Is DAA treatment failure still an issue ?

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Conference

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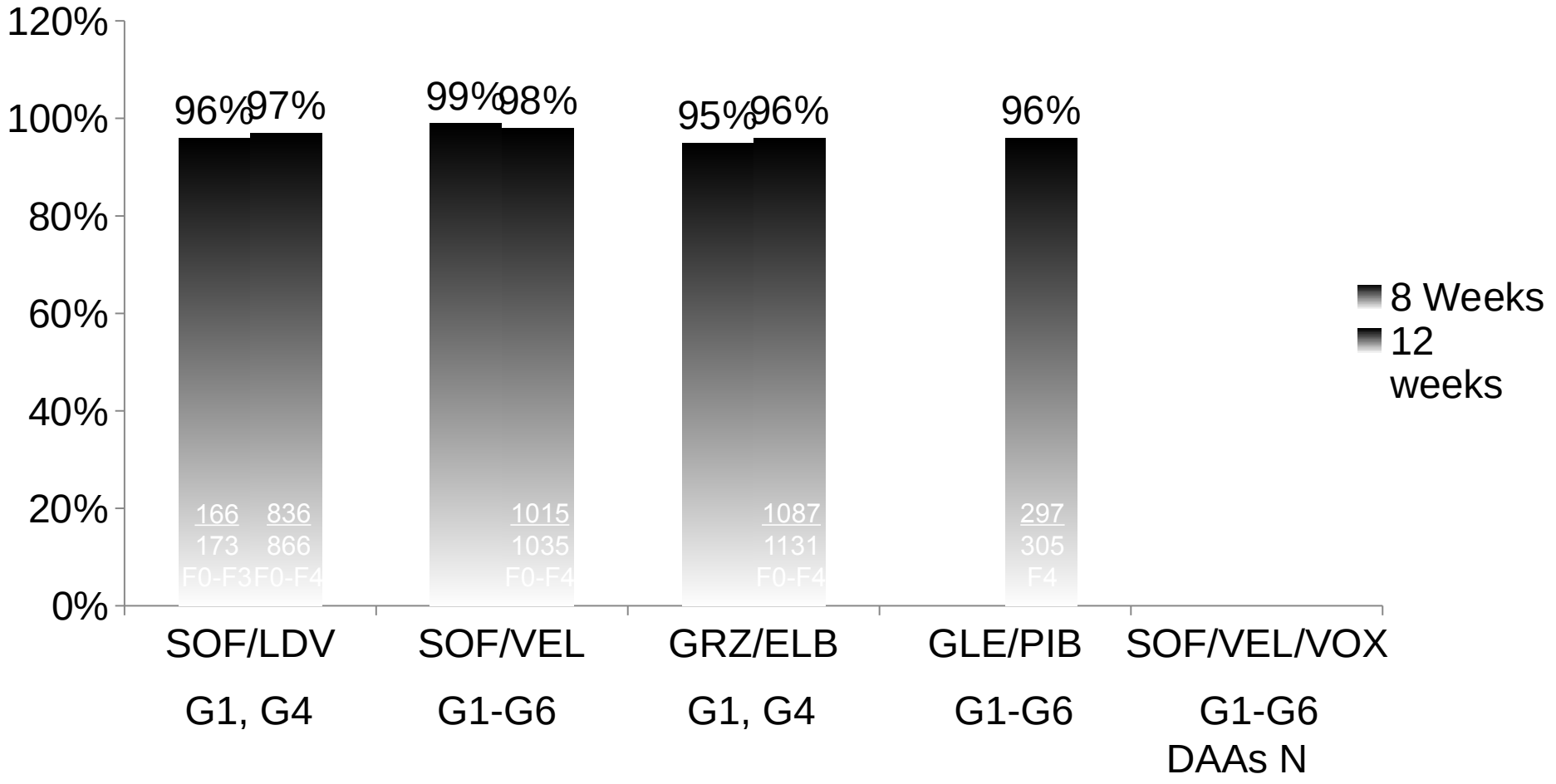
Agence autonome de l'Inserm

Disclosures

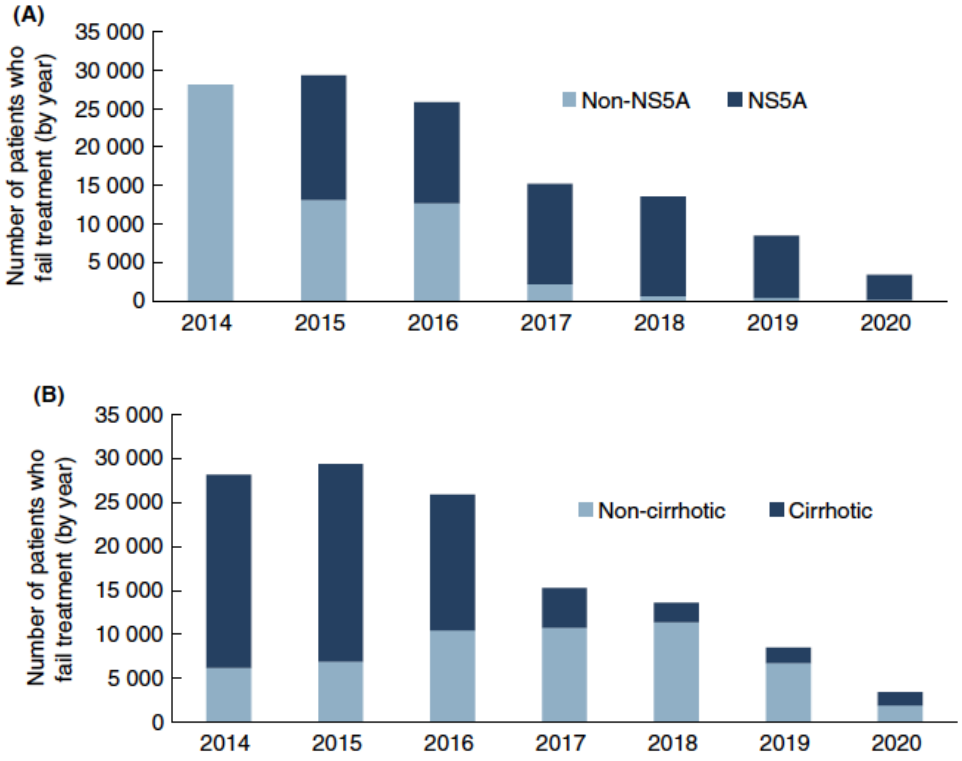
- Board member for : MSD, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, AbbVie, GSK, Vertex, Idenix, Intercept
- Speaker for : MSD, Janssen, Gilead, BMS, Abbvie, Intercept

SVR is not anymore the challenge and failure is rare

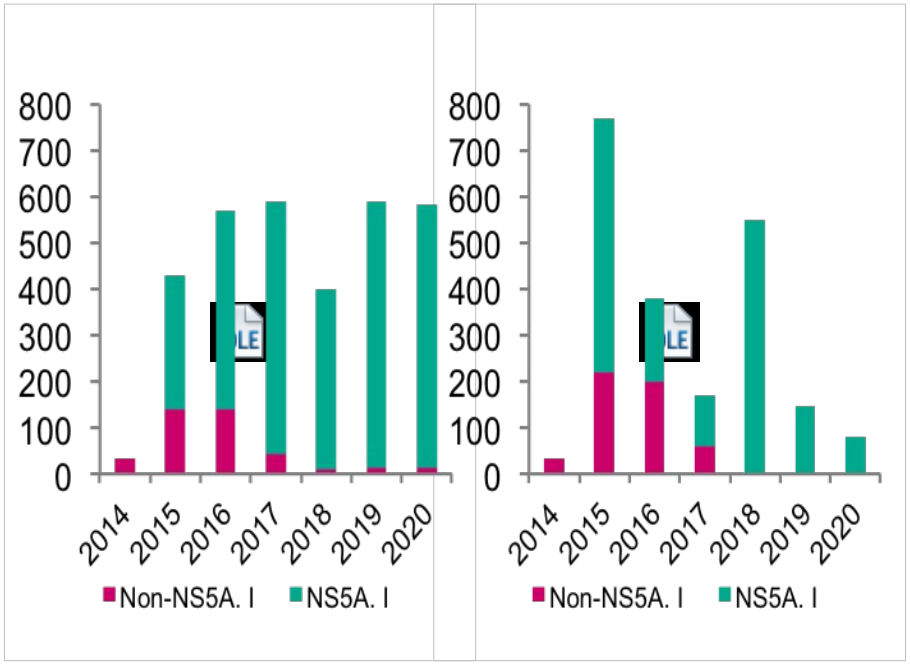


Lawitz E et al EASL 2017; Abs THU-273. Afdhal N et al. NEJM 2014:370: 1889-98.Afdhal N et al. NEJM 2014; 370: 1483-93, Kowdley KU et al. NEJM 2014; 370: 1979-88. Agarwal K et al EASL 2016;: SAT-295. Feld JJ et al NEJM 2015; 373: 2599-607. Komatsu TE et al. Gastroenterology 2016. Puoti M et al. EASL 2017; SAT-233. Gane EJ et al. AASLD 2017 abs 73. Roberts SK et al EASL 2017; SAT-280,. Jacobson I et al. Gastroenterology 2017; 153: 113-122.

