Need to assess HCV resistance profile before the initiation of DAAs therapy

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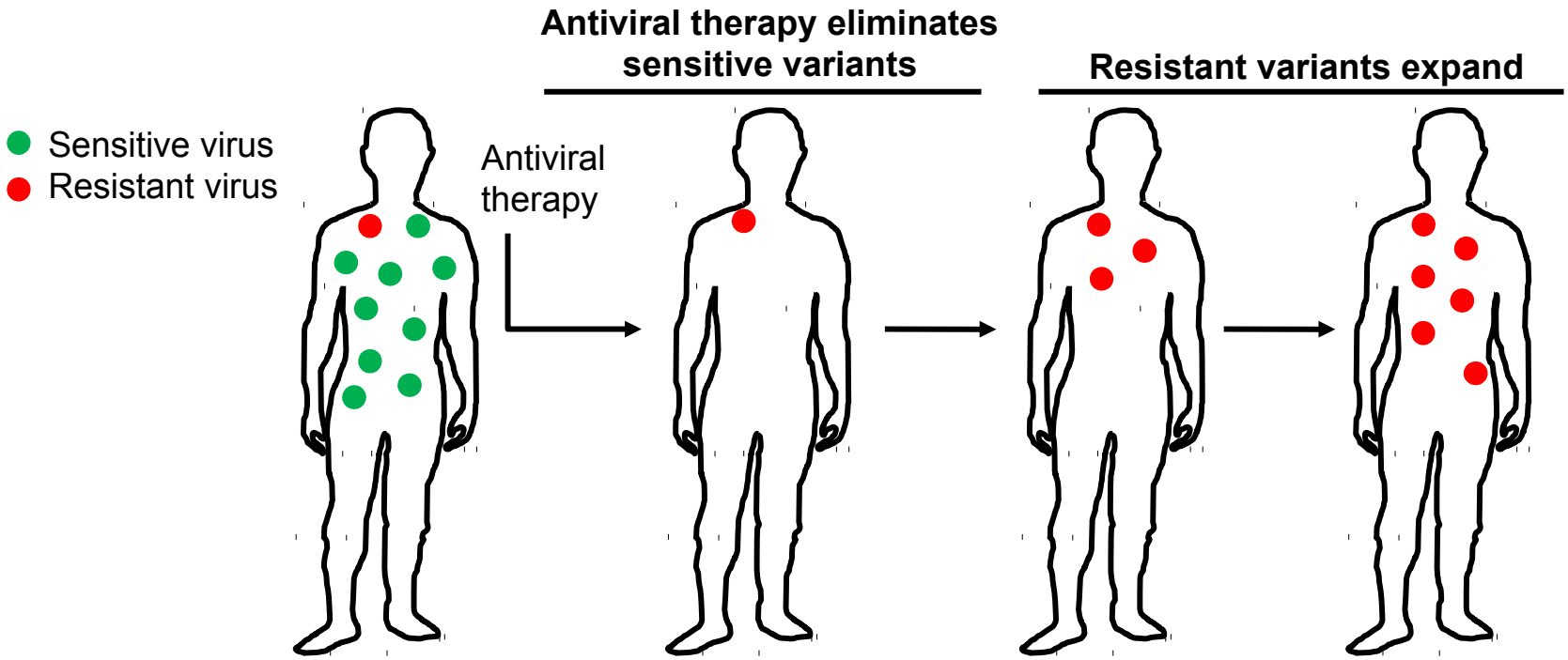
Disclosures

