Role of resistance and resistance testing for managing HCV

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Conflict of Interest

Jürgen Rockstroh has received:

- Honoraria for lectures and/or consultancies from Abbott, AbbVie, Bionor, BMS, Cipla, Gilead, Janssen, Merck and ViiV.
- Research grants from Dt. Leberstiftung, DZIF, NEAT ID.

Deutsche Leberstiftung

DZIF

neatid

General aspects of DAA resistance

General aspects

- The advent of direct-acting agents (DAAs) has improved treatment of HCV but may be limited by primary drug resistance and also development of RAS (resistance-associated substitutions) in the setting of virological failure

Not All Direct-Acting Antivirals are Created Equal

Characteristic	Protease Inhibitor*	Protease Inhibitor**	NS5A Inhibitor	Nuc Polymerase Inhibitor	Non-Nuc Polymerase Inhibitor
Resistance profile					
Pangenotypic efficacy					
Antiviral potency					
Adverse events					

 Good profile  Average profile  Least favorable profile

*First generation. **Second generation.

Prevalence of Baseline GT1a NS5A RAVs: Impact of RAV Definition and Sensitivity of Detection

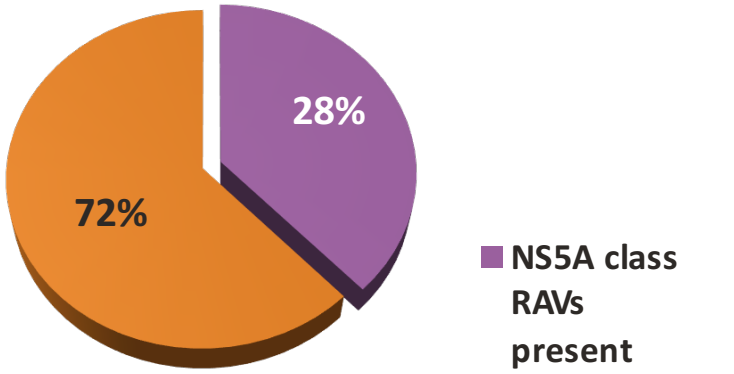
NS5A Inhibitor Class RAVs detected in this study at amino acid positions:

M28(all), Q30(all), L31(all), P32L, H58D/R, and Y93(all)

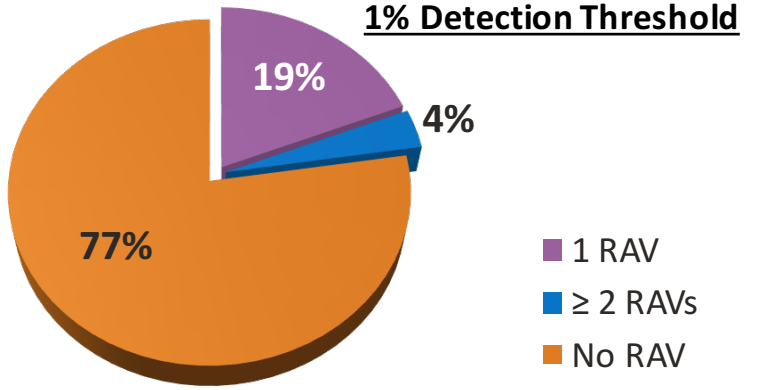
Ombitasvir-specific RAVs detected in this study:

M28T/V, Q30E/R, H58D, Y93C/F/H/L/N

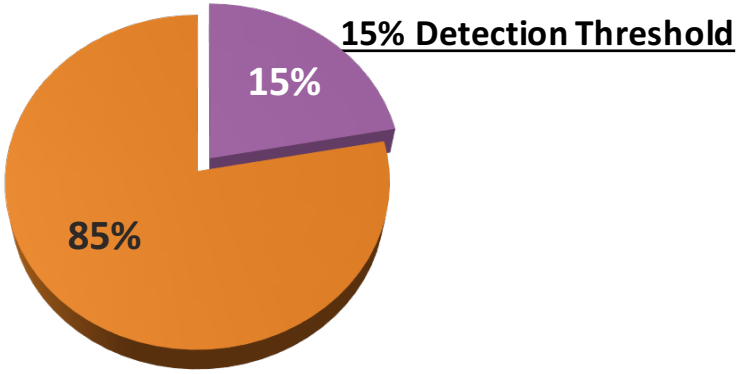
1% Detection Threshold



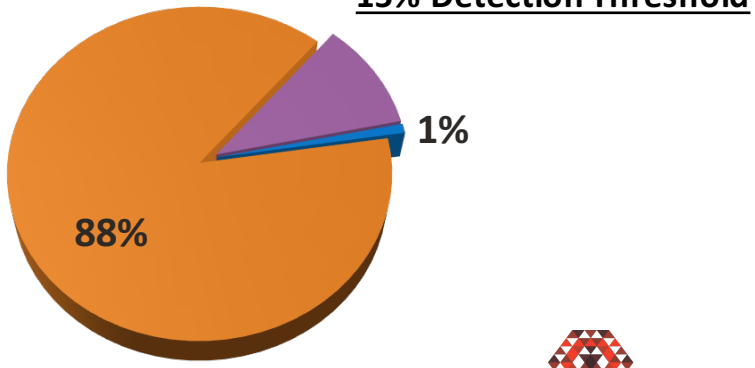
1% Detection Threshold



15% Detection Threshold



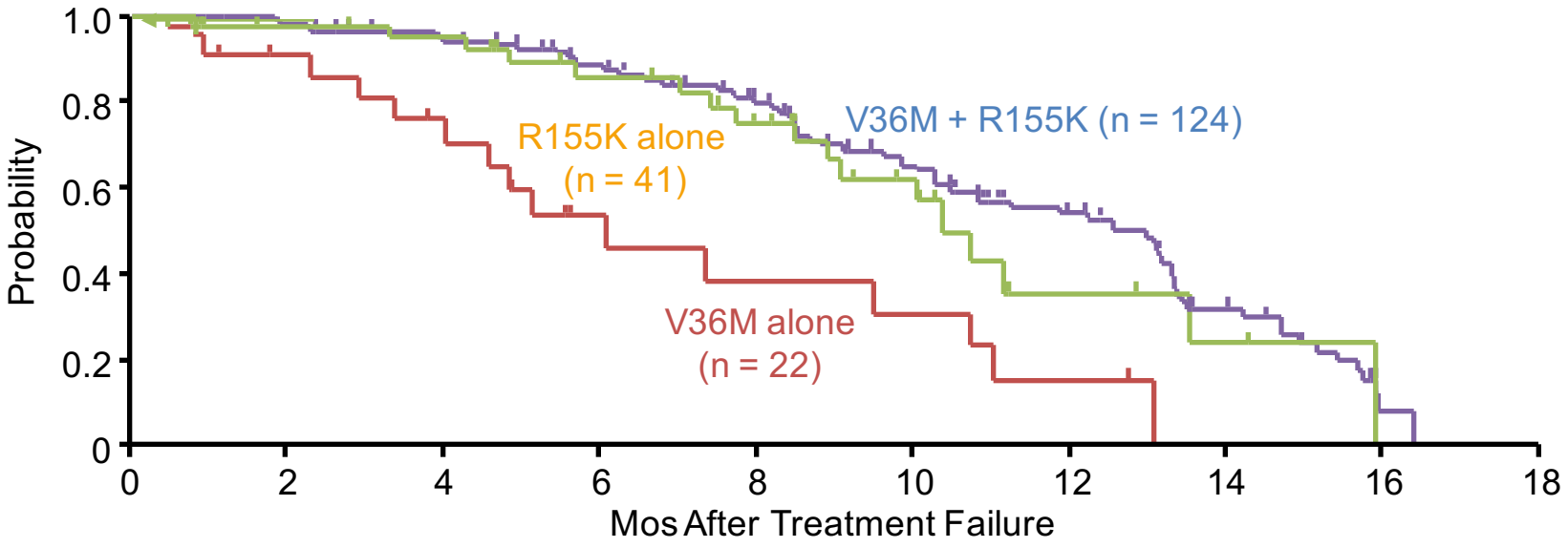
15% Detection Threshold



Sulkowski M, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 539LB.

