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HCV: Il punto sulle resistenze ai DAA sul trattamento nei pazienti con pregresso fallimento ai DAA

Convegno Internazionale
GIORNATE INFETTIVOLOGICHE "LUIGI SACCO" 2018
MILANO, 14-15 GIUGNO 2018
OSPEDALE LUIGI SACCO POLO UNIVERSITARIO – ASST FATEBENEFRATELLI SACCO
AULA MAGNA POLO LITA

Management of treatment failures

- Management of DAA Experienced
  - Epidemiology
  - Causes of Treatment failure
  - Patients profile
  - Re-treatment “ a la carte”: role of RAS testing
  - Re treatment with a fixed menu: data from registration studies
  - Overview of International recommendations

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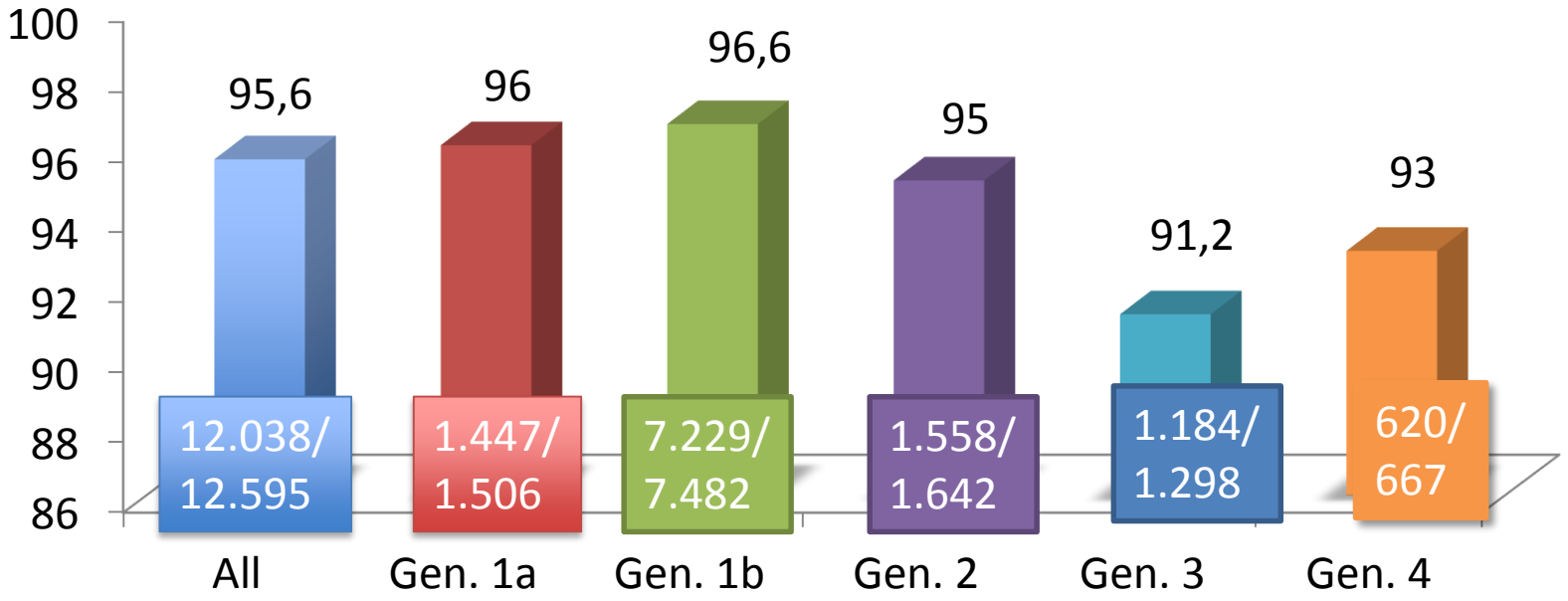
SVR12 in 12.595 HCV infected patients in 4 Italian Regional Registries

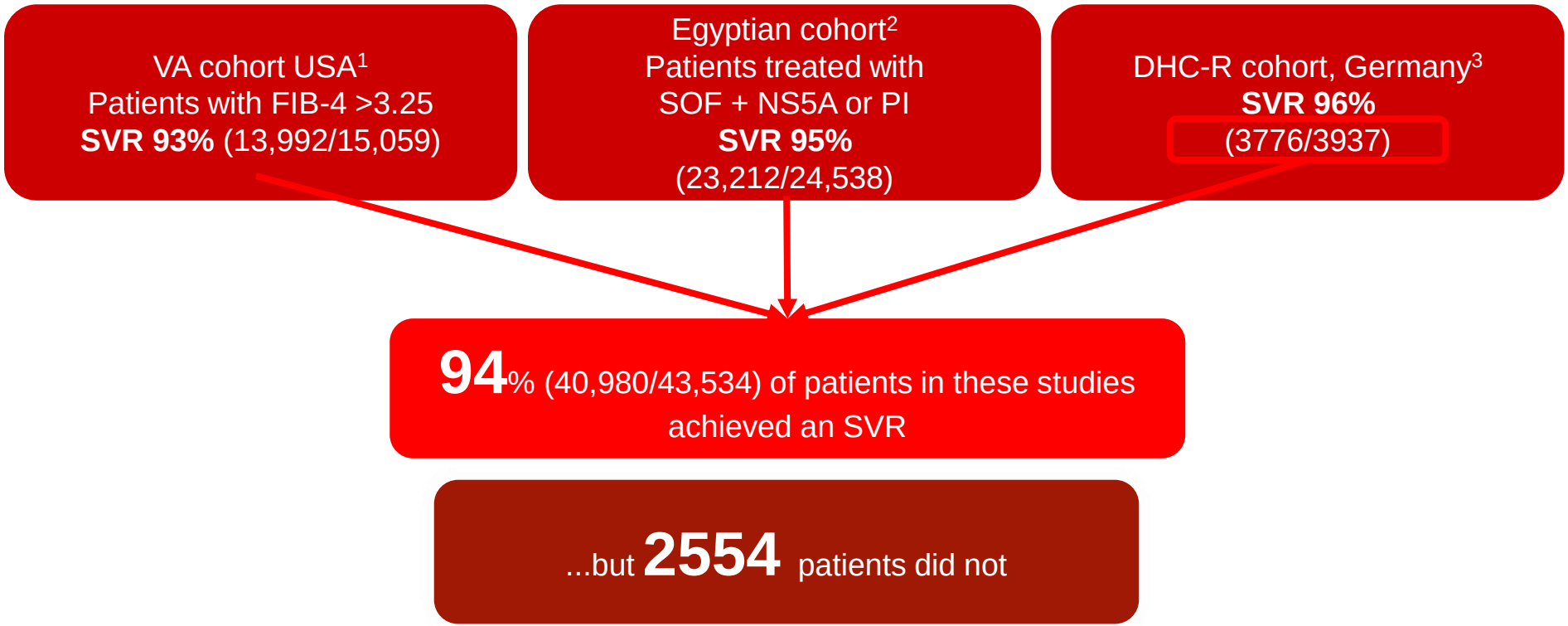
(66% F4 and 28% F3 stratified according to HCV Genotypes)



Viganò M et al DLD 2017

But 557 subjects did not achieved SVR

Patients who have experienced DAA treatment failure are a small but important HCV patient population



1. Backus LI, et al. Hepatology 2017;doi: 10.1002/hep.29408;
2. Gomaa A, et al. Hepat Med 2017;9:17–25;
3. Welzel TM, et al. ILC 2016; Poster #SAT-274

VA: Veterans Affairs; DHC-R: German Hepatitis C Registry

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Failure & Susceptibility to antiviral therapy.

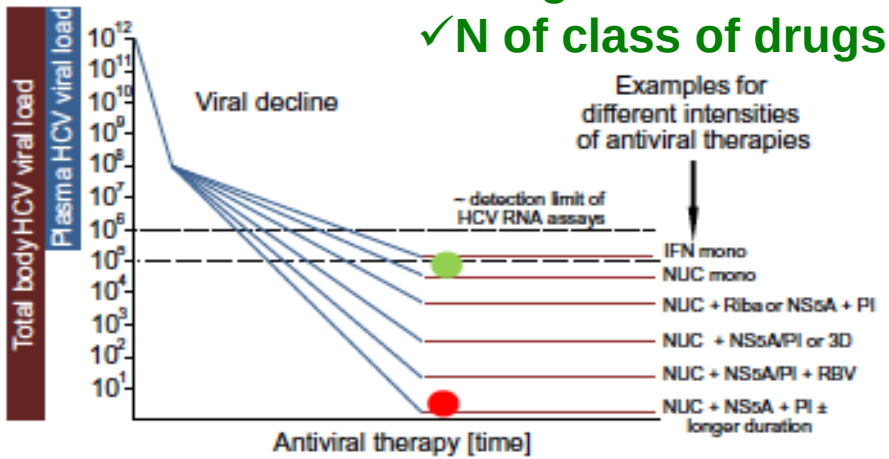
Different levels of suppression of HCV RNA are required for final eradication of the virus by the immune system

Depending on:

- viral- related factors:
  - **HCV Genotypes**
  - **RASs**
  - **Viremia**
- host-related factors:
  - **IL28b, IP-10, ISG→ Previous IFN failure**
  - **Fibrosis**
  - **Age & gender**

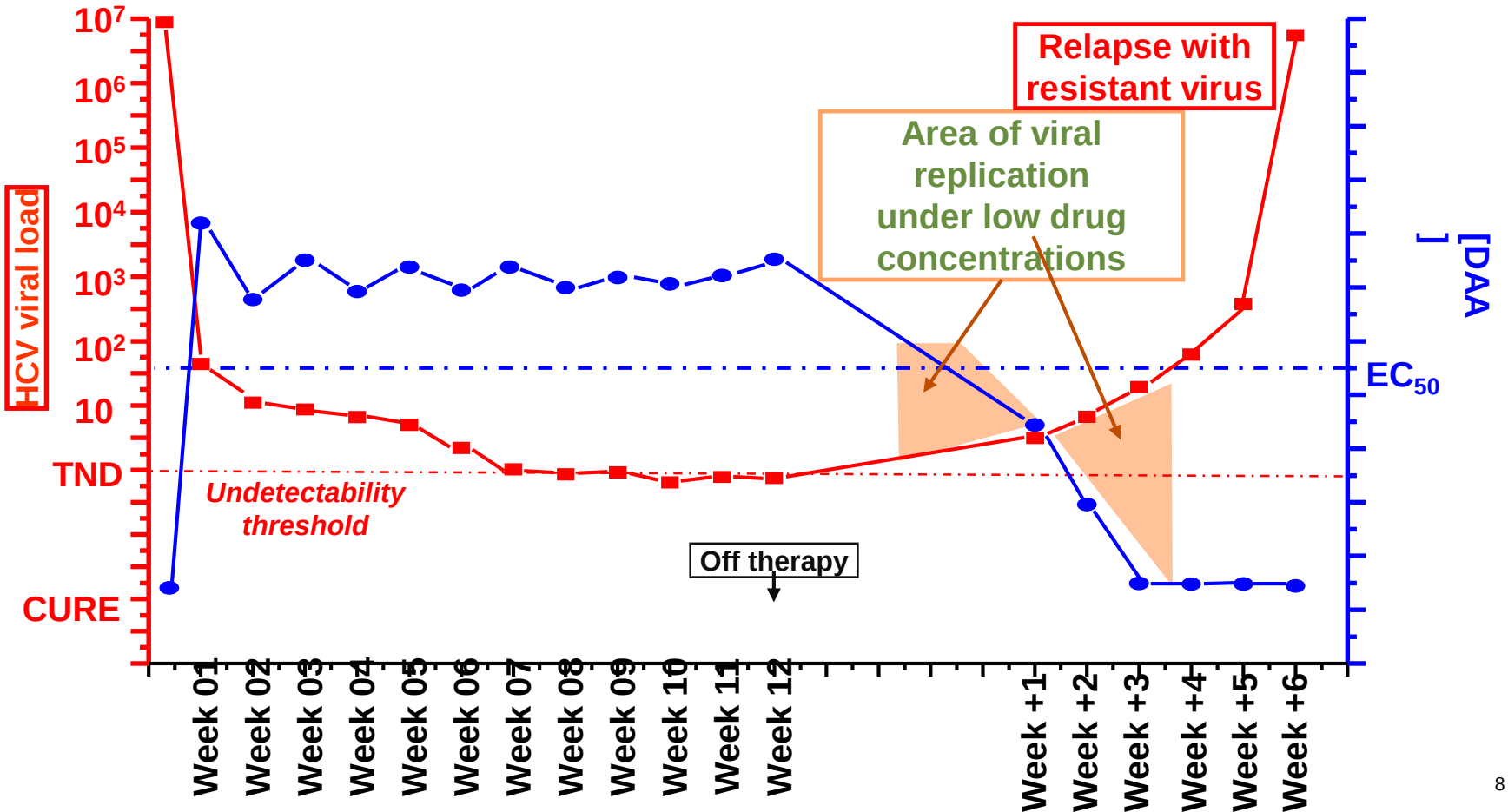
Failure:
- **Breakthrough**
- **Relapse**

Treatment Modulation by:
- ✓**Ribavirin use**
- ✓**Length of treatment**
- ✓**N of class of drugs**



Modified from Sarrazin C et al J Hepatol 2016

Relapse and resistance during DAA-based anti-HCV therapy



Management of treatment failures

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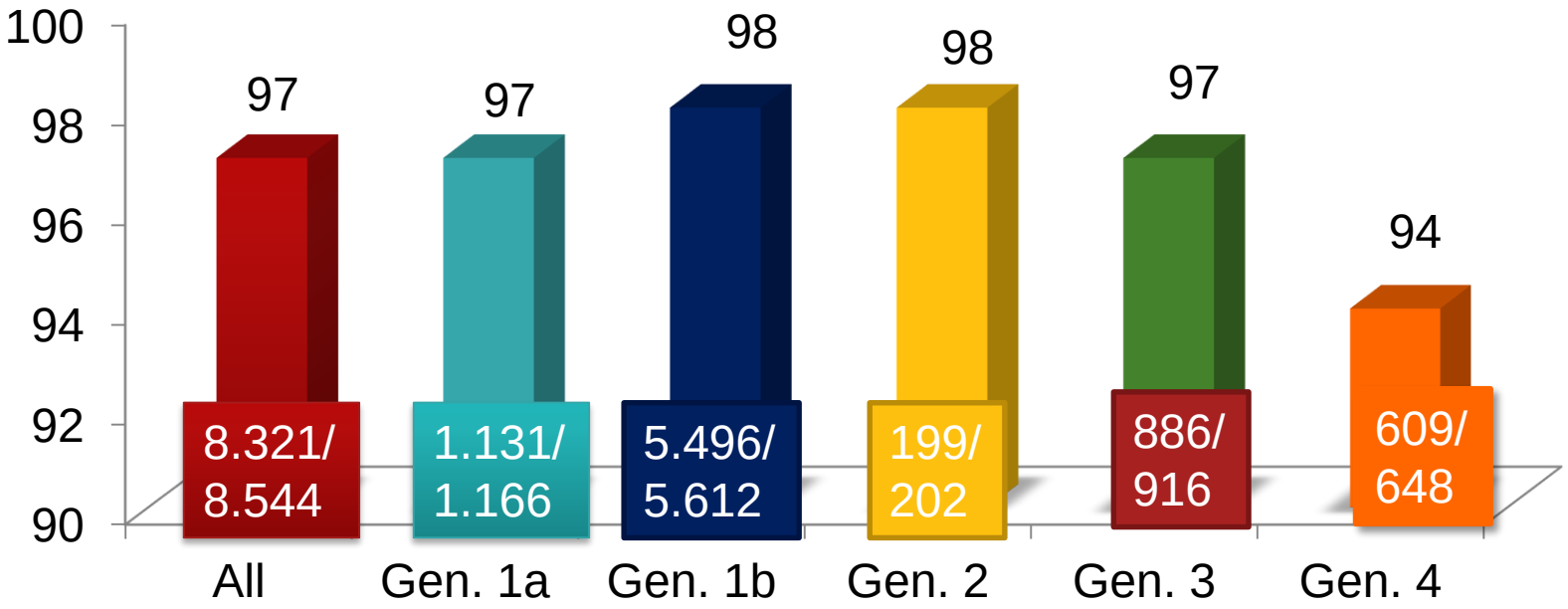
SVR12 in 8.544 HCV infected patients **treated according to EASL 2016 recommendations** in 4 Italian Regional Registries

(66% F4 and 28% F3 stratified according to HCV Genotypes)



But 223 (3%) subjects did not achieved SVR

Viganò M et al DLD 2017

Effectiveness of hepatitis C antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma

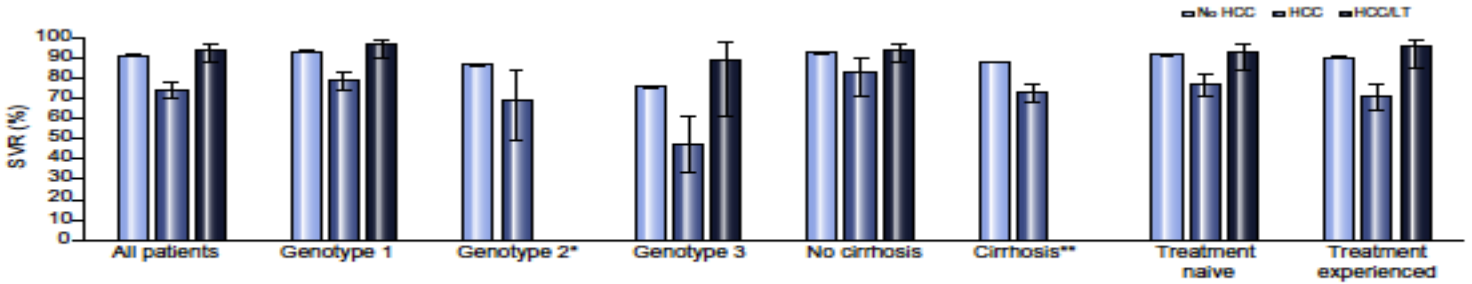


Fig. 1. SVR rates among patients with HCC, HCC/LT, and no HCC. SVR, sustained virologic response; HCC, hepatocellular carcinoma; HCC/LT, HCC with previous liver transplantation. *Bar not shown due to small subgroup <5 patients; **Bar not shown because all patients with HCC/LT were considered to be non-cirrhotic.