Advisor and/or speaker for

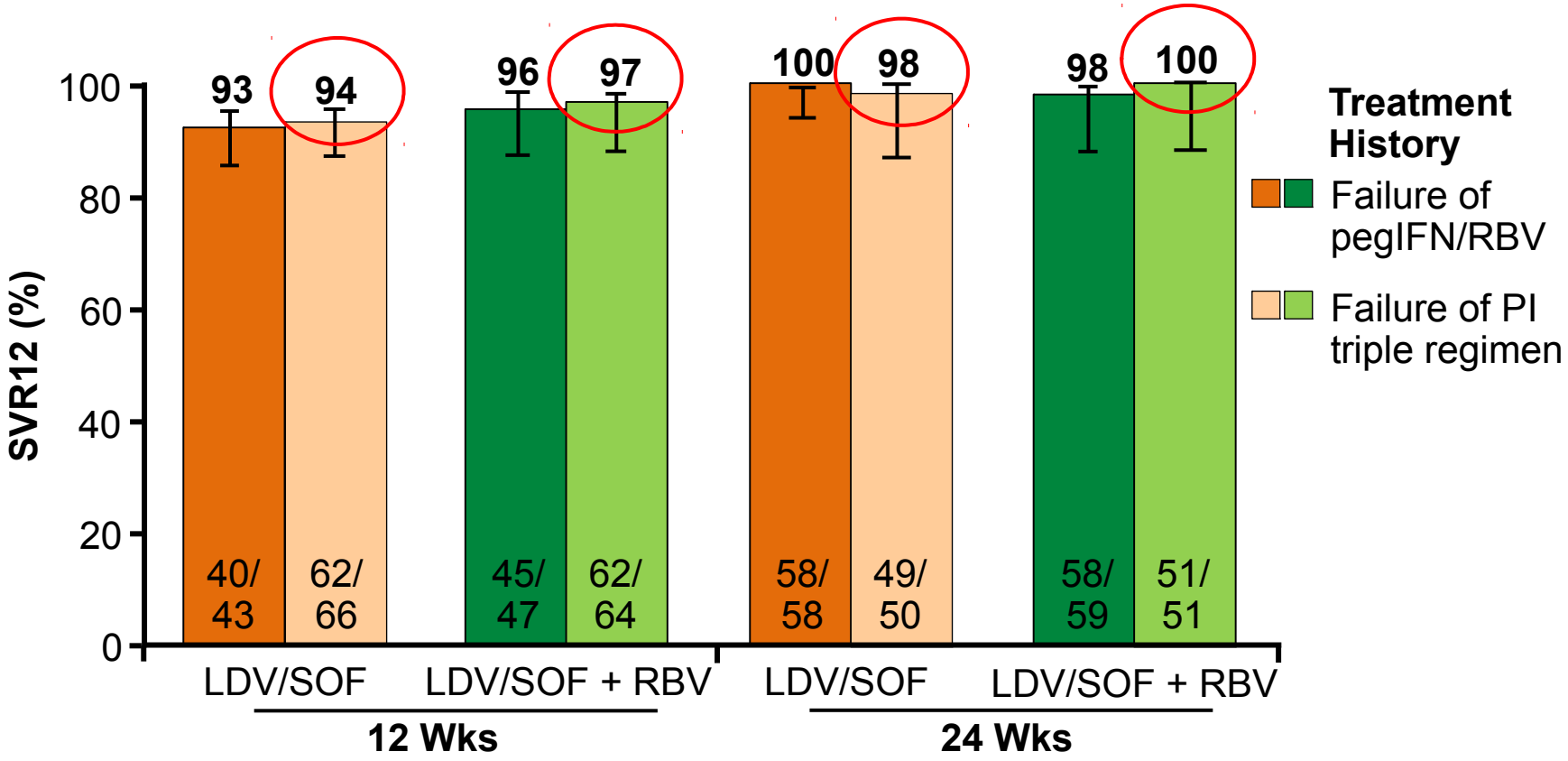
AbbVie, Bristol-MyersSquibb, Gilead, Janssen, Merck, Novartis, Roche

Resistance Associated Variants (RAVs) are present before the treatment and can be selected during therapy



Afdhal NH. www.clinicaloptions.com/hepatitis

LDV/SOF ± RBV effective in Boceprevir or Telaprevir experienced patients with NS3 RAVs (ION-2 study)