Framework of DAAs failure in 2020



Number of patients who failed DAAs regimen with or without NS5A.I in France, between 2014 and 2020



124,000 patients will be DAA failure in USA
47,000 patients will be DAAs failure in 5 European country.
Since 2015, near all patients will be NS5A failure

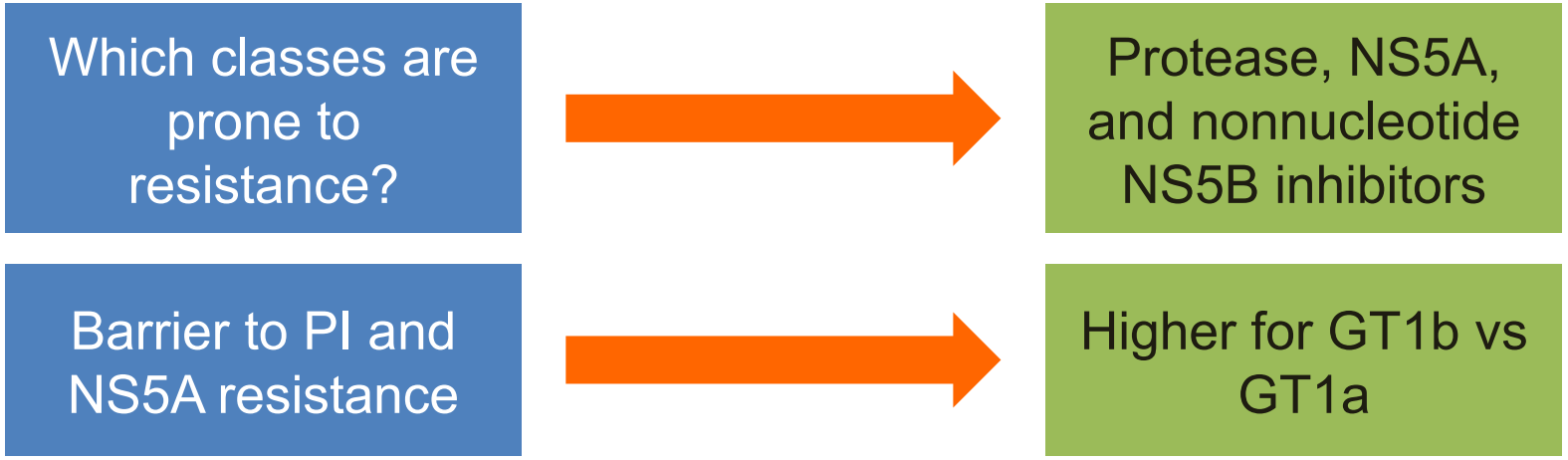
Chhatwal J et al. Aliment Pharmacol Ther 2018; 47: 1023-1031
Chhatwal J et al., EASL 2017 abstr. FRI-233

Reasons for DAAs failure

- **Treatment regimen**
  - Specific DAAs (intrinsic barrier for specific HCV strains)
  - Duration of treatment , adherence to treatment
  - Ribavirin
- **Cirrhosis**
  - Hepatic sanctuaries with low drug exposure due to distorted liver architecture and portal shunting of drug-rich blood
- Host innate immunity
  - IFN-lambda-4/IL-28B
- **Resistance associated substitutions**
  - Burden of liver infection (% hepatocytes infected estimated by HCV RNA level)
  - Specific RASs present and their impact on selected DAAs
  - Proportion of hepatocytes infected with HCV with RASs (estimated by % of the circulating population)

Courtesy from Mark Sulkoswsi

Resistance Considerations



- **Most patients with failure of current DAAs have emergent resistance-associated substitutions (RASs)**
  - NS5A RASs persist much longer than PI RASs
- 15% of patients have baseline NS5A RASs with variable effects on GT1a response
- Second-generation drugs designed to cover RASs

EASL Clinical Practice Guidelines

- The utility of HCV resistance testing prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown.
  - If reliable resistance testing is performed, retreatment can be guided by probabilities of response according to the resistance team (B2).
- Patients who failed on a regimen containing SOF + SMV should be retreated with a combination of SOF + NS5A inhibitor (B1).
- Patients infected with HCV genotype 2,3, 5 and 6 who failed on a regimen containing an NS5A inhibitor should be retreated with SOF/VEL + RBV for 24 weeks
- Patients infected with HCV genotype 1 or 4 who failed on a regimen containing an NS5A inhibitor should be retreated with (B1):
  - a combination of SOF + PrOD +RBV
  - a combination of SOF + EBR/GZV + RBV
  - a combination of SOF + SMV + DCV + RBV
  - 12 weeks for genotype 1b or 4 patients with METAVIR score F0 to F2
  - 24 weeks plus ribavirin for all patients with genotype 1a and for genotype 1b and 4 patients with METAVIR score F3 or with compensated cirrhosis)

EASL Recommendations on treatment of hepatitis C 2016. J Hepatol 2017; 66: 153-194

AASLD/ IDSA recommendations 2018 for treatment failures

GT	Failed treatment	GZR/ELB	SOF/LDV	SOF/VEL	GLE/PIB	SOF/VEL/VOX
G1	NS3+PR		**12**w(F0-F3)	**12**w	**12**w	
	Non NS5A			12w (1b)	12w	**12**w
	NS5A				16w (Iia,B)	**12**w
G2	SOF+RBV			**12**w	**12**w	
	DAAs					**12w**
G3	DAAs					**12**w (+RBV if F4)
G4	DAAs					**12**w
G5/G6	DAAs					**12**w

EASL recommendations 2018 for treatment failures

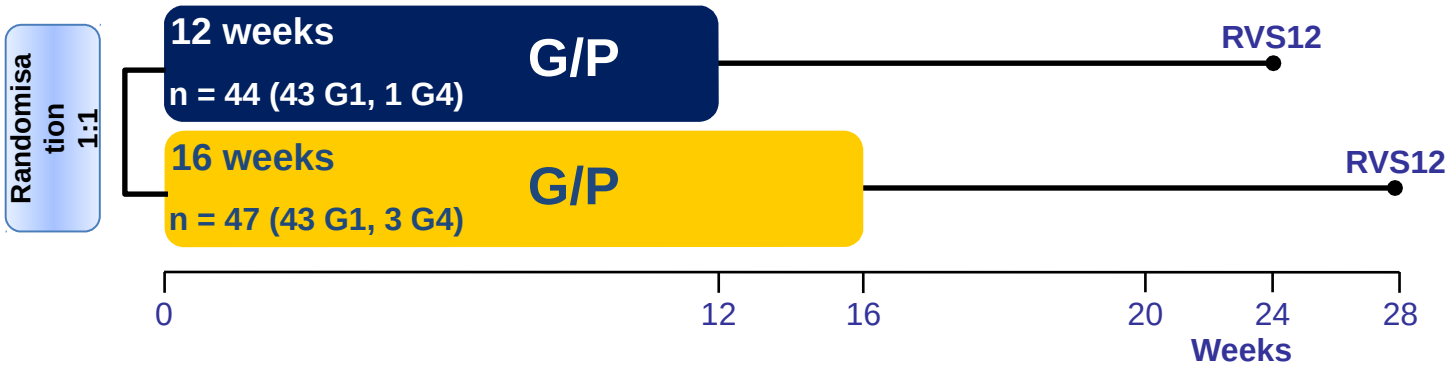
GT	Failed treatment	GZR/ELB	SOF/LDV	SOF/VEL	GLE/PIB	SOF/VEL/VOX
G1	DAAs				**12**w **+SOF**	**12**w
G2	DAAs				**12**w**+SOF**	**12**W
G3	DAAs				**12**W**+SOF**	**12**w
G4	DAAs				**12**W**+SOF**	**12**w
G5/G6	DAAs				**12W+SOF**	**12**w

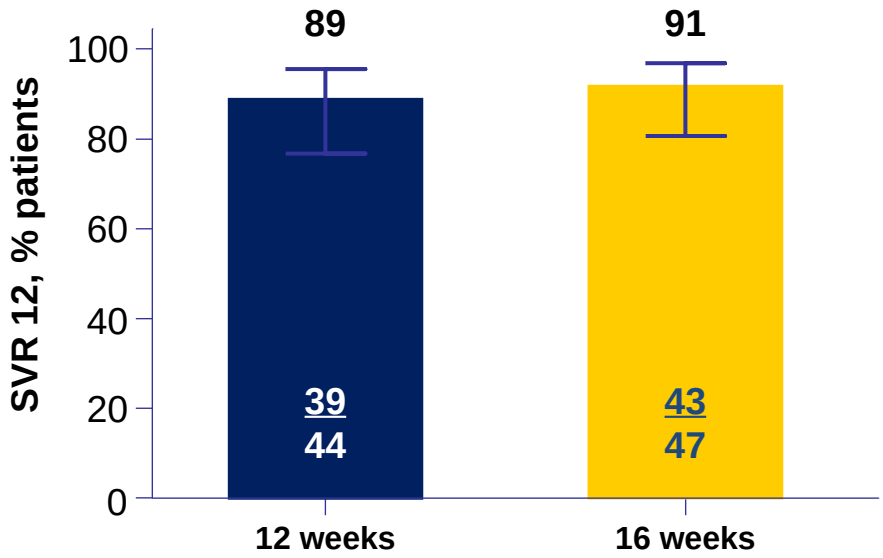
Pts who failed twice DAAs with NS5A RASs: SOF/VEL/VOX +RBV or SOF+GLE/PIB+RBV 12w