Table 3. Association between HCC and SVR in multivariable logistic regression models.

	All patients (n = 15,573)		Genotype 1 (n = 12,493)		Genotype 2 (n = 1,868)		Genotype 3 (n = 1,084)	
	AOR (95% CI)†	p value	AOR (95% CI)†	p value	AOR (95% CI)†	p value	AOR (95% CI)†	p value
No HCC	1	–	1	–	1	–	1	–
HCC	0.38 (0.29, 0.48)	<0.001	0.34 (0.26, 0.45)	<0.001	0.59 (0.25,1.38)	0.224	0.41 (0.22, 0.76)	0.005
HCC/LT	1.57 (0.75, 3.28)	0.23	1.89 (0.68,5.20)	0.21	0.10 (0.01, 0.82)	0.03	2.7 (0.58, 12.6)	0.20

† AOR: Adjusted odds ratio, by multivariable logistic regression modeling including age, gender, race/ethnicity, alcohol use disorders, genotype, subgenotype, HCV regimen, baseline HCV viral load, diabetes, treatment naive/experienced, cirrhosis, decompensated cirrhosis, platelet count, bilirubin, and albumin. HCC, hepatocellular carcinoma; HCC/LT, HCC with previous liver transplantation.

Beste LA J Hepatology 2017; 67: 32-39

Baseline characteristics of 310 HCV failures in Italy included in the "VIRONET" analysis

Patients, N		310
Males, N (%)		240 (77.4)
Age (years), Median (IQR)		58 (52-69)
Liver Transplant, N (%)[a]		7 (3.4)
Hepatocellular carcinoma, N (%)[a]		28 (12.1)
Cirrhotic patients, N (%)		251 (81.0)
Stiffness at baseline (kPa), Median (IQR)		17.9 (12.5-25.9)
HIV coinfection, N (%)[a]		14 (6.2)
Naïve patients, N (%)[a]		47 (34.1)
Treatment experienced, N (%)[a]		91 (65.9)
	Breakthrough	7 (7.7)
	Non-responder	35 (38.5)
	Relapse	29 (31.9)
	Other	20 (21.9)
	DAA experienced[a]	22 (15.9)
Unknown previous treatment		172 (55.5)
Baseline HCV-RNA (logIU/ml), Median (IQR)[a]		6.0 (5.4-6.5)
Baseline ALT (IU/ml), Median (IQR)[a]		76 (52-131)
	1a	70 (22.6)
	1b	119 (38.4)
HCV genotype/subtype	2 (a-b-c)	33 (10.6)
	3 (a-h)	52 (16.8)
	4 (a-d-n-v)	36 (11.6)

[a]Values were calculated according to the information available; IQR, interquartile range

Di Maio VC et al., EASL 2017

HCV sequencing is useful for identifying RASs but also the "correct" genotype: 15/310 (4.8%) patients were found infected with a different HCV genotype at failure

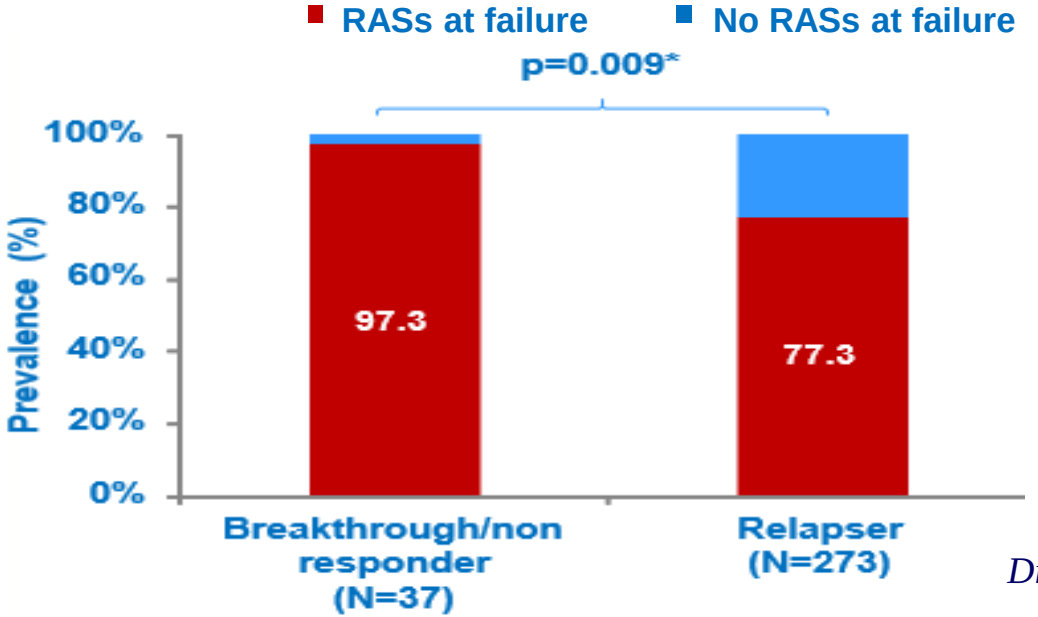
Notably, 10 patients previously classified as infected with HCV-1 were actually infected with HCV-2 and HCV-3, 9/10 failed a 3D+RBV regimen and all presented RASs at failure

ID Patient	Pre-therapy genotype by commercial assay	Genotype by sequencing at failure	DAA regimen	DAA response	Failure RASs		
					NS3	NS5A	NS5B
1497	**1a**	**3a**	3D+RBV	Non-responder		**Y93H**	
2150	**1a**	**3a**	3D+RBV	Breakthrough	**Q80K**	**Y93H**	
2068	**1b**	**3a**	3D	Non-responder	**Q80K**	**Y93H**	
1424	**1b**	**3a**	3D+RBV	Non-responder		**Y93H**	
2140	**1b**	**3a**	3D+RBV	Non-responder		**A30K**	
2353	**1**	**3a**	3D	Non-responder		**Y93H**	
1823	**1b**	**2c**	3D+RBV	Non-responder	**D168V**		
2020	**1b**	**2c**	3D	Non-responder	**D168V**	**F28C**	
2623	**1b**	**2c**	3D	Relapse		**F28C**	
2890	**1b**	**2c**	SMV+SOF	Relapse		**L31M**	
2204	2	1b	LDV+SOF+RBV	Relapse		R30Q+L31I+Y93H	C316N
2886	2	1b	SOF+RBV	Relapse	Y56F		C316N
2153	2	3a	SOF+RBV	Relapse		A30K+L31F	
1111	4	1a	2D+RBV	Breakthrough	V36M+Y56H	M28T	
45	4	3a	SMV+SOF	Relapse	D168K		

Di Maio VC et al., EASL 2017

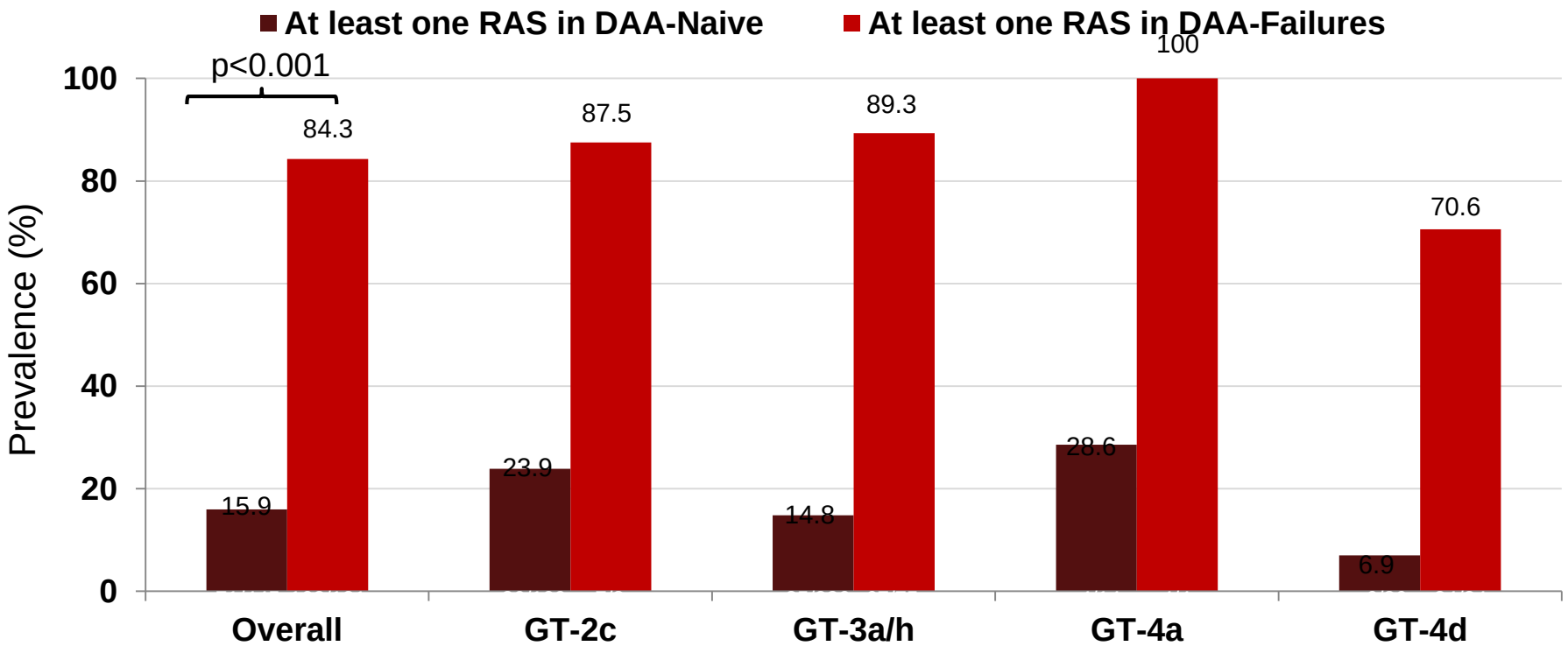
Overall, 247/310 patients (79.7%) showed at least one RAS related to the DAA-regimen at failure

RASs prevalence at failure was significantly higher in breakthrough/non-responders



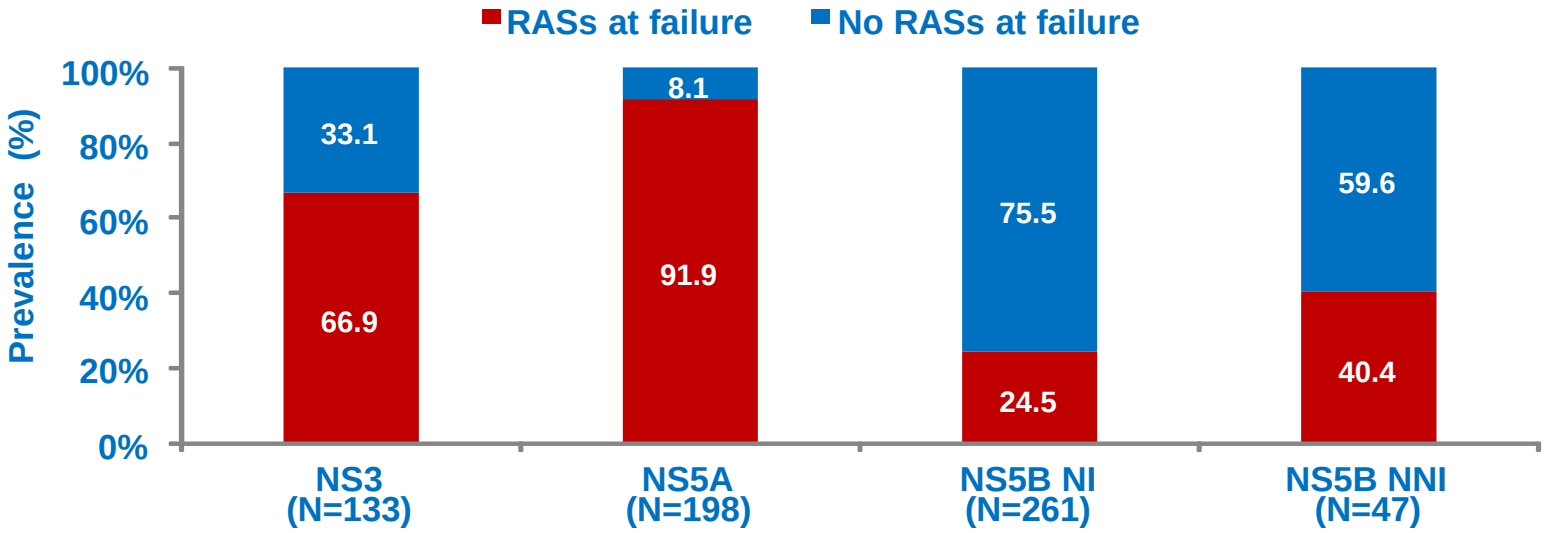
Di Maio VC et al., EASL 2017 & J Hepatol. 2017