Stopping Rules—The Facts: Multiple Mutations May Be More Troublesome

- Loss of detectable resistance in patients with resistant variant(s) at failure of TVR + pegIFN/RBV (analysis includes only patients with follow-up data)



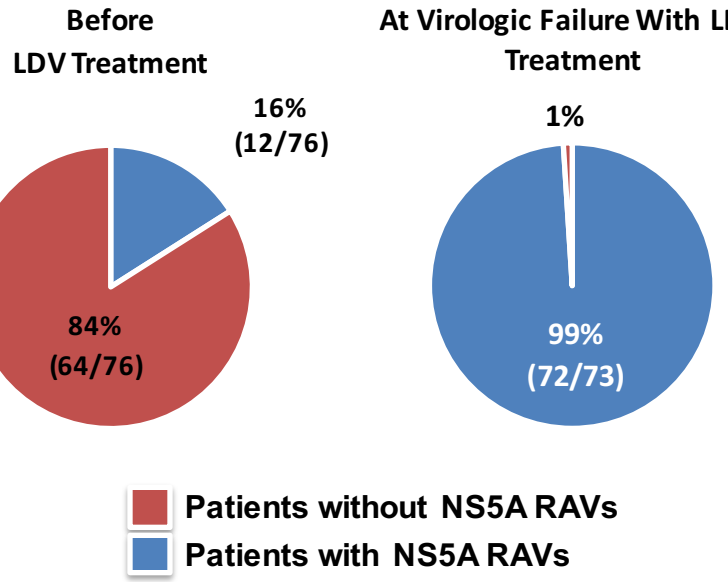
	V36M Alone*	R155K Alone†	V36M + R155K
% of 1a failures (WT: 16%)	10	20	46
Median mos to loss (95% CI)	6 (4-9)	10 (9-13)	13 (10-13)

*Comparison of V36M vs V36M + R155K: $P < .0001$. †Comparison of R155K vs V36M + R155K: $P = .48$.

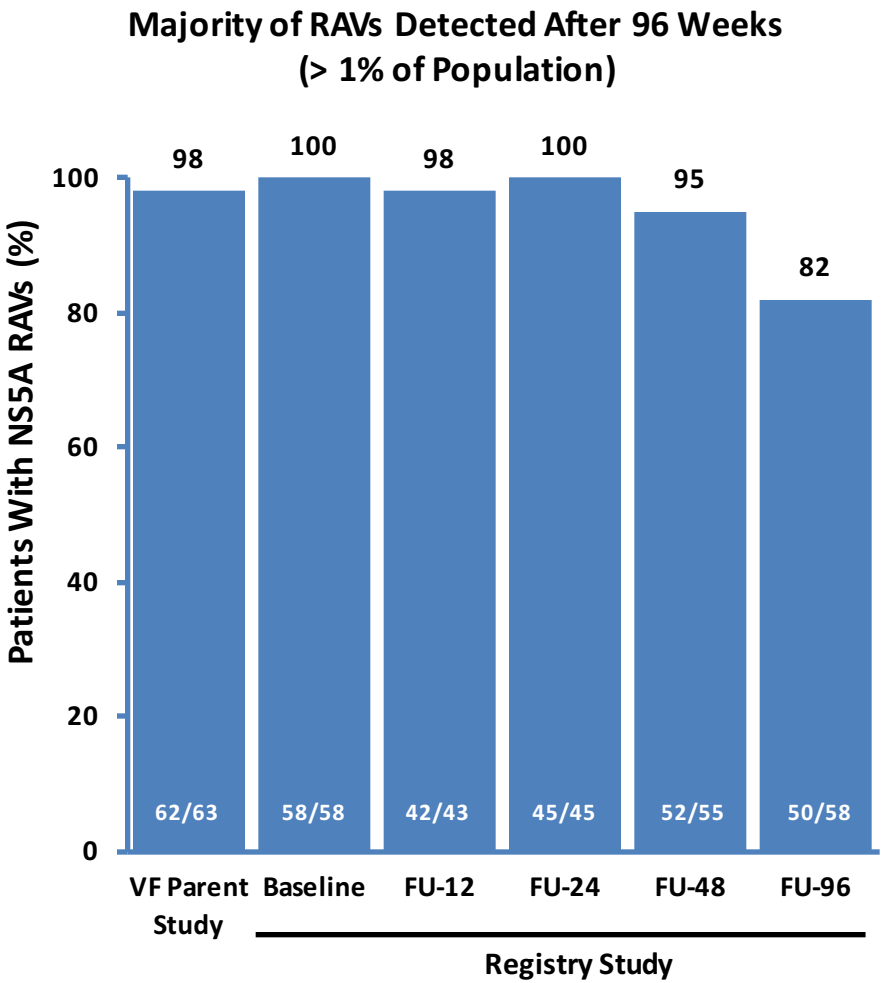
Sullivan J, et al. EASL 2011. Abstract 8.

Long-Term Persistence of HCV NS5A Variants After Treatment With LDV

- NS5A RAVs in patients who failed HCV treatment with ledipasvir (LDV) in the absence SOF
  - Positions 24, 28, 30, 31, 32, 58, 93 that confer >2.5-fold reduced susceptibility to LDV *in vitro* were included