Pts with decompensated cirrhosis : SOF/VEL+ RBV 24w

EASL recommendations. J Hepatol 2018 on line

Glecaprevir/pibrentasvir (G/P) in DAAs failure*(1)*



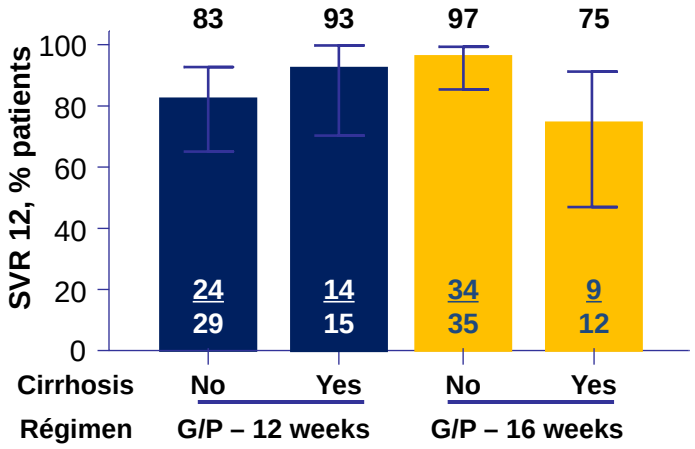


	12 weeks	16 weeks
Breakthrough	1 (2 %)	4 (9 %)
Virological relapse	4 (9 %)	0

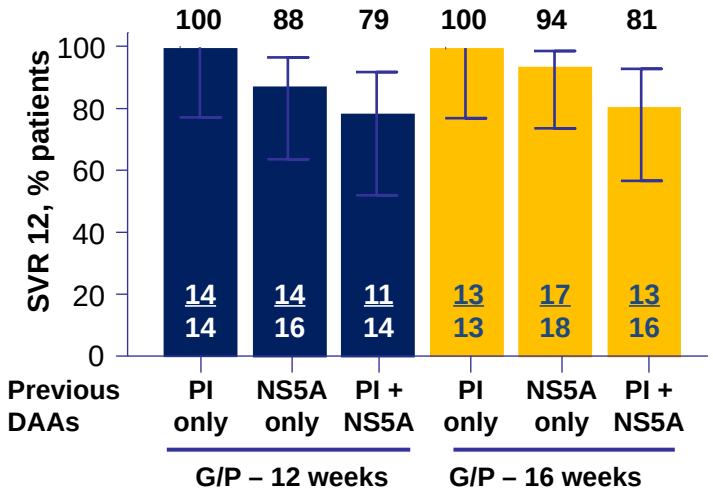
Poordard F. et al.. EASL 2017, Abs. PS-156
Poordard F; et al. Hepatology 2017; 66: 389-397

Glecaprevir/pibrentasvir (G/P) in DAAs failure*(2)*

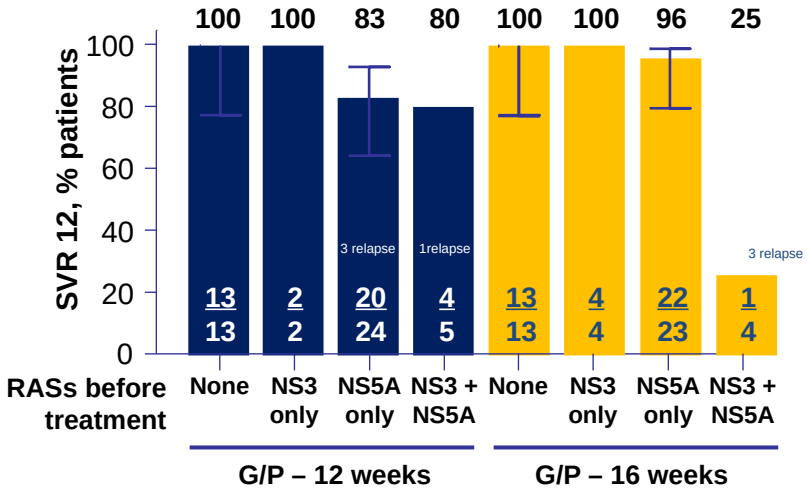
Impact of cirrhosis



Impact of previous DAAs regimen



Impact of RASs

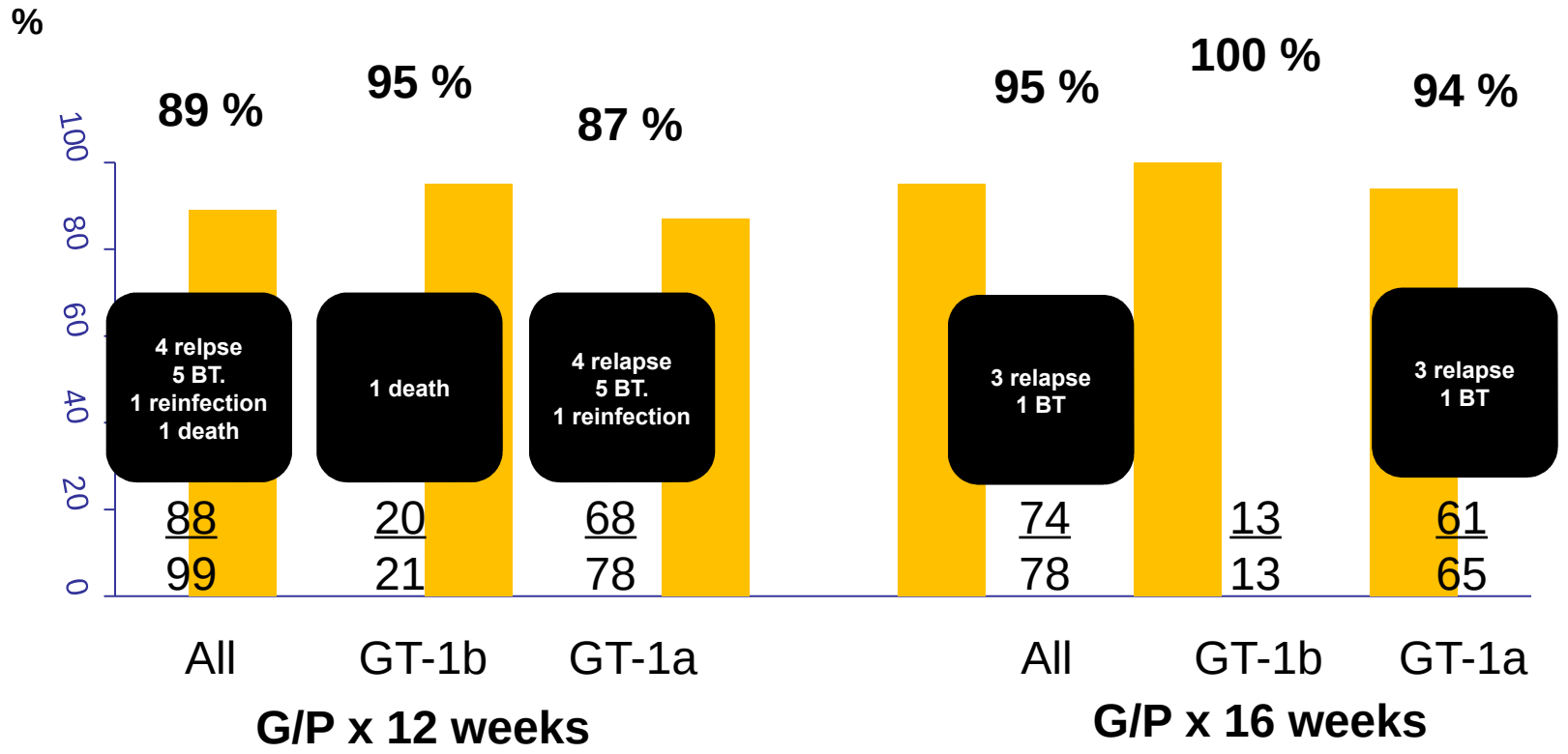


Not an optimal option for NS5A failure especially in those who harbor NS5A +NS3 RASs

Poordard F. et al.. EASL 2017, Abs. PS-156
Poordard F; et al. Hepatology 2017; 66: 389-397

GLE/PIB in genotype 1 patients who failed DAAS regimen with NS5A I.

