Management delle epatiti virali

Come gestire le poche migliaia di fallimenti alla terapia anti-HCV con DAA?

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TOR VERGATA

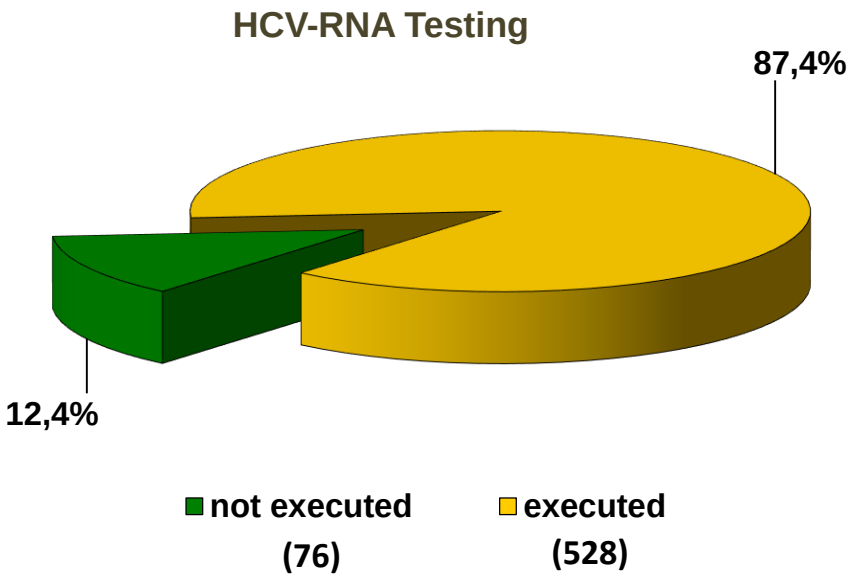
Even in the era of DAAs,~ 47,000 patients would fail to achieve SVR in Europe before 2020

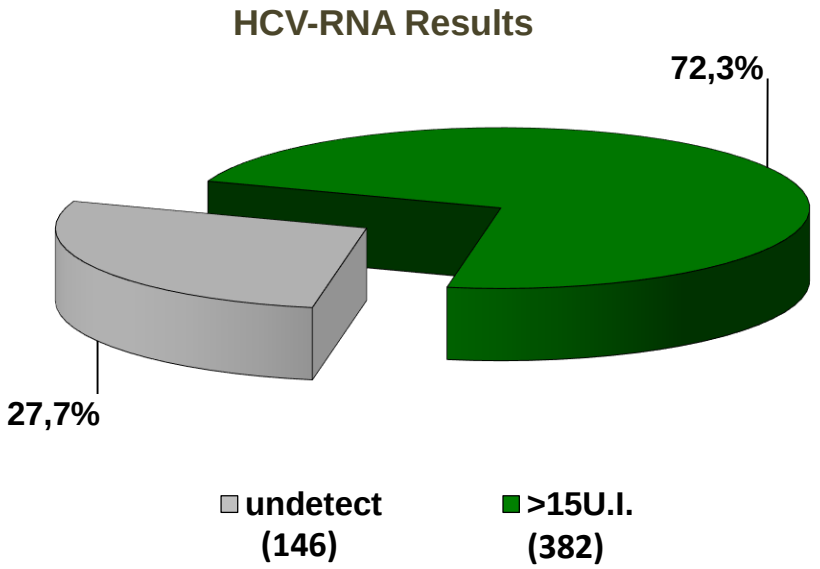
	France	Germany	Italy	Spain	UK
Number of patients who receive treatment (2014 – 2020)	102,555	92,166	207,917	156,980	94,971
• PR (%)	14,411 (14.1%)	3,596 (3.9%)	14,022 (6.7%)	9,023 (5.7%)	9,484 (10.0%)
• NS5A (%)	83,019 (81.0%)	69,771 (75.7%)	158,881 (76.4%)	136,107 (86.7%)	77,785 (81.9%)
• Non-NS5A (%)	5,125 (5.0%)	18,799 (20.4%)	35,014 (16.8%)	11,850 (7.5%)	7,702 (8.1%)
• Treatment failure (%)	13,226 (12.9%)	9,291 (10.1%)	23,224 (11.2%)	15,193 (9.7%)	9,999 (10.5%)
Among treatment failures					
• PR (%)	8,015 (60.6%)	1,369 (14.7%)	5,759 (24.8%)	4,864 (32.0%)	3,990 (39.9%)
• NS5A (%)	4,322 (32.7%)	4,126 (44.4%)	9,381 (40.4%)	7,900 (52.0%)	3,861 (38.6%)
• Non-NS5A (%)	889 (6.7%)	3,796 (40.9%)	8,084 (34.8%)	2,429 (16.0%)	2,148 (21.5%)
• Cirrhotic (%)	6,408 (48.5%)	4,426 (47.6%)	14,722 (63.4%)	7,586 (49.9%)	3,201 (32.0%)
• Genotype 1	9,281 (70.2%)	4,641 (50.0%)	16,353 (70.4%)	11,150 (73.4%)	4,578 (45.8%)
• Genotype 2	716 (5.4%)	649 (7.0%)	5,161 (22.2%)	436 (2.9%)	466 (4.7%)
• Genotype 3	2,087 (15.8%)	3,672 (39.5%)	867 (3.7%)	2,988 (19.7%)	4,582 (45.8%)
• Genotype 4-6	1,142 (8.6%)	329 (3.5%)	843 (3.6%)	619 (4.1%)	373 (3.7%)

Chhatwal J et al., EASL 2017 poster #FRI-233

PrHep-EU 2014

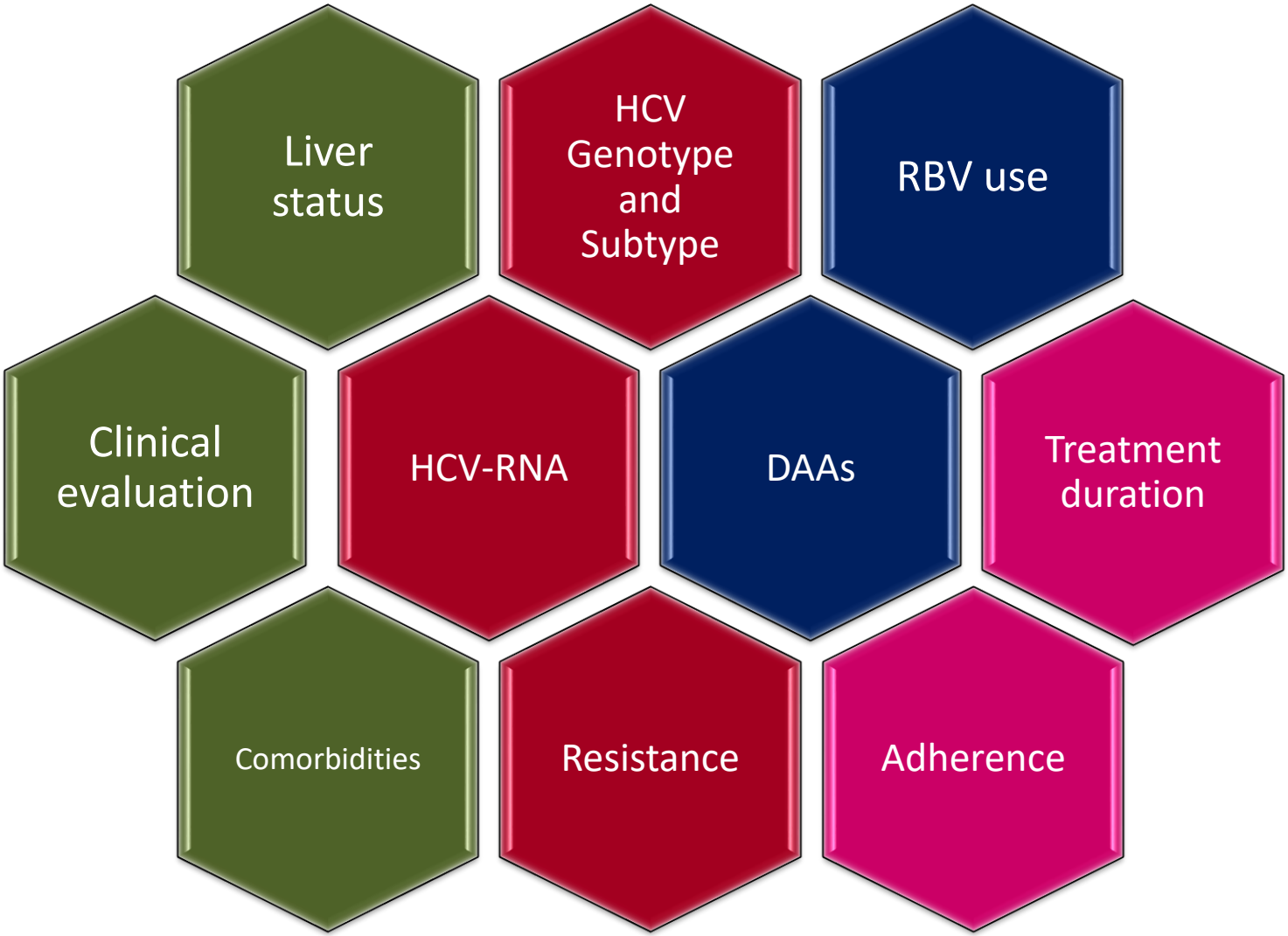
HCV Viral Load [604 HCVAb+ inmates]:

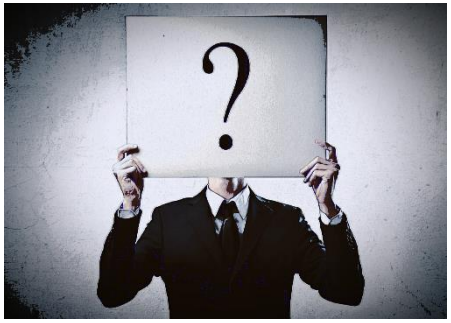




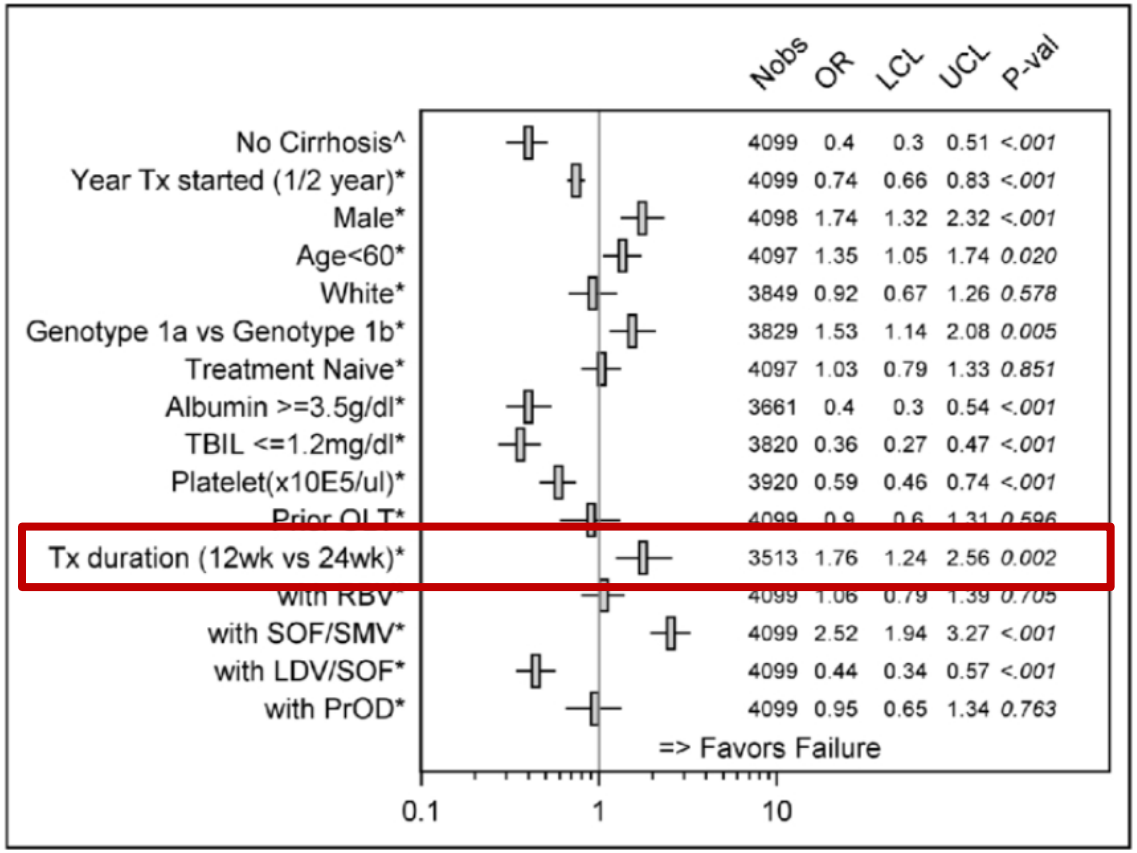
Courtesy of prof. S. Babudieri

“Viral”, “patient” and “treatment” parameters have to be taken into account for possible DAA failure