At DAA failure, 84.3% of patients infected with non-1 GTs had at least 1 RAS



Di Maio VC et al., EASL 2018

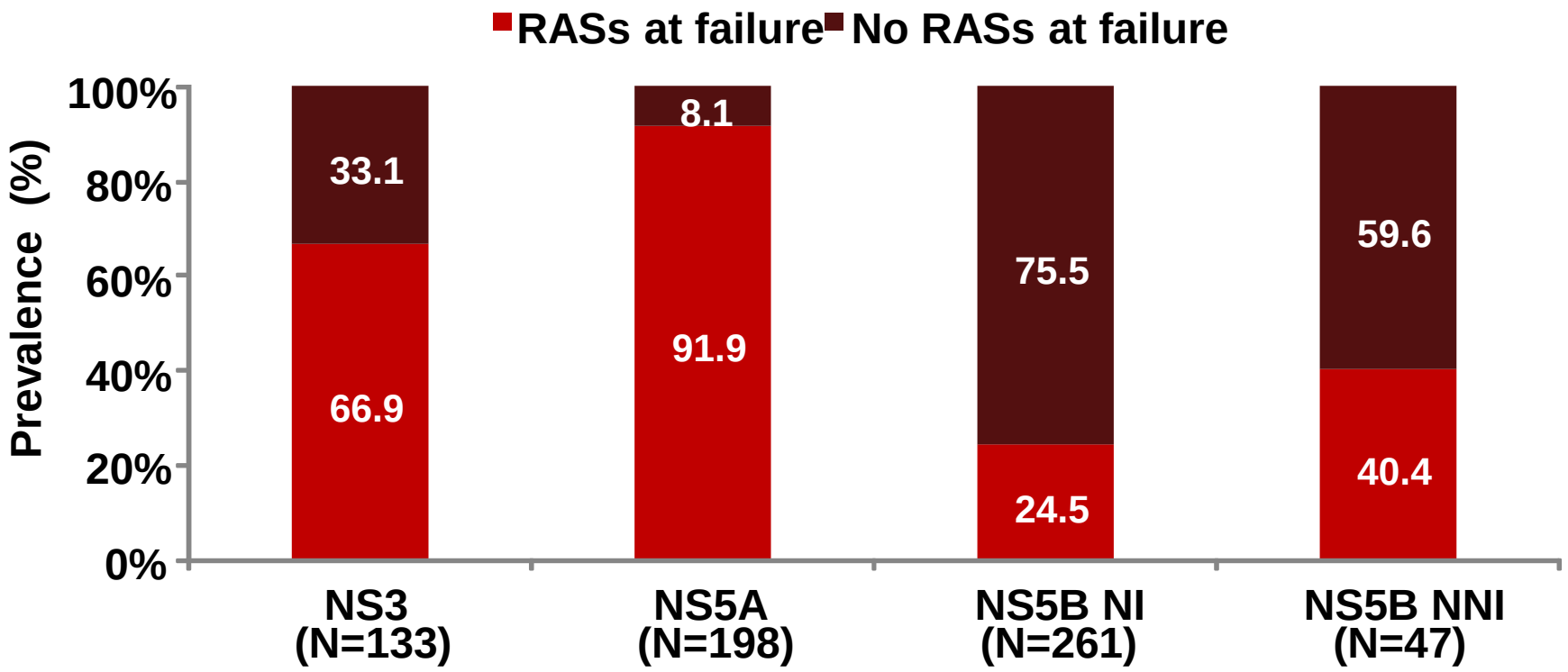
RASs prevalence was found in all genes tested: NS5A very frequent (92%), NS3 frequent (67%), NS5B less common (24-39%)



NI, Nucleotide inhibitor; NNI Non-Nucleoside Inhibitor

Di Maio VC et al., EASL 2017 & J Hepatol. 2017

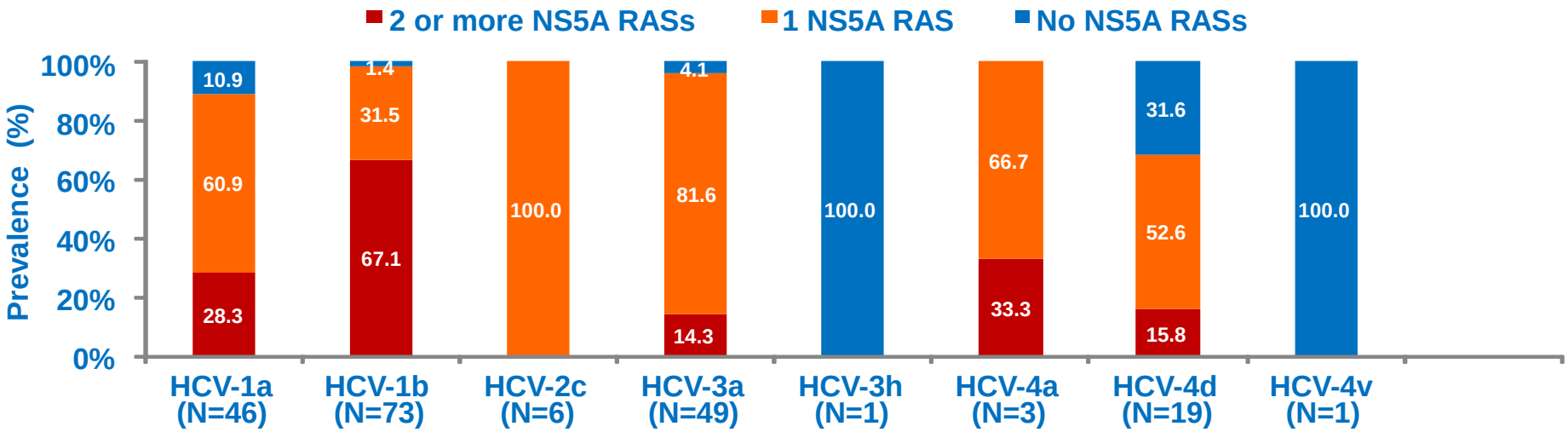
67% of NS3-failures and **92% of NS5A-failures** were associated with RASs emergence



NI, Nucleotide inhibitor; NNI Non-Nucleoside Inhibitor

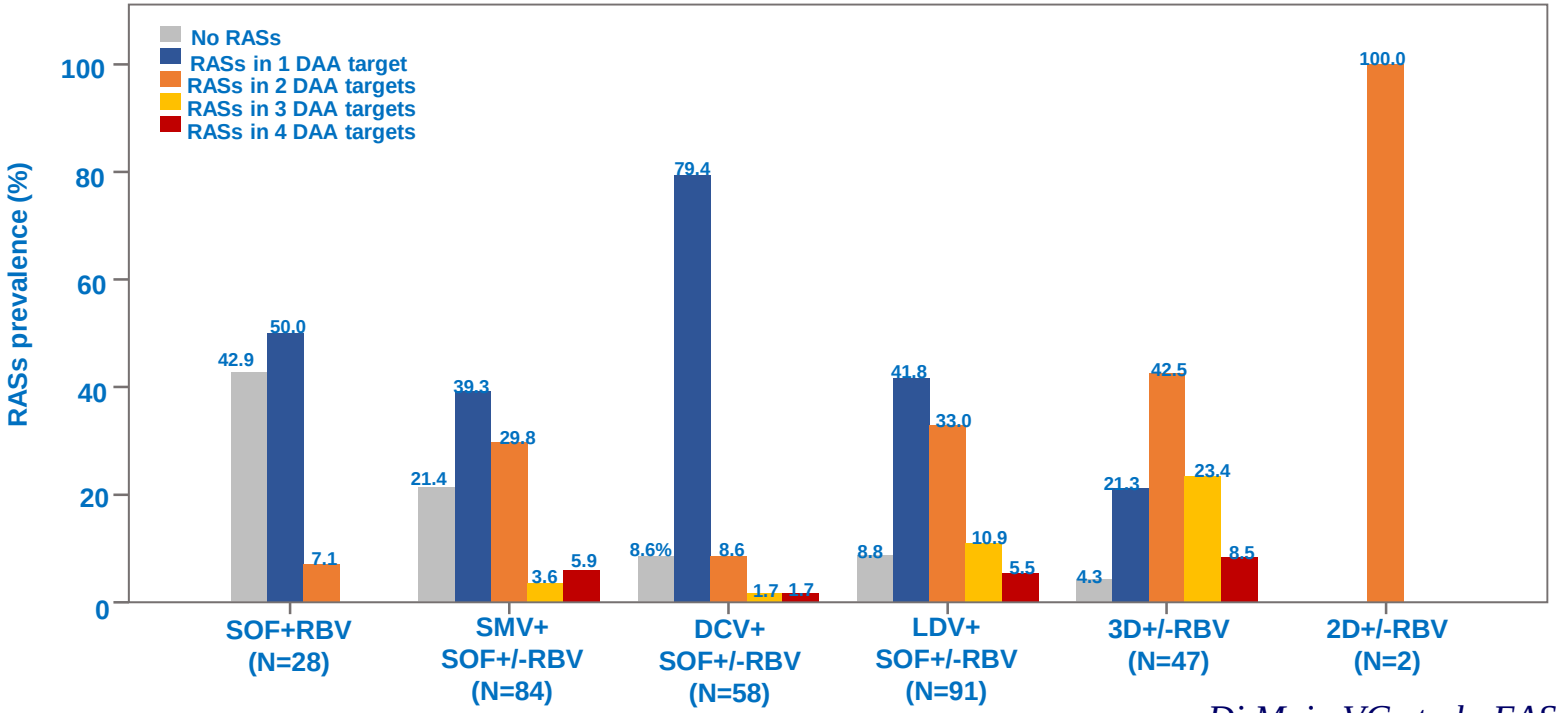
Di Maio VC et al., J Hepatol 2018

73/198 (36.9%) of NS5A-failing patients presented ≥2 NS5A-RASs



Di Maio VC et al., EASL 2017 & J Hepatol. 2017

Notably, 125/282 (44.3%) patients treated with ≥2 DAA classes showed RASs on ≥2 DAA-targets at failure



Di Maio VC et al., EASL 2017 & J Hepatol. 2017

Overall, the NS5B RAS S282T was detected in 9/277 (3.2%) of sofosbuvir failures

Prevalence of S282T was higher in SOF HCV-4 failing patient 4/35 (11.4%) compared to SOF HCV-1b failing patients 4/107 (3.7%; p= n.s.)

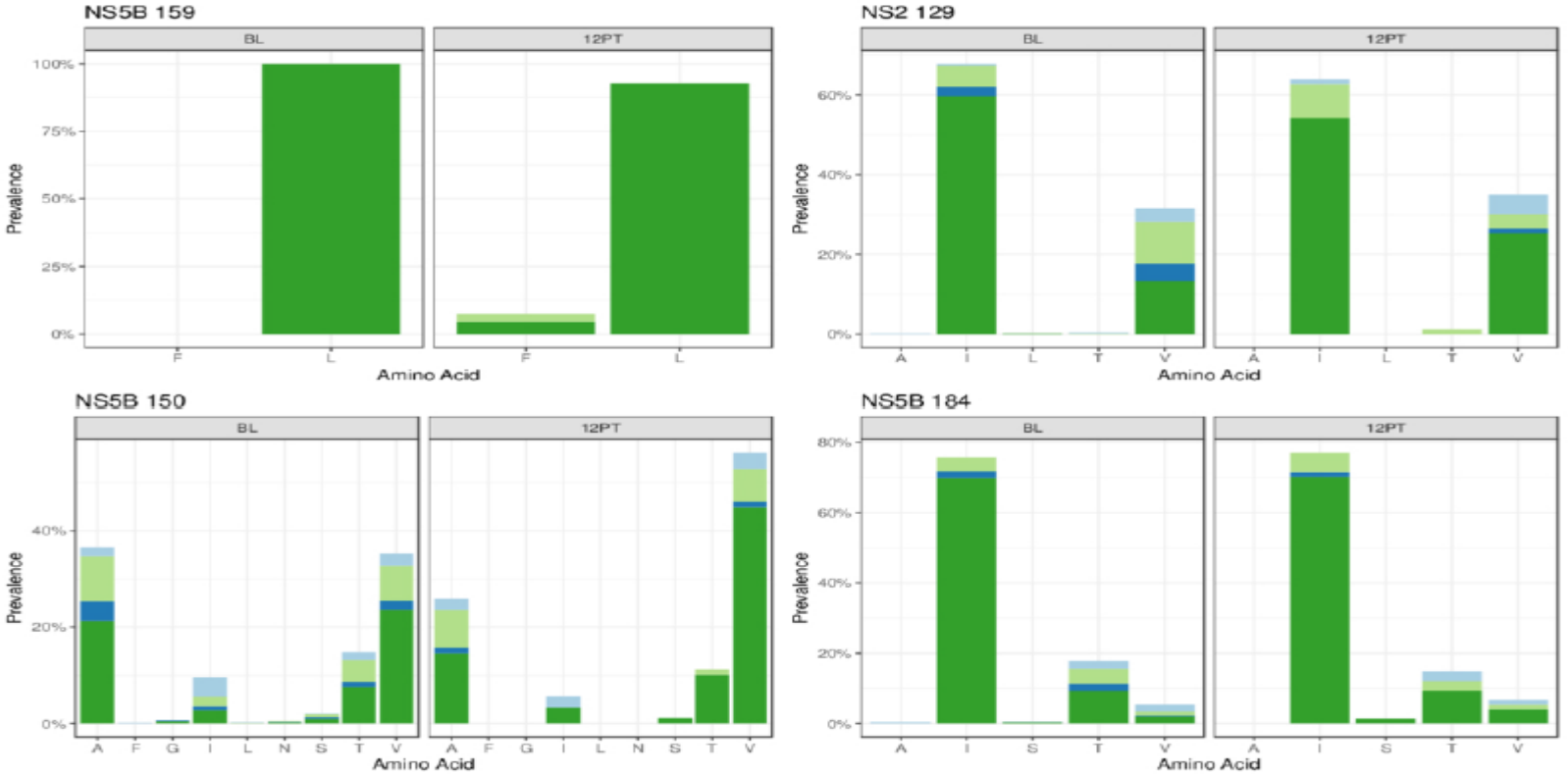
DAA Regimen	HCV geno/ subtype	DAA Outcome	Baseline RASs			Failure RASs		
			NS3	NS5A	NS5B	NS3	NS5A	NS5B
SMV+SOF	1b	Non-responder			L159F+C316N	D168V	L31M	L159F+**S282T**+C316N
SMV+SOF	4a	Breakthrough				Q80R+D168E		**S282T**
LDV+SOF	1b	Relapse					L31I+Y93H	L159F+**S282T**+C316N
LDV+SOF	1b	Relapse				Y56F+Q80L	Y93H	L159F+**S282T**+C316N
LDV+SOF	1b	Relapse					L28M+A92T/A+Y93C	**S282T/S**+S556G
LDV+SOF	4a	Breakthrough					L30H	**S282T**
LDV+SOF	4a	Breakthrough		V28M+Y93H			V28M+Y93H	**S282T**
LDV+SOF+RBV	4d	Breakthrough					L28V	**S282T**
DCV+SOF	3a	Relapse				D168Q	Y93H	**S282T**
SOF+RBV	2a	Relapse					L31M	**S282R+C316T+L320C**

Baseline resistance test not available

n.s., not significant

Di Maio VC et al., ICAR 2017

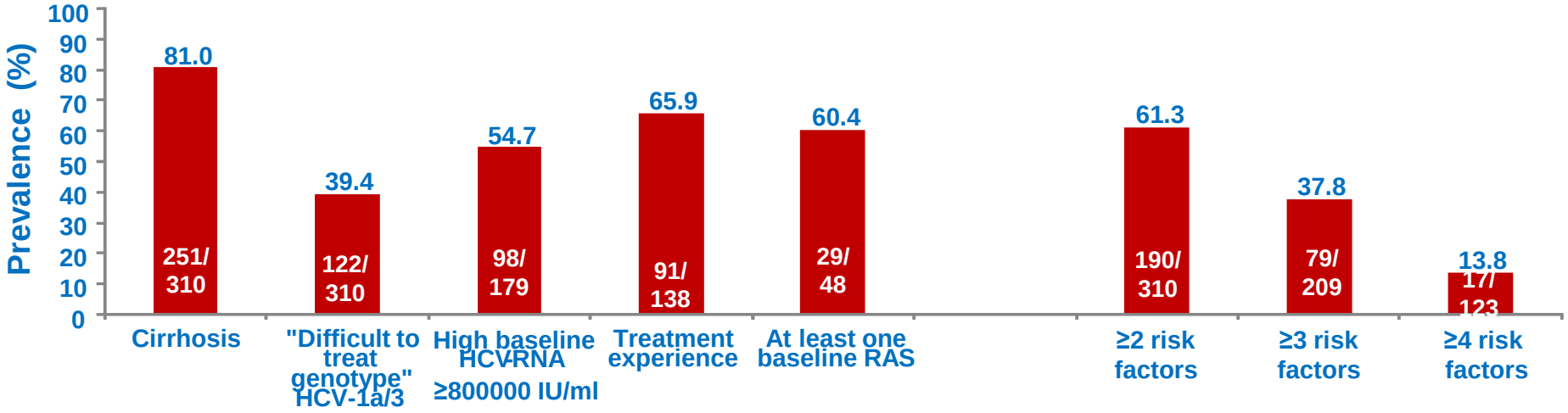
The L159F RAS and putative RASs NS2 I129V and NS5B A150V were significantly enriched in 12-weeks post treatment samples



Smith D et al., EASL 2018

2 or more failure risk factors were present at baseline in the majority of failing patients

60% of our failing patients already had natural RASs at DAA baseline



Di Maio VC et al., EASL 20
& J Hepatol[22] *20*

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Conditions for a broad use of HCV resistance testing in clinical practice

- A **standardized assay** should be available as a **purchasable kit**, **externally validated** for its performance and **easy to routinely used** in any virology laboratory with experience in molecular biology. Whatever the technology used, the assay should be able to reliably report the presence of RASs with **a validated and repeatable sensitivity of 15%** equivalent to population sequencing. (ii)
- **Interpretation and reporting** of HCV resistance data should be **homogenized and standardized** through **recommendations by an international organization.**
- **Clinically relevant RASs** should be **clearly identified**, and only these RASs should be reported and used for treatment decisions.
- **Guidelines** should be provided by international societies to guide **treatment decisions based on resistance testing results**, on the basis of data from **clinical trials and real-life studies** reporting strong predictive values of the different RAS profiles.