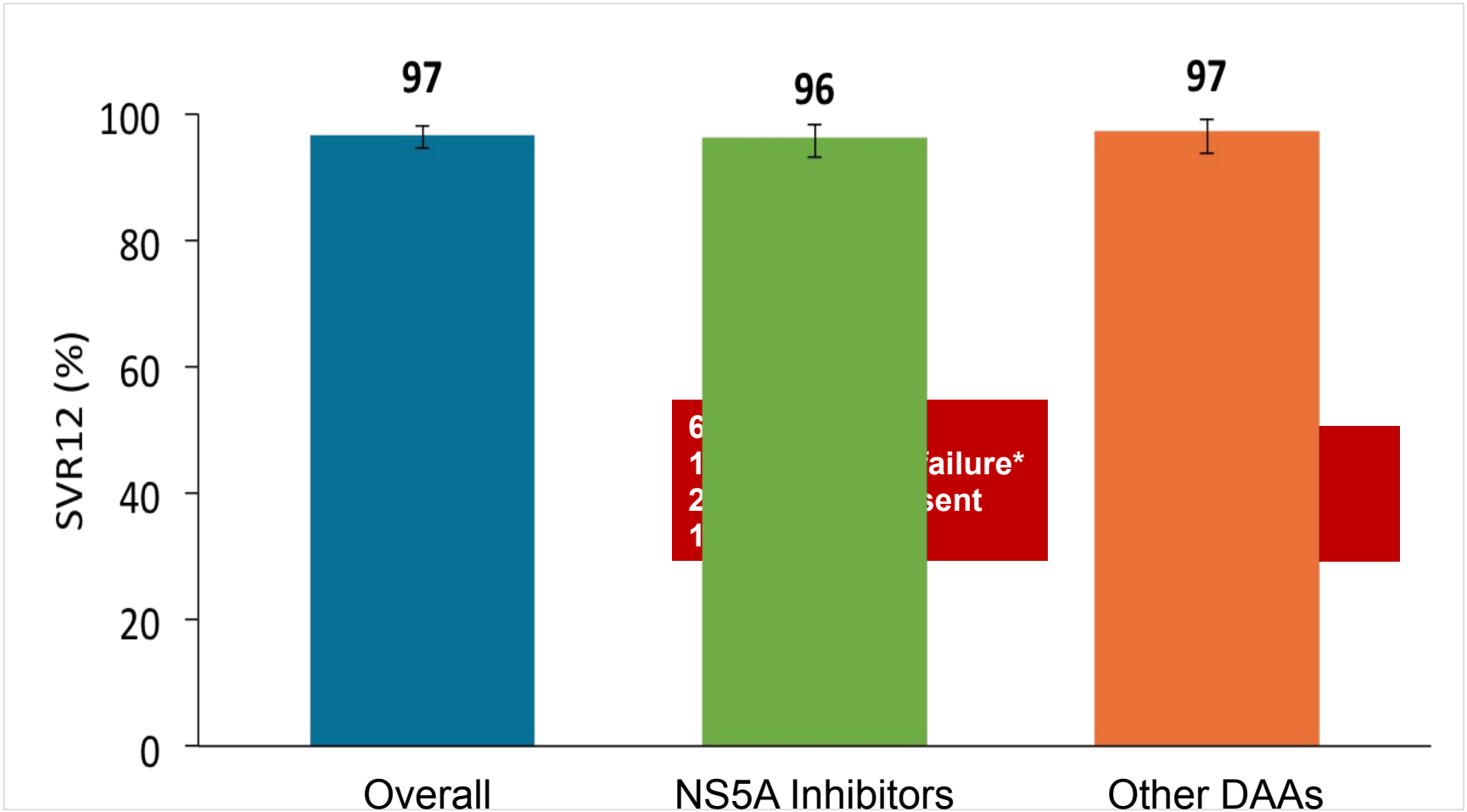
SVR 12 according to subtypes and treatment duration



➔ **G/P 12 or 16 weeks may be an option for patients with GT-1b but not in patients with GT-1a**

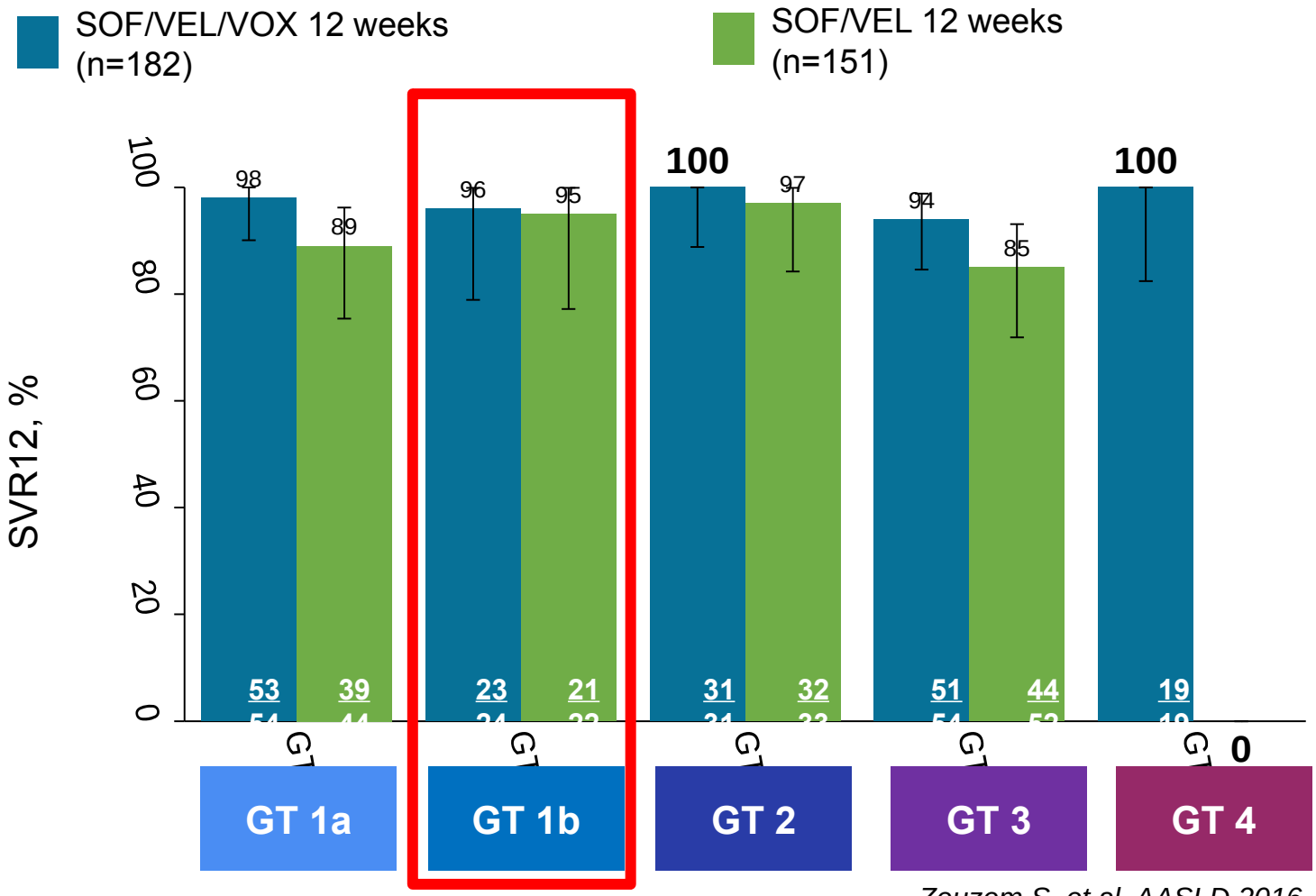
Sulkowski M et al., AASLD 2018, Abs. 226

SOF/VEL/VOX 12 weeks in DAA-experienced Patients



Bourliere M, ….,Zeuzem S et al. NEJM 2017; 376: 2134-214

sofosbuvir/velpatasvir/voxilaprevir versus sofosbuvir/velpatasvir in G1-6 patients who failed DAAs regimen without NS5A.I