Baseline predictors of virological failure in HCV TARGET Cohort



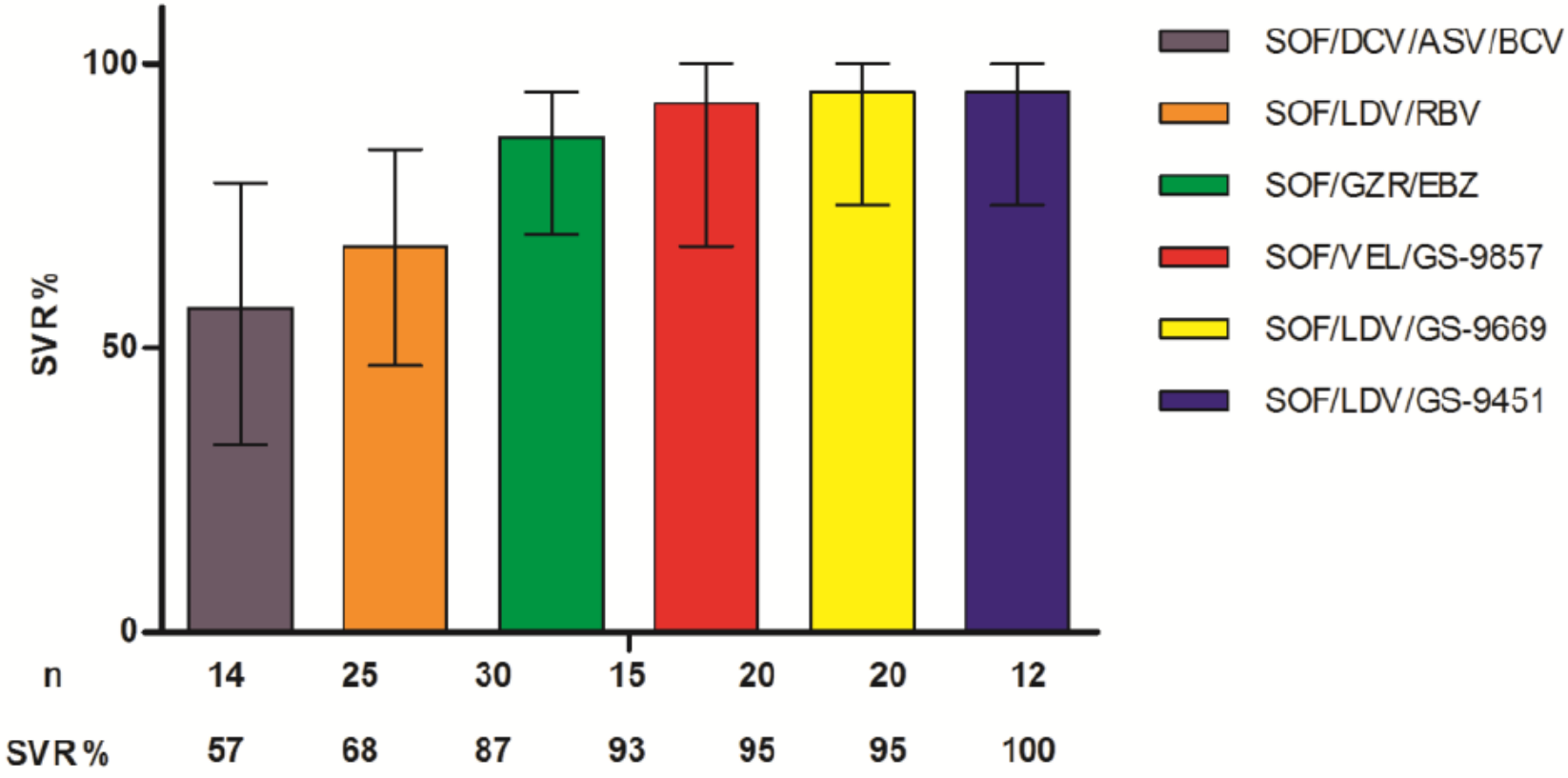
Thinking about a DAA-failing patients, you have to expect:

- Male
- Cirrhotic
- Low albumin
- High bilirubin
- Low platelet count
- Treated with «subotimal» DAA combinations
- Treated with short regimens

Sulkowski MS et al., EASL 2017

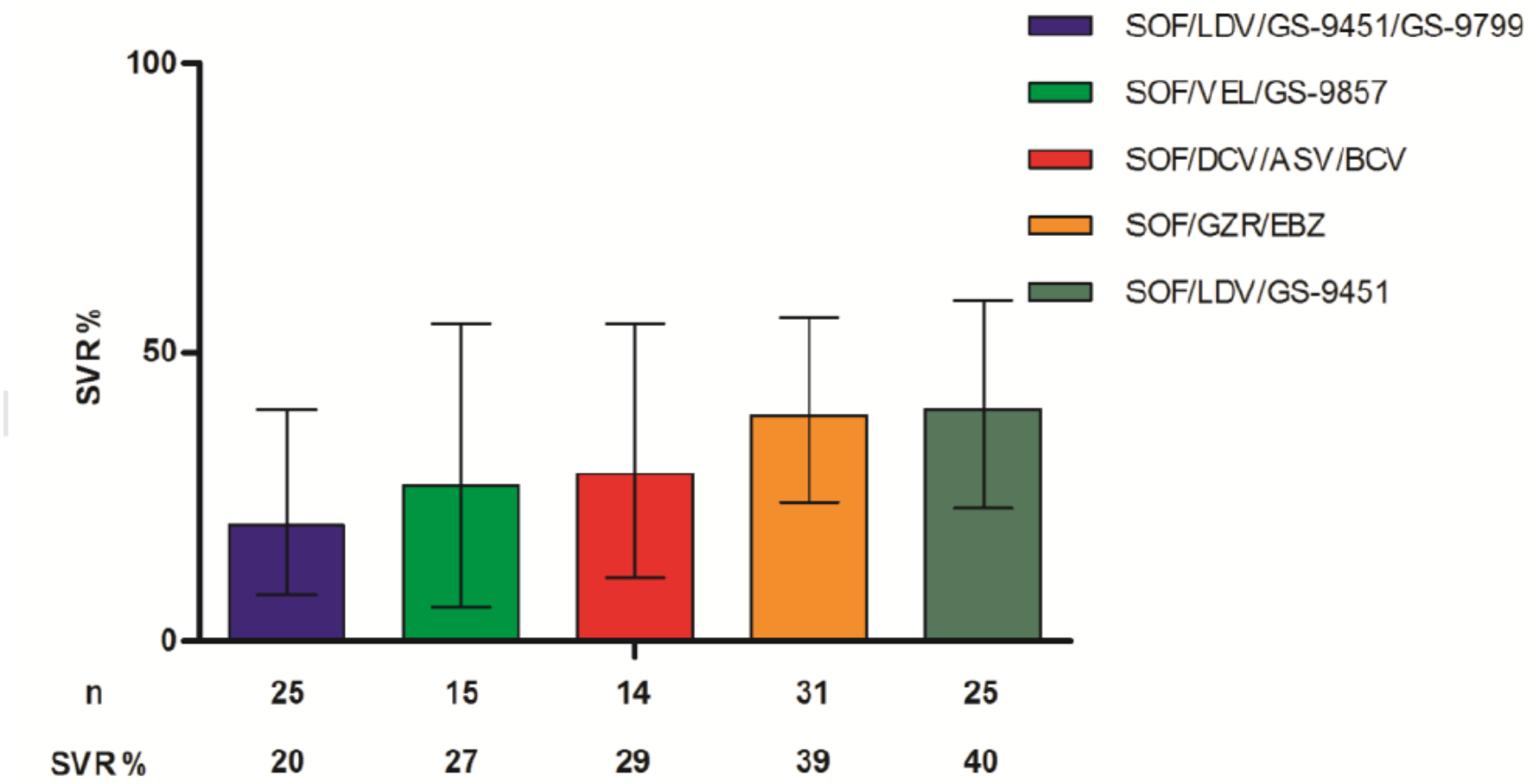
No one-size-fits-all: 6 weeks DAA therapies in GT1

Several small studies have demonstrated the feasibility of 6 weeks of SOF therapy in combination with an NS5A inhibitor and a protease inhibitor for HCV GT 1 … but with variable efficacy.



El Sherif O et al., J Viral Hepat. 2017

4 weeks of therapy with various combinations of the currently available DAAs appears to be sub-optimal in phase 2 trials in GT1



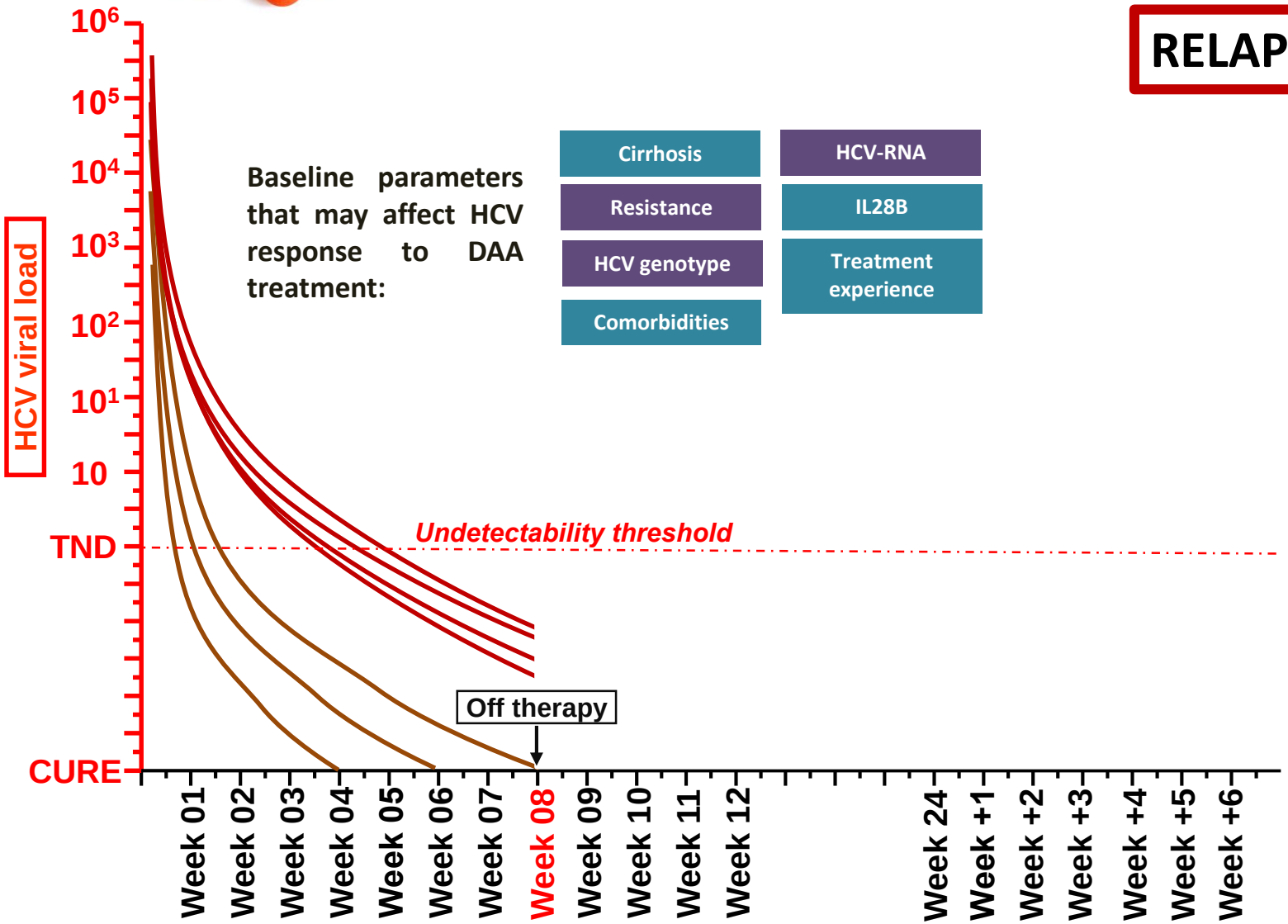
El Sherif O et al., J Viral Hepat. 2017

How «short» can we go?

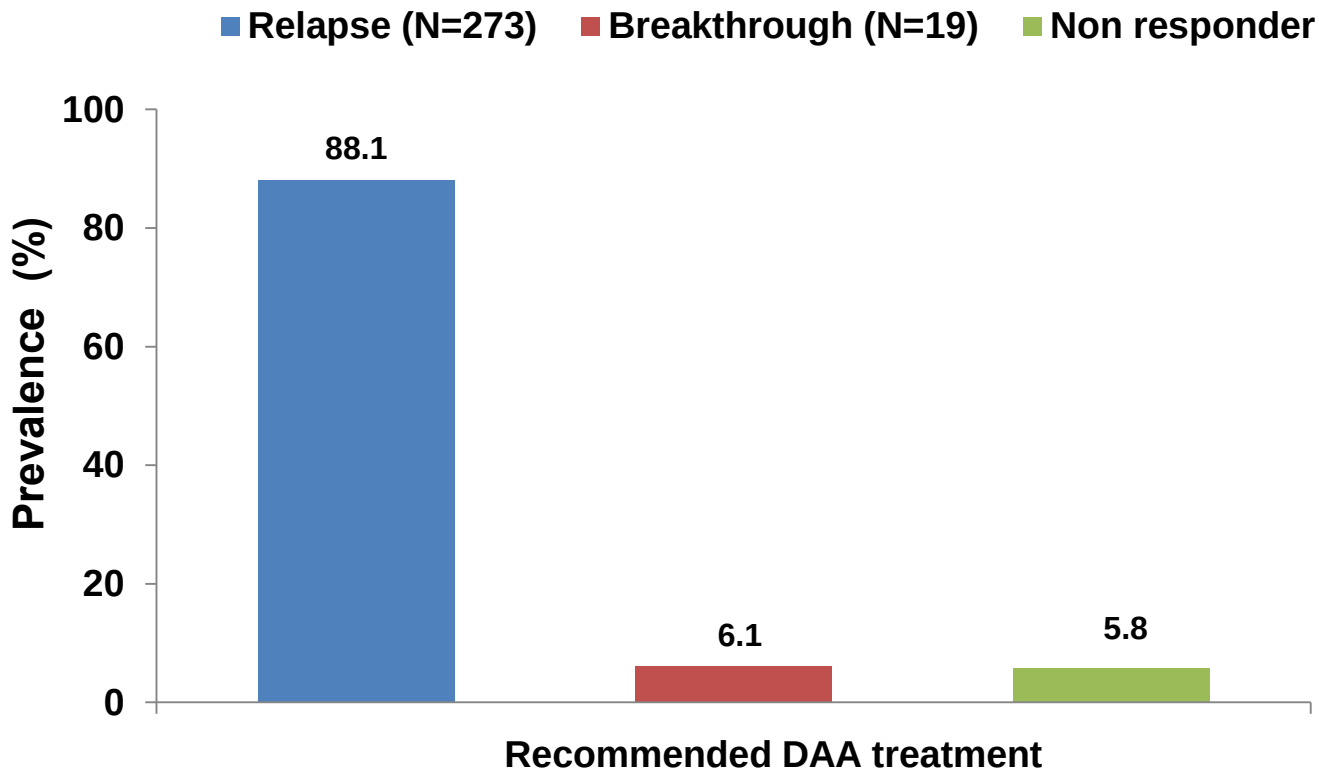
RELAPSE!!!