Pawlotsky JM Gastroenterology 2016

HCV Virology Italian Resistance Network Study Group: VIRONET-C

VIRONET-C BOARD: F Ceccherini-Silberstein (President), A Craxì (President), M Andreoni, CF Perno, M Puoti, M Zazzi.

STEERING COMMITTEE: S Bonora, M Brunetto, A Callegaro, MR Capobianchi, V Cento, G Gaeta, G Raimondo, T Santantonio.

PARTICIPATING VIROLOGISTS and PHYSICIANS: A Aghemo (Milano); A Alberti (Padova); P Andreone (Bologna); M Andreoni (Roma); G Angarano (Bari); M Angelico (Roma); A Antinori (Roma); G Antonelli (Roma); M Aragri (Roma); S Babudieri (Sassari); P Bagnarelli (Ancona); F Baldanti (Pavia); F Baldelli (Perugia); G Barbarini (Pavia); B Bartolini (Roma); ML Biondi (Milano); E Boeri (Milano); S Bonora (Torino); V Borghi (Modena); S Brillanti (Bologna); M Brunetto (Pisa); R Bruno (Pavia); S Bruno (Milano); B Bruzzone (Genova); F Caccuri (Brescia); AP Callegaro (Bergamo); V Calvaruso (Palermo) MR Capobianchi (Roma); N Caporaso (Napoli); G Cariti (Torino); A Caruso (Brescia); C Caudai (Siena); F Ceccherini-Silberstein (Roma); V Cento (Milano); A Ciaccio (Monza); A Ciancio (Torino); A (Parma); A Focà (Catanzaro); G Foti (Reggio Calabria); S Galli (Bologna); GB Gaeta (Napoli); E Galmozzi (Milano); AR Garbuglia (Roma); W Gennari (Modena); V Ghisetti (Torino); A Giacometti (Ancona); A Giorgini (Milano); A Gori (Monza); A Grieco (Roma); A Lai (Milano); A Licata (Palermo); P Lampertico (Milano); M Levrero (Roma); R Lionetti (Roma); F Maggiolo (Bergamo); S Malandrin (Monza); N Marascio (Catanzaro); S Marenco (Genova); C Mastroianni (Latina), S Menzo (Ancona); V Messina (Caserta); V Micheli (Milano); L Monno (Bari); F Morisco (Napoli); G Morsica (Milano); C Mussini (Modena); LA Nicolini (Genova); V Pace Palitti (Pescara); S Paolucci (Pavia); S Parisi (Padova); G Parruti (Pescara); C Pasquazzi (Roma); A Pellicelli (Roma); MO Pensi (Terni-Foligno); CF Perno (Milano); M Persico (Salerno); S Petta (Palermo); E Polilli (Pescara); T Pollicino (Messina); ML Ponti (Cagliari); G Portella (Napoli); T Prestileo (Palermo); M Puoti (Milano); M Quartini (Terni); G Raimondo (Messina); MC Re (Bologna); M Rendina (Bari); G Rizzardini (Milano); D Romagnoli (Baggiovara); T Ruggiero (Torino); MG Rumi (Milano); FP Russo (Padova); M Sanguinetti (Roma); R Santangelo (Roma); T Santantonio (Foggia); V Sangiovanni (Napoli); M Siciliano (Roma); A Soria (Monza); L Sticchi

https://www.vironetc.org/

Validazione Nazionale Test Resistenza HCV
NS3, NS5A, NS5B – GT1,2,3,4

I Fase (conclusa Febbraio 2018)

- 21 Centri Sanger Sequencing
- 1 Centro next generation sequencing

Validazione Nazionale
Test Resistenza HCV

Sanger Sequencing

1. Microbiologia e Virologia, ASST Papa Giovanni XXIII, Bergamo
2. Microbiologia Clinica, Virologia e Diagnostica delle Bioemergenze, ASST Fatebenefratelli Sacco, Milano
3. Microbiologia e Virologia, San Raffaele, Milano
4. Microbiologia e Virologia, Ospedale Maggiore Policlinico, Università di Milano, Milano
5. Virologia Molecolare, Fondazione Policlinico San Matteo, Pavia
6. Laboratorio di Microbiologia e Virologia - ospedale Amedeo di Savoia ASL Città di Torino, Torino
7. Microbiologia e Virologia, Azienda Ospedaliero Universitaria Policlinico di Modena, Modena
8. Microbiologia, Ospedale S.Orsola-Malpighi, Bologna
9. UO Igiene, IRCCS AOU San Martino - IST, Genova
10. Virologia, Ospedali riuniti di Ancona, Ancona
11. Virologia, Azienda Ospedaliero Universitaria di Pisa, Pisa
12. Epatologia, Azienda Ospedaliero Universitaria di Pisa, Pisa
13. Virologia, Policlinico S. Maria alle Scotte, Siena
14. Virologia, INMI Lazzaro Spallanzani, Roma
15. Microbiologia, Policlinico Universitario Agostino Gemelli, Roma
16. Virologia Molecolare, Fondazione Policlinico Tor Vergata, Roma
17. Microbiologia e Virologia, Azienda Ospedaliera dei Colli, Cotugno - Napoli
18. Malattie Infettive, Seconda Università di Napoli, Napoli

Validazione Nazionale
Test Resistenza HCV

The sequencing protocols used by the 22 centers allowed full coverage of NS3 and NS5A positions associated with resistance.

With respect to next-generation sequencing results, 12 labs had 0-1 RAS discordance, 3 labs had 2 discordances, and 1 lab had 4 discordances.

- Accuracy for NS3 sequencing ranged from 83.3% to 100%.

https://www.vironetc.org/

Validazione Nazionale Test Resistenza HCV
NS3, NS5A, NS5B – GT1,2,3,4

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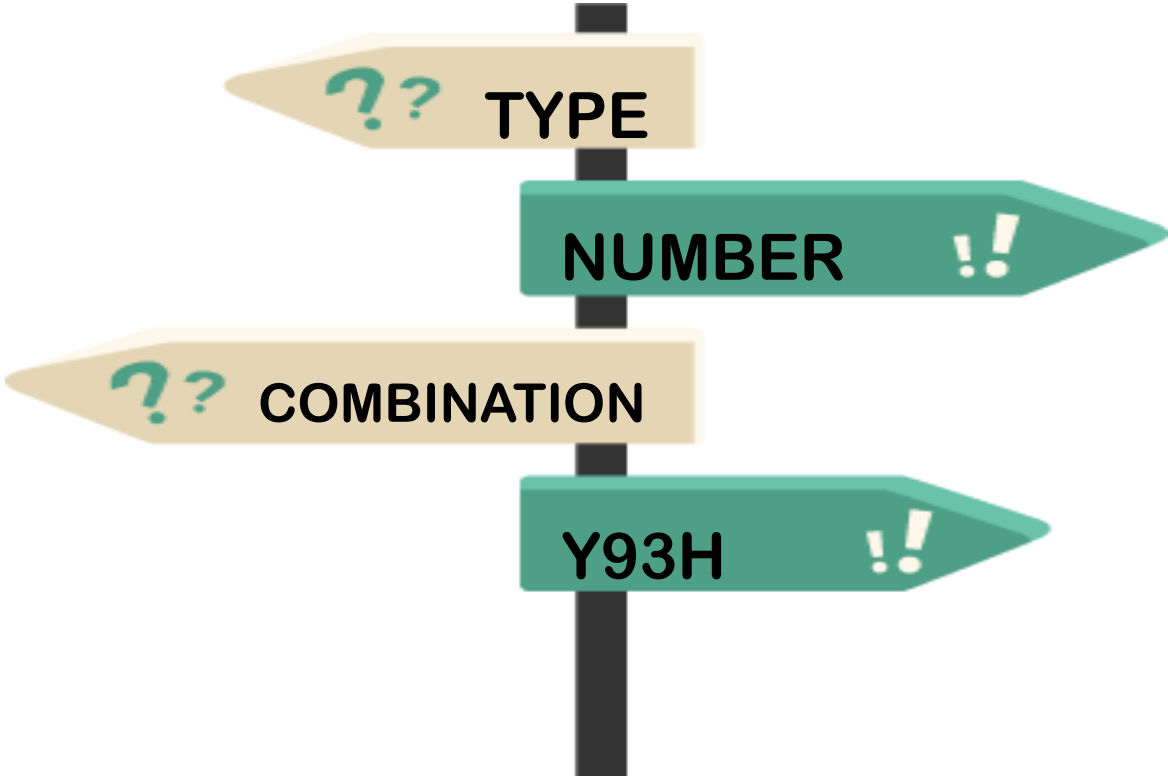
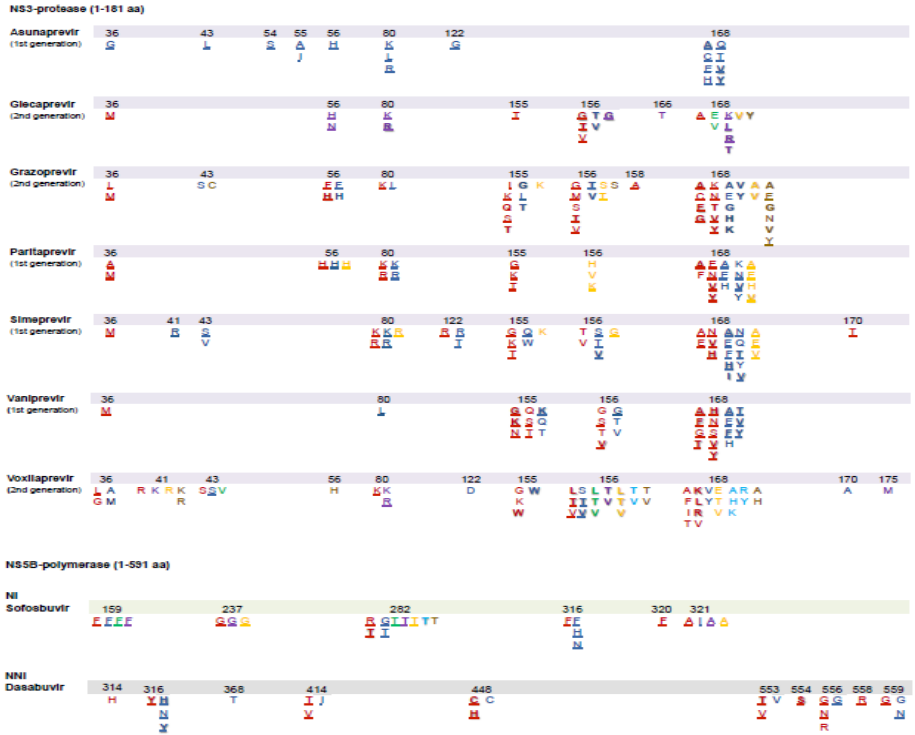
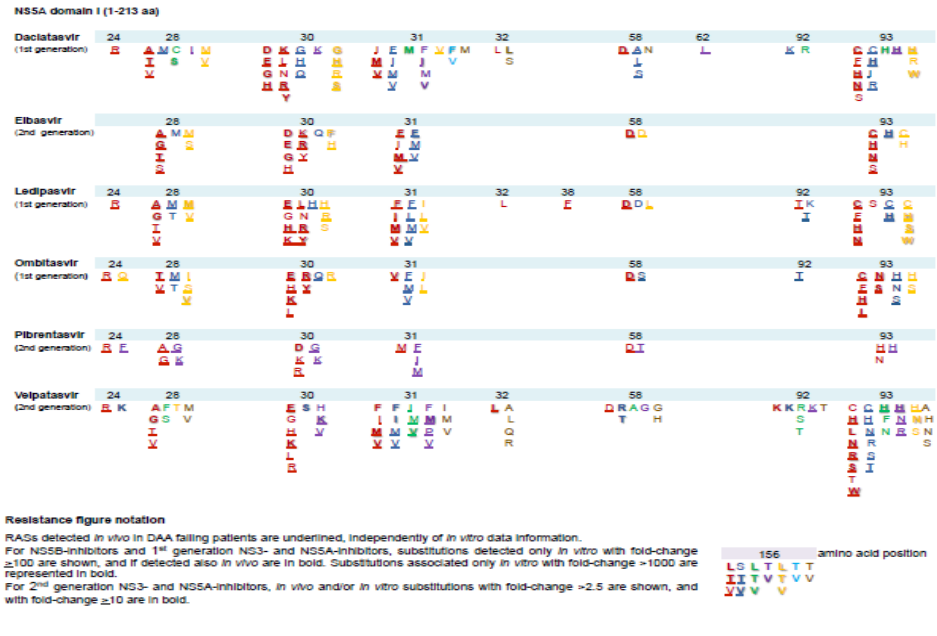
HCV Resistance Issue After Failure: what should I look at?

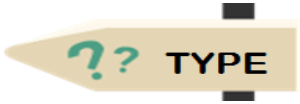


A stunning number of RASs have been reported in literature





Sorbo MC et al., Drug Res Updates 2018



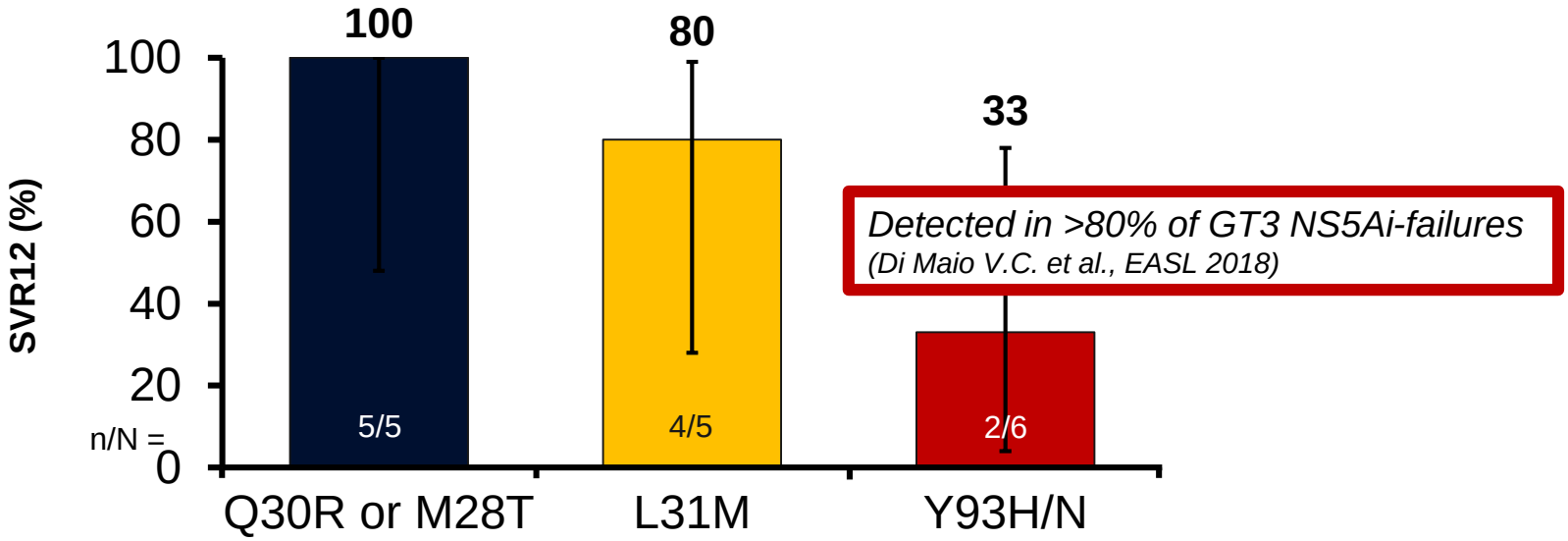
Not all NS5A RASs are created equal

Fold Change	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Ledipasvir	20x	> 100x	> 100x/ > 100x	> 1000x/ > 10,000x		> 100x/--
Ombitasvir	> 1000x	> 100x	< 3x / > 100x	> 10,000x/ > 10,000x	< 10x	20x/50x
Daclatasvir	> 100x	> 1000x	> 100x/ > 1000x	> 1000x/ > 10,000x	< 10x	20x/50x
Elbasvir	20x	> 100x	> 10x / > 100x	> 1000x/ > 1000x	< 10x	> 100x/--
Pibrentasvir	< 3x	< 3x	< 3x	< 10x	< 3x	< 3x
Velpatasvir	< 10x	< 3x	20x/50x	> 100x/ > 1000x	< 3x	< 3x/--

Wang C, et al. Antimicrob Agents Chemother. 2012;56:1588-1590. Cheng G, et al. EASL 2012. Abstract 1172. Zhao Y, et al. EASL 2012. Abstract A845. Yang G, et al. EASL 2013. Abstract 1199. Ng T, et al. CROI 2014. Abstract 639. Asante-Appiah E, et al. AASLD 2014. Abstract 1979. Krishnan P, et al. Antimicrob Agents Chemother. 2015;59:979-987. Fridell RA, et al. Hepatology. 2011;54:1924-1935. Liu R, et al. Antimicrob Agents Chemother. 2015;59:6922-6929. Lawitz EJ, et al. Antimicrob Agents Chemother. 2016;60:5368-5378; Sorbo CM, et al. Drug Res Update 2018.