Almost all patients developed NS5A RAVs at treatment failure

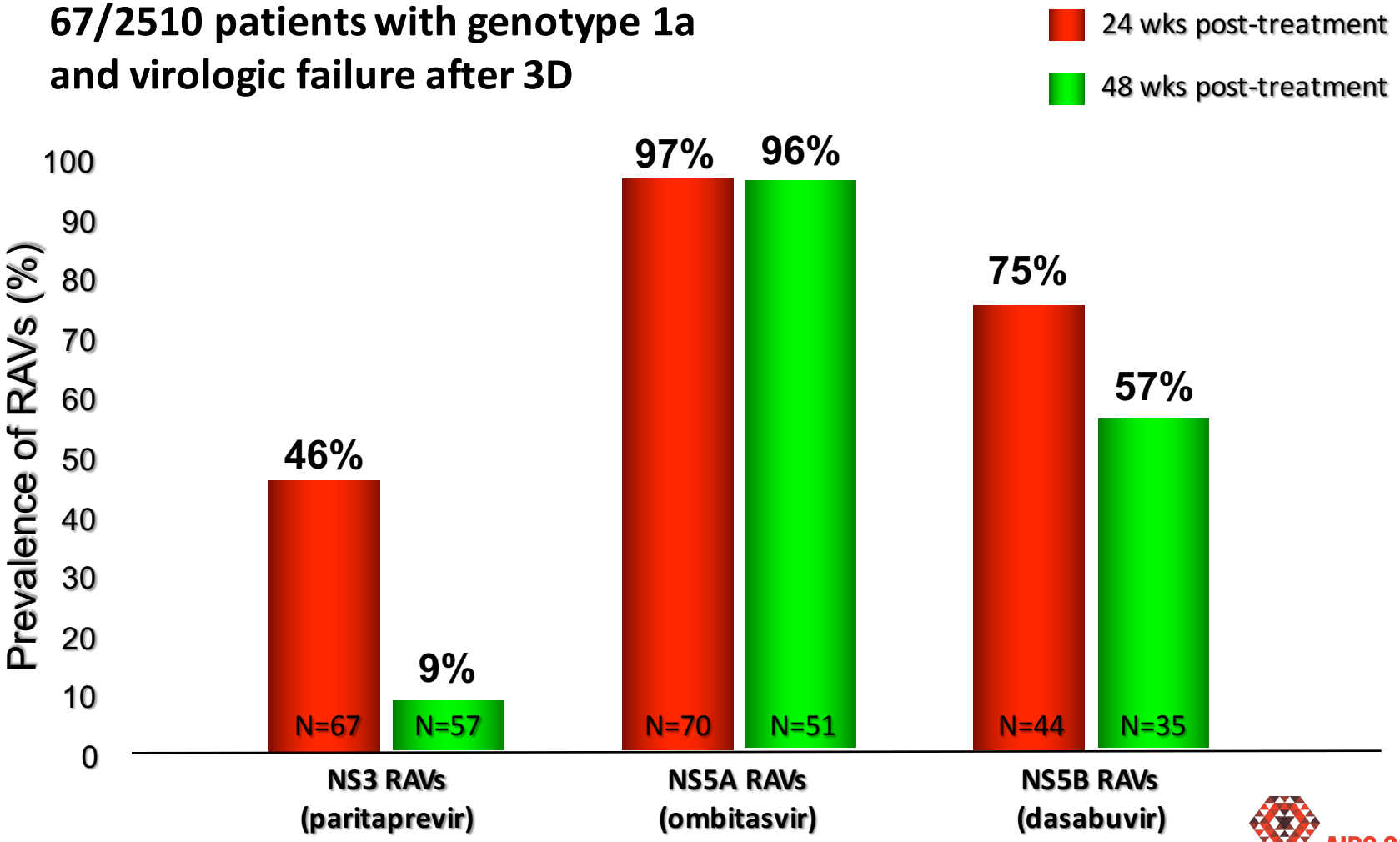


NS5A RAVs persisted in majority of patients for 96 weeks

Wyles D, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O059.

Persistence of RAVs in Patients who Relapsed after 3D

67/2510 patients with genotype 1a and virologic failure after 3D



(Krishnan et al., EASL 2015)

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What do the guidelines say?

EASL JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver *

- The HCV genotype and genotype 1 subtype (1a/1b) must be assessed prior to treatment initiation and will determine the choice of therapy **(A1)**
- *IL28B* genotyping has no role in the indication for treating hepatitis C with the new DAAs **(A1)**
- HCV resistance testing should not be performed prior to therapy, because the SVR rates are very high both in patients without and with detectable amounts of resistance-associated variants by means of population sequencing at baseline (with the exception of patients infected with subtype 1a who receive the combination of PegIFN-α, ribavirin and simeprevir) **(A1)**
- The utility of HCV resistance testing (i.e. the determination of the sequence of the DAA target region) prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown **(B2)**

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What does the label say?

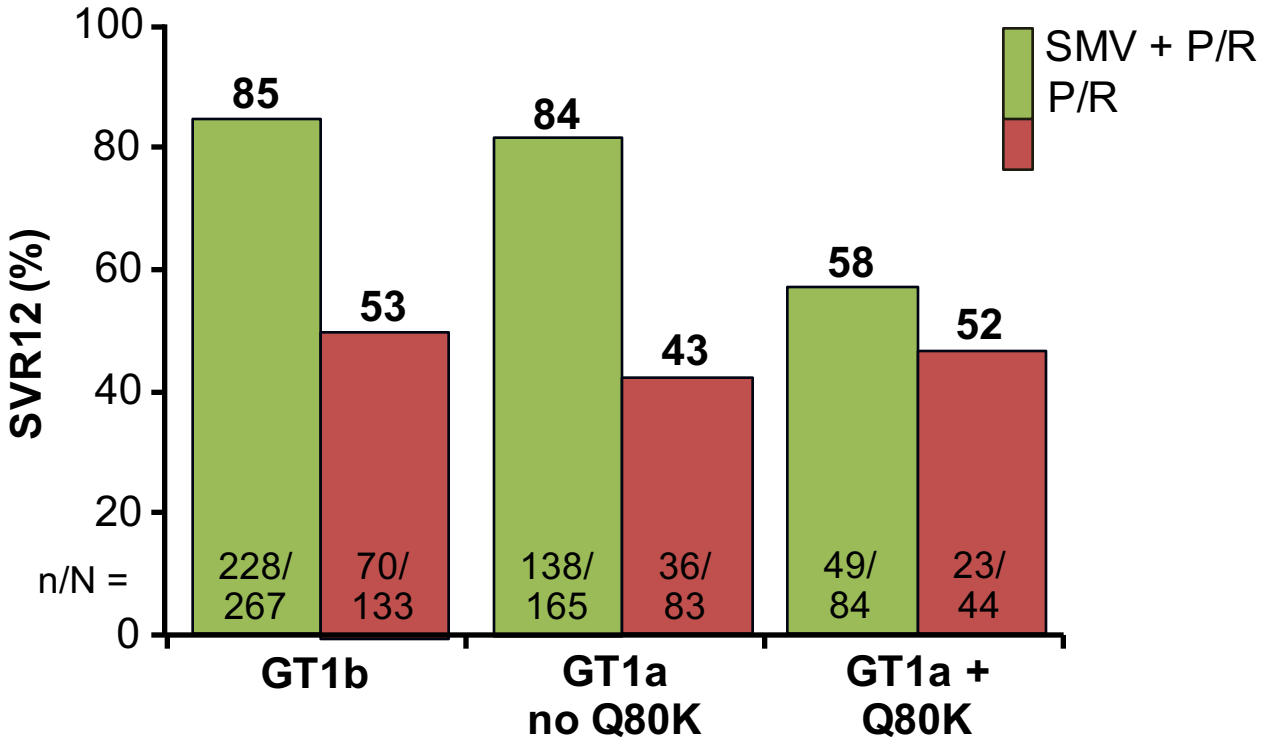
What does the label say?

- When considering OLYSIO (Simeprevir) combination treatment with peginterferon alfa and ribavirin in HCV genotype 1a patients, patients should be tested for the presence of virus with the NS3 Q80K polymorphism before starting treatment

- Zepatier label USA: Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended.

- Daklinza® (daclatasvir) and Sunvepra® (asunaprevir) licensed in Japan

QUEST: No Benefit of Simeprevir if Q80K Positive

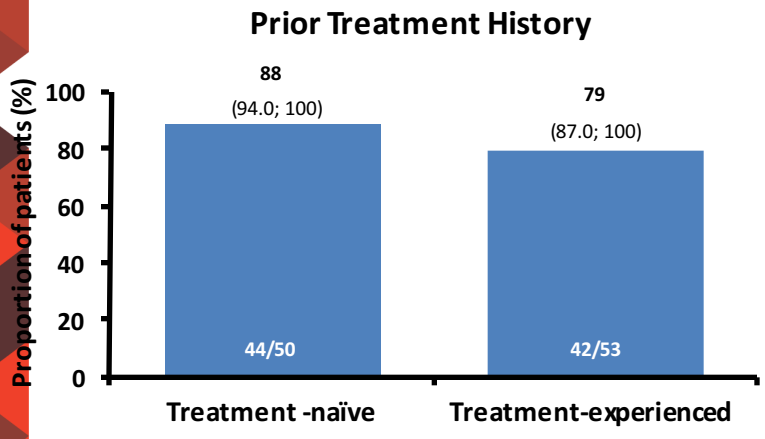


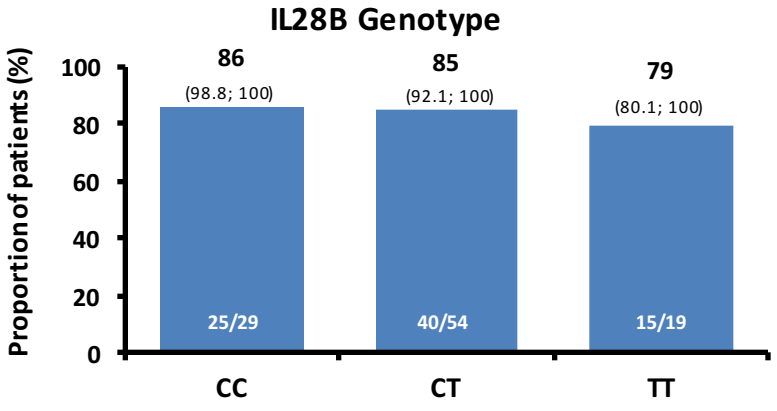
Q80K present in 34% of GT1a patients
No benefit of simeprevir if Q80K positive

