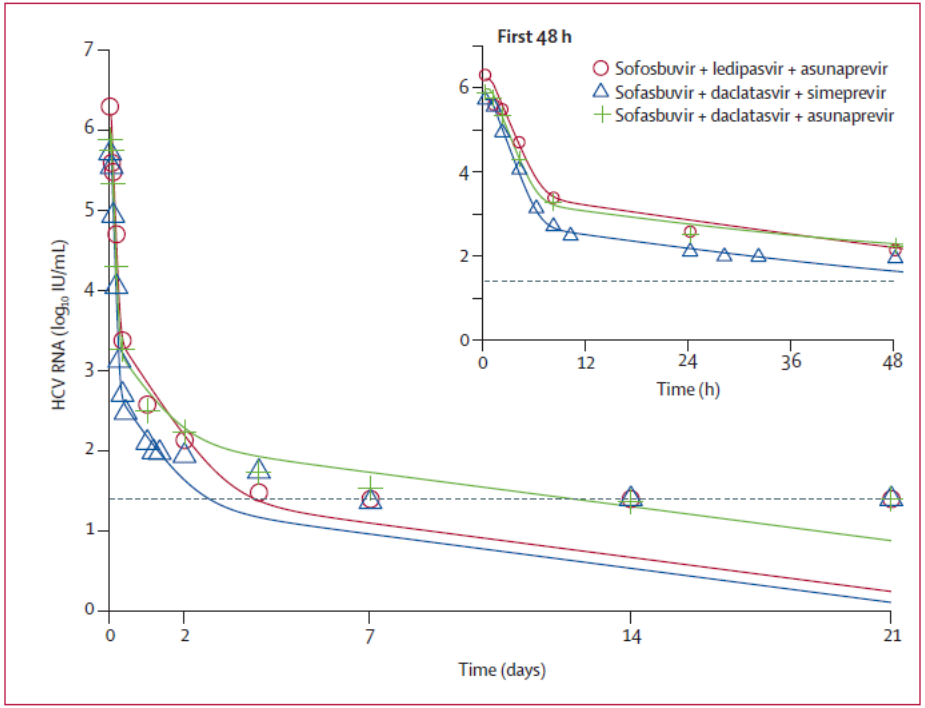
GT1b, treatment naive, F0-2, mean age 31-41 years, RNA<500 IU/mL day 2 (18/26)



Lau G, et al. Lancet Gastro Hepatol 2016

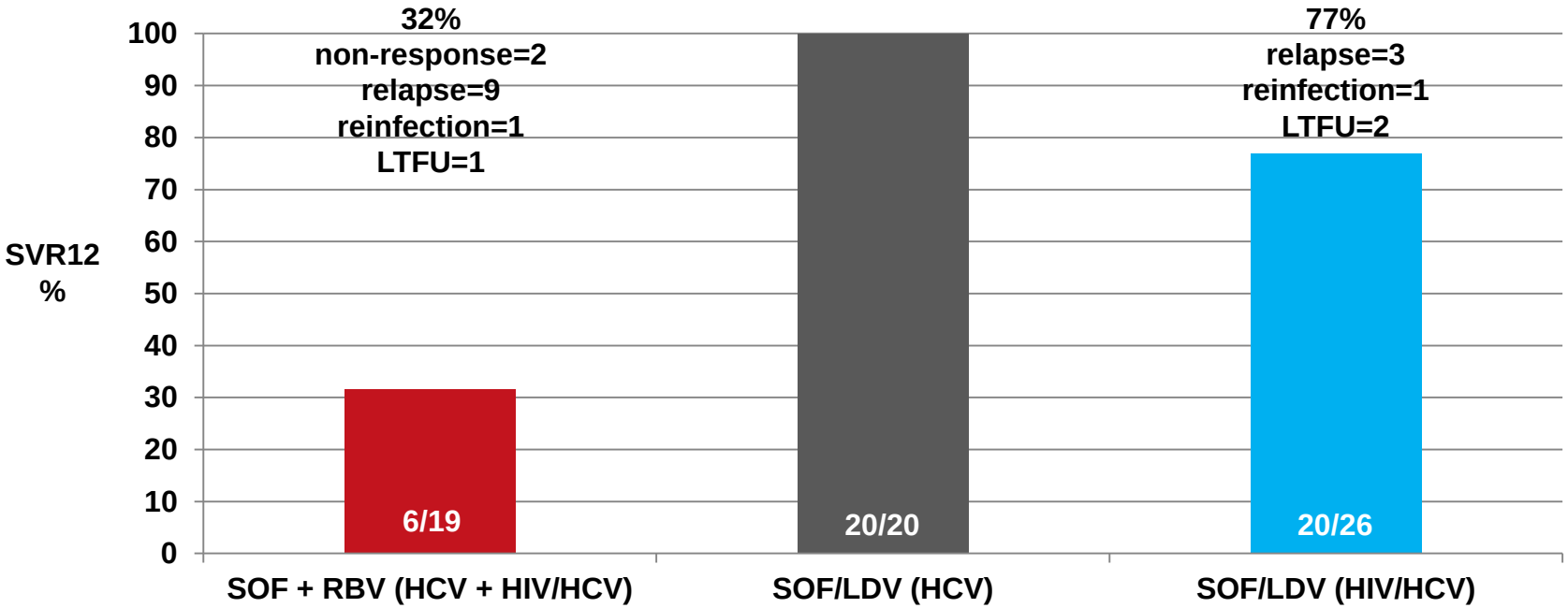
Ultra-short DAA therapy: response-guided 3 weeks