Differential impact of NS5A RASs during retreatment with a cross-resistant regimen

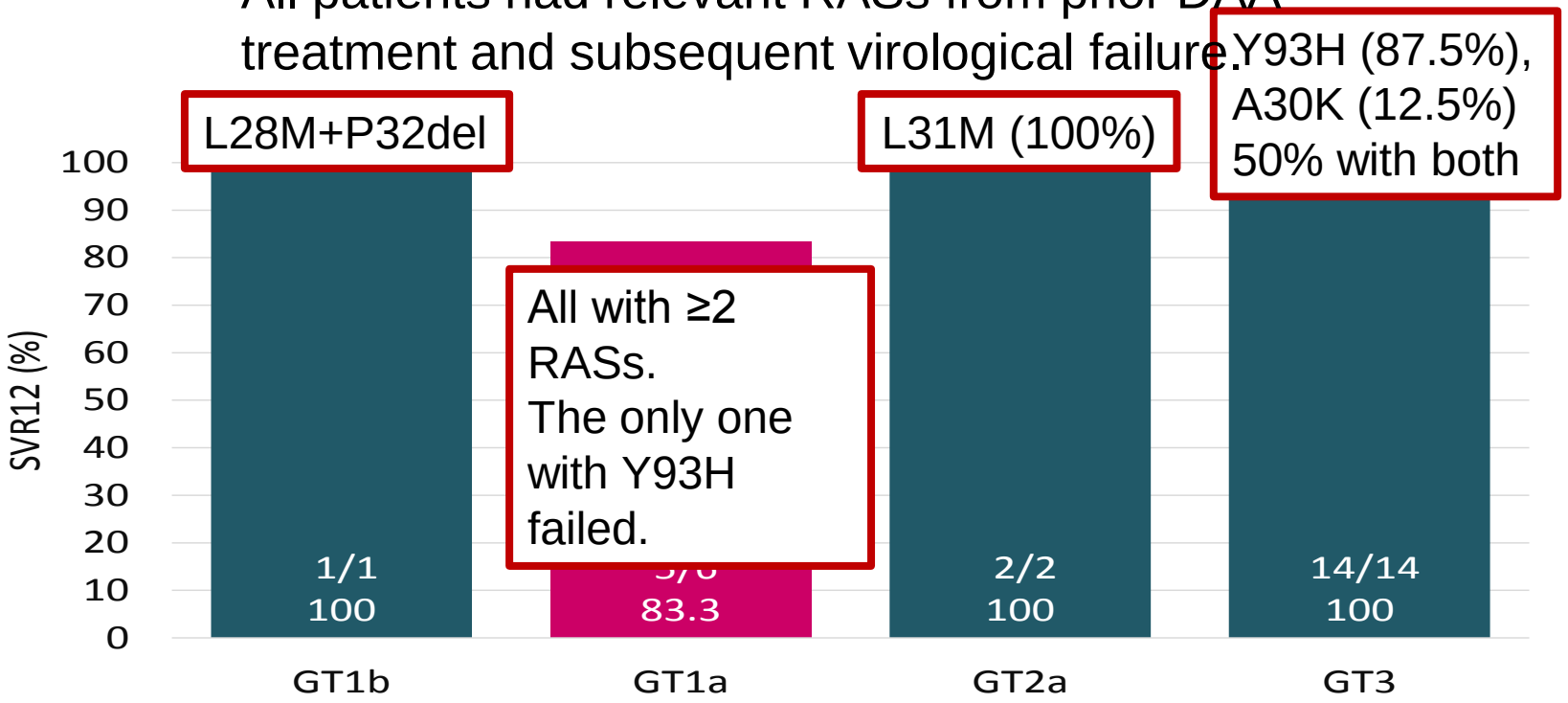
- 8-wk or 12-wk LDV/SOF-based treatment failures retreated with LDV/SOF for 24 wks (N = 41)



Lawitz E, et al. EASL 2015. Abstract O005.

96% SVR12 in G/P failures following G/P+SOF retreatment

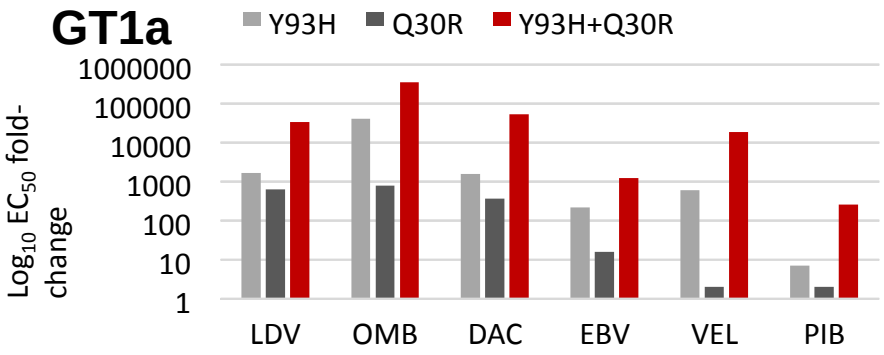
All patients had relevant RASs from prior DAA treatment and subsequent virological failure.

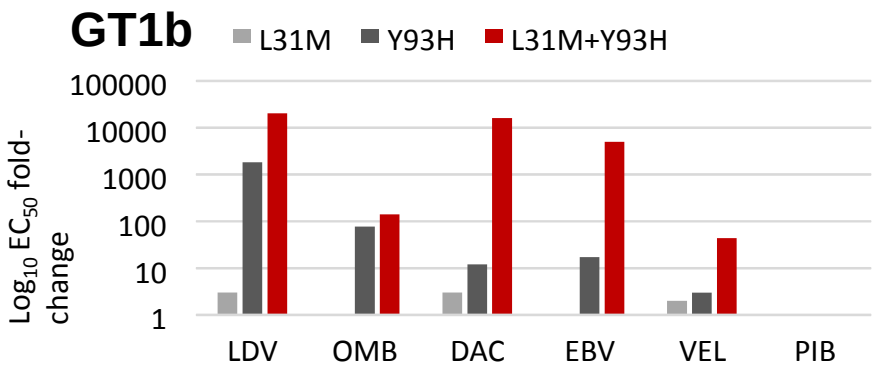


Wyles D, et al. EASL 2018. Abstract PS-040

NS5Ai EC_{50} exponentially increases when 2 or more RASs are present at the same time

	RASs	EC_{50} fold-change					
		LDV	OMB	DAC	EBV	VEL	PIB
GT1a	**Y93H**	1677	41383	1600	220	609	7
	Q30R	632	800	365	16	2	2
GT1b	**L31M**	3	1	3	1	2	1
	Y93H	1807	77	12	17	3	1

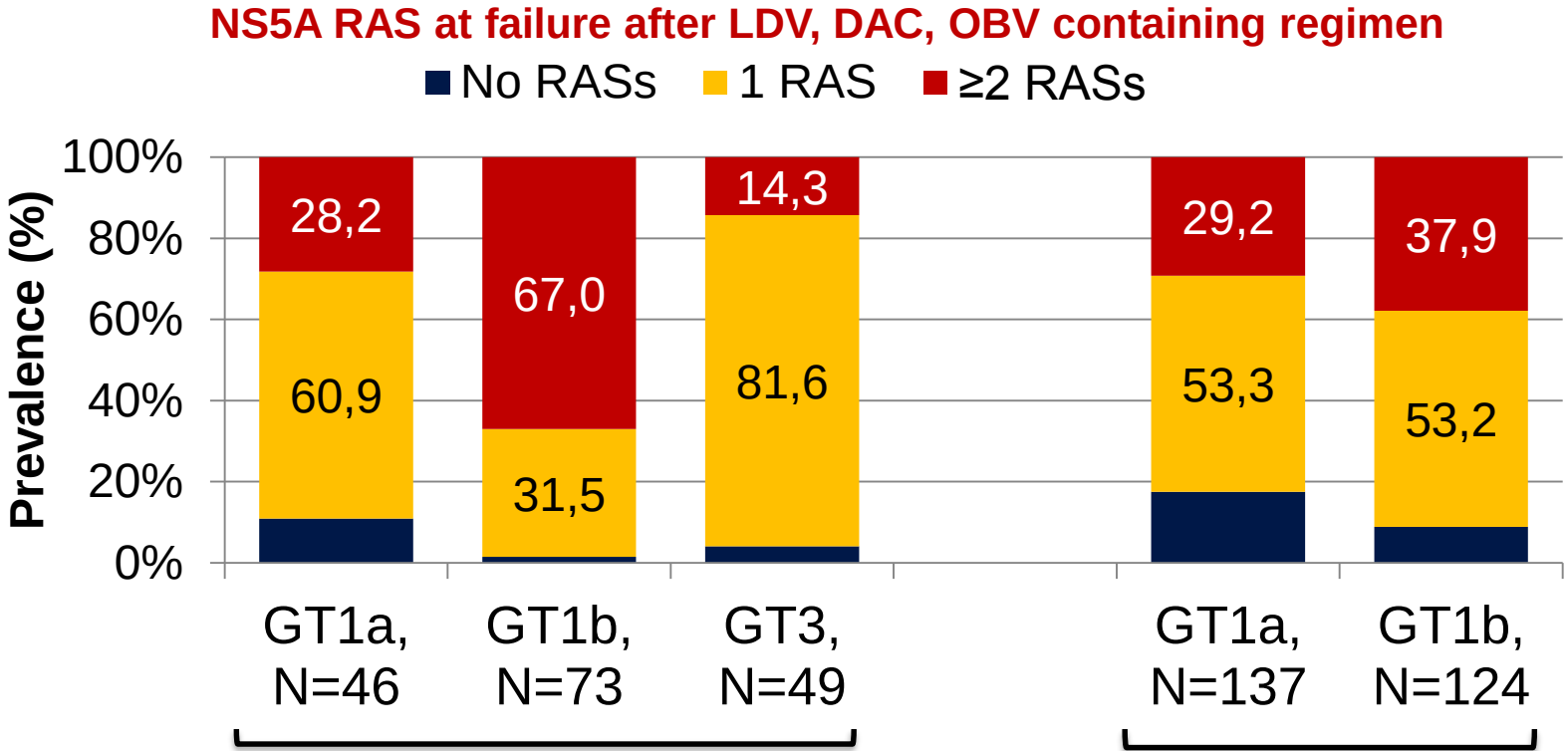




Harrington et al, Hepatology 2017; Sorbo MC et al., Drug Res Update 2018

NUMBER !!

Prevalence of single and multiple NS5A resistance associated substitutions in after NS5A-inhibitor failure



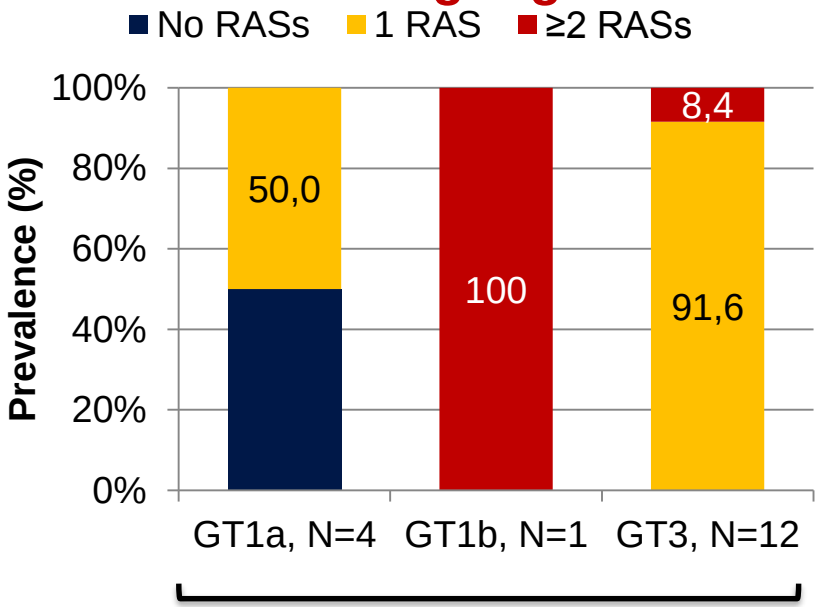
Di Maio VC, et al., J Hepatol. 2018 Mar;68(3):597–600.

Dietz J, et al., Gastroenterology. 2018 Mar;154(4):976–988.

NUMBER !!

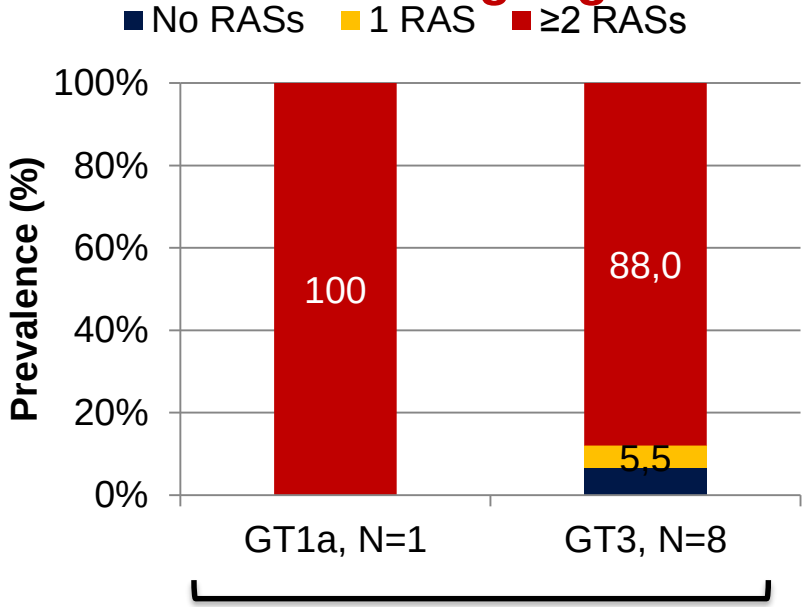
Prevalence of single and multiple NS5A resistance associated substitutions in after NS5A-inhibitor failure

NS5A RAS at failure after VEL containing regimen



Hezode C, et al., J Hepatol. 2018 May;68(5):895–903.