Baseline parameters that may affect HCV response to DAA treatment:

- Cirrhosis
- HCV-RNA
- Resistance
- IL28B
- HCV genotype
- Treatment experience
- Comorbidities



In our real-life experience, 88% of 310 DAA-failures were **relapsers**

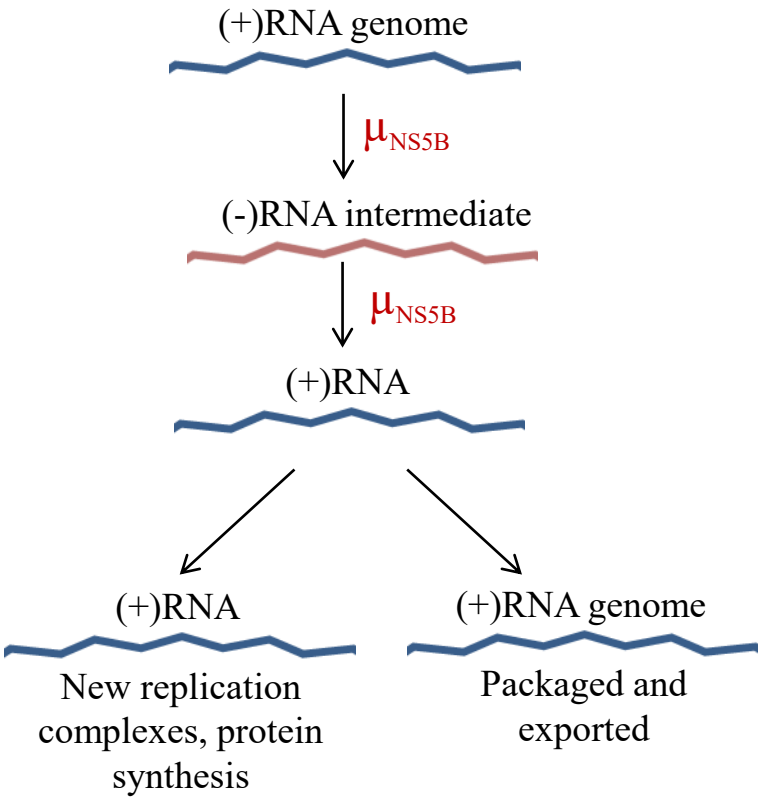


- **SMV+SOF+/-RBV (N=84)**
- **3D+/-RBV (N=47)**
- **2D+/-RBV (N=2)**
- **LDV+SOF+/-RBV (N=91)**
- **DCV+SOF+/-RBV (N=58)**
- **SOF+RBV (N=28, HCV-2)**

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

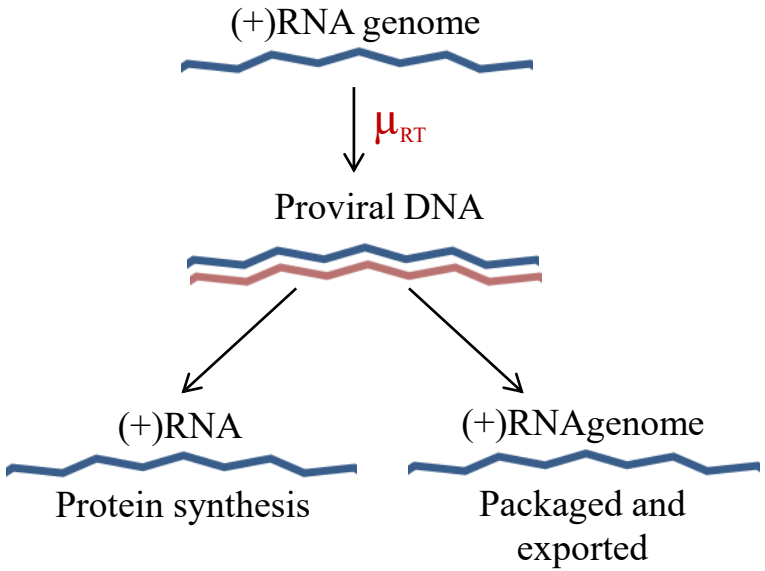
HCV

Double passage by viral NS5B polymerase to create a (+)RNA template for protein synthesis



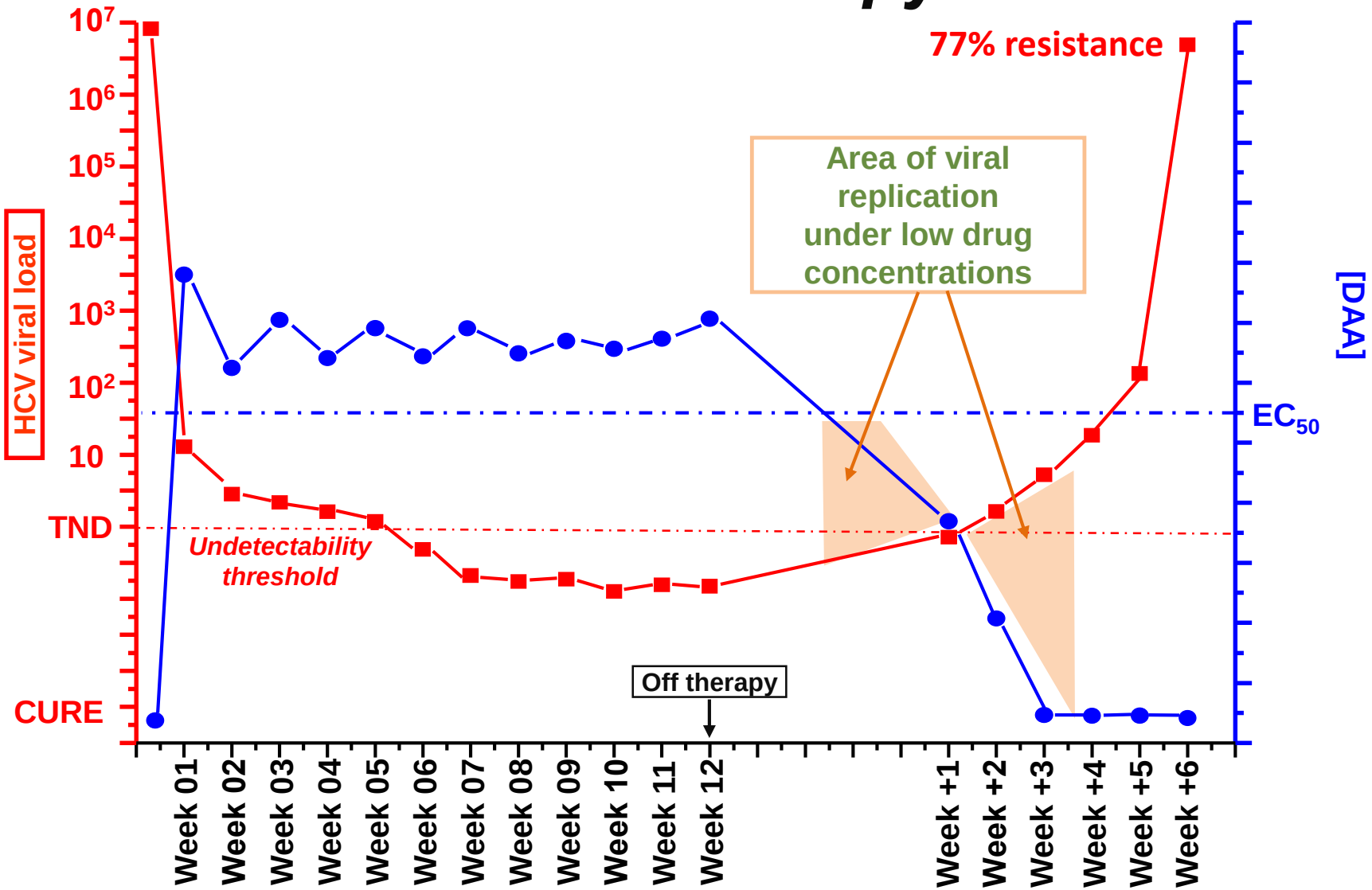
HIV

Single passage by viral reverse-transcriptase (RT) to create proviral DNA and then a (+)RNA template for protein synthesis

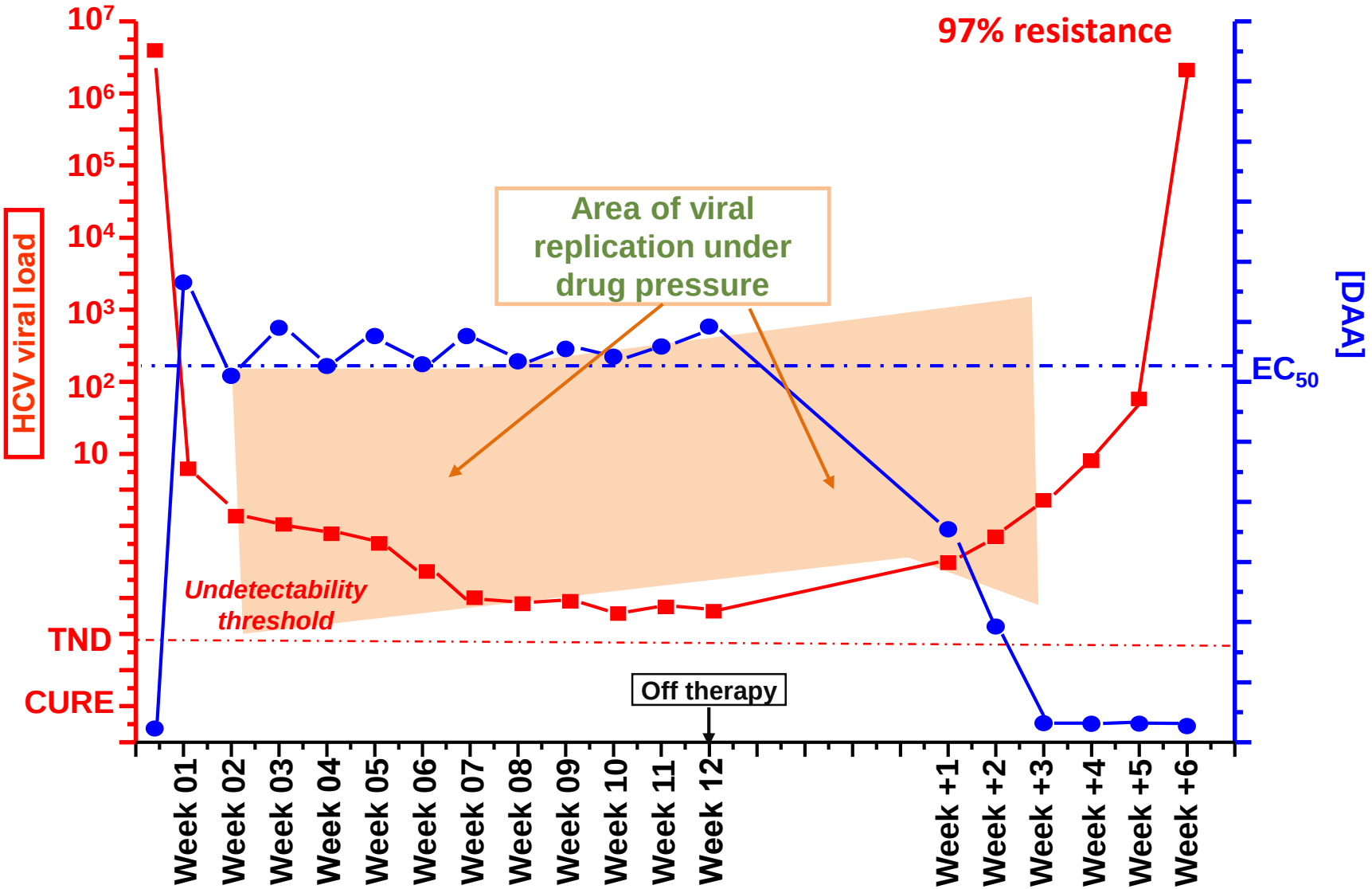


Regardless of NS5B/RT mutational rates, quasispecies complexity is higher in HCV in respect to HIV ...