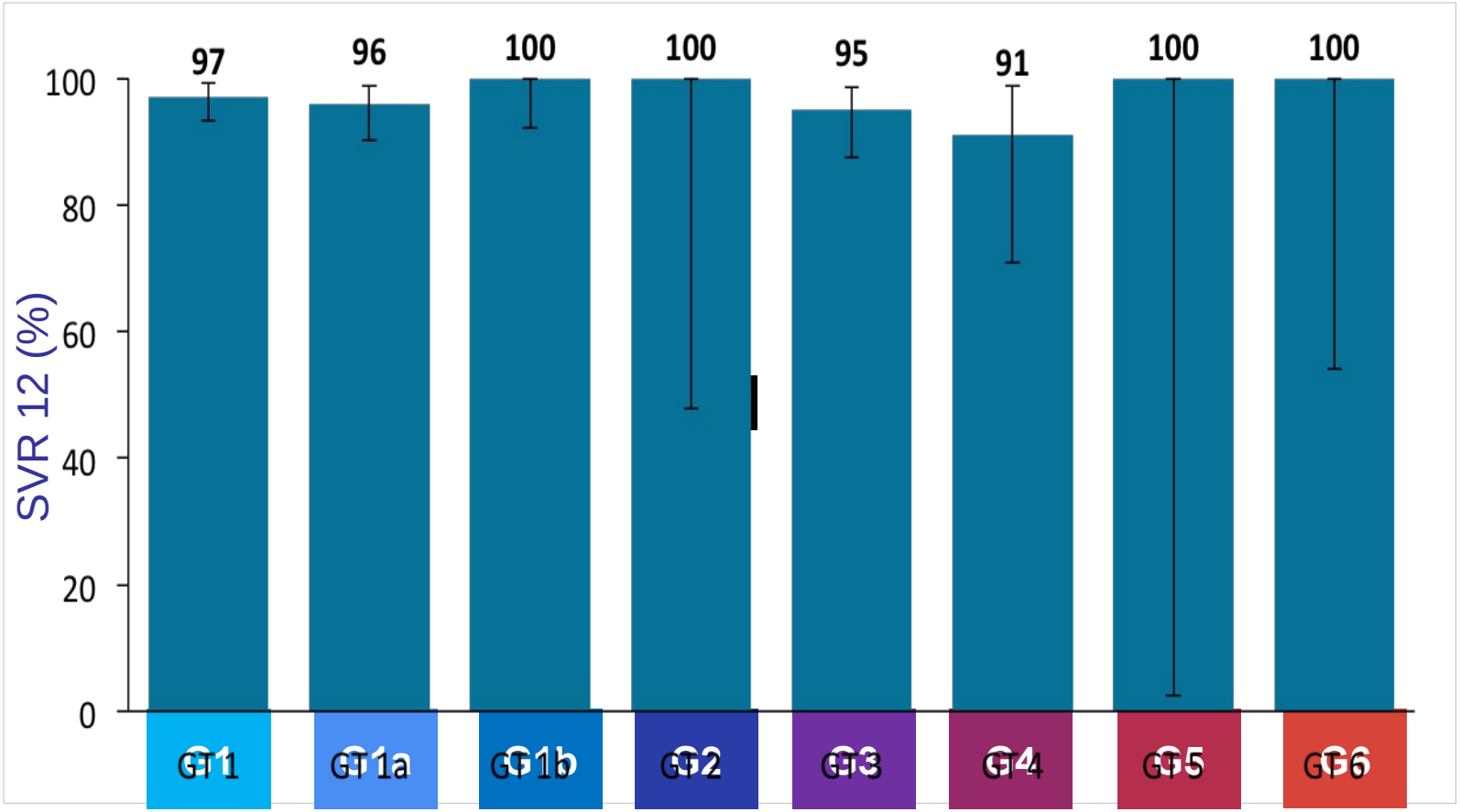


Zeuzem S, et al. AASLD 2016, Abs. 109 actualis

Bourliere M,...,Zeuzem S et al. NEJM 2017; 376: 2134-214

POLARIS-1 : sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in patients who failed DAAs regimen with NS5A.I

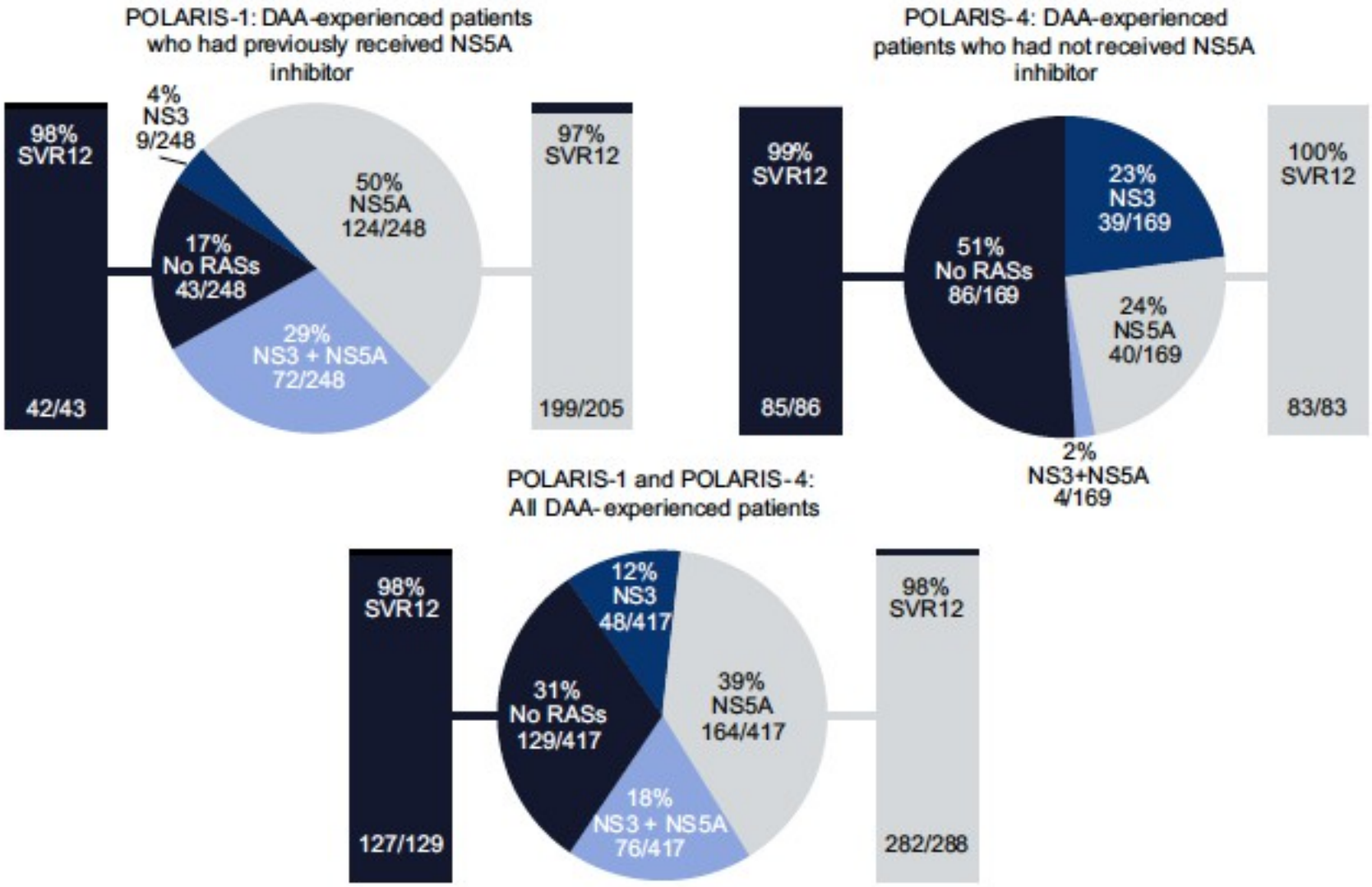
SVR 12



➔ **6 patients relapse (1 G1a, 4 G3 and 1 G4) all F4**

Bourliere M et al. NEJM 2017; 376: 2134-2146

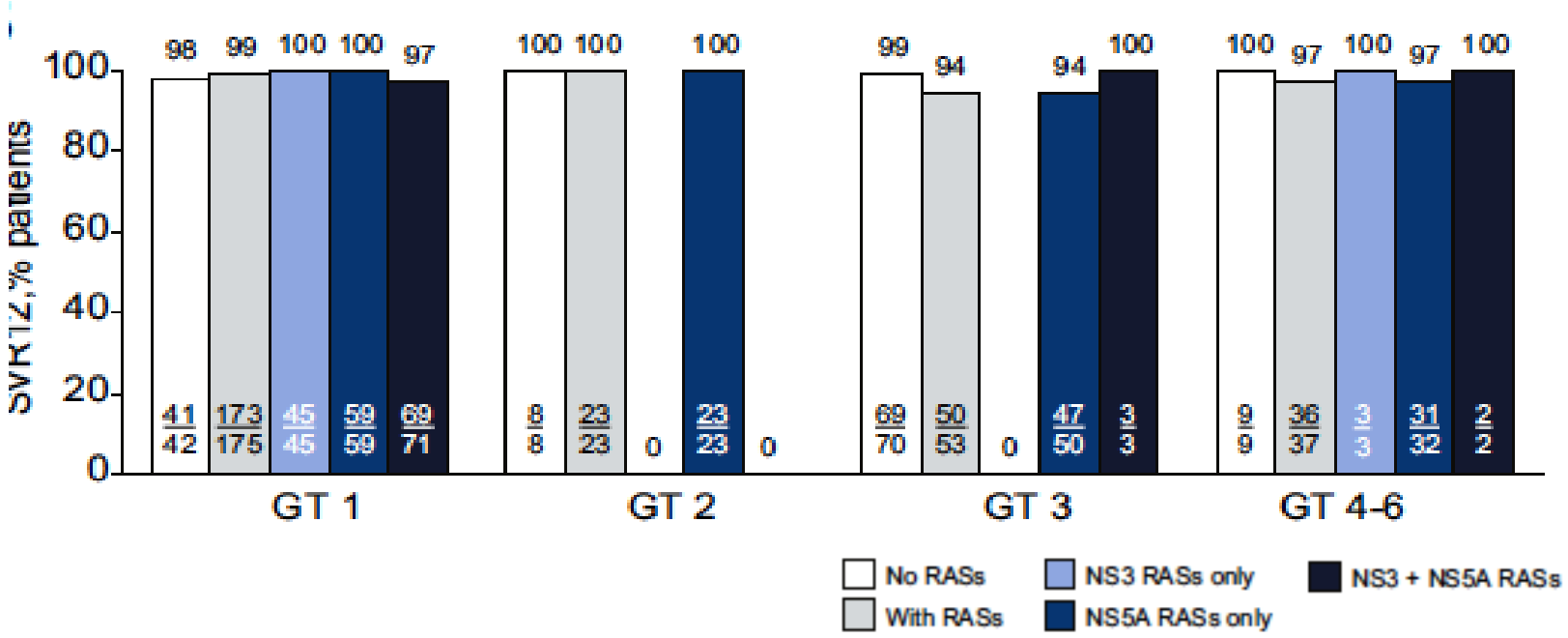
No impact of RASs on high efficacy of SOF/VEL/VOX for 12 weeks in DAA experienced patients