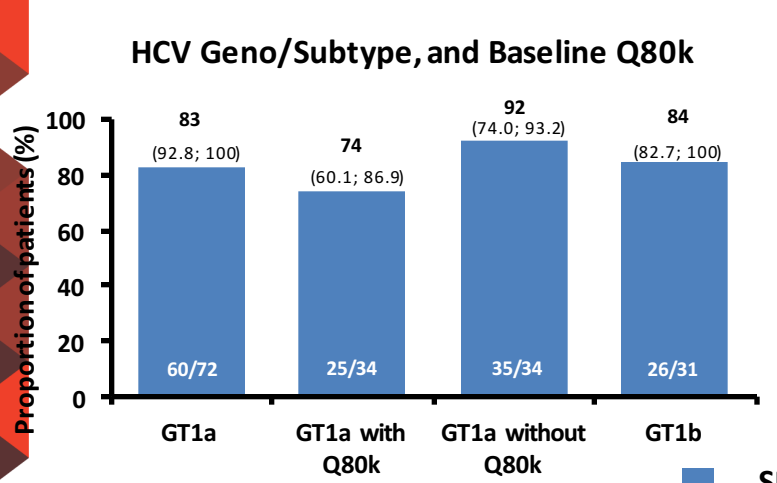
Jacobson I, et al. AASLD 2013. Abstract 1122.

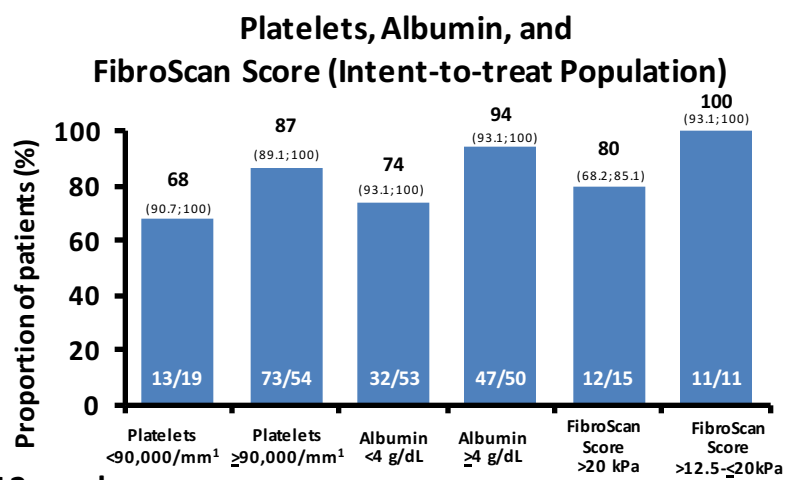
OPTIMIST 2: SMV + SOF in HCV Mono-Infx with GT1 and Cirrhosis

- **SVR12 Rates (95% CI) by:**









Lawitz E, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TULBPE11.

C-EDGE TN + C-EDGE CO-INFECTION: NS3/4A Resistance Associated Variants

Resistance analysis population (290 GT1a; 172 GT1b)†

	RAV Status in Patients with Baseline Sequence % (n/m)		SVR12 All Patients % (N/n)		SVR12 NS3 RAVs ≤5-fold potency loss		SVR12 NS3 RAVs >5-fold potency loss	
Genotype 1a RAVS								
Baseline NS3 RAVS	53.4	(155/290)	96.1	(149/155)	96.1	(149/155)	0	0/0
No baseline NS3 RAVs	46.6	(135/290)	93.3	(126/135)	—	—	—	—
Genotype 1b RAVS								
Baseline NS3 RAVS	17.4	(30/172)	96.7	(29/30)	96.1	(25/26)	100	(4/4)
No baseline NS3 RAVs	82	(142/172)	99.3	(141/142)	—	—	—	—

†The resistance analysis population includes all patients from the full analysis set who have sequencing data available and who either achieved SVR12 or met criteria for virologic failure

N = number of patients who achieved SVR12

m = number of patients with evaluable baseline sequence

n = number of patients with or without a baseline RAV

Signature NS3 loci included the substitutions V36A/G/L/M/I, T54A/C/G/S, V55A/I, Y56H, Q80K/R, V107I, 122A/G/R, I132V, R155X, A156S/T/V/F/G/L, V158I, D168X, I/V170A/F/T/V, and M175L.

The following NS3 RAV(s) are considered to have >5-fold resistance to GZR based on GT1a replicons: Y56H, R155G/T/W, A156G/T/V/L, D168A/G/T/V/L/I/F/Y/E/H/K/R .

C-EDGE TN + C-EDGE CO-INFECTION: NS5A Resistance Associated Variants

Resistance analysis population (294 GT1a; 173 GT1b)†

	RAV Status in Patients with Baseline Sequence % (n/m)		SVR12 All Patients % (N/n)		SVR12 NS5A RAVs ≤5-fold potency loss		SVR12 NS5A RAVs >5-fold potency loss	
Genotype 1a RAVS								
Baseline NS5A RAVS	9.9	(29/294)	65.5	(19/29)	87.5	(14/16)	38.5	(5/13)
No baseline NS5A RAVs	90.1	(265/294)	98.1	(260/265)	—	—	—	—
Genotype 1b RAVS								
Baseline NS5A RAVS	13.3	(23/173)	95.7	(22/23)	100	(1/1)	95.5	(21/22)
No baseline NS5A RAVs	86.7	(150/173)	99.3	(149/150)	—	—	—	—

†The resistance analysis population includes all patients from the full analysis set who have sequencing data available and who either achieved SVR12 or met criteria for virologic failure