Relapse and resistance during DAA-based anti-HCV therapy

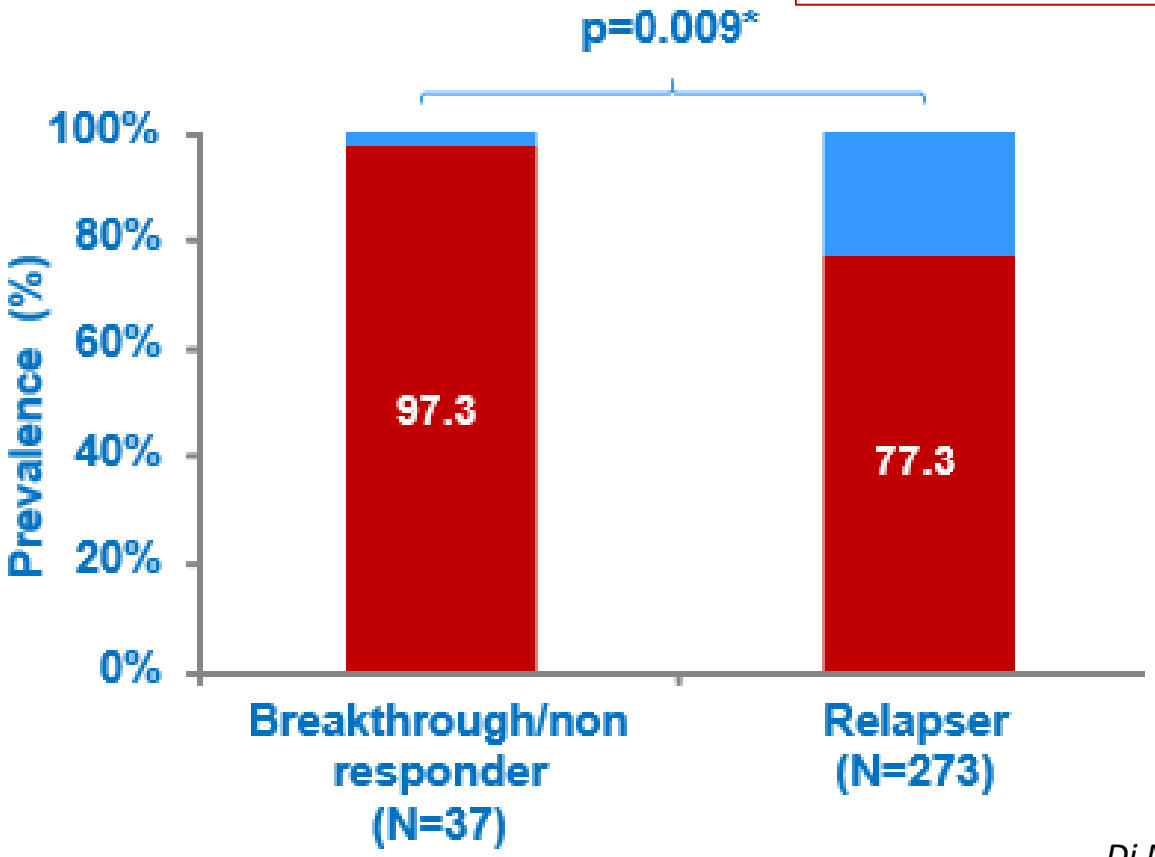


No response/Breakthrough and resistance during DAA-based anti-HCV therapy



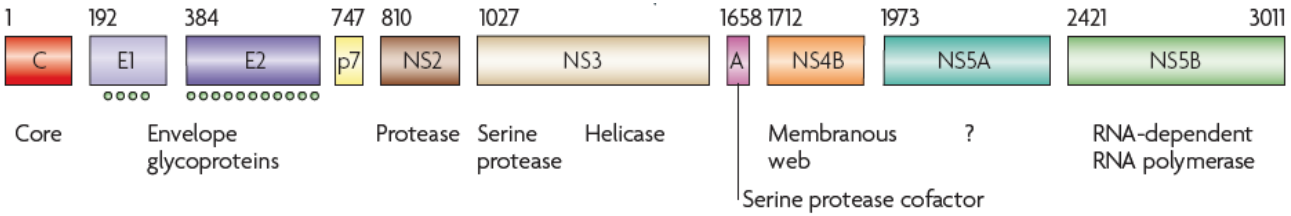
RASs prevalence at failure was significantly higher in breakthrough/non-responders

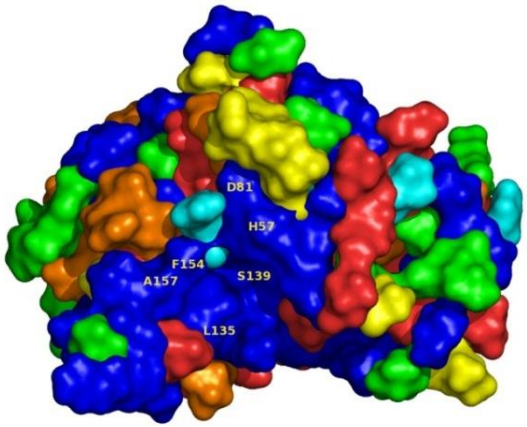
→ 24.3% of breakthroughs and non-responses were related to wrong GT assignments …

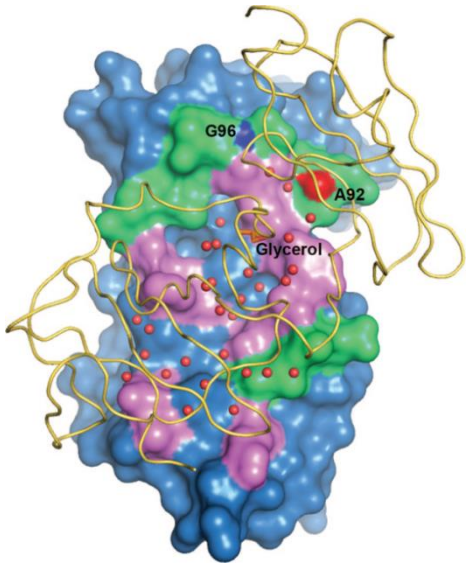


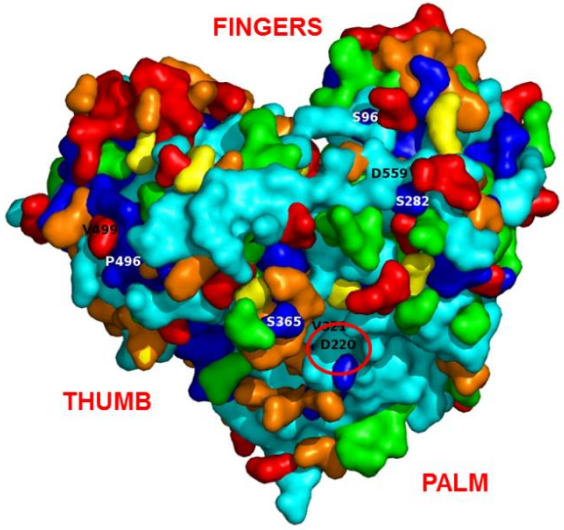
Di Maio VC et al., EASL 2017
Di Maio VC et al., accepted J Hepatol 2017

TARGETS OF DAA TREATMENT







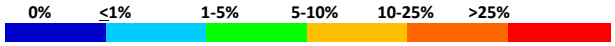


47% amino acids of HCV PROTEASE NS3 are conserved among all HCV-genotypes

46% amino acids of HCV NS5A are conserved among all HCV-genotypes

55% amino acids of HCV POLYMERASE NS5B are conserved among all HCV-genotypes

Amino acid variability:



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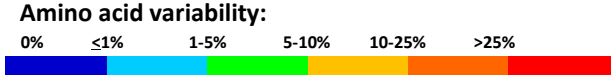
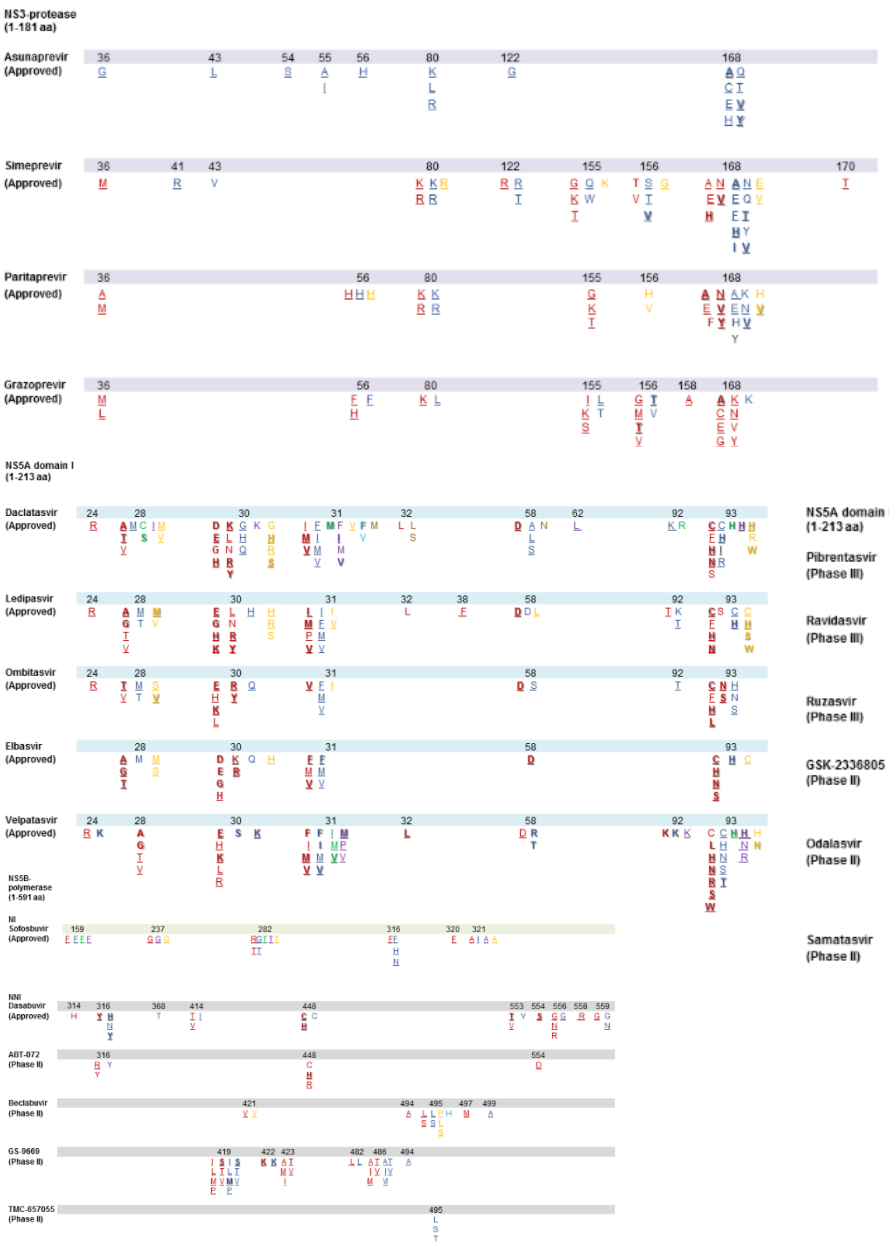


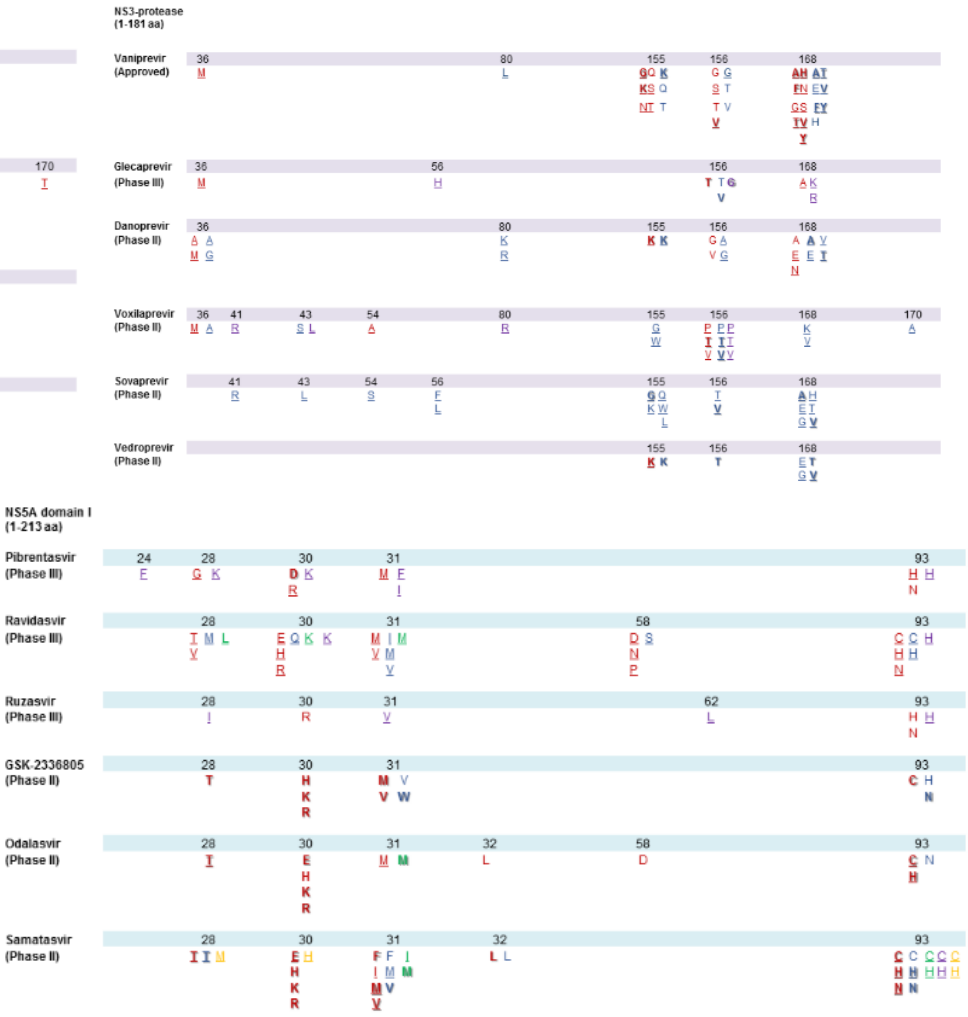
Cento et al., PLoS ONE 2012

Love et al., J Vir 2009

Di Maio et al., AAC 2014

HCV … more than 100 RASs have been reported





Sorbo MC et al., manuscript submitted

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Chhatwal J et al., EASL 2017 poster #FRI-233