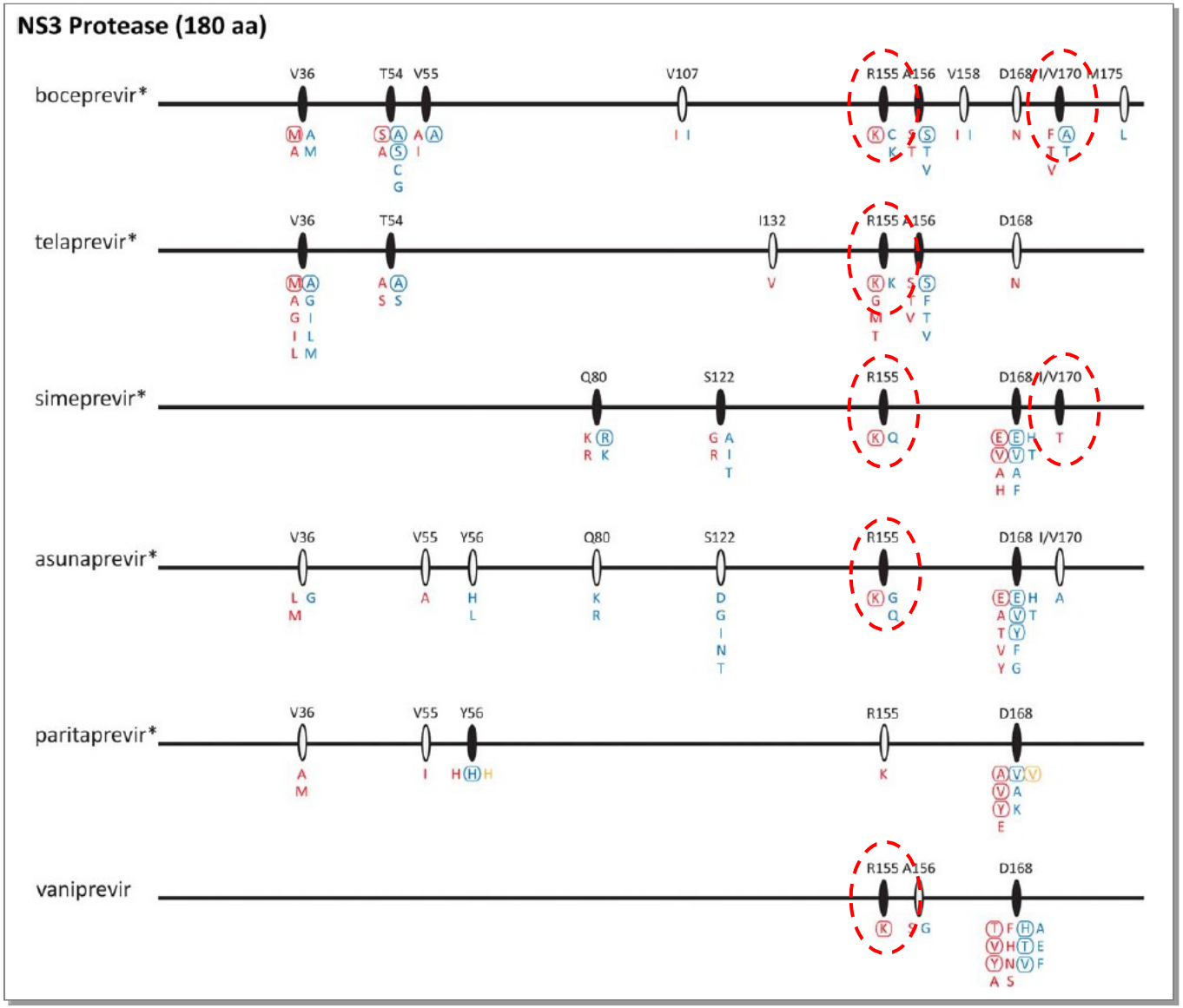
- Virologic failure: 1 breakthrough in 24-wk LDV/SOF + RBV due to nonadherence; 11 relapses (7 in 12-wk LDV/SOF, 4 in 12-wk LDV/SOF + RBV)
- 14% of pts had NS5A RAVs at baseline; 89% of these achieved SVR12;
- **71% of pts had NS3 RAVs at baseline; 98% of these achieved SVR12**

Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

NS3 resistance associated substitutions observed with treatment

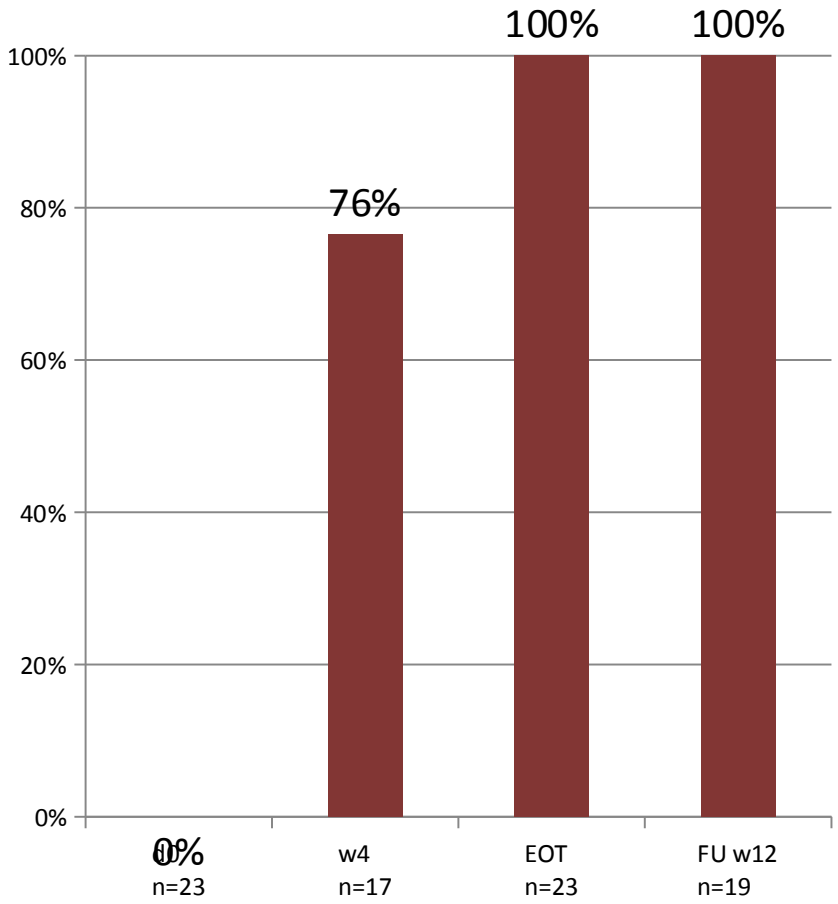
substitution in non-SVR

<10% ≥10%



Lontok E, et al. *Hepatology*. 2015; 62(5):1623-1632

SVR after treatment of triple regimen failures with OBV/PTV/r±DSV±RBV in real life AMBER-CEE study



Patients from:
Poland (16), Lithuania (6), Bulgaria (1)
N=23
Age: 33 to 70 (53±9)
Genotype1b: 83%
Triple regimen:

- boceprevir: 12
- telaprevir: 9
- daclatasvir: 2

Type of non-response

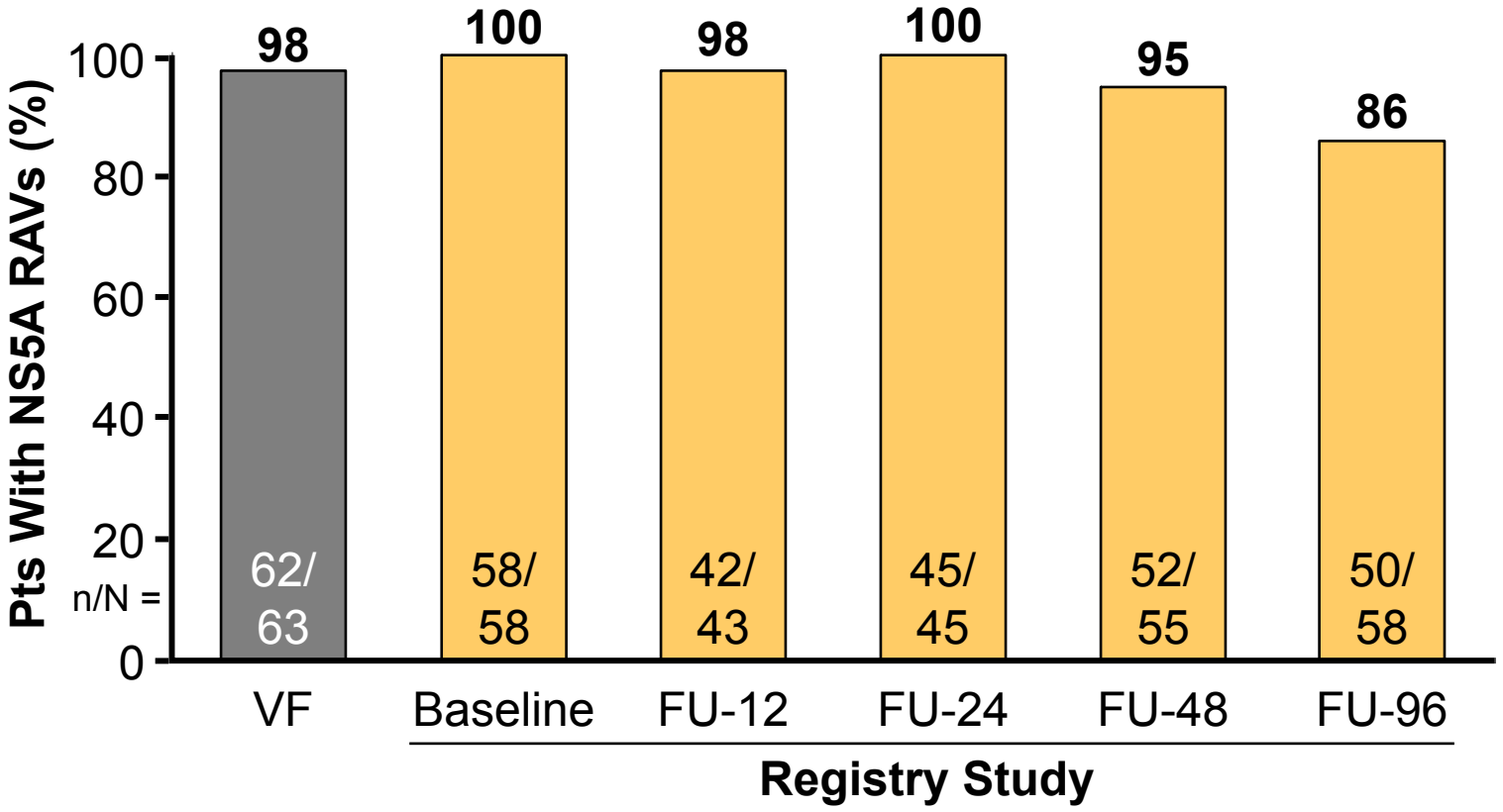
- null: 6
- partial: 9
- relapse: 7
- unknown: 1