N = number of patients who achieved SVR12

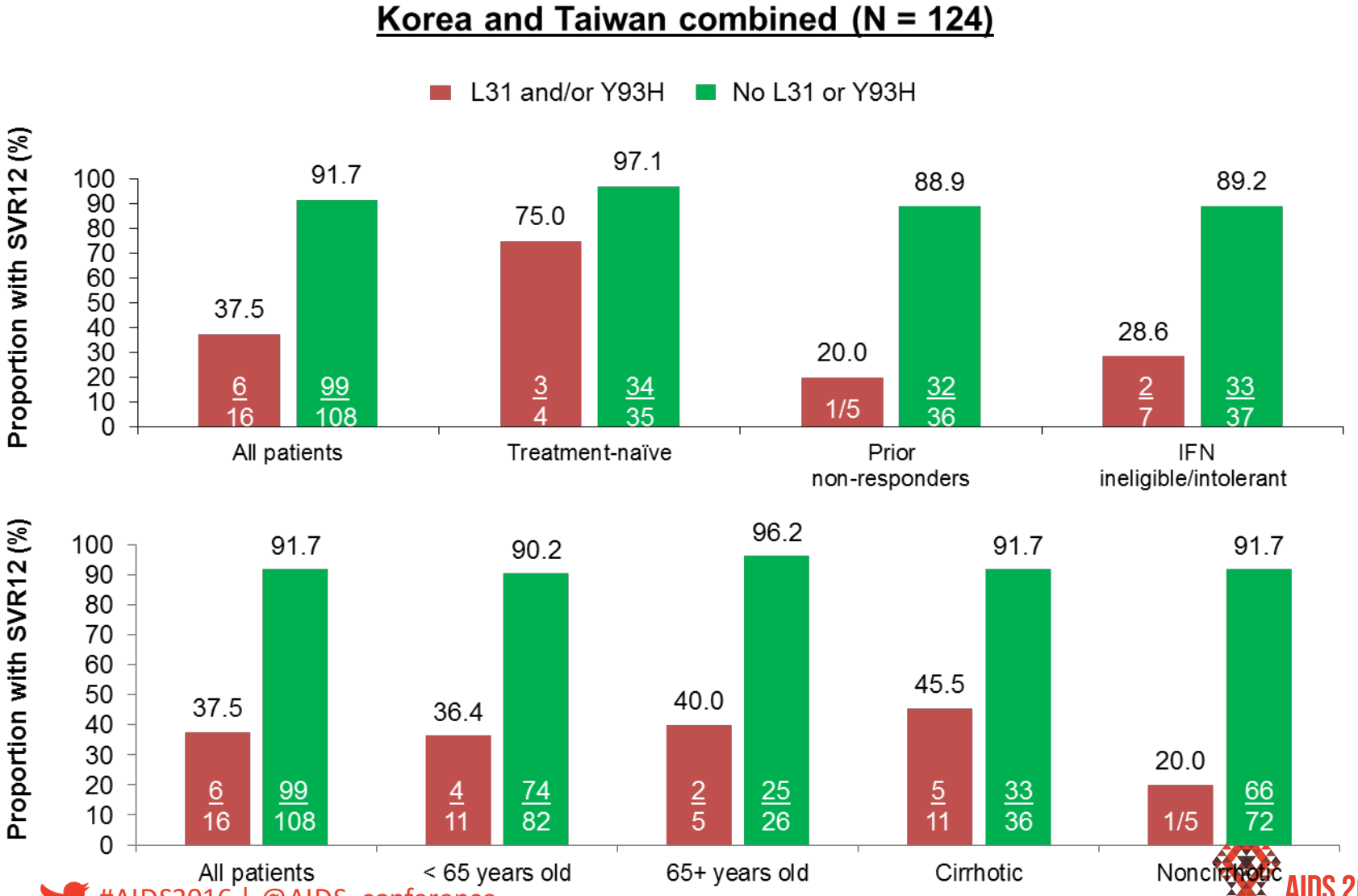
m = number of patients with evaluable baseline sequence

n = number of patients with or without a baseline RAV

Signature NS5A loci included the substitutions M28T/V/A, Q30E/H/R/G/K/L/D, L31M/V/F, H58D, and Y93C/H/N/S for GT1a and the substitutions L28T/V/A, R30E/H/G/K/L/D, L31M/V/F, P58D and Y93C/H/N/S for GT1b.

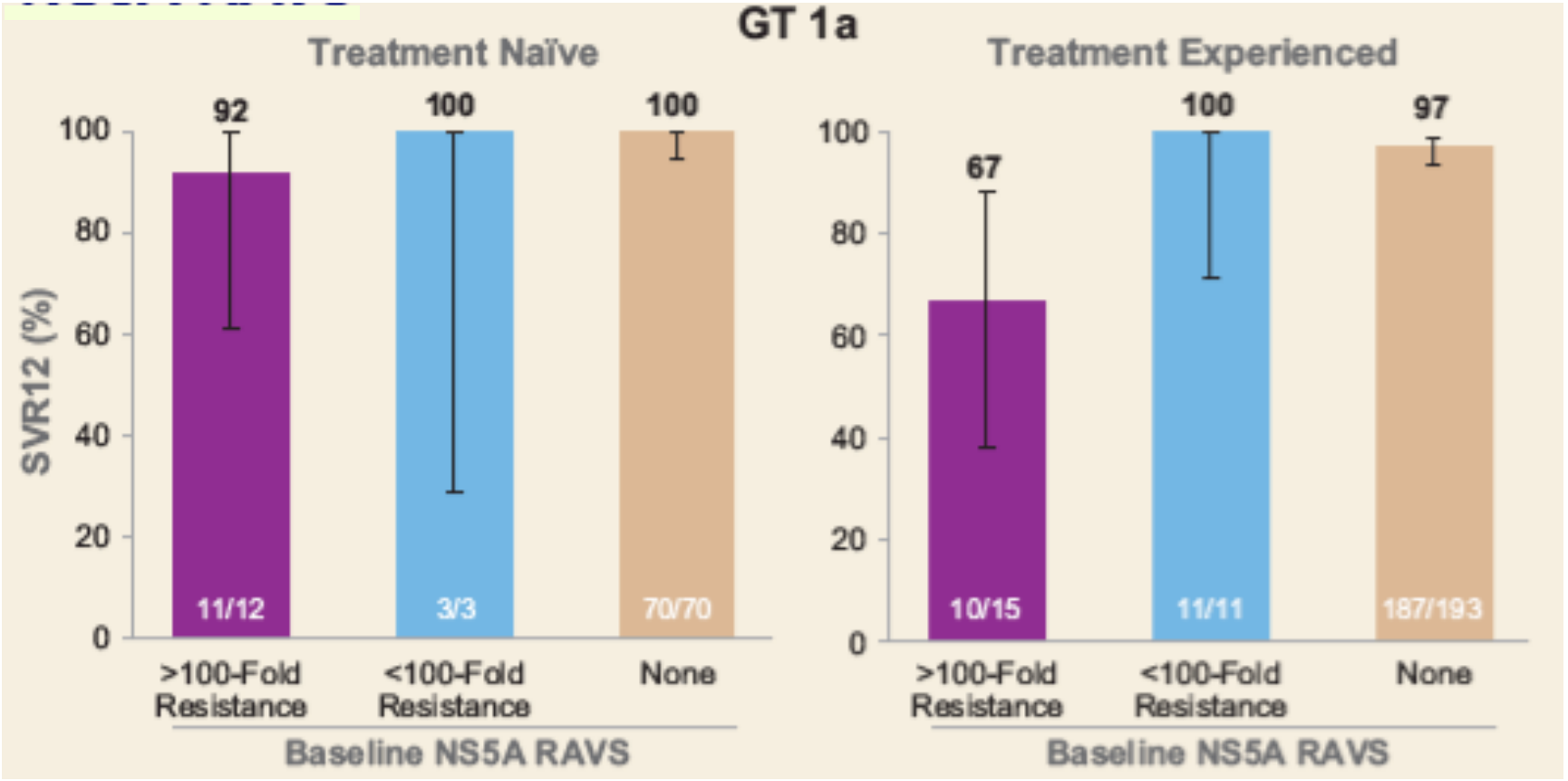
Based on the available GT1a replicon data, the following variants are considered to have >5-fold resistance to EBR: M/L28T/A, Q/R30E/H/R/G/K/L/D, L31M/V/F, H58D, Y93C/H

Daclatasvir + Asunaprevir: High SVR across all patient types without baseline L31 and/or Y93H polymorphisms