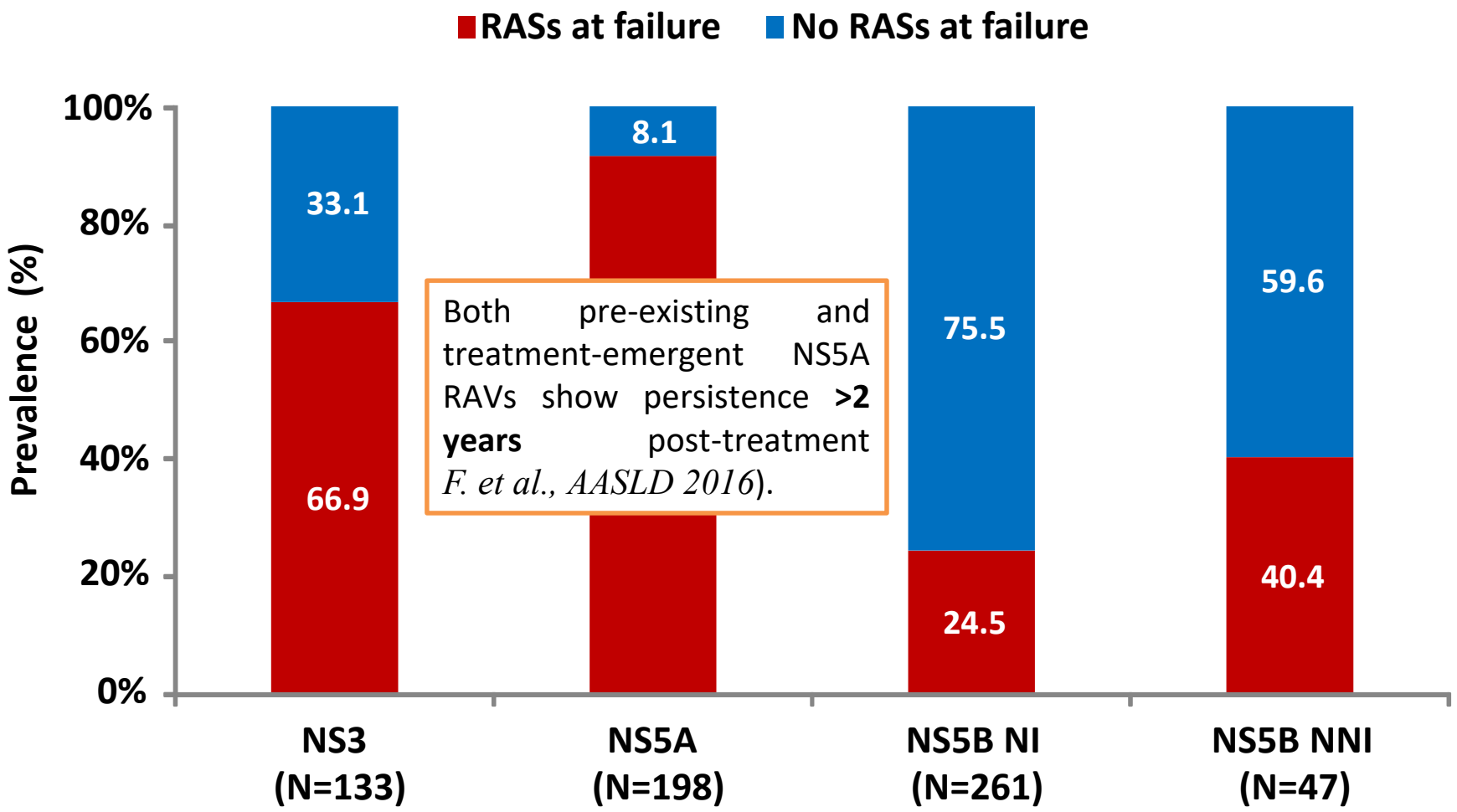
ALL 1st line DAA regimens include an NS5A inhibitor

HCV GT	Recommended Regimens	
	Treatment Naive	**IFN/RBV Experienced**
1a	▪ **EBR**/GZR* ▪ **LDV**/SOF ▪ SOF/**VEL**	▪ **EBR**/GZR* ▪ **LDV**/SOF + RBV ▪ SOF/**VEL**
1b	▪ **EBR**/GZR ▪ **LDV**/SOF ▪ **OBV**/PTV/RTV/DSV ER ▪ **OBV**/PTV/RTV+ DSV BID ▪ SOF/**VEL**	▪ **EBR**/GZR ▪ **LDV**/SOF + RBV ▪ **OBV**/PTV/RTV/DSV ER ▪ **OBV**/PTV/RTV+ DSV BID ▪ SOF/**VEL**
	No Cirrhosis	**Compensated Cirrhosis**
2	▪ SOF/**VEL**	▪ SOF/**VEL**
3	▪ **DCV**/SOF ▪ SOF/**VEL**	▪ **DCV**/SOF ± RBV ▪ SOF/**VEL** ± RBV
4	▪ **OBV**/PTV/RTV + RBV ▪ SOF/**VEL** ▪ **EBR**/GZR* ▪ **LDV**/SOF	▪ **OBV**/PTV/RTV + RBV ▪ SOF/**VEL** ▪ **EBR**/GZR* ▪ **LDV**/SOF ± RBV
5 or 6	▪ SOF/**VEL** ▪ **LDV**/SOF	▪ SOF/**VEL** ▪ **LDV**/SOF

*Only if no baseline NS5A elbasvir RASs detected.

AASLD/IDSA. HCV guidance. April 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., EASL 2017
Di Maio VC et al., accepted J Hepatol 2017

Broad Cross-Resistance With Currently Available NS5A Inhibitors

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/--
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.

In HIV treatment, resistance testing at failure is recommended by all guidelines

Drug-resistance testing is **recommended** in patients on combination ART with **HIV RNA levels >1,000 copies/mL** (AI). In patients with HIV RNA **levels >500 copies/mL but <1,000 copies/mL, Testing may not be successful** but should still be considered (**DHHS adult & adolescent guidelines, 2016**).

EACS European AIDS Clinical Society

Perform resistance testing on failing therapy (usually routinely available for HIV-VL levels > 350-500 copies/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations

European Guidelines, 2015

IMPIEGO	RACCOMANDAZIONE (FORZA/EVIDENZA)	RAZIONALE
Per pazienti in fallimento con viremia >200 copie/mL al fine di impostare al meglio la cART successiva.	[AI]	E' essenziale che il test venga eseguito mentre la terapia fallita è ancora in corso, al fine di evitare il rischio di falsi negativi.
Per pazienti in fallimento con viremia 50-200 copie/mL il test è ugualmente consigliato per una corretta impostazione della cART successiva.	[AII]	In pazienti che falliscono una cART con viremia 50-200 copie/mL il test fornisce risultati affidabili e riproducibili, informativi della resistenza emergente a bassi livelli di viremia e predittivi di ulteriore rialzo della viremia. L'efficienza di amplificazione e interpretazione è già circa del 70% con viremia intorno alle 50-200 copie/mL, mentre è > 90% con viremie 500-1000 copie/mL.

Italian Guidelines, December 2015

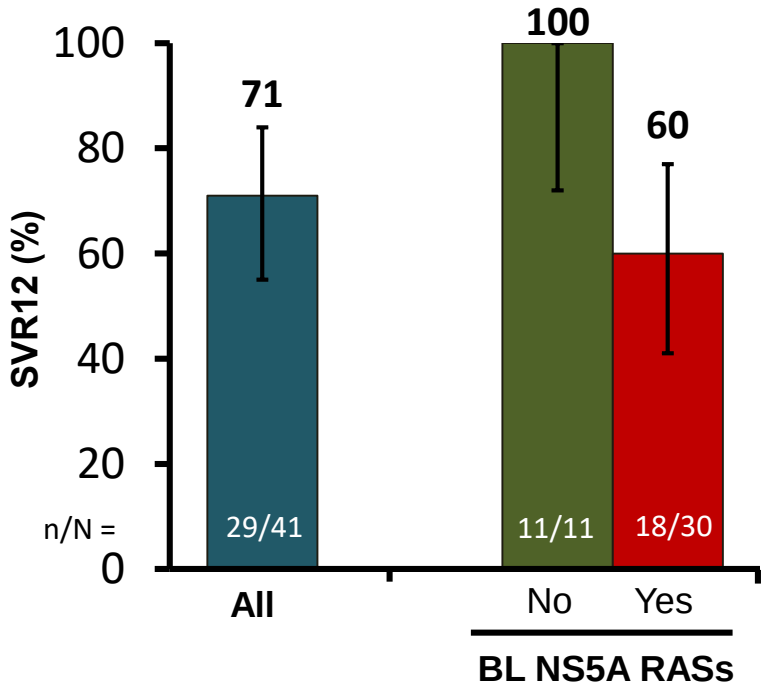
RASs at virological failure and retreatment options - Statements

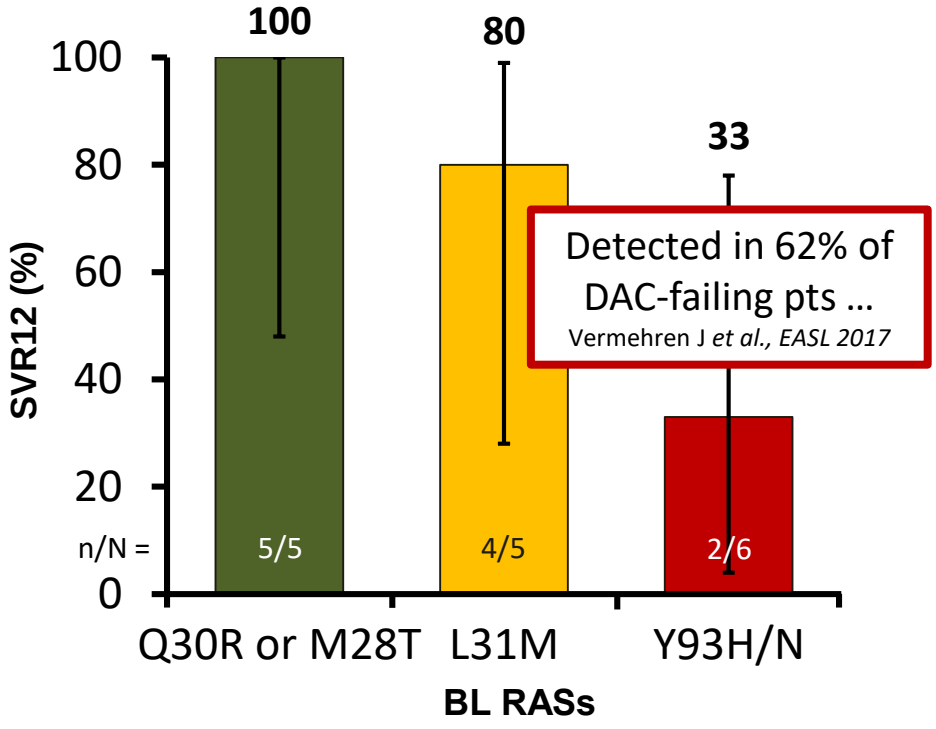
- Resistance testing after treatment failure in all 3 genes (NS3, NS5A, NS5B [for the two different classes of nucleoside and non-nucleoside inhibitors] independently from the failure regimen) is mandatory in order to optimize retreatment strategy.
- HCV sequencing can be based on Sanger population method or by ultra-deep sequencing using a cut-off of 15% prevalence. It can confirm the previous genotype and subtype assignment, but can also attribute a different HCV-genotype highlighting cases of previous wrong genotype assignation by commercial assays or occurrence of potential re-infection instead of virological relapse, avoiding then inappropriate retreatment regimens.
- Resistance testing should be performed as soon as possible after documentation of failure, provided that HCV RNA has reached a value of at least 1000 IU/mL, according to the threshold limits for virology laboratories for HCV sequencing.
- Clinical and virological information required for resistance test performance and interpretation should be provided contextually with blood samples.

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

NS5A RASs Associated With Retreatment Failure 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.