GT1b, treatment naive, F0-2, mean age 31-41 years, RNA<500 IU/mL day 2 (18/26)



Lau G, et al. Lancet Gastro Hepatol 2016

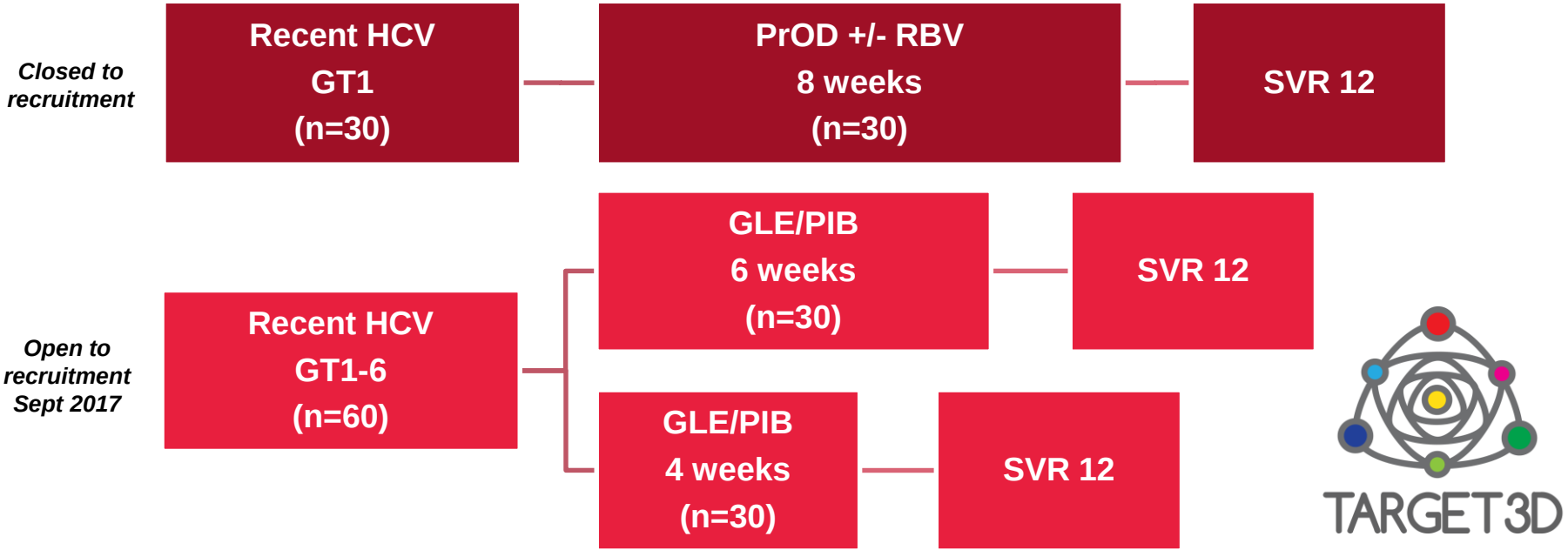
Acute/recent HCV: DAA regimens 6 weeks



Martinello et al. Hepatology 2016; Deterding et al. Lancet ID 2016; Rockstroh et al. Lancet Gastro Hep 2017