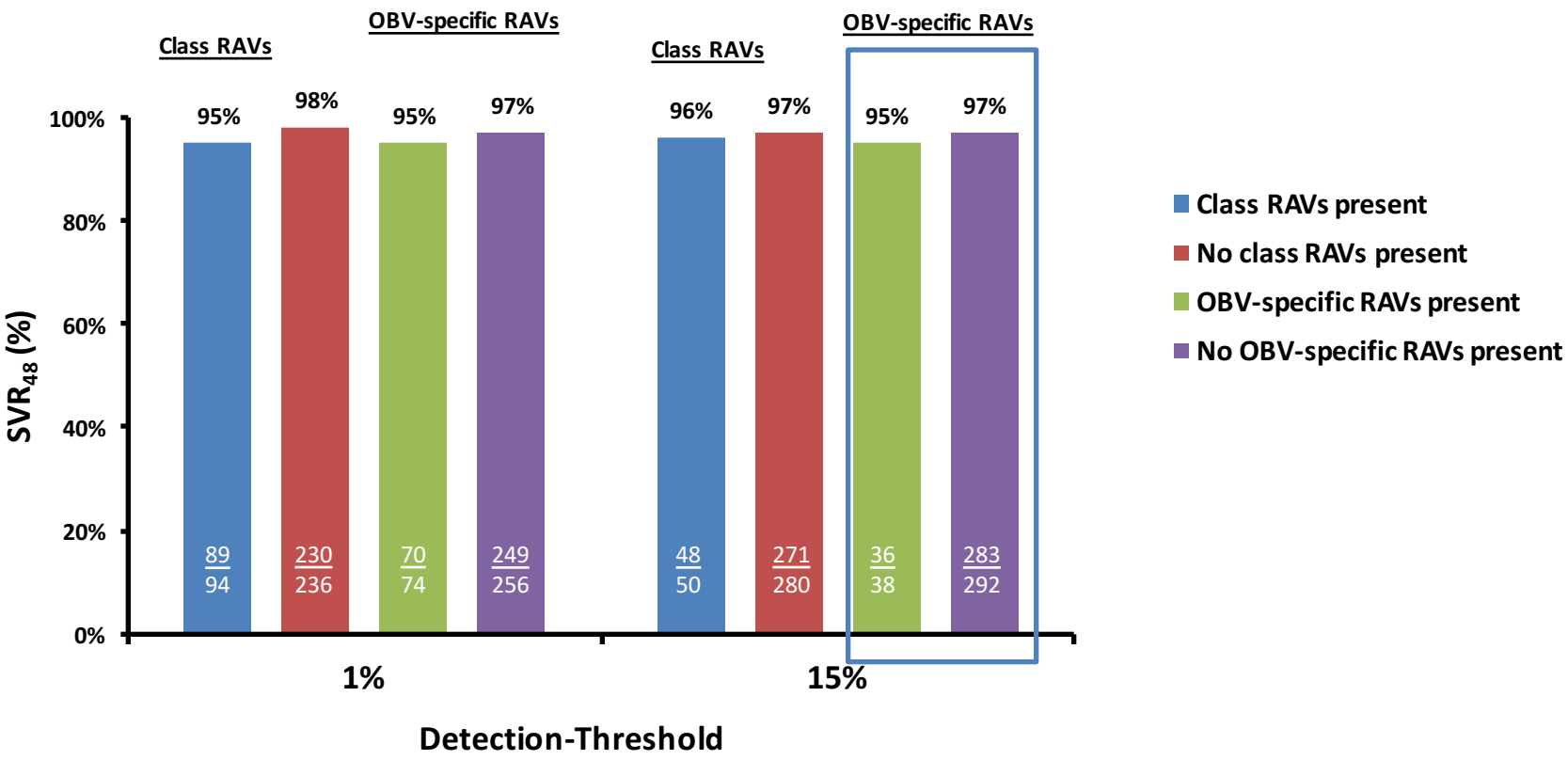
McPhee et al. APASL 2015. Poster 1549; Kao JH..**Ahn SH**. The Liver Week 2015.

SVR to Sofosbuvir/Ledipasvir According to NS5A RAVs (513 cirrhotic patients)



Sarrazin et al., EASL 2015

Impact of Baseline GT1a NS5A Class RAVs and Ombitasvir-specific RAVs on SVR Rate



Similar SVR rates were observed irrespective of the presence or absence of baseline variants

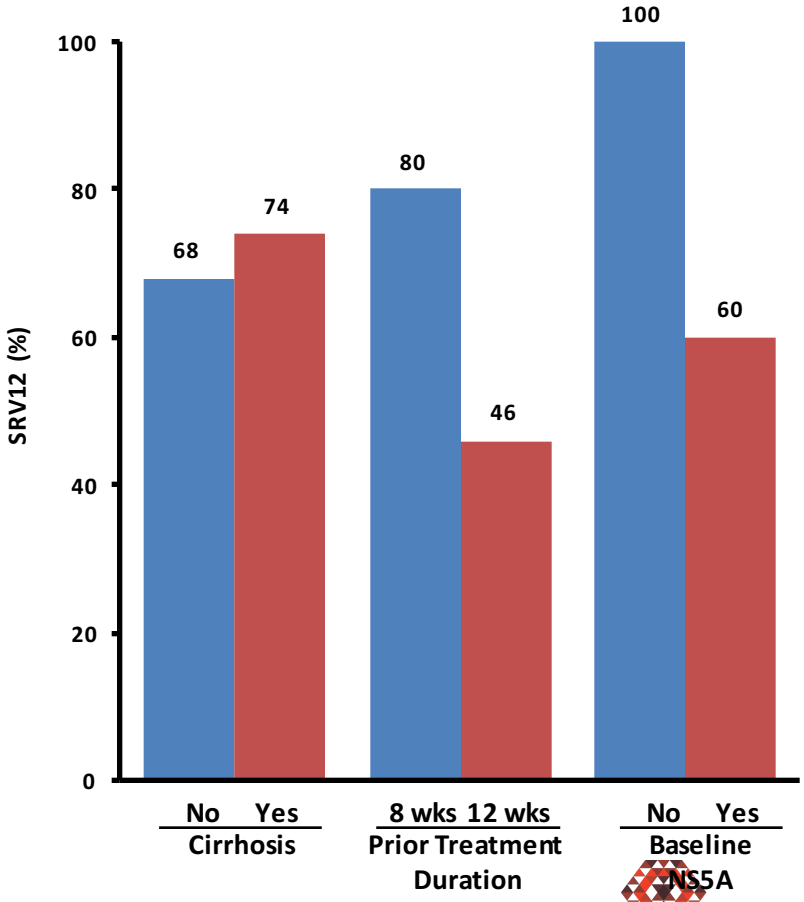
Sulkowski M, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 539LB.

Can a resistance test guide treatment decision making in patients with prior failure of DAA based therapy?

Retreatment of Patients Who Failed 8 or 12 Weeks of LDV/SOF-Based Regimens With LDV/SOF for 24 Weeks