Retreatment framework for GT1 DAA failures

GT1

Genetic region:	**NS5A**
Predicted subtype:	**1b (Similarity of DNA to closest reference = 92.13%)**
Codons covered in *NS5A* region:	**1 - 203**
Mutations in *NS5A* region:	**K6R, S17T, L34V, Q54H, K78R, A92T, V138I, V164A, V174T, Q176L, A197T, S201?**
Warnings *NS5A* region:	**Sequence contains deletions.**
Reference used:	**D90208**

Drug Resistance

Drugs	Scored mutations	Resistance analysis	
Daclatasvir	**92T**	**substitution on scored position**	
Elbasvir	**none**	**susceptible**	
Ledipasvir	**92T**	**substitution on scored position**	
Ombitasvir	**none**	**susceptible**	
Velpatasvir	**none**	**susceptible**	

Detailed Mutation Information

	Mutation	Resistance analysis
Daclatasvir		
	92T	**substitution on scored position**
Ledipasvir		
	92T	**substitution on scored position**

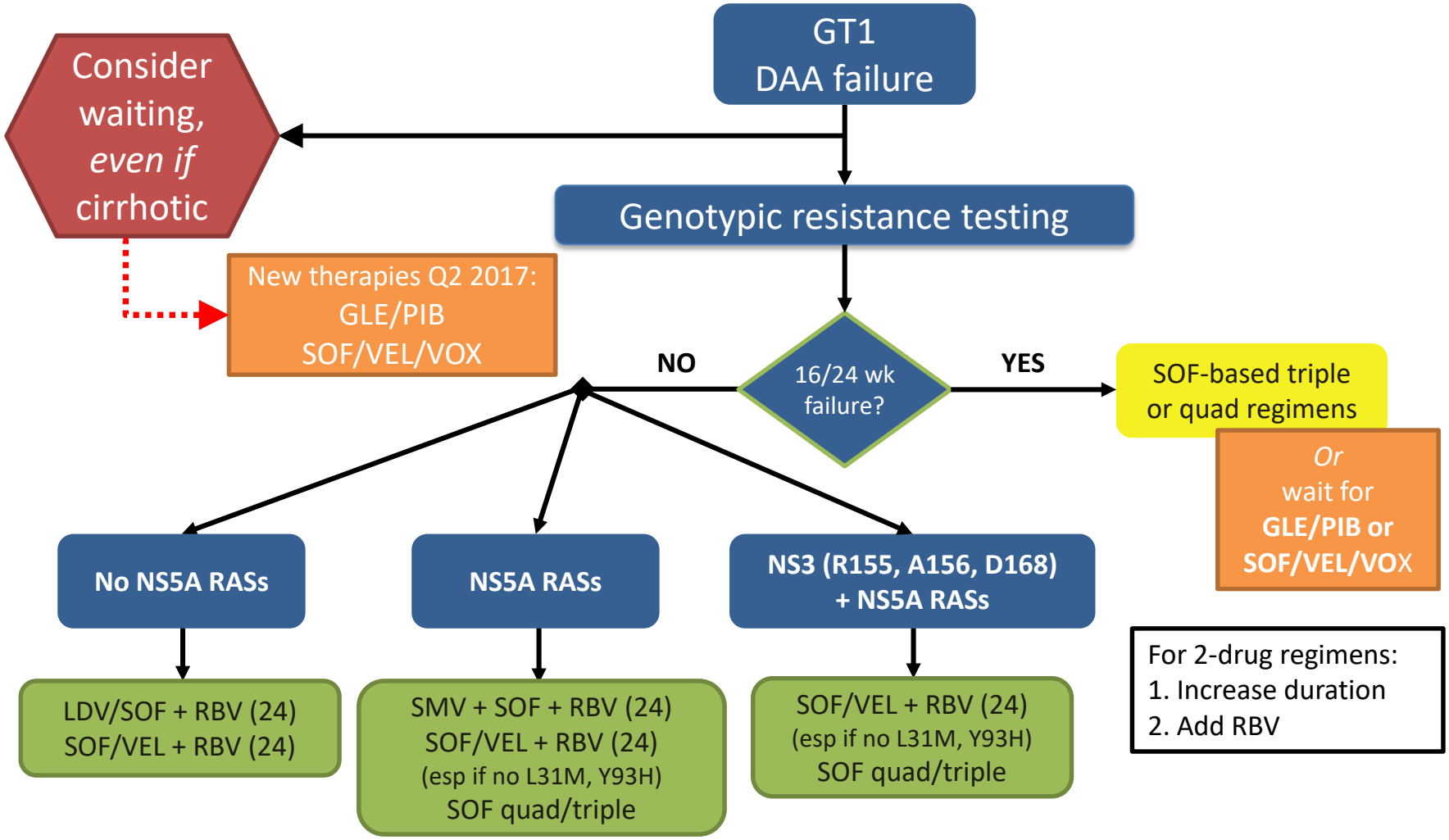
Interpretation of Resistance Classes

Resistance class	Description	
Resistant	Well-characterized resistance-associated mutation	
Reduced susceptibility	Association to resistance, insufficient evidence for clinical outcome (characterized resistance variant in other HCV genotypes)	
Substitution on scored position	Uncharacterized substitution on a scored position	
Susceptible		
Not licensed for genotype	Drug not licensed for the predicted genotype.	

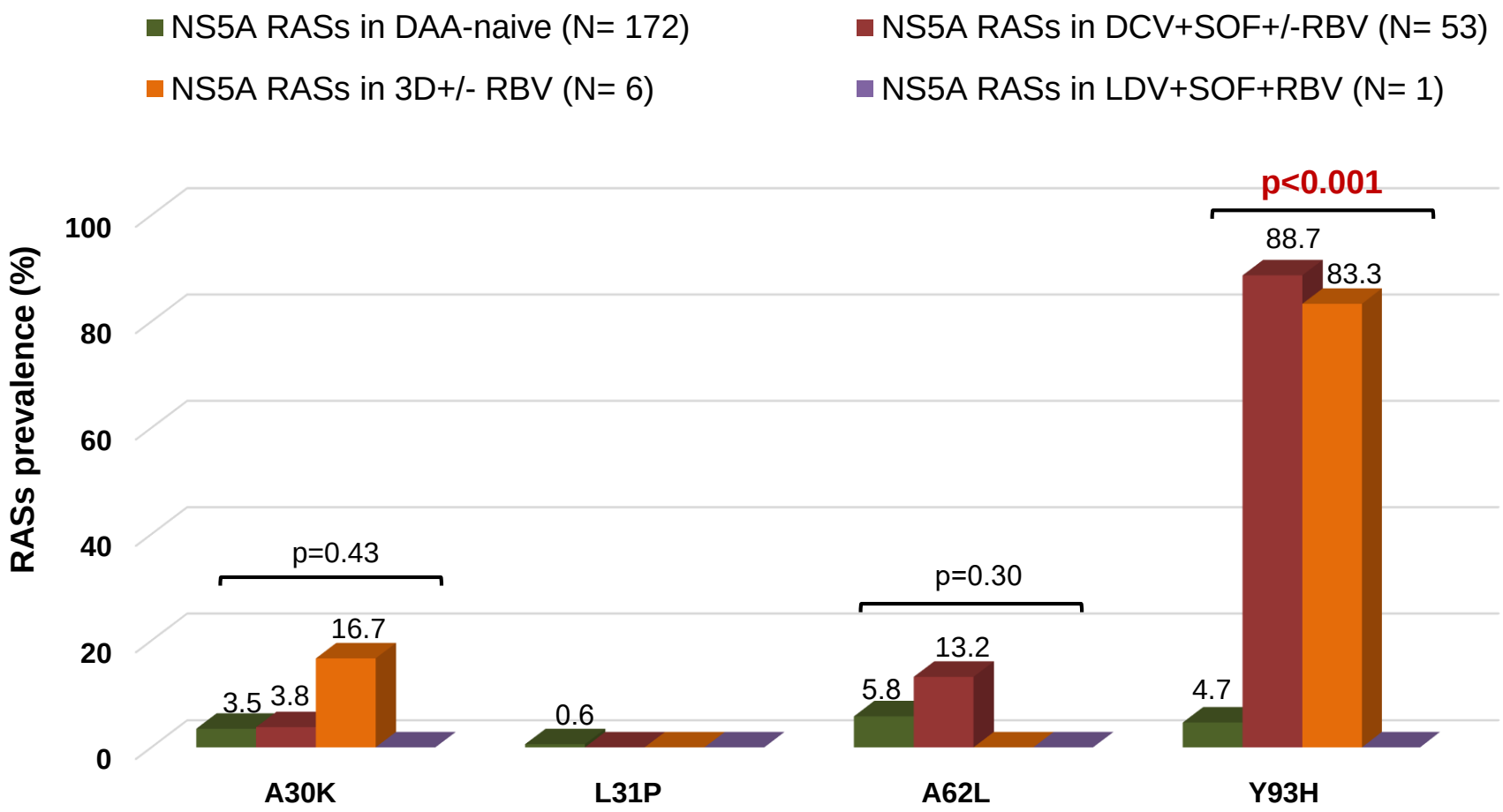
News

but is indicating a reduced therapy success probability. If possible, a regimen with fully active drugs should be chosen.

Retreatment framework for GT1 DAA failures



The **Y93H** was the most prevalent RAS detected in **GT-3** patients after NS5Ai-failure



Median sampling time point after EOT (weeks):

- 3D+/-RBV: 5.4 (1.3-10.6)
- DCV+SOF+/-RBV: 16.0 (10.1-20.7)

Barbaliscia S. et al., ICAR 2017

Roles of RBV and Longer Tx Duration in Overcoming Resistance (?) in DAA-experienced pts Treated with VEL/SOF

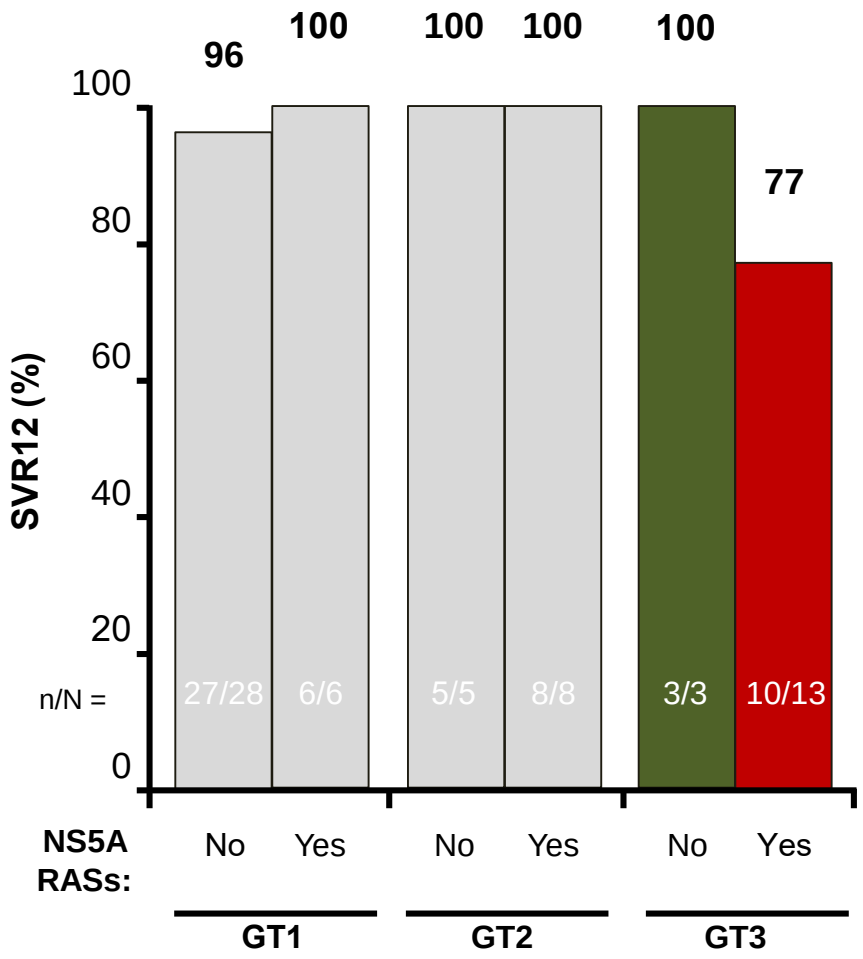
- Single-arm trial

HCV-infected pts without SVR in previous phase II trials of SOF/VEL (n = 41) or SOF/VEL + VOX (n = 28) → **SOF/VEL 400/100 mg + RBV** (N = 69)

Wk 24

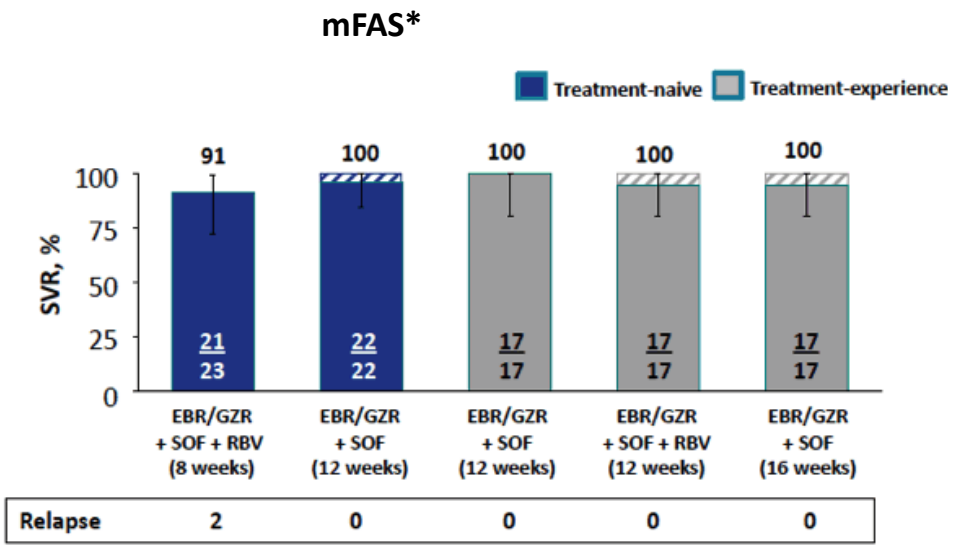
- Cirrhosis: 26%; previous relapse: 99%
- Only 18% of GT1 with NS5A RASs
- Previous treatment: 41% VEL 25 mg, 74% < 12 wks

Overall SVR_{12}: GT1 (n = 34): 97%; GT2 (n = 14): 91%; **GT3 (n = 17): 76% → 82% in pts with Y93H**



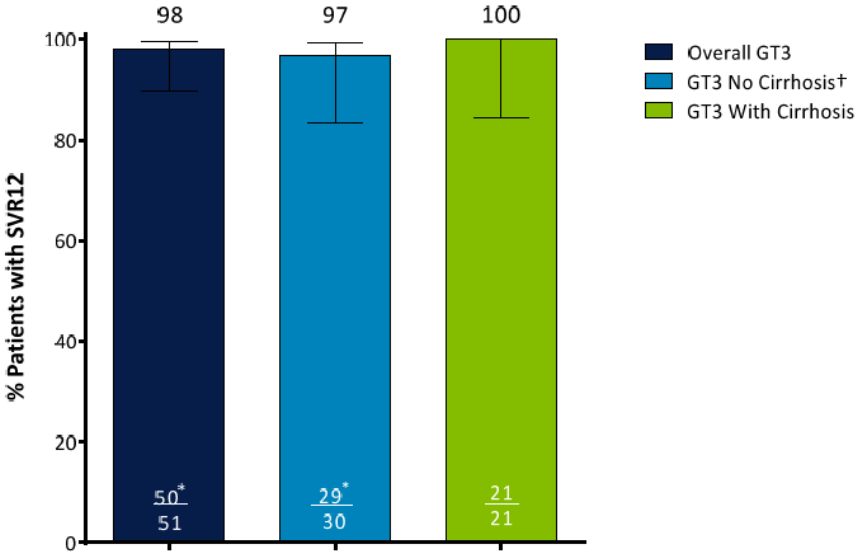
Gane EJ, et al. EASL 2016. Abstract PS024
EASL Recommendations on Treatment of Hepatitis C 2016

C-ISLE: SVR With EBR/GZR + SOF ± RBV for GT3 HCV in Pts With Compensated Cirrhosis



*Modified full analysis set excludes discontinuations not related to study drugs. 3 pts discontinued for administrative reasons.