Sarrazin C et al. J Hepatol 2018 ; 69:1221-1230

No impact of RASs on high efficacy of SOF/VEL/VOX for 12 weeks in DAA experienced patients

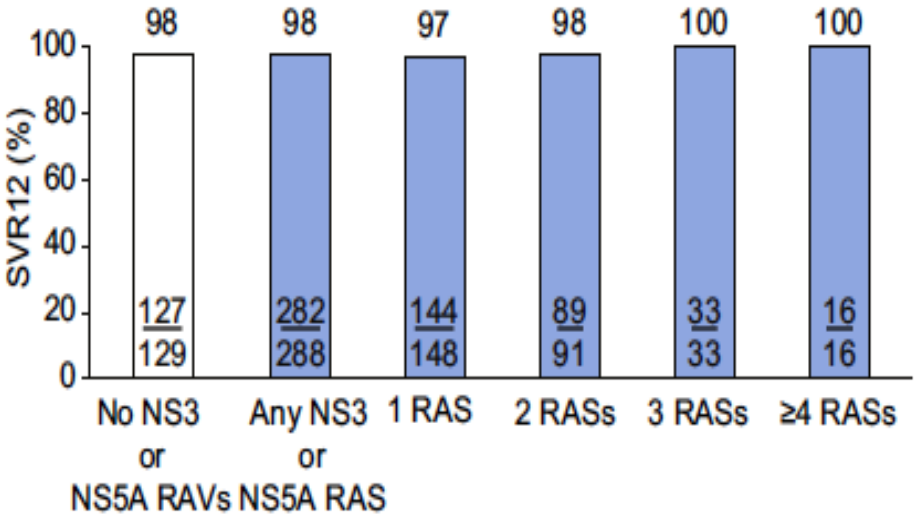
SVR according to genotype and baseline RAS



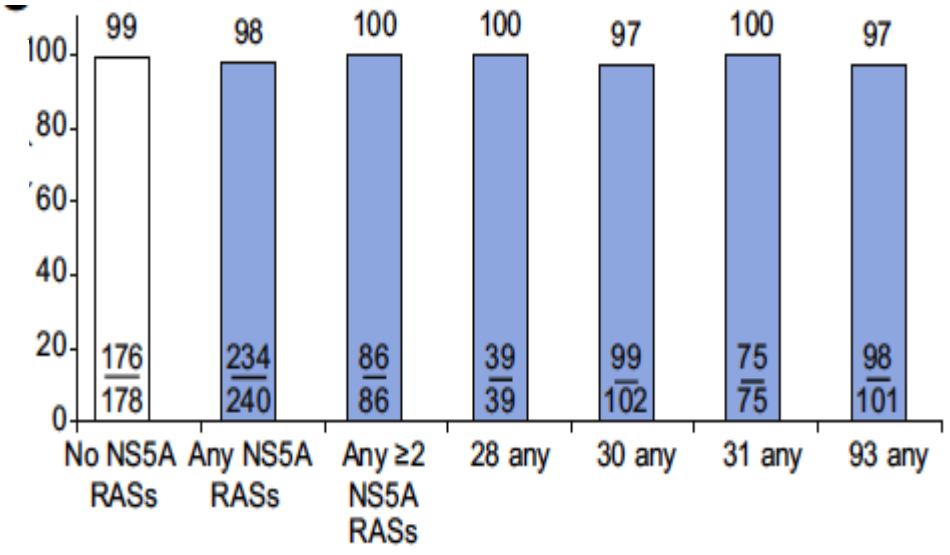
Sarrazin C et al. J Hepatol 2018 ; 69:1221-1230

No impact of RASs on high efficacy of SOF/VEL/VOX for 12 weeks in DAA experienced patients

SVR according to the number of baseline RAS



SVR according NS5A RAS position



Sarrazin C et al. J Hepatol 2018 ; 69:1221-1230

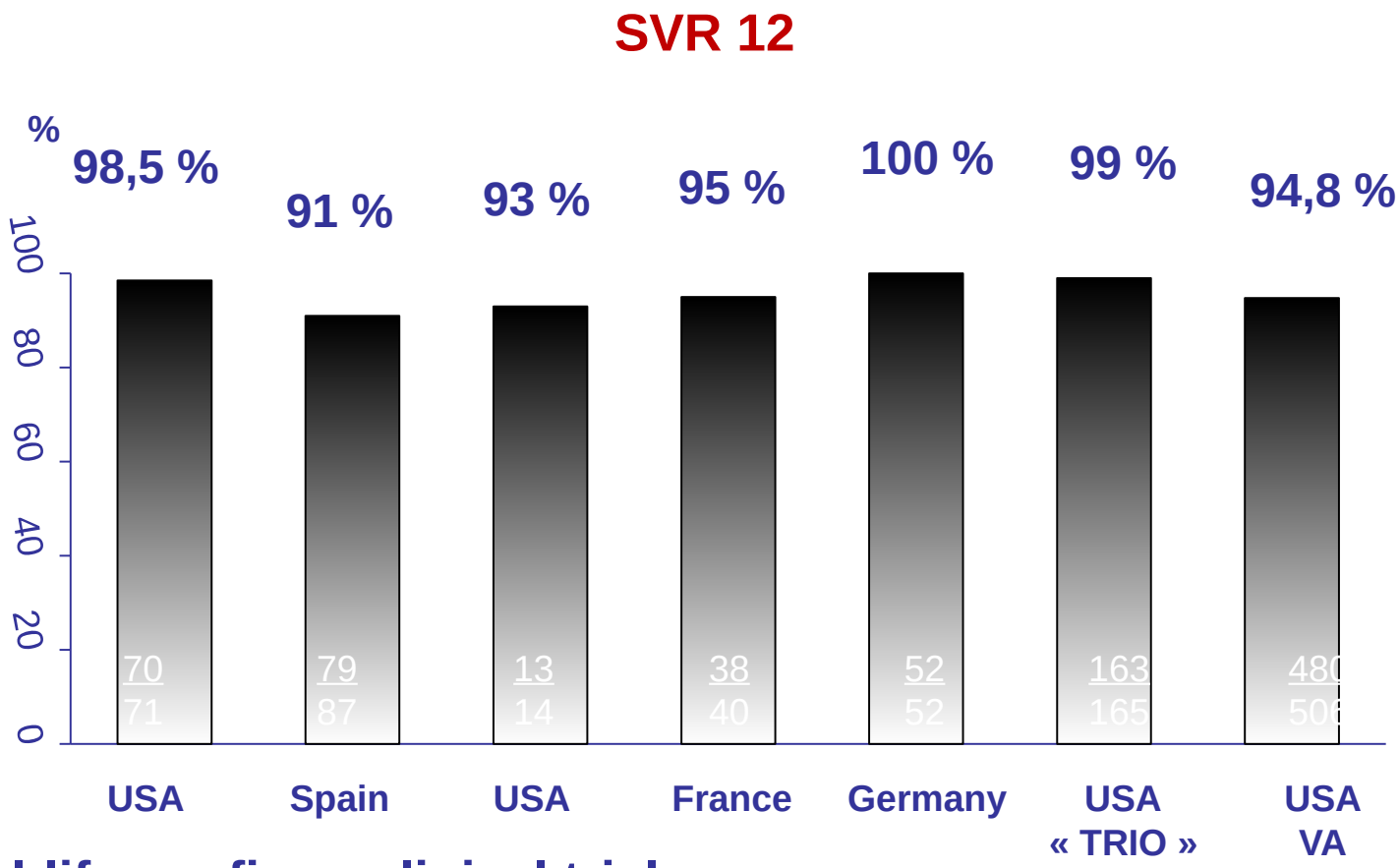
Is there any issue with emergent RASs in patients who failed SOF/VEL/VOX ?