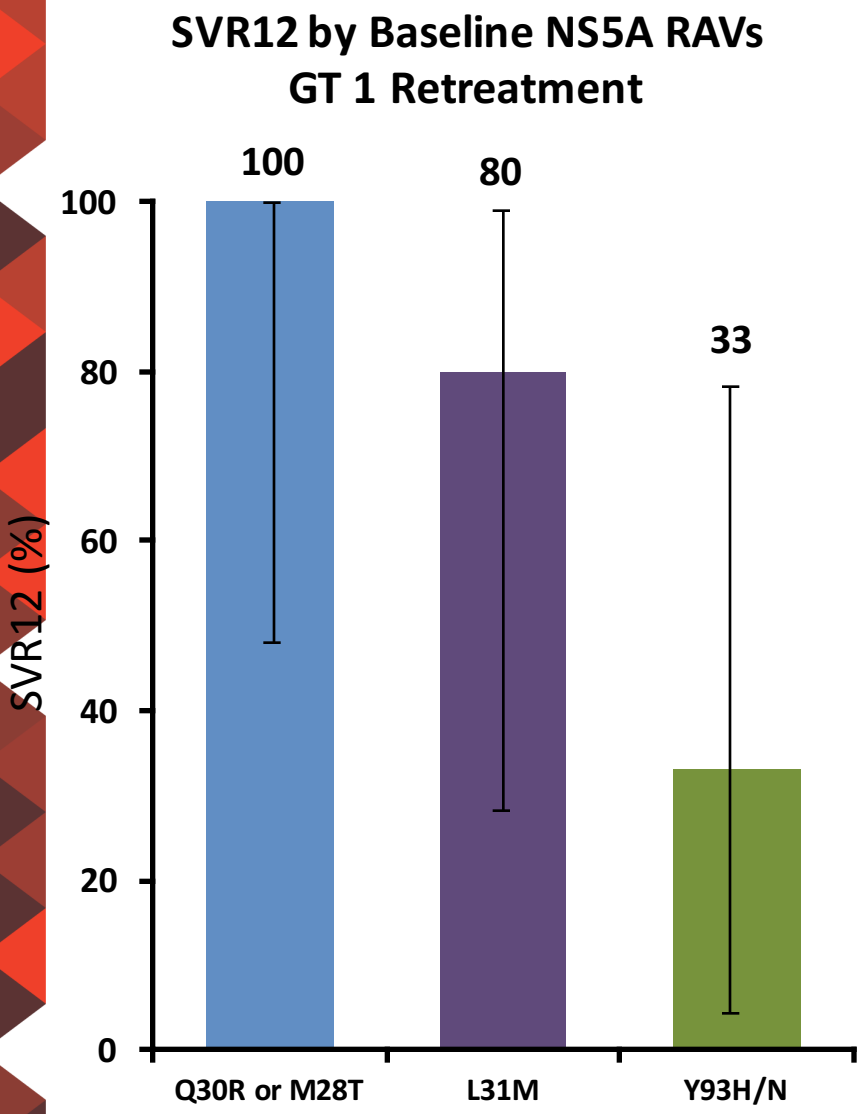
	LDV/SOF 24 Weeks N=41
Mean age, y (range)	58 (35-71)
Male, n (%)	34 (83)
Black/African American, n (%)	10 (24)
IL28B non-CC, n (%)	38 (93)
GT 1a, n (%)	34 (83)
Mean HCV RNA, log_{10}IU/mL (range)	6.2 (4.5-7.4)
Cirrhosis, n (%)	19 (46)
Presence of NS5A RAVs	15 (79)
Prior HCV treatment, n (%)	
LDV/SOF ± RBV	33 (80)
LDV/SOF + GS-9669	8 (20)
Prior HCV treatment duration, n (%)	
8 weeks	30 (73)
Presence of NS5A RAVs	19 (63)
12 weeks	11 (27)
Presence of NS5A RAVs	11 (100)

SVR according to baseline parameters



Lawitz E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O005.

Results and Analysis

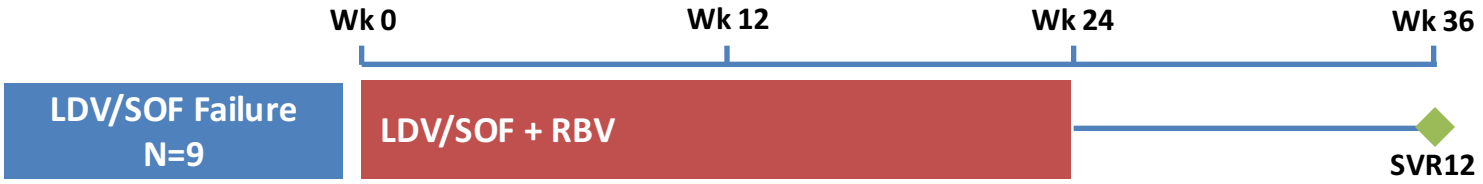


- Prior to re-treat
  - No NS5B resistance associated (S282T) or treatment-emergent (L159F, V321A) variants were detected
- At second virologic failure
  - 4 of 12 (33%) patients had NS5B variants detected
    - S282T (n=2)
    - L159F (n=1)
    - Double-mutant S282T + L159F (n=1)

Lawitz E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O005.

Re-treatment after failure to LDV/SOF

- **9 patients without SVR in ION-4 after 12 weeks of LDV/SOF**



GT	NS5A RAVs Before Primary Study (%)	NS5A RAVs at Virologic Rlapse After Primary Study (5)	SRV12
1a	None	None	Yes
1a	None	None	Yes
1a	L31M (>99), H58D (92)	L31M (>99), H58D (92)	Yes
1a	Y93F (1), Y93N (10)	Y93N (<99)	Yes
1a	L31M (>99), Y93N (<25)	L31M (>99), Y93N (>99)	Yes
1a*	None	Y93N (>99)	Yes
1b	Y93H (>99)	L31I (11), Y93H (>99)	Yes
1b	None	L31V (>99)	Yes
1a	None	L31M (>99)	No

SVR in 8/9; 1 relapse 4 weeks after EOT: GT1a, no cirrhosis

Cooper C, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 573.

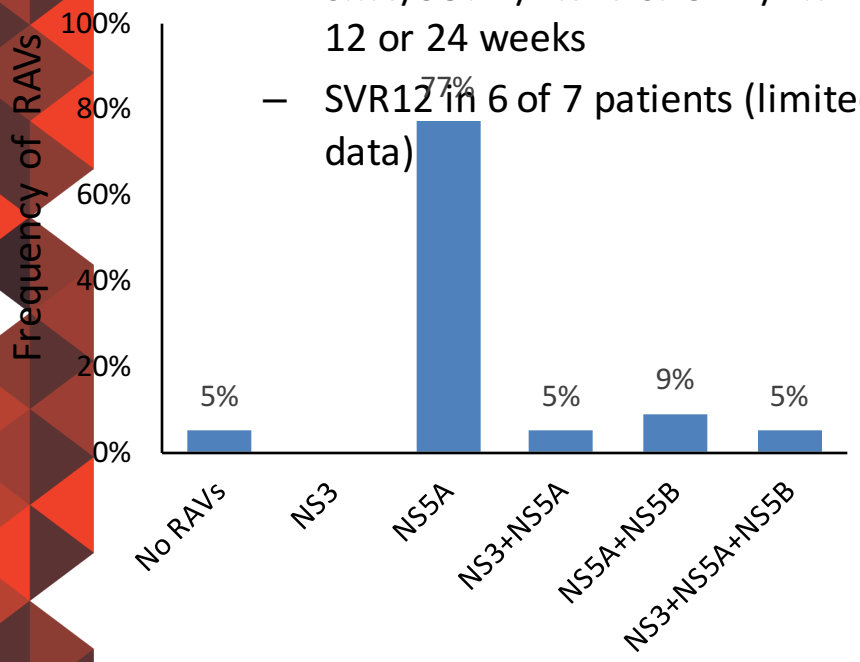
Retreatment of Patients Who Failed DAA-combination Therapies - Real-world Experience From a Large Hepatitis C Resistance Database

- Subset of the European resistance database (n=3549) with persons who failed DAAs outside of clinical trials (N=310) – drug-class specific RASs (NS3, NS5A, NS5B) associated with > 2-fold increase in EC50
- Assess HCV guidelines approach to re-treatment:
  1. Use active DAAs
  2. Add RBV
  3. Longer duration