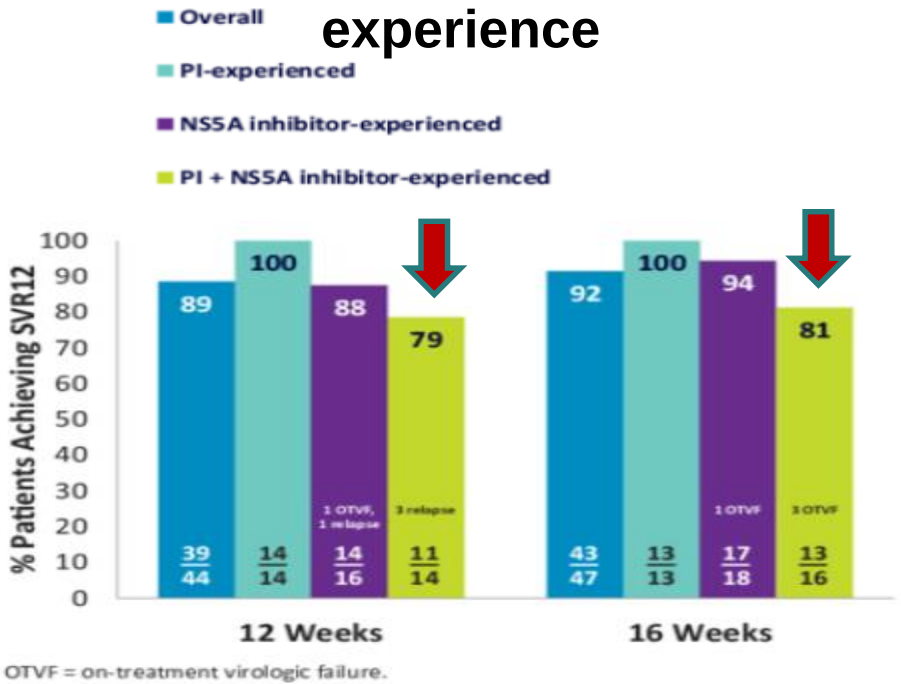
NS5A RAS at failure after PIB containing regimen



Puoti M, et al., J Hepatol. 2018 Mar 15.

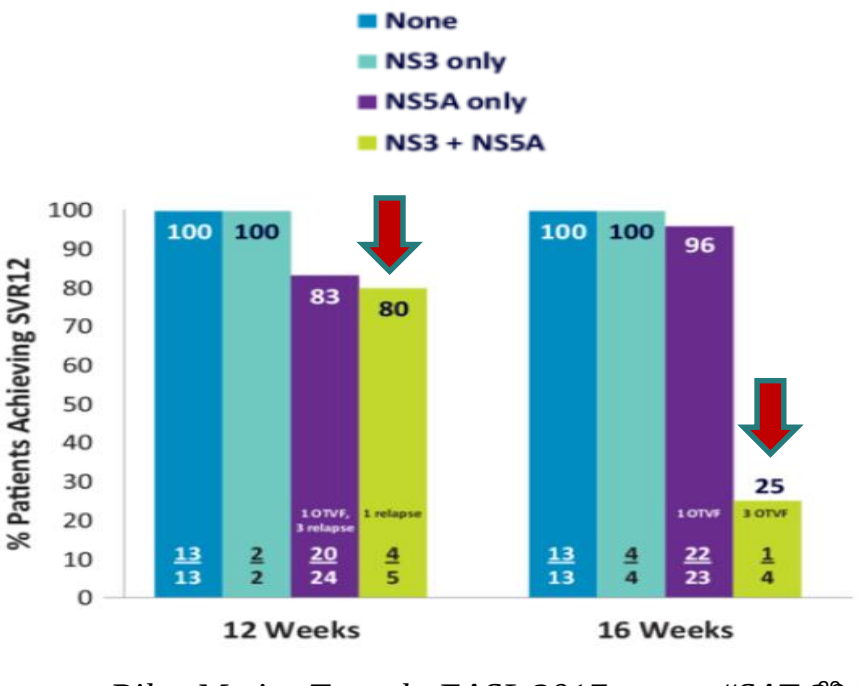
MAGELLAN-I: efficacy of glecaprevir/pibrentasvir in DAA-experienced patients can be reduced by double-class RASs

SVR_{12} rate by prior DAA-experience



OTVF = on-treatment virologic failure.

SVR_{12} rate by baseline RASs

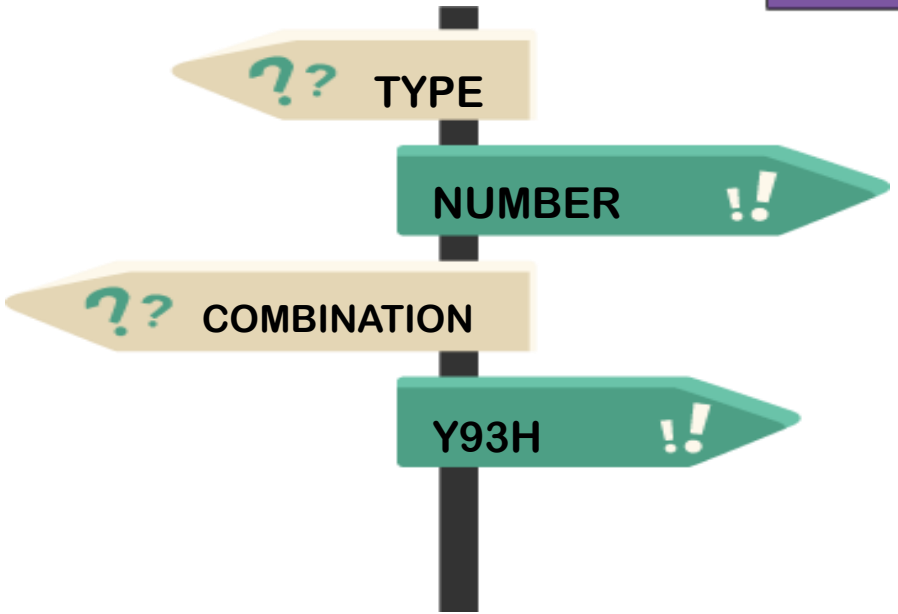


Pilot-Matias T. et al., EASL 2017 poster #SAT-204

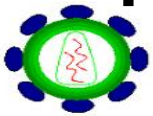

Digestive
and Liver
Disease


JOURNAL
OF HEPATOLOGY
EASL Recommendations
Treatment of Hepatitis C 2018

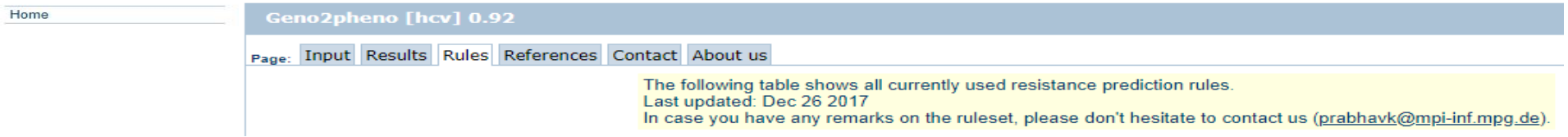

DRUG
RESISTANCE
Updates


TYPE
NUMBER
COMBINATION
Y93H

https://hcv.geno2pheno.org/

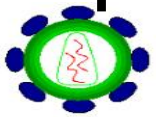


DZIF HEINRICH HEINE UNIVERSITÄT DÜSSELDORF HIV-GRADE max planck institut informatik



- Geno2pheno$_{[HCV]}$ is the first web-based, freely accessible server offering **detailed sub-genotyping** of HCV as well as **analysis of DAA-susceptibility for each drug target**.
- The server and algorithms are updated regularly in order to incorporate knowledge derived from comprehensive review of the latest literature and conference reports on both licensed and upcoming drugs. In addition, we are integrating viral and clinical data from our collaborating partners.
- Geno2pheno$_{[HCV]}$ is widely popular and has received more than 38,000 queries in 2017.

https://hcv.geno2pheno.org/



DZIF HIV-GRADE

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Home

Geno2pheno [hcv] 0.92

Page: Input | Results | Rules | References | Contact | About us

NEW Resistance associated rules were last updated on Dec 26 2017. In case you observe any problems, please don't hesitate to contact us (prabhavk@mpi-inf.mpg.de)

Sequence Information

Identifier:	1
Genetic region:	NS5A
Predicted subtype:	1b (Similarity of DNA to closest reference = 91.81%)
Codons covered in *NS5A* region:	1 - 195
Mutations in *NS5A* region:	K6R, L28M, L34V, K44R, Q62H, C80?, I90V, Y93H, V164A, E171D, V174S, L183P
Warnings *NS5A* region:	Sequence contains deletions.
Reference used:	D90208

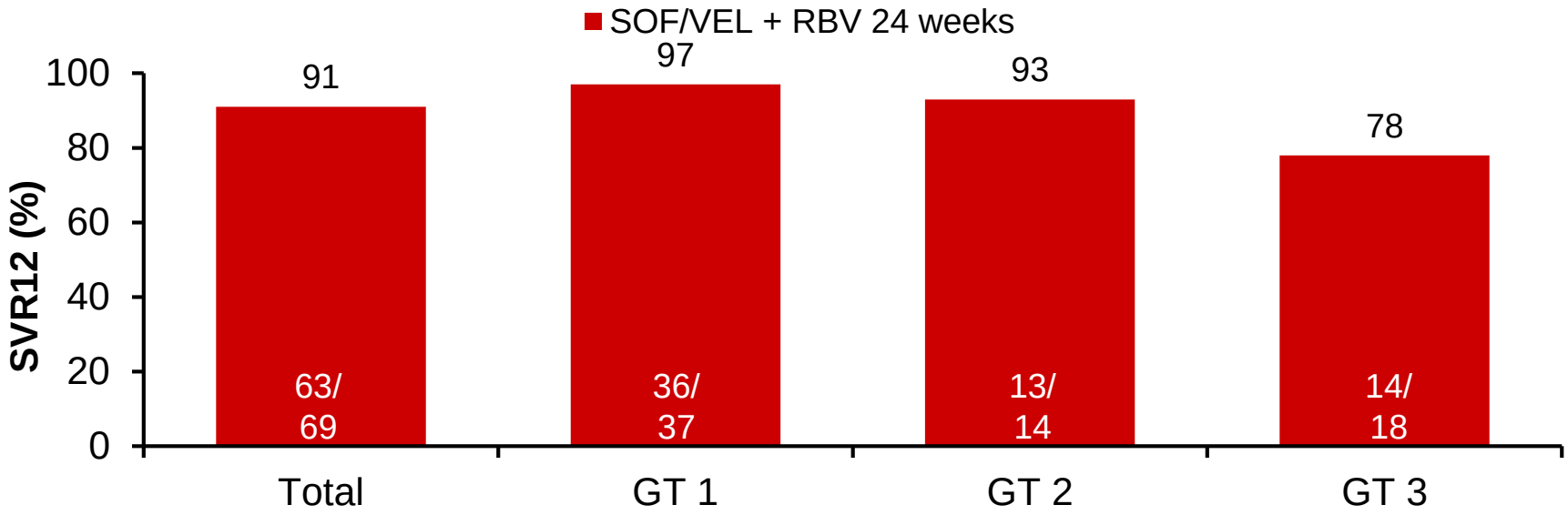
Drug Resistance

Drugs	Scored mutations	Resistance analysis	
Daclatasvir	28M,93H	resistant	
Elbasvir	93H	resistant	
Ledipasvir	28M,93H	resistant	
Ombitasvir	28M,93H	resistant	
Pibrentasvir	none	susceptible	
Velpatasvir	93H	resistant	

Management of treatment failures

- Management of DAA Experienced
  - Epidemiology
  - Causes of Treatment failure
  - Patients profile
  - Re-treatment “ a la carte”: role of RAS testing
  - Re treatment with a fixed menu: data from registration studies
  - Overview of International recommendations

SOF/VEL + RBV for 24 weeks in NS5A inhibitor-experienced patients

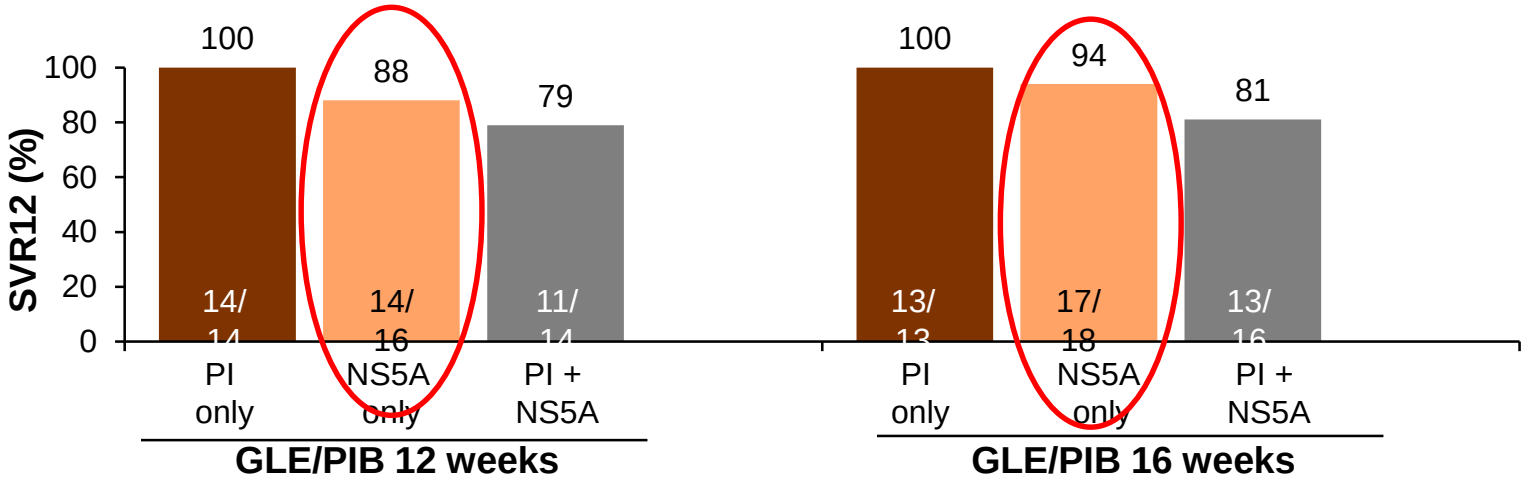


Gane E, et al. Hepatology 2017;66:1083–9

Efficacy of GLE/PIB in DAA-experienced GT 1 patients

MAGELLAN-1, part 2: randomised, open-label, Phase 2 study

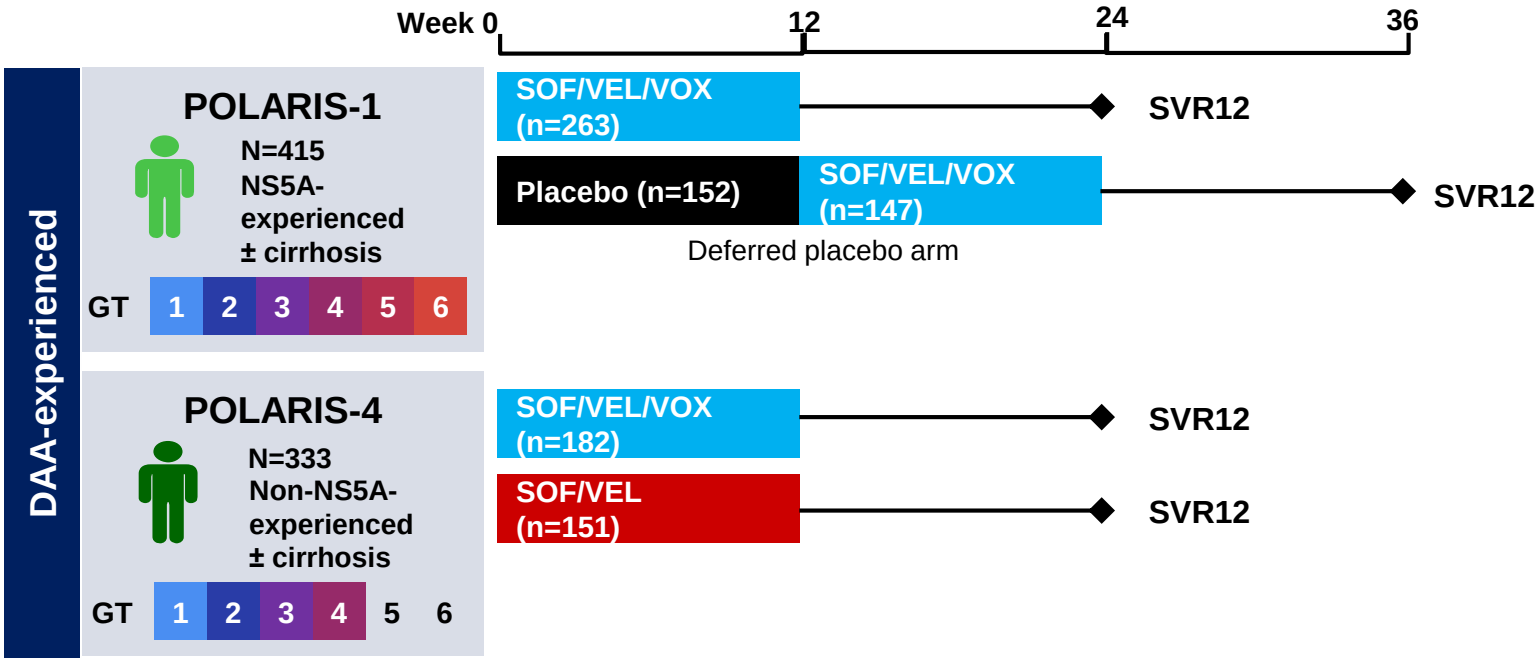
Virological response in PI- and/or NS5A inhibitor-experienced patients without and with cirrhosis