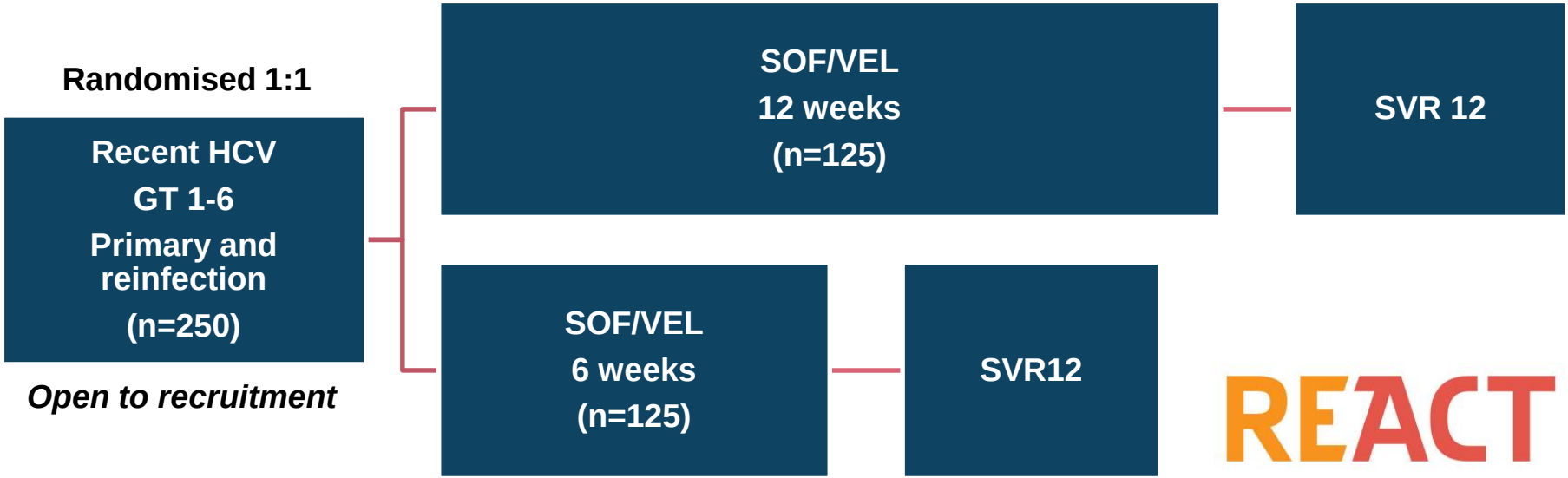
TARGET3D: Treatment of recently AcquiRed hepatitis C with the 3D regimen or GLE/PIB

Open label, multi-centre, sequential (Australia, NZ, UK)



REACT: A randomised study of interferon-free treatment for recently acquired hepatitis C in people who inject drugs and people with HIV co-infection

Phase III randomised, open-label, non-inferiority trial (AUS, NZ, NA, Europe)



Acknowledgements

UNSW Australia
A/Prof. Jason Grebely
A/Prof. Gail Matthews
Prof. Andrew Lloyd
Dr. Behzad Hajarizadeh
Dr. Maryam Alavi
Dr. Tanya Applegate
Ms. Pip Marks
Dr. Marianne Martinello
Prof. Carla Treloar

Collaborators
Prof. Margaret Hellard (Australia)
Prof. Ed Gane (New Zealand)
Dr. Philip Bruggmann (Switzerland)
Prof. Olav Dalgard (Norway)
Prof. Julie Bruneau (Canada)
Dr. Jordan Feld (Canada)
Prof. Alain Litwin (USA)
Prof. Juergen Rockstroh (Germany)
Dr. Mark Nelson (UK)
Ms. Tracy Swan (USA)