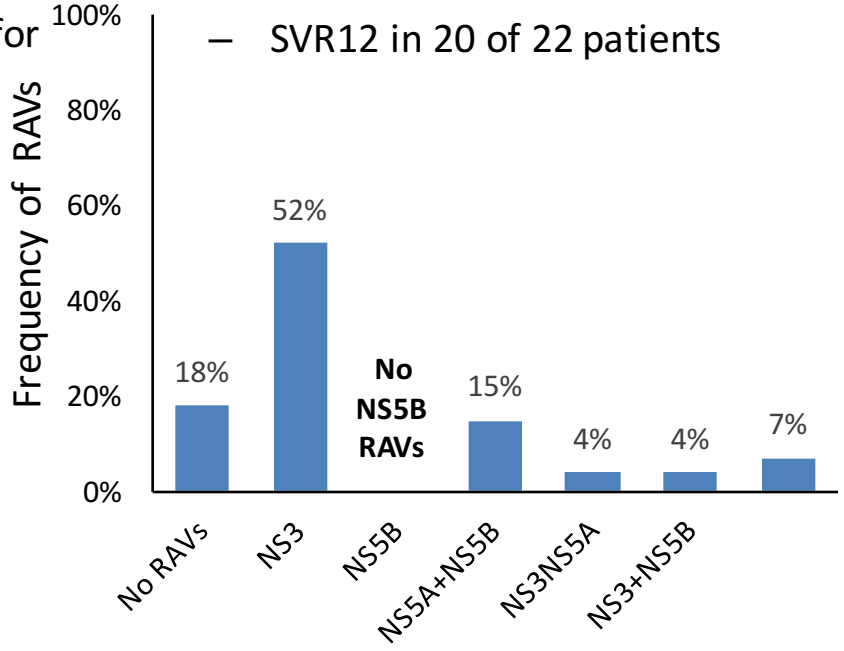
N = 310	SMV/SOF ± RBV N=55	LDV/SOF ± RBV n=114	DCV/SOF ± RBV n=51	RTV/OBV ± RBV n=30	SOF + RBV n=60
Mean age, y (range)	58 (43-75)	57 (34-77)	55 (31-71)	55 (34-58)	52 (27-65)
Men, n (%)	43 (78)	94 (82)	42 (82	26 (87)	47 (78)
Cerrhosis, n (%)	37 (71)	62 (57)	33 (70)	11 (37)	21 (44)
+RBV, n (%)	10 (55)	39 (34)	8 (16)	19 (63)	60 (100)
Prior IFN Therapy	39 (76)	67 (67)	20 (76)	21 (70)	27 (63)
G, n (%)					
1	49 (89)	90 (79)	29 (57)	27 (90)	-
2	-	-	-	-	27 (45)
3	1 (2)	15 (13)	20 (39)	-	33 (55)
4	5 (9)	9 (8)	2 (4)	3 (10)	-
Treatment duration 8/12/24 weeks, n	-/53/1	12/80/20	-/25/26	-/29/1	-/26/29

Retreatment after DAA Failure

- 22 of 119 patients with **G1 and NS5A treatment failure** (DCV or LDV + SOF)
- Retreatment with with PI containing regimen
  - SMV/SOF +/- RBV or 3D +/- RBV for 12 or 24 weeks
  - SVR12 in 6 of 7 patients (limited data)



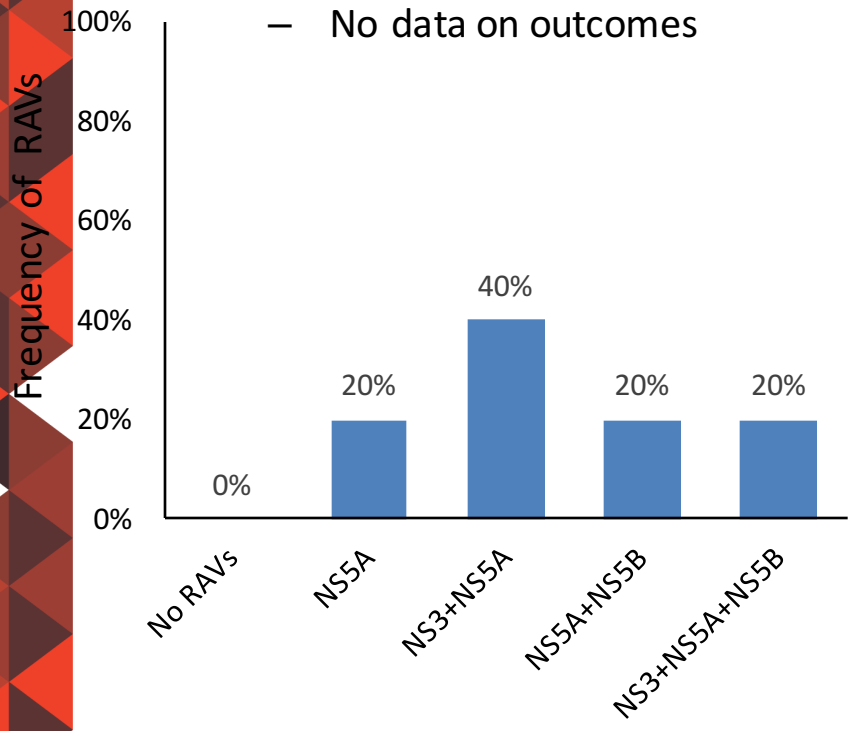
- 27 of 49 patients with **G1 and SMV/SOF treatment failure**
- Retreatment with NS5A containing regimen
  - LDV/SOF (n=23) or 3D (n=4) +/- RBV
  - SVR12 in 20 of 22 patients



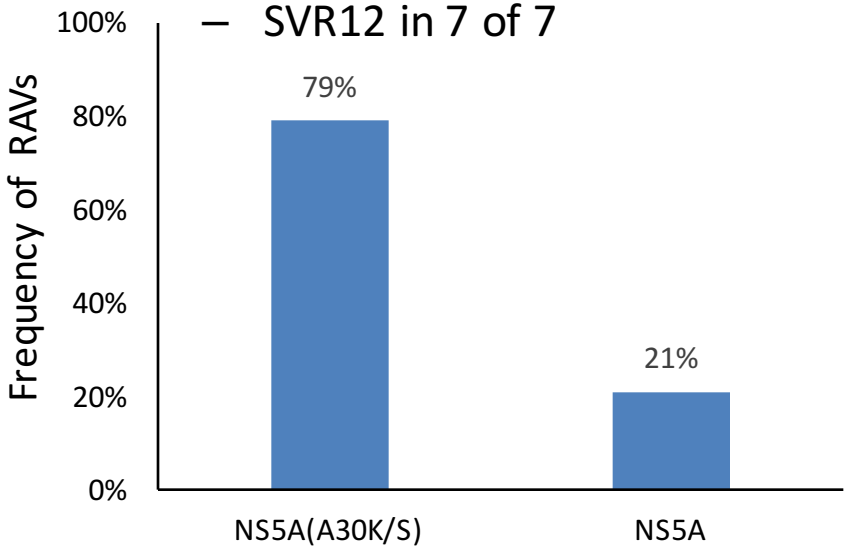
Vermehren J, et al. 51st EASL; Barcelona, Spain; April 13-17, 2016. Abst. PS103.

Retreatment after DAA Failure (cont'd)

- 5 of 27 patients **with G1 and 3D treatment failure**
  - Retreatment with SOF based regimen
  - No data on outcomes



- 14 of 23 patients with **genotype 3 and SOF/RBV treatment failure**
  - Retreatment with DCV (n=13) or LDV (n=1) + SOF +/- RBV
  - SVR12 in 7 of 7



  - DAA failures – male sex, cirrhosis, prior PR
  - 73 patients (28%) started RAS-driven retreatment
  - Preliminary data promising

Vermehren J, et al. 51st EASL; Barcelona, Spain; April 13-17, 2016. Abst. PS103.

Summary

- After IFN-free treatment failure, HCV variants resistant to protease inhibitors progressively disappear by population sequencing, replaced by wild-type virus
- In contrast, viruses resistant to NS5A inhibitors and to NNIs persist for years
- In most patients who fail to achieve an SVR on an IFN-free regimen, viruses that are resistant to one or more of the DAAs administered are present as the dominant species at the time of relapse
- By means of population sequencing, HCV RAVs at baseline may have an impact on the rate of SVR with IFN-free regimens in patients with negative host factors
- The addition of ribavirin and extending treatment duration appears to minimize the impact of pre-existing RAVs on SVR