Poordad F, et al. ILC 2017; Abstract #PS156

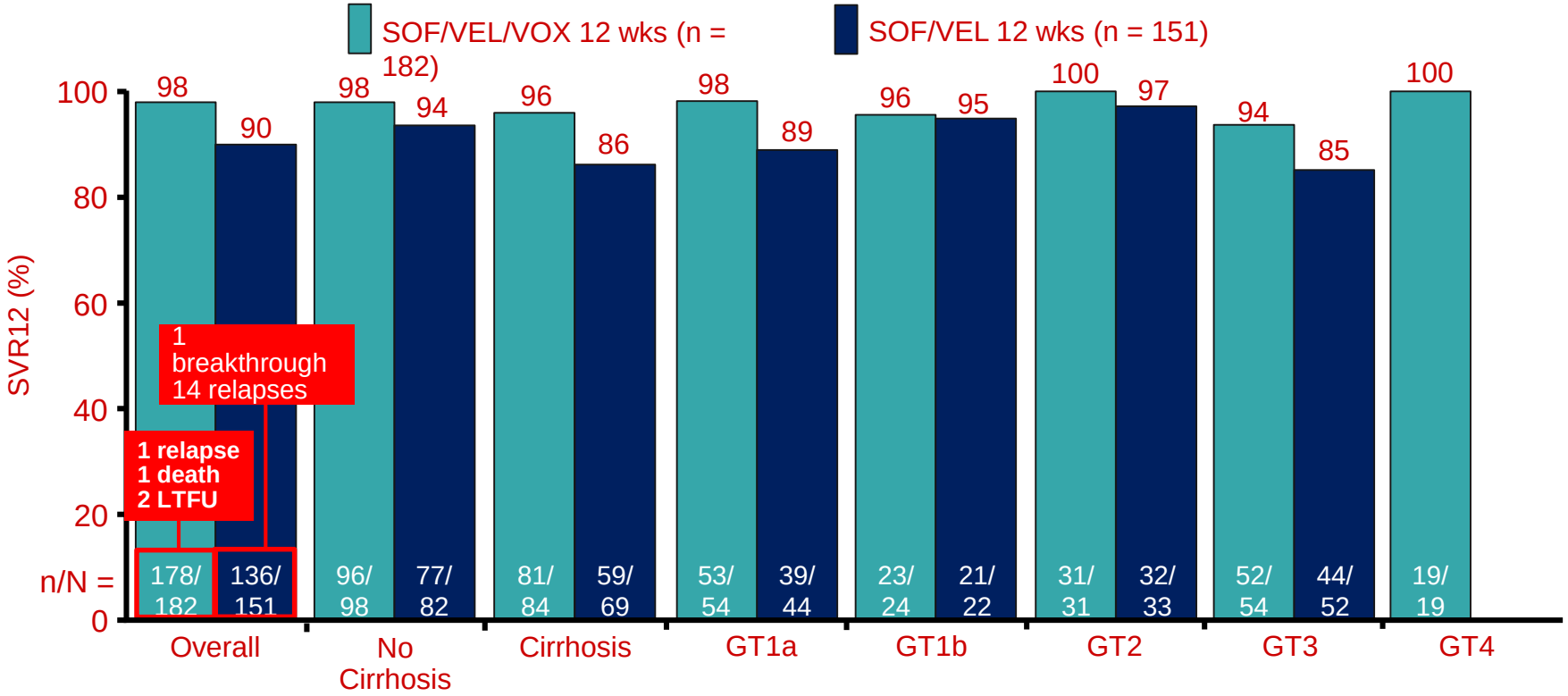
GLE/PIB is not approved in the EU for the re-treatment of patients with prior exposure to NS3/4A and/or NS5A inhibitors

SOF/VEL/VOX for 12 weeks in GT 1–6
DAA-experienced patients: POLARIS-1 and -4



Bourliere M, et al. N Engl J Med 2017;376:2134–46;
Bourliere M, et al. AASLD 2017; Poster #1178

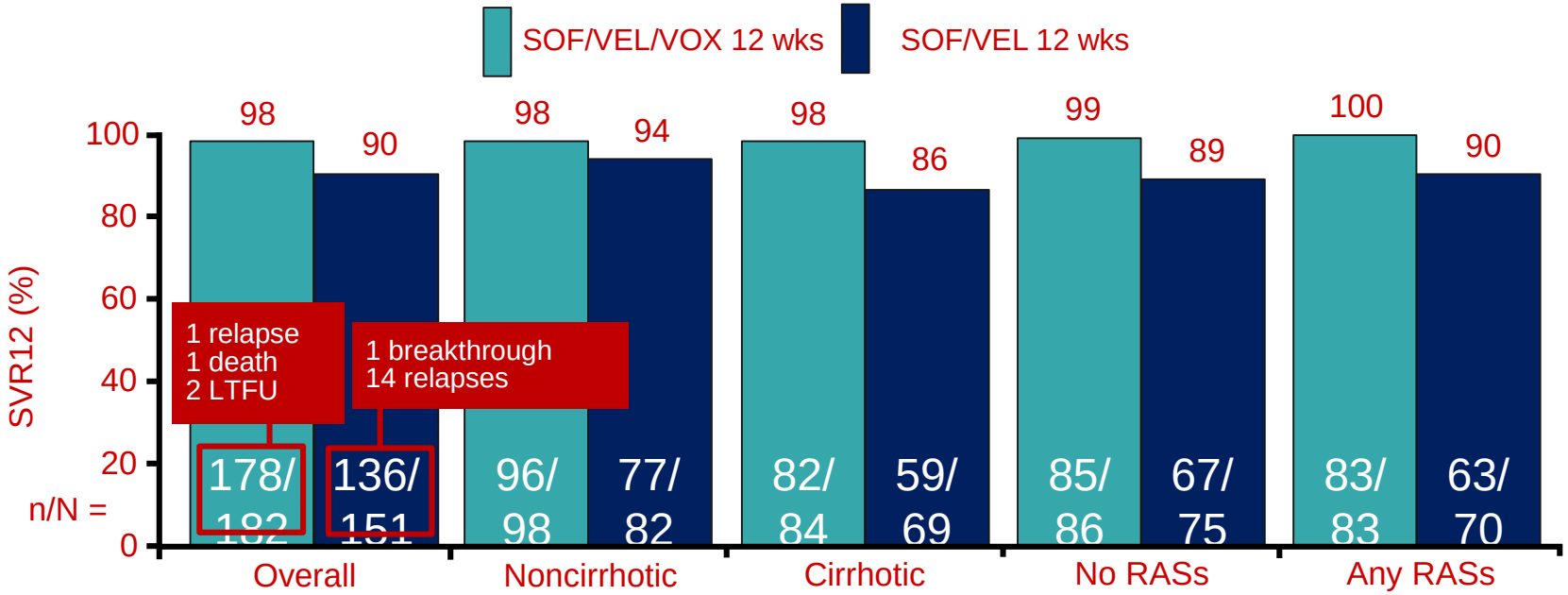
POLARIS-4: SVR12 With SOF/VEL/VOX for 12 Wks in Non-NS5A Inhibitor, DAA-Exp'd Pts



Bourlière M, et al. N Engl J Med. 2017;376:2134-2146. Zeuzem S, et al. AASLD 2016. Abstract 109.

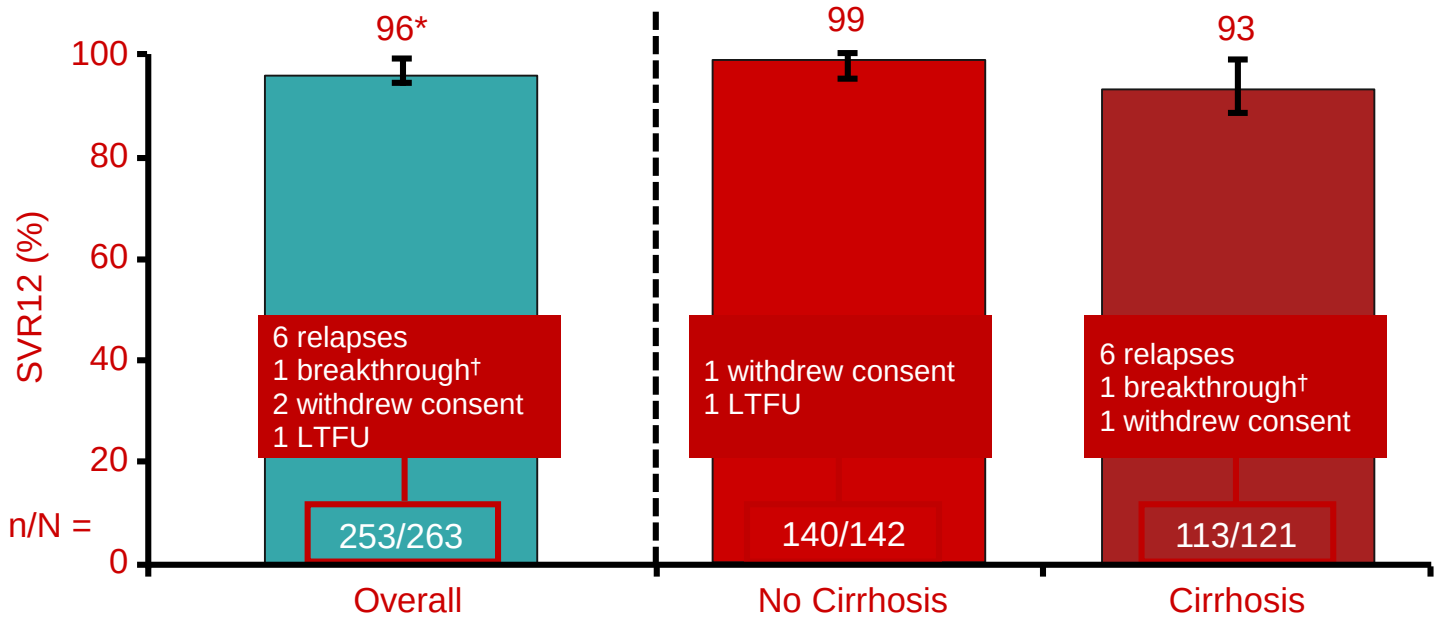
POLARIS-4: SVR12 With SOF/VEL/VOX for 12 Wks in Non-NS5A Inhibitor, DAA-Exp'd Pts

SOF/VEL/VOX: *P* < .001 for superiority vs prespecified 85% goal; SOF/VEL: *P* = .09



Bourlière M, et al. N Engl J Med. 2017;376:2134-2146. Zeuzem S, et al. AASLD 2016. Abstract 109.

POLARIS-1: SVR12 With SOF/VEL/VOX for 12 Wks in NS5Ai experienced: overall and by Cirrhosis Status

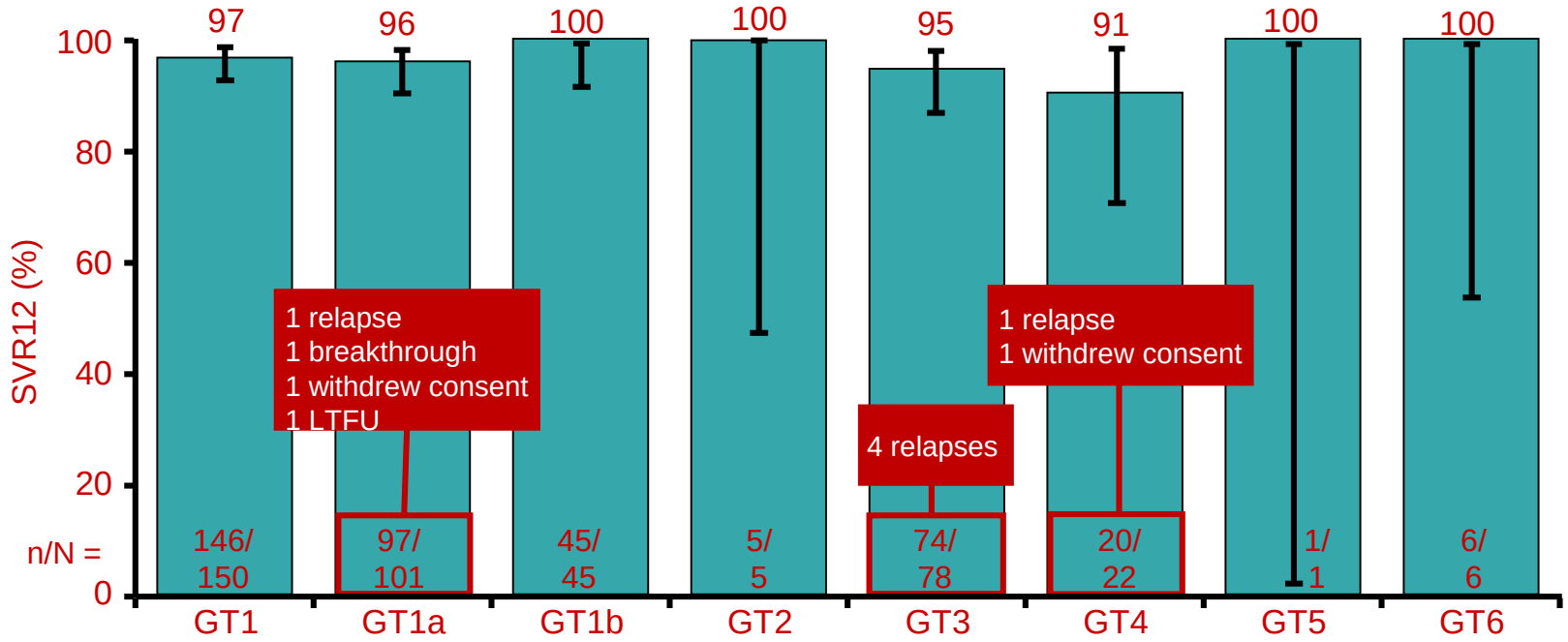


*P < .001 for superiority vs prespecified 85% performance goal for SOF/VEL/VOX.
†Exposure was consistent with nonadherence.

Bourlière M, et al. N Engl J Med. 2017;376:2134-2146. Bourlière M, et al. AASLD 2016. Abstract 194.