Study	GT	Cirrhosis	NS3 RASs		NS5A RASs		NS5B NI RASs	
			Baseline	Relapse	Baseline	Relapse	Baseline	Relapse
Polaris-1	1a	Yes	Q80K >99%	Q80K >99%	Q30T	Q30T, **L31M Y93H**	None	None
	1a	Yes	Q80K >99%	Q80K >99%	Y93N 98%	Y93N 99%	None	None
	3a	Yes	None	None	Y93H 72%	Y93H 99%	E237G 97%	NA
	3a	Yes	None	None	Y93H 31%	Y93H 99%	None	None
	3a	Yes	None	None	A30K 99%	A30K 99%	None	None
	3a	Yes	None	None	None	None	None	None
	4d	Yes	None	None	L30R	L30R **Y93H**	None	None
Polaris-4	1a	Yes	None	None	None	None	None	None
Deferred Polaris-1	1a	No	Q80K	Q80K	M28T Q30H	M28T Q30H	None	None
	1a	Yes	T54S V55I	T54S V55I	Q30Q/L Y93Y/H	Q30L Y93H	None	None
	1a	No	None	**Y56H D168A/V**	Y93N	**L31L/N** Y93N	None	None
	1a	No	Q80K	**V36V/A** Q80K	M28T Q30H H58N	M28T Q30H H58N	None	None

Sarrazin C et al. J Hepatol 2018 ; 69:1221-1230

Bourliere. M et al. Lancet HG 2018: 3 : 559-65

SOF/VEL/VOX in DAAs failures « real-life data »

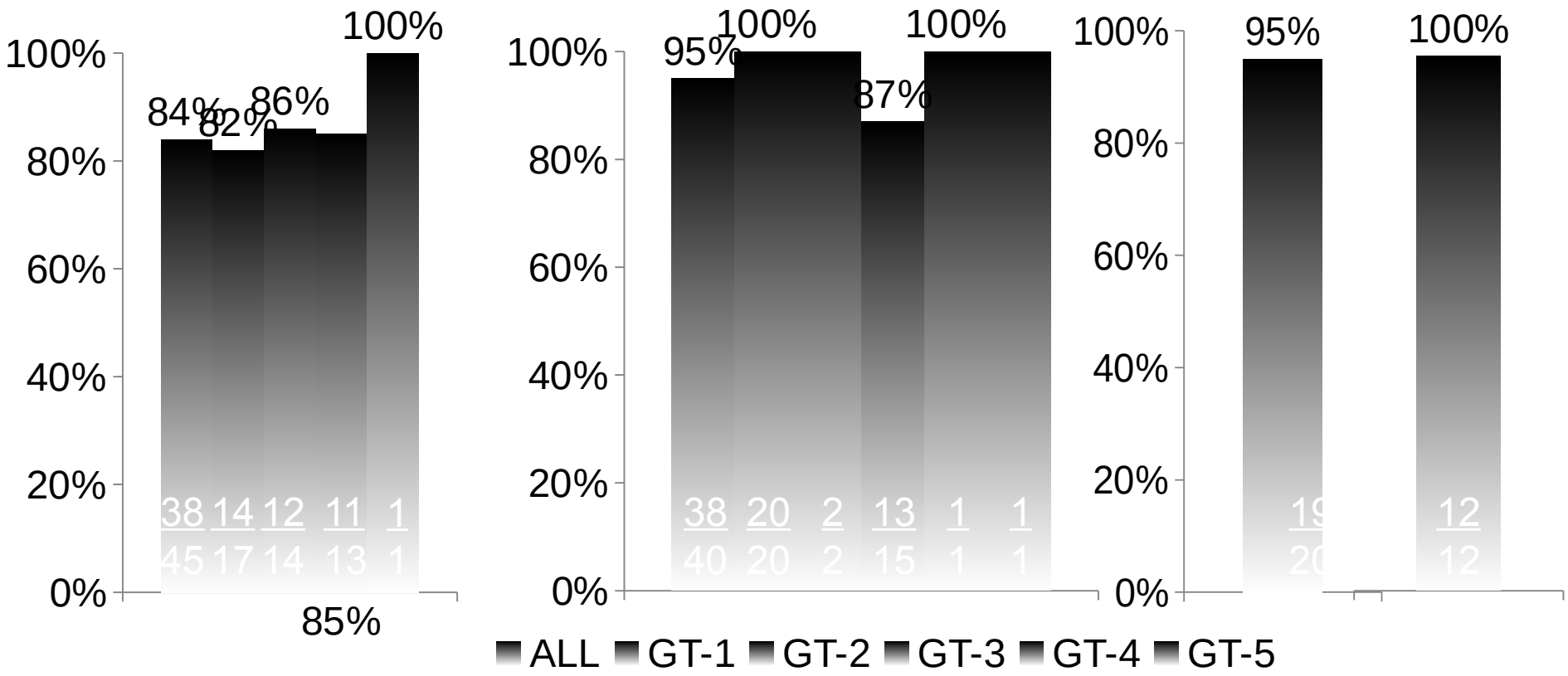


➔ **Real-life confirms clinical trials**

Covert E et al. AASLD 2018, Abs. 583
Llaneras J et al. AASLD 2018, Abs. 683
Pearlman B et al. AASLD 2018, Abs. 607

Hézode C et al. AASLD 2018, Abs. 629
Vermehren J et al. AASLD 2018, Abs. 676
Bacon B et al. AASLD 2018, Abs. 706
Belperio PS et al., AASLD 2018, Abs. 227

SOF/VEL/VOX in patients who failed SOF/VEL is there an issue ?



USA – VA cohort

Belperio PS, et al. AASLD 2018, Abs. 227

POLARIS 1-4

Ruane P et al; GHS 2018
Bourliere M et al NEJM 2017

USA Germany TRIO

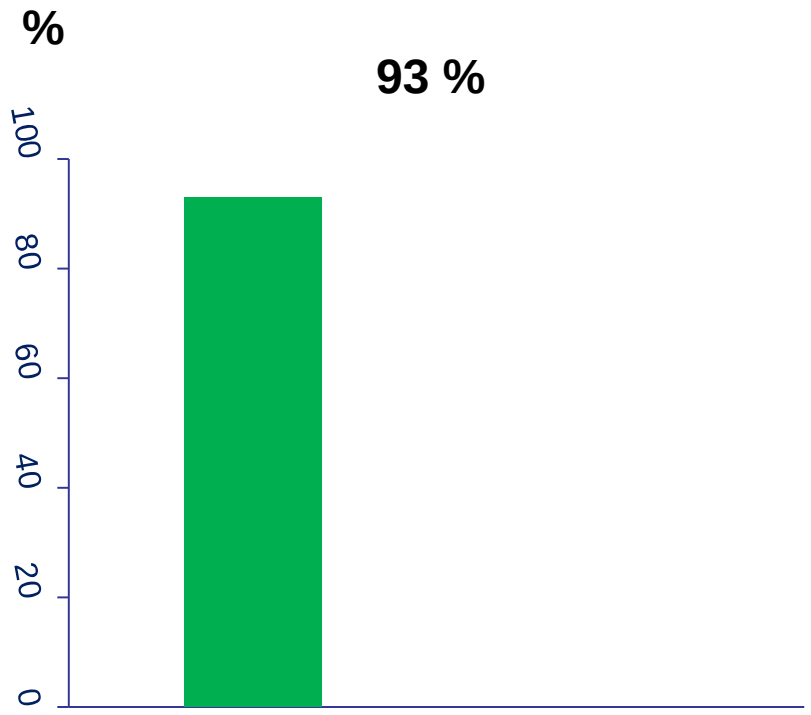
Bacon B, et al AASLD 2018, Abs. 706
Vermehren J, et al AASLD 2018, Abs. 676

SOF/VEL/VOX in patients who failed GLE/PIB

- 14 patients who failed Glecaprevir/pibrentasvir regimen were retreated with SOF/VEL/VOX 12 weeks

Patients charateristics

	n = 14
Cirrhosis	**7 (50 %)**
Genotype 1a Cirrhosis Relapsers	**5 (36 %)** 2/5 5/5
Genotype 3 Cirrhosis Relapsers Breakthrough	**9 (64 %)** 5/9 7/9 2/9
RAS at baseline NS5A NS3 NS5A +NS3 None	**12 (86 %)** 5 (36 %) 1 (7 %) 6 (43 %) 2 (14 %)



1 woman HCV GT3 without cirrhosis and initial RAS A30K relapse at 4 weeks

➔ **SOF/VEL/VOX achieve High SVR in G/P failure**

Pearlman B et al., AASLD 2018, Abs. 607

Sofosbuvir plus glecaprevir/pibrentasvir in G/P failure

- **MAGELLAN-3**, Evaluate efficacy and safety of sofosbuvir + G/P + ribavirin for 12 or 16 weeks in patinets who failed a prvious treatment with G/P

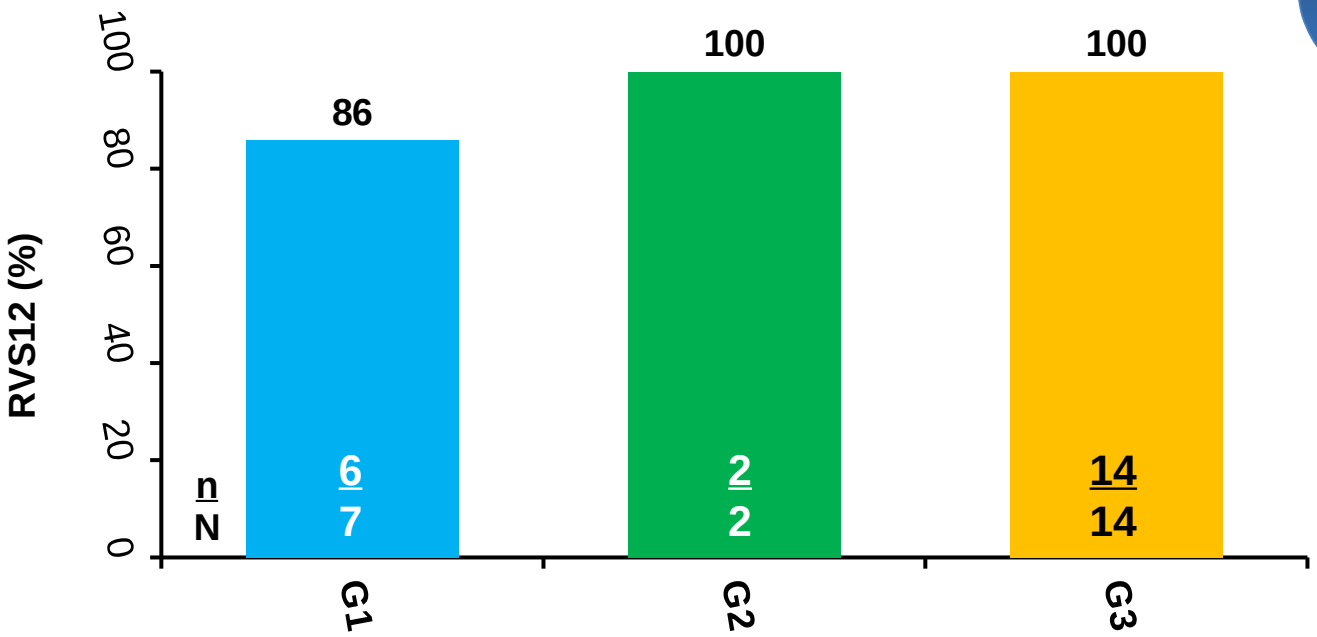
Study design and patient's characteristic