QUARTZ II-III: SVR With OBT/PTV/r + SOF ± RBV for 12 weeks in GT3 HCV pts



High SVR rates in treatment-experienced, cirrhotic/non cirrhotic pts with GT3, but no NS5A-experienced pts included

Foster GR, et al. AALSD 2016. Abstract 74.
Shafran S. et al., J Hepatology 2017

New pan-genotypic regimens are on their way to the market

Regimen	NS5B Polymerase Nucleotide Inhibitor (. . . buvir)	NS3/4A Protease Inhibitor (. . . previr)	NS5A Inhibitor (. . . asvir)
Sofosbuvir/velpatasvir/voxilaprevir	SOF	VOX	**VEL**
Glecaprevir/pibrentasvir	--	GLE	**PIB**
~~Grazoprevir/ruzasvir/uprifosbuvir~~	~~UPR~~	~~GZR~~	~~**RZR**~~
AL-335 + odalasvir + simeprevir	AL-335	SMV	**ODV**

Not all NS5A RASs are created equal

HCV Drug	Fold-Change								
	RASs in HCV Genotype 1a						RASs in HCV Genotype 1b		
	M28T	Q30R	L31M	L31V	Y93H	Y93N	L31V	Y93H	Y93N
Daclatasvir	>100×	>1000×	>100×	>1000×	>1000×	>10,000×	<10×	20×	50×
Elbasvir	20×	>100×	>10×	>100×	>1000×	>1000×	<10×	>100×	NA
Ledipasvir	20×	>100×	>100×	>100×	>1000×	>10,000×	>20×	>100×	NA
Ombitasvir	>1000×	>100×	<3×	>100×	>10,000×	>10,000×	<10×	20×	50×
Pibrentasvir	<3×	<3×	<3×	<3×	<10×	<10×	<3×	<3×	<3×
Ruzasvir[b]	<10×	<10×	<10×	<10×	<10×	<10×	<10×	<10×	<10×
Velpatasvir	<10×	<3×	20×	50×	>100×	>1000×	<10×	<3×	NA

Abbreviations: EC_{50}, median effective concentration; HCV, hepatitis C virus; NA, data not available; RAS, resistance-associated substitution.

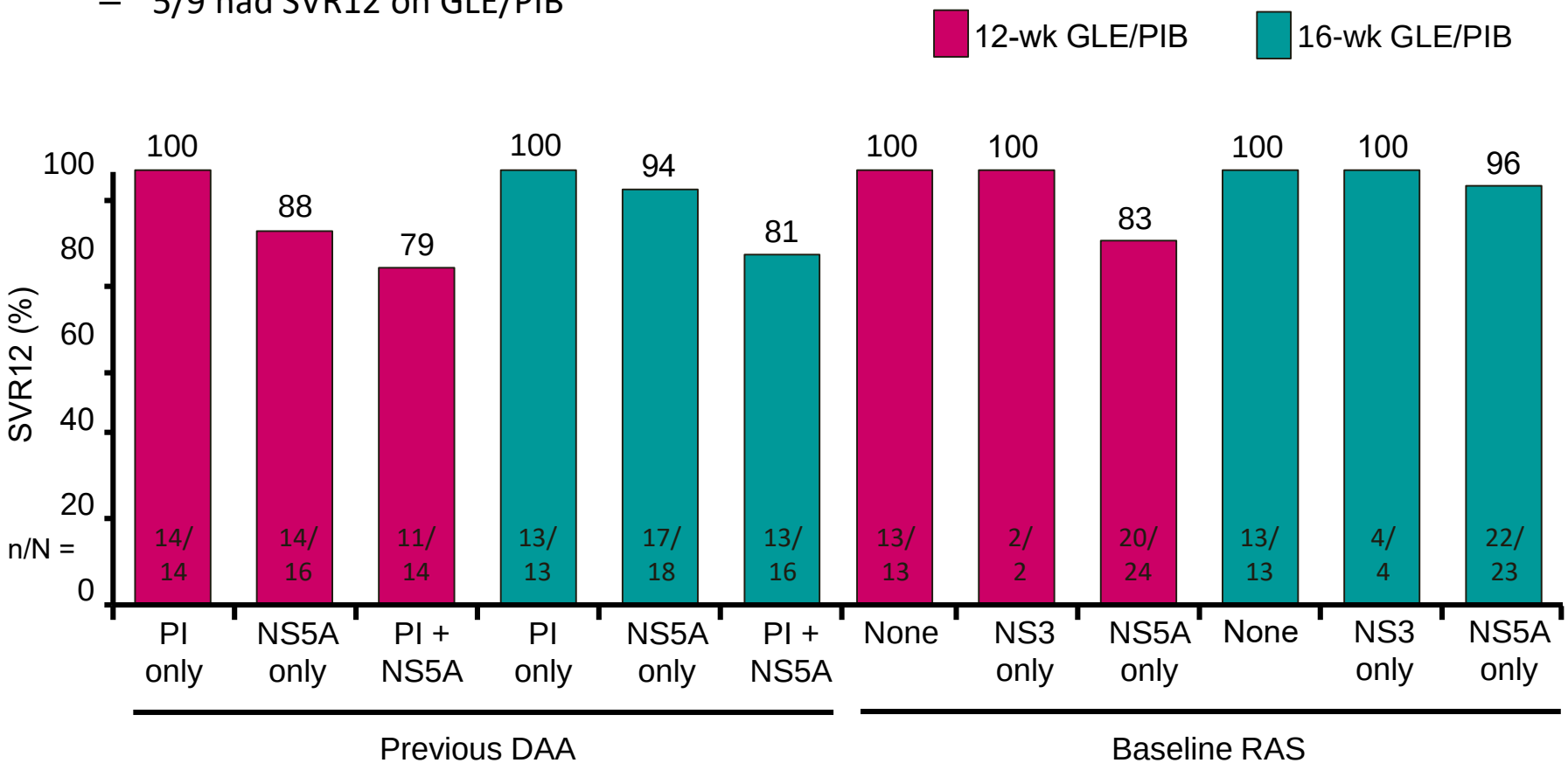
[a]RASs highlighted in red are more likely to confer a clinical impact due to the high fold-change. RASs highlighted in orange have an intermediate impact on efficacy. RASs highlighted in shades of green are not likely to have a clinically significant impact.

[b]Investigational drug.

Wyles DL et al., HCV Drug Resistance, 2017

MAGELLAN-1: Glecaprevir/Pibrentasvir in GT1 or 4 HCV With Previous DAA Failure

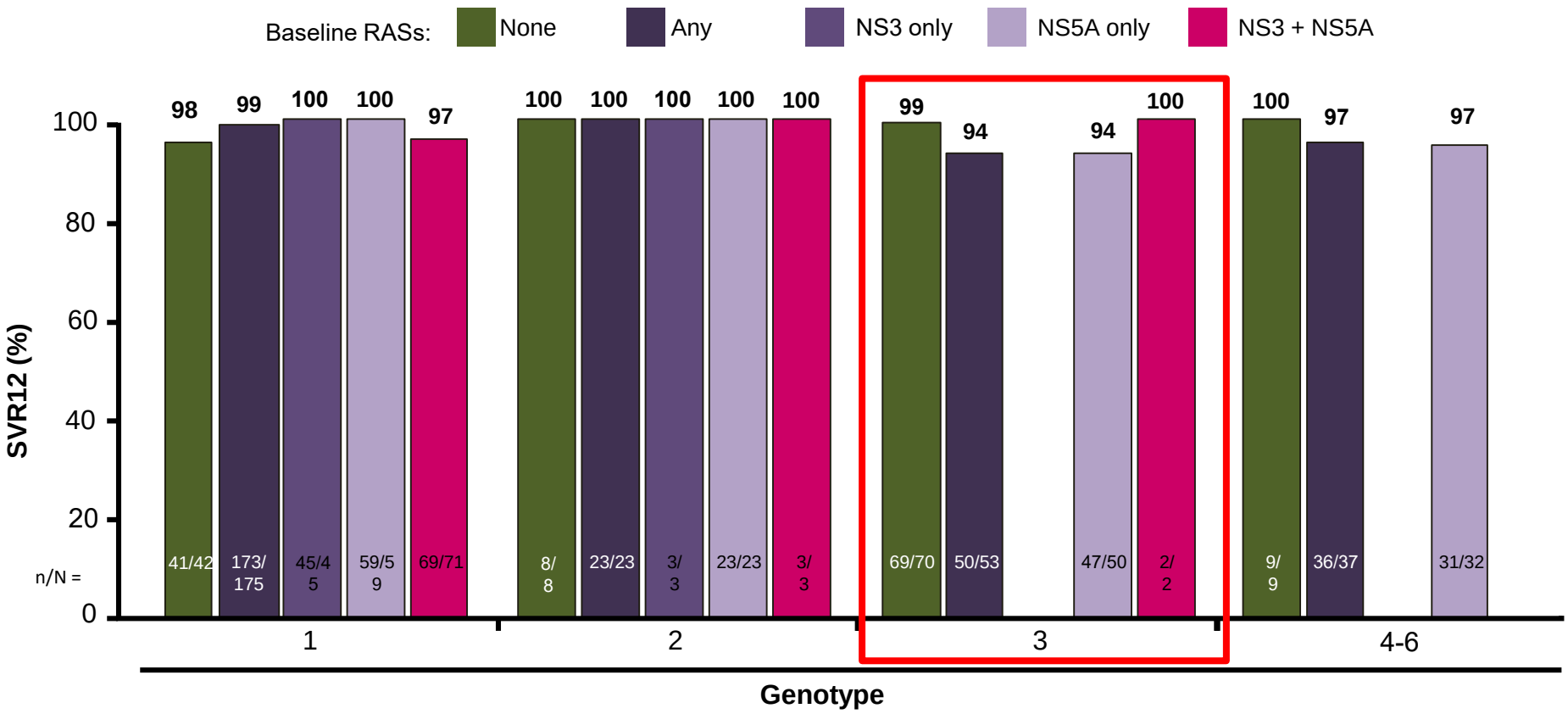
- Of pts with NS3 and NS5a RASs, 9/9 had previous failure with PI + NS5A
  - 5/9 had SVR12 on GLE/PIB



Poordad F, et al. EASL 2017. Abstract PS-156.

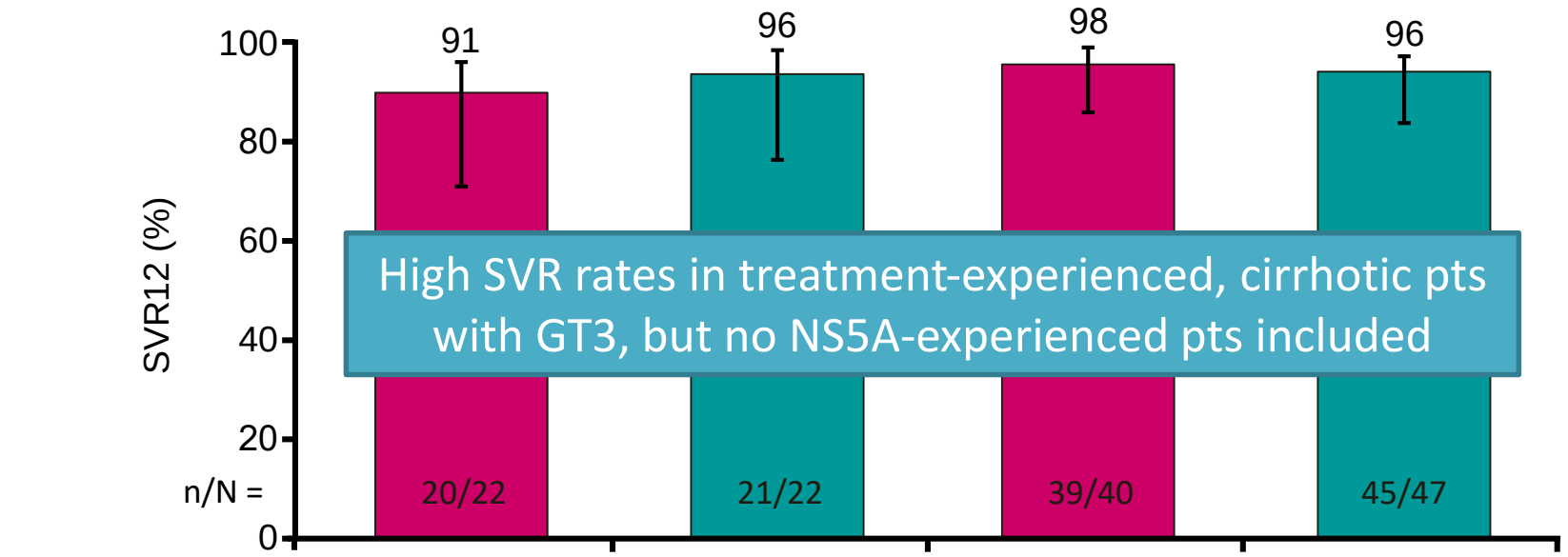
POLARIS-1 and -4: Impact of Baseline RASs on 12-Wk SOF/VEL/VOX in DAA-Experienced Pts

Integrated analysis of data from SOF/VEL/VOX arms of 2 phase III trials of DAA-experienced pts with (n = 263) and without (n = 182) previous NS5A inhibitors



Sarrazin, et al. EASL 2017. Abstract THU-248.

SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB for Pts With GT3 HCV ± Cirrhosis



Tx Wks	12	16	12	16
Cirrhosis	-	-	+	+
Tx Experienced	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
LTFU	0	0	1	0

Wyles DL, et al. AASLD 2016. Abstract 113.

Slide credit: clinicaloptions.com

Hepatology. 2017 Jul 7. doi: 10.1002/hep.29358. [Epub ahead of print]

Grazoprevir, Ruzasvir, and Uprifosbuvir for HCV After NS5A Treatment Failure.

Wyles D[1], Wedemeyer H[2], Ben-Ari Z[3], Gane EJ[4], Hansen JB[5], Jacobson IM[6], Laursen AL[7], Luetkemeyer A[8], Nahass R[9], Pianko S[10], Zeuzem S[11], Jumes P[12], Huang HC[12], Butterton J[12], Robertson M[12], Wahl J[12], Barr E[12], Joeng HK[12], Martin E[12], Serfaty L[13]; C-CREST Part C and C-SURGE Investigators.

C-SURGE

GT1 patients who failed treatment with LDV/SOF or GZR/EBR. Overall, 43% were cirrhotic, 86% had GT1a infection. At baseline, NS5A RASs were present in 31/43 (72%) and 46/49 (94%) participants in the 16-

C-CREST

24 patients underwent retreatment: 23 were F0-F2, 2 had GT1 infection, 14 had GT2 infection, and 8 had GT3 infection.

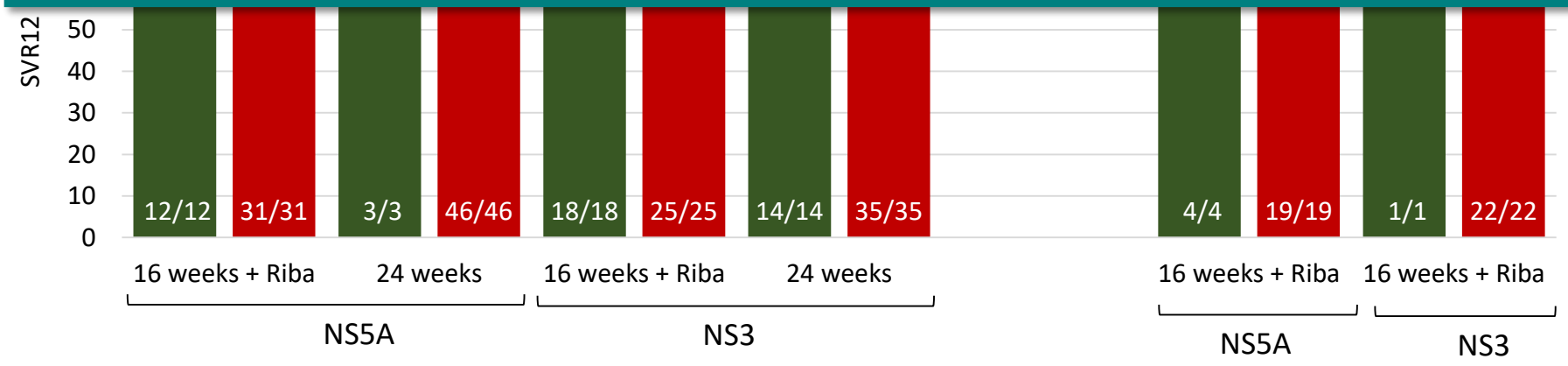
Merck Discontinues MK-3682B and MK-3682C Development Programs

SEPTEMBER 29, 2017

Company to Focus on Maximizing the Potential of ZEPATIER® (Elbasvir and Grazoprevir)

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE:MRK), known as MSD outside of the United States and Canada, today announced its strategic decision to discontinue the development of the investigational combination regimens MK-3682B (grazoprevir/ruzasvir/ uprifosbuvir) and MK-3682C (ruzasvir/uprifosbuvir) for the treatment of chronic hepatitis C virus (HCV) infection. This decision was made based on a review of available Phase 2 efficacy data and in consideration of the evolving marketplace and the growing number of treatment options available for patients with chronic HCV infection, including ZEPATIER® (elbasvir and grazoprevir).

"Remarkable progress has been made in the fight against hepatitis C infection, and Merck is enormously proud of the role we have had in that fight over the past 30 years," said Dr. Eliav Barr, senior vice president, global clinical development, infectious diseases and vaccines, Merck Research Laboratories. "We will continue to study ZEPATIER to understand even more about its role in treating chronic hepatitis C infection and will continue to work with others to help bring ZEPATIER to appropriate patients with chronic hepatitis C genotype 1 or 4 infection, the genotypes which make up the majority of patients with chronic hepatitis C infection."



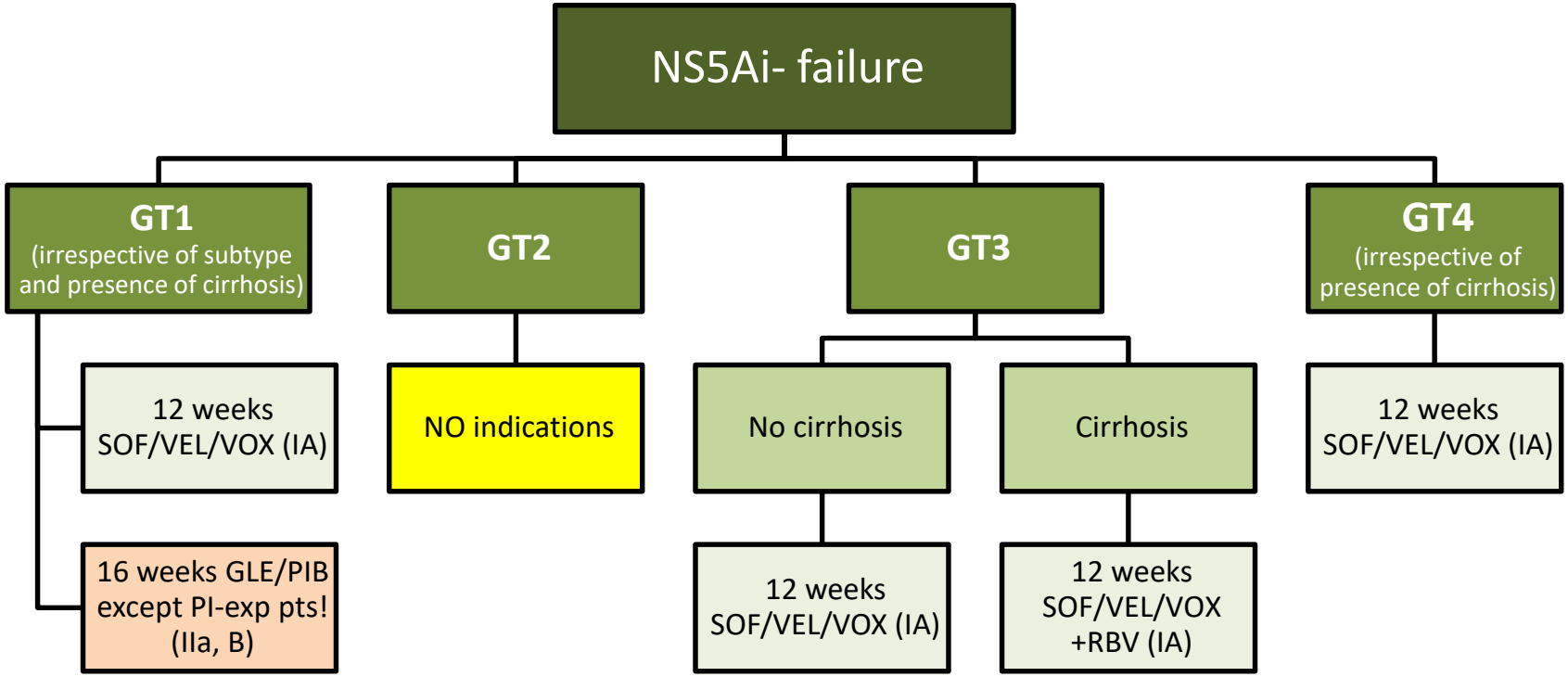
Wyles D. et al., Hepatology, 2017

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Update 21 Sept 2017



The Wall to HCV Cure and Eradication

HIV	Post OLT	BMI	Genotype 1	High VL
Black	Age >65	Renal failure	IFN experience	DDIs
IL28b TT	Cost & access	Cirrhosis	DAA experience	Genotype 3

Even in the era of DAAs,~ 47,000 patients would fail to achieve SVR in Europe before 2020

	France	Germany	Italy	Spain	UK
Number of patients who receive treatment (2014 – 2020)	102,555	92,166	207,917	156,980	94,971
• PR (%)	14,411 (14.1%)	3,596 (3.9%)	14,022 (6.7%)	9,023 (5.7%)	9,484 (10.0%)
• NS5A (%)	83,019 (81.0%)	69,771 (75.7%)	158,881 (76.4%)	136,107 (86.7%)	77,785 (81.9%)
• Non-NS5A (%)	5,125 (5.0%)	18,799 (20.4%)	35,014 (16.8%)	11,850 (7.5%)	7,702 (8.1%)
• Treatment failure (%)	13,226 (12.9%)	9,291 (10.1%)	23,224 (11.2%)	15,193 (9.7%)	9,999 (10.5%)
Among treatment failures					
• PR (%)	8,015 (60.6%)	1,369 (14.7%)	5,759 (24.8%)	4,864 (32.0%)	3,990 (39.9%)
• NS5A (%)	4,322 (32.7%)	4,126 (44.4%)	9,381 (40.4%)	7,900 (52.0%)	3,861 (38.6%)
• Non-NS5A (%)	889 (6.7%)	3,796 (40.9%)	8,084 (34.8%)	2,429 (16.0%)	2,148 (21.5%)
• Cirrhotic (%)	6,408 (48.5%)	4,426 (47.6%)	14,722 (63.4%)	7,586 (49.9%)	3,201 (32.0%)
• Genotype 1	9,281 (70.2%)	4,641 (50.0%)	16,353 (70.4%)	11,150 (73.4%)	4,578 (45.8%)
• Genotype 2	716 (5.4%)	649 (7.0%)	5,161 (22.2%)	436 (2.9%)	466 (4.7%)
• Genotype 3	2,087 (15.8%)	3,672 (39.5%)	867 (3.7%)	2,988 (19.7%)	4,582 (45.8%)
• Genotype 4-6	1,142 (8.6%)	329 (3.5%)	843 (3.6%)	619 (4.1%)	373 (3.7%)

Chhatwal J et al., EASL 2017 poster #FRI-233

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.

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Validazione Nazionale GRT HCV

Valeria Cento, Tina Ruggiero, Francesca Ceccherini-Silberstein, Maurizio Zazzi
per il **Gruppo Validazione GRT**

Centri attivi fase I

1. Microbiologia e Virologia, ASST Papa Giovanni XXIII, Bergamo
2. Microbiologia Clinica, Virologia e Diagnostica delle Bioemergenze, ASST Fatebenefratelli Sacco, Milano
3. Malattie Infettive, San Raffaele, Milano
4. Microbiologia e Virologia, San Raffaele, Milano
5. Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Università di Milano, Milano
6. Virologia Molecolare, Fondazione Policlinico San Matteo, Pavia
7. Laboratorio di Microbiologia e Virologia - ospedale Amedeo di Savoia ASL Città di Torino, Torino
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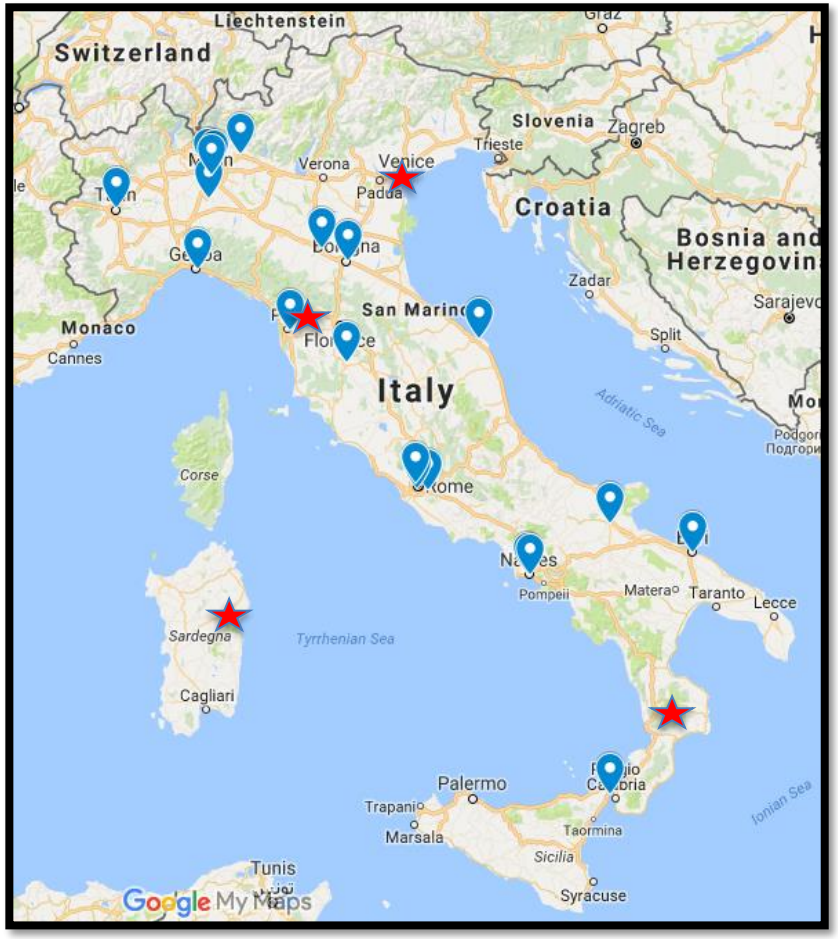

Roma 9 Giugno 2017