POLARIS-1: SVR12 by Genotype With 12-Wk SOF/VEL/VOX in NS5A Inhibitor–Experienced Pts

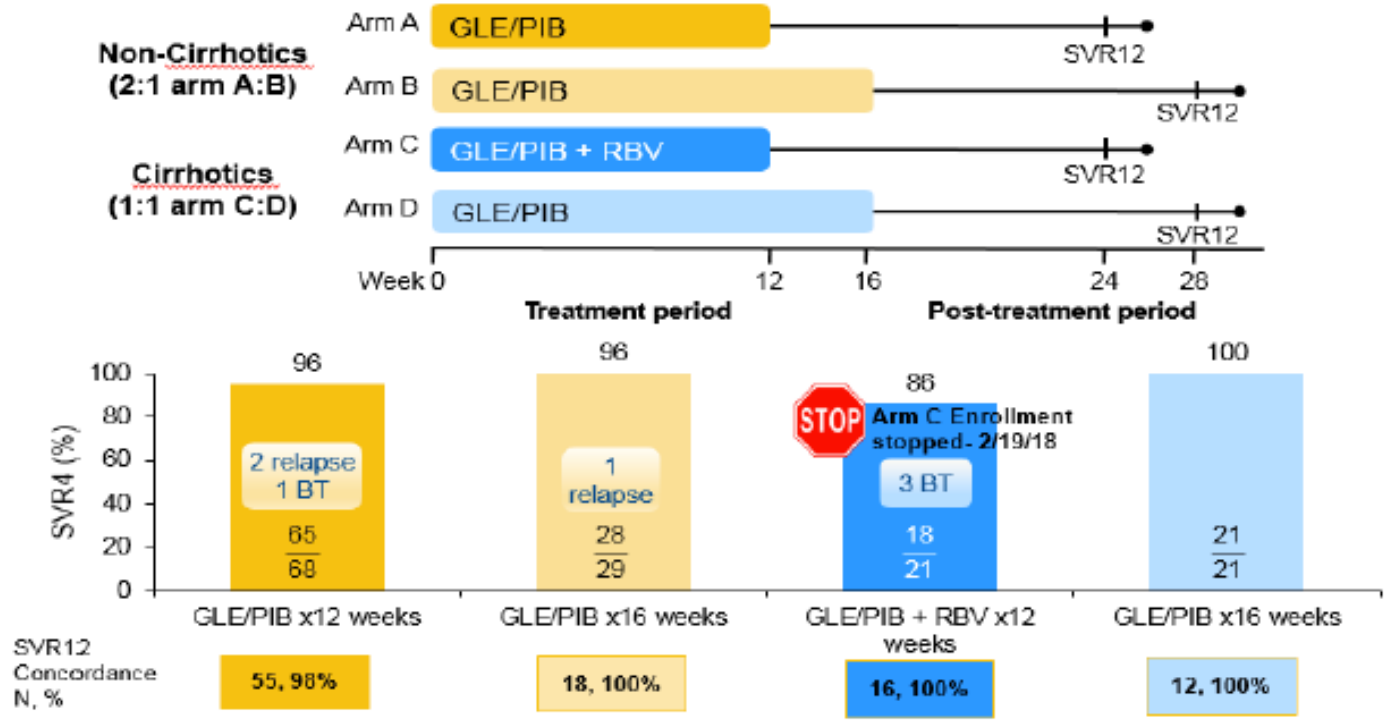
Only 1 GT4 pt developed a treatment-emergent RAS (NS5A Y93H)



Bourlière M, et al. N Engl J Med. 2017;376:2134-2146. Bourlière M, et al. AASLD 2016. Abstract 194.

Phase 3b, open-label, randomized study of glecaprevir /pibrentasvir +/- RBV for HCV GT1 subjects who previously failed an NS5A Inhibitor + SOF

- Phase 3b, multi-center, randomized, open-label, pragmatic study



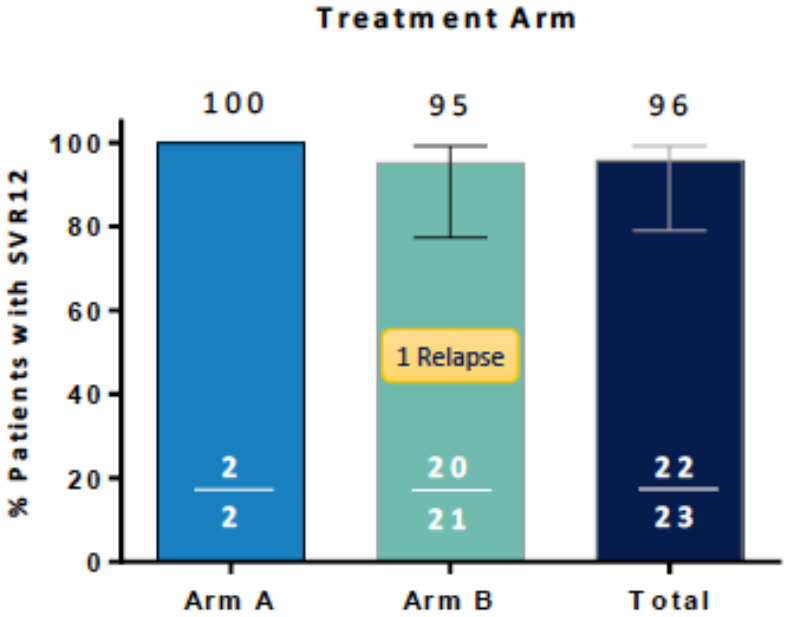
GLE, glecaprevir; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; BT, breakthrough

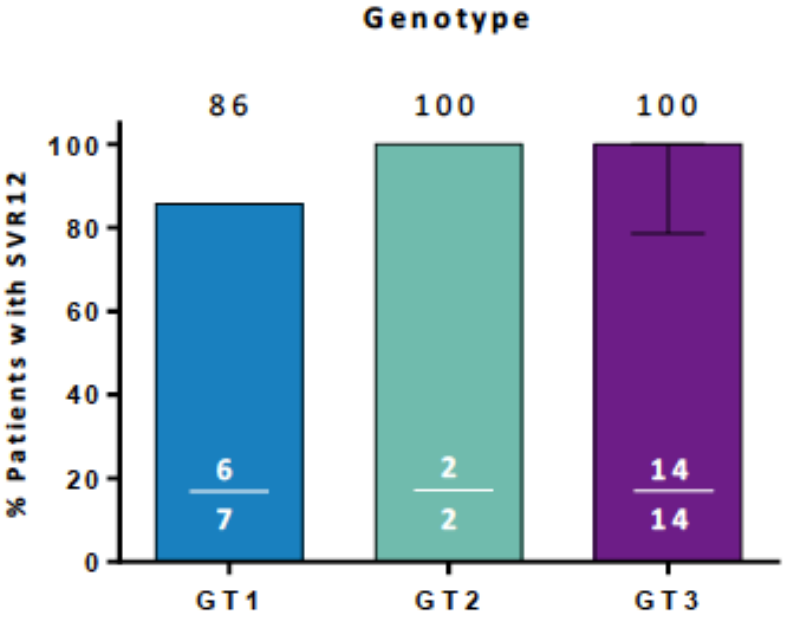
HCV-TARGET Network Study

Lok A et al. ILC 2018;LBO-008

Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C. Magallen-3 study

Phase 3 ongoing study evaluating the efficacy and safety of G/P +SOF+ RBV patients who previously failed G/P treatment.





- 30% had cirrhosis, 26% failed PI and/or NS5Ai before G/P treatment failure, and 65% had ≥2 NS5A RAS at baseline

Arm A: Non GT 3, Non Cirrhosis G/P+SOF+RBV 12 wks

Arm B: Any GT with or without Cirrhosis G/P+SOF+RBV 16 weeks

Wyles D et al. ILC 2018

Management of treatment failures

- Management of PEG-IFN +RBV experienced
- Management of DAA Experienced
  - Epidemiology
  - Causes of Treatment failure
  - Patients profile
  - Re-treatment “ a la carte”: role of RAS testing
  - Re treatment with a fixed menu: data from registration studies
  - Overview of International recommendations

Is Resistance Testing Needed When Retreating Pts Who Failed DAA-Containing Regimens?

Regimen	AASLD/IDSA RAS Testing Recommendations for Treatment-Experienced Pts
GLE/PIB	▪ Not recommended
SOF/LDV	▪ Consider for pts with GT1a HCV; if significant resistance present, extend treatment and add RBV or select a different regimen
SOF/VEL	▪ Recommended for pts with GT3 HCV; if Y93H mutation present, add RBV to regimen
SOF/VEL/VOX	▪ Not recommended

AASLD/IDSA. HCV guidance. September 2017.

Retreatment of Persons in Whom Prior Therapy Failed

Previous Regimen	PR + NS3i						SOF + R ± PEGIFN ± NS3i									
Genotype	1a		1b		4		1a		1b		2		3		4	
Liver disease stage	NC	C	NC	C	NC	C	NC	C	NC	C	NC	C	NC	C	NC	C
SOF/LDV 12 w	■		■													
SOF/LDV+R 12 w		■		■			■		■							
SOF+VEL 12 w	■	■	■	■					■	■	■	■				
G/P 12 w	■	■	■	■			■	■	■	■	■	■				
EBR/GZR +R 12 w	■	■	■	■												
EBR/GZR + R 16 w if bl NS5ARAS	■	■														
SOF/VEL/VOX 12 w + RBV														■		
SOF/VEL/VOX 12 w					■	■	■	■					■		■	■

■ Recommended
■ Alternative

HCV guidance: recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org/ (accessed October 2017)

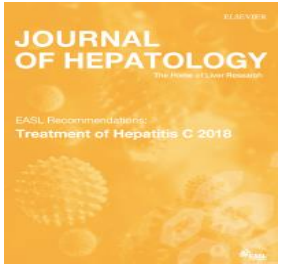
Retreatment of Persons in Whom Prior Therapy Failed

Previous Regimen	NS5Ai containing regimen										NS5A i+ NS3i
Genotype	1a		1b		2		3		4		All
Liver disease stage	NC	C	NC	C	NC	C	NC	C	NC	C	NC & C
G/P 16 w	■	■	■	■	■	■					?
SOF/VEL/VOX 12 w + RBV								■			?
SOF/VEL/VOX 12 w	■	■	■	■	■	■	■		■	■	?

■ Recommended
■ Alternative

HCV guidance: recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org/ (accessed October 2017)

EASL Recommendations on Treatment of Hepatitis C 2018



- **Recommendations**
  - HCV resistance testing prior to retreatment in patients who failed after any of the DAA-containing treatment regimens is useful to guide retreatment by probabilities of response, according to the resistance profile observed in the context of a **multidisciplinary team** including experienced treaters and virologists (**B2**).

AdHoc Working Party – Statements 2017 (… and 2018)

- Resistance testing after treatment failure in all 3 genes (independently from the failure regimen) is **mandatory** in order to optimize retreatment strategy.
  - NS3
  - NS5A
  - NS5B: for the two different classes of nucleoside and non-nucleoside inhibitors.

Viganò M, Perno CF, and Craxì A on behalf of AdHoc Working Party, Dig Liv Dis 2017

EASL Recommendations on Treatment of Hepatitis C 2018

Adapted from Update April 2018

NS5Ai- failure

RASs testing

In the context of a multidisciplinary team including experienced treaters and virologists

RASs with low fold-change

«**Easy**» patients

12 weeks SOF/VEL/VOX (A1)

Complex RASs

«**Difficult**» patients

12 weeks GLE/PIB + SOF (B2)

Catastrophic RASs

«**Very difficult**» patients (double NS5Ai-failures)

12, 16 or 24 weeks SOF/VEL/VOX + RBV (C2)

12, 16 or 24 weeks GLE/PIB + SOF + RBV (C2)

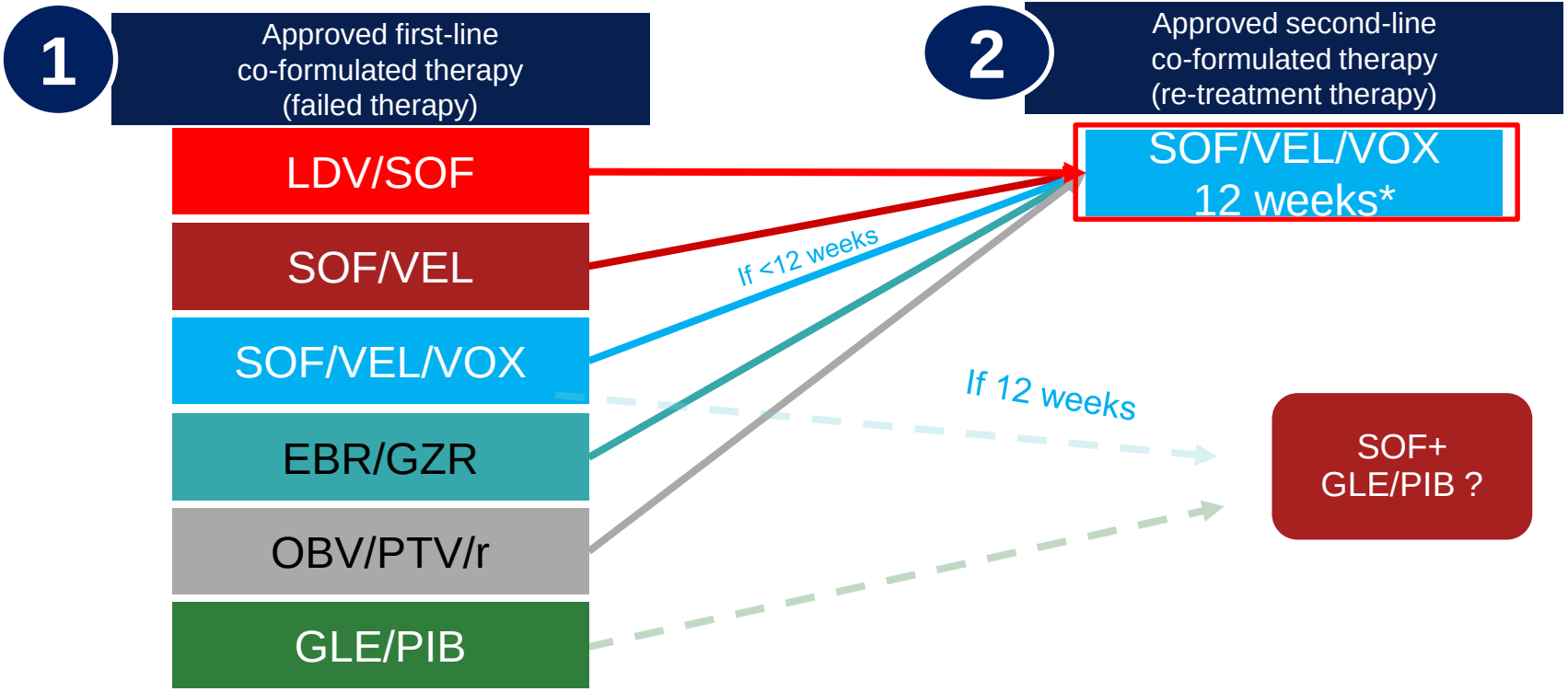
Decompensated cirrhosis

24 weeks SOF/VEL + RBV (B2)

Re-treatment: a la carte

- Identify at least 2 antivirals active according to resistance testing
- Deferral of re-treatment
  - No advanced liver disease
  - Options with 2 active drugs will be available in the next future
  - Active HCC
  - ON LT waiting list
- Prolong treatment duration and/or add Ribavirin if multiple predictors of poor response are present
  - Advanced liver disease
  - Very High HCVRNA
  - Reduced activity of prescribed drugs according to RASs testing
  - IL28 non CC

Re-treatment: fixed menu



*SOF/VEL/VOX has not been tested in patients who have experienced treatment failure with GLE/PIB or SOF/VEL/VOX 12 weeks s

With an effective treatment and re-treatment strategy, the vast majority of patients could achieve an SVR

SVR 96%

1000 people treated with SOF-based regimens

SVR 97%

Treat 40 who require re-treatment with SOF/VEL/VOX*

Overall

Up to 999/1000 eligible patients could achieve an SVR

With the potential for an up to 99.9% SVR at the population level, elimination of HCV could become a reality!

Flamm S, et al. ILC 2017; Poster #SAT-279; Curry M, et al. ILC 2017; Oral #102; Terrault N, et al. Gastroenterology 2016;151:1131–40; Khalili M, et al. ILC 2017; Poster #SAT-222; Vermehren J, et al. ILC 2017; Poster #FRI-247; Welzel TM, et al. ILC 2016; Poster #SAT-274; Roberts S, et al. ILC 2017; Poster #SAT-280

*SOF/VEL/VOX is not recommended in patients with moderate or severe hepatic impairment (CTP B or CTP C). This is a concept slide based on a real-world SVR of 96% calculated from 9391 patients treated with LDV/SOF ± RBV and SOF/VEL ± RBV in the TRIO, HCV-TARGET and DHC-R cohorts. Re-treatment SVR of 97% with SOF/VEL/VOX is reported in the POLARIS-1–4 integrated analysis

HCV Virology Italian Resistance Network Study Group: VIRONET-C

VIRONET-C BOARD: F Ceccherini-Silberstein (Vice-President), A Craxì (President), M Andreoni, CF Perno, M Puoti, M Zazzi.

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