RAS s at baseline	GT- non 3 without cirrhosis 12 weeks (n = 2)	GT-3+ GT-non 3 + cirrhosis 16 weeks (n = 21)	All (n = 23)
NS3 only	0	0	0
NS5A only	2 (100)	16 (76,2)	18 (78,3)
NS3 + NS5A	0	5 (23,8)	5 (21,7)
None	0	0	0

Wyles D. et al. , EASL 2018, Abs. PS-04

Sofosbuvir plus glecaprevir/pibrentasvir in G/P failure

SVR-12 according to genotype



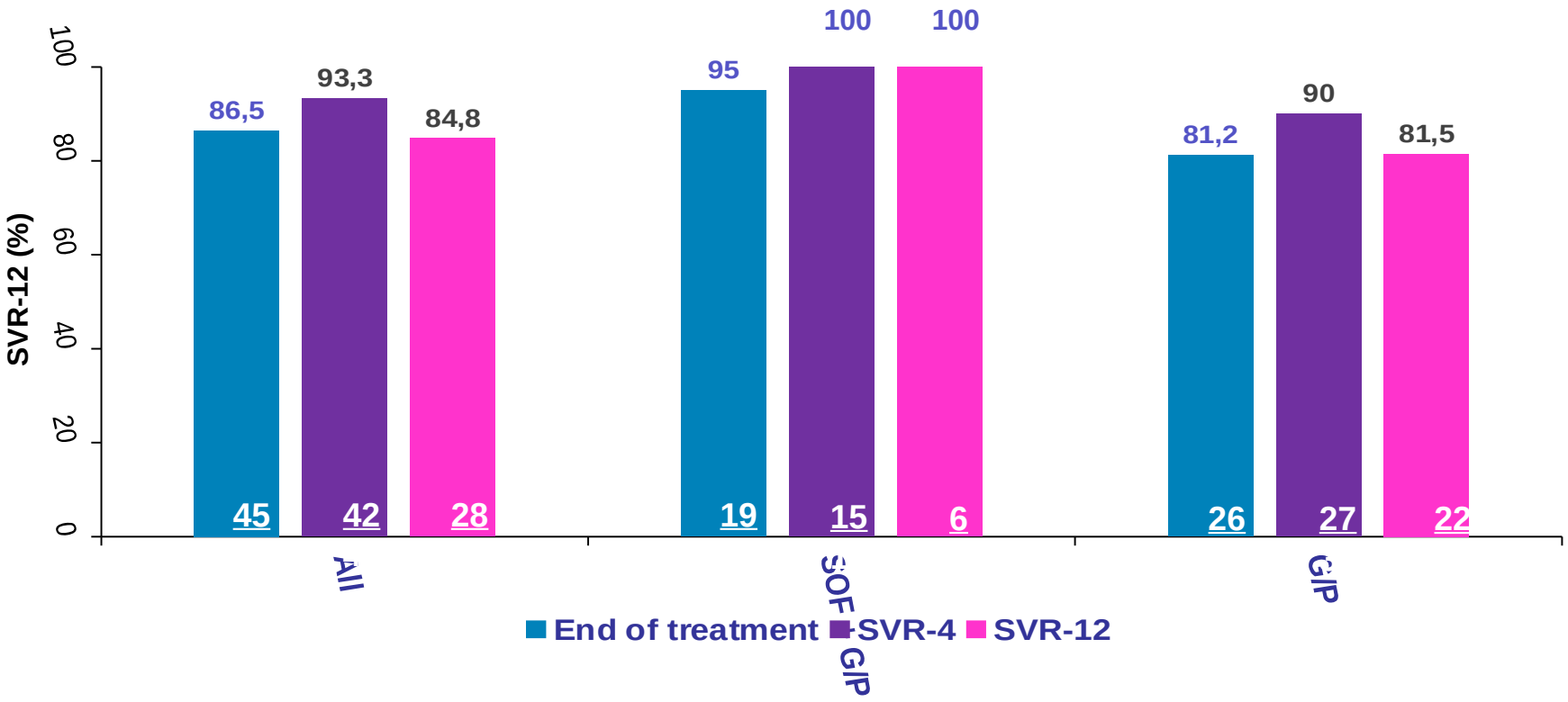
1 relapse patient

- GT-1a
- Compensated cirrhosis
- Failure to SOF/LDV then to G/P

➔ **SOF +G/P +RBV for 16 weeks is an option for GT-3 who have failed previous treatment with G/P**

Wyles D et al, EASL 2018, Abs. PS-04

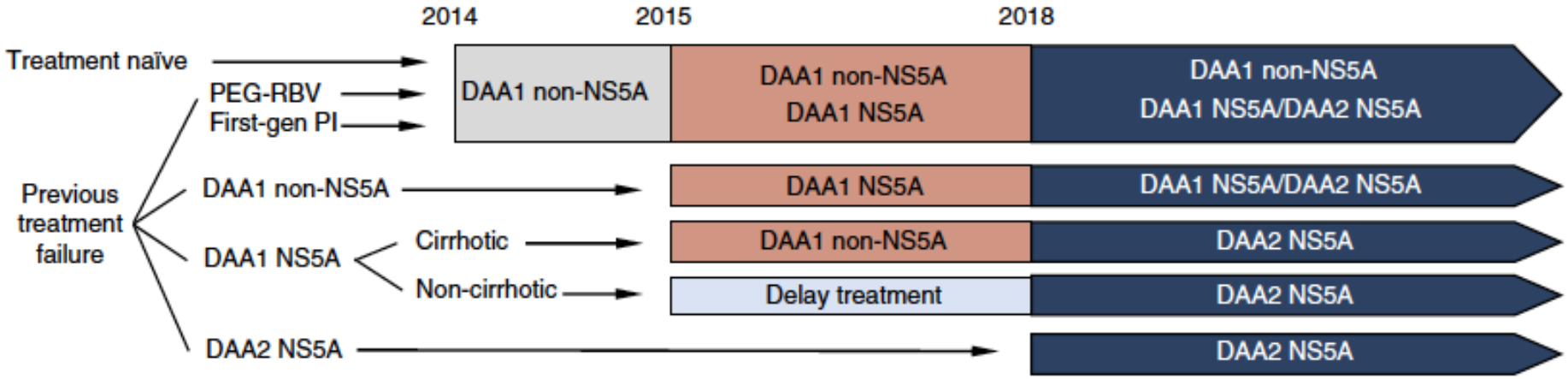
Sofosbuvir plus glecaprevir/pibrentasvir in DAAs failure
In the French ATU
Virological response



➔ **SOF + G/P treatment for 12 weeks is a therapeutic option in DAAs failures**

de Lédinghen V. et al. EASL 2018, Abs. THU-29

We have options for any DAAs failure in 2019



DAA1 non NS5A : SOF+PEG±RBV, SOF±RBV, SOF+SMV±RBV,
DAA1 NS5A : LDV/SOF±RBV, SOF+DCV±RBV, DCV+PEG±RBV, OBV/PTVr+DSV±RBV, OBV/PTVr±RBV, EBR/GZR±RBV, SOF/VEL.
DAA2 NS5A : SOF/VEL/VOX, glecaprevir/pibrentasvir, SOF+ glecaprevir/pibrentasvir

Chhatwal J et al. Aliment Pharmacol Ther 2018; 47: 1023-1031

Conclusions

Approach to persons with HCV failure

- Consider re-infection as a cause of recurrent viremia
- Assess adherence/persistence prior regimen
- Assess Genotype
- Assess liver disease stage: No cirrhosis, cirrhosis CTP A or B/C
- No cirrhosis and single DAA failure
  - Retreat with least two DAAs predicted to be active based on prior DAA use or directly use triple regimen for 12w (SOF/VEL/VOX or SOF+G/P)
  - RAS testing not recommended
- Cirrhosis or prior therapy with both NS5A and NS3 protease inhibitor (not really useful so far !!)
  - RAS testing recommended?
  - Consider triple regimens SOF/VEL/VOX or SOF+G/P
  - Consider Ribavirin and extended duration (16 or 24w)