Period between DAA in triple nad IFN-free: 10-280 wks.

Flisiak R. et al. HepDart 2015: 122

Durability of NS5A RAVs after virologic failure

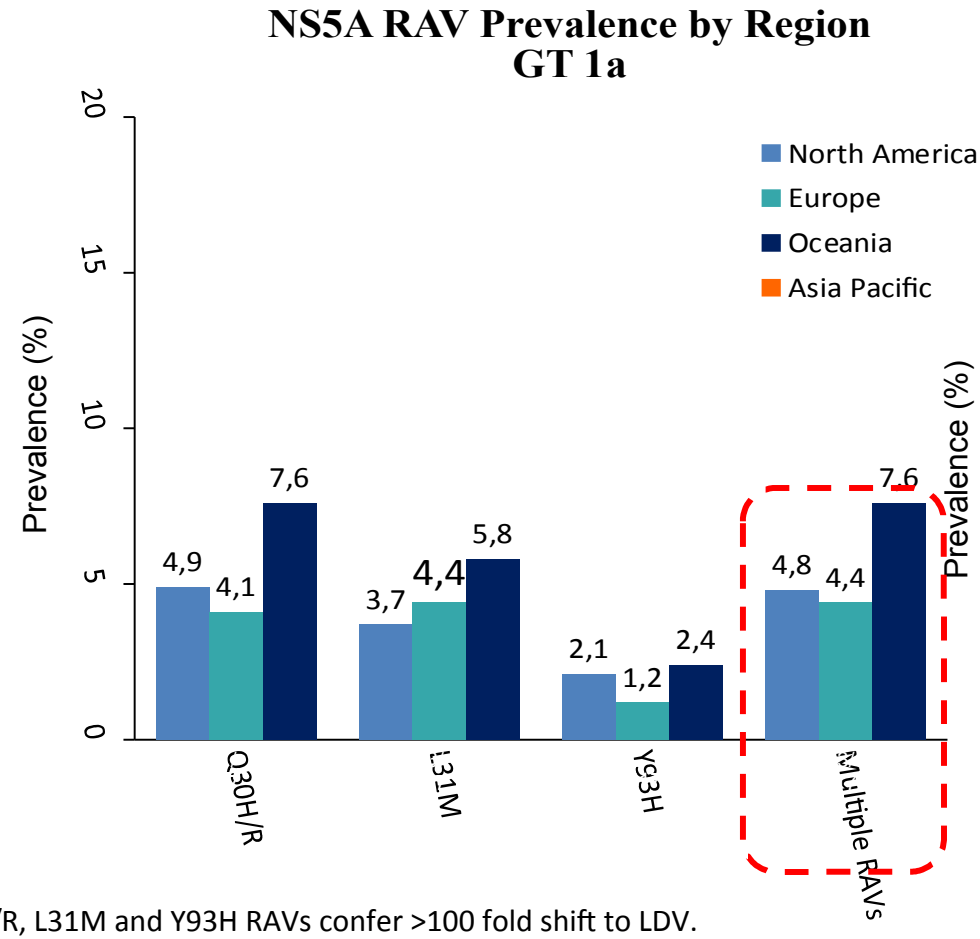
- Patients with NS5A RAVs not achieving SVR after receiving LDV without SOF
- NS5A RAVs persisted in majority of pts for 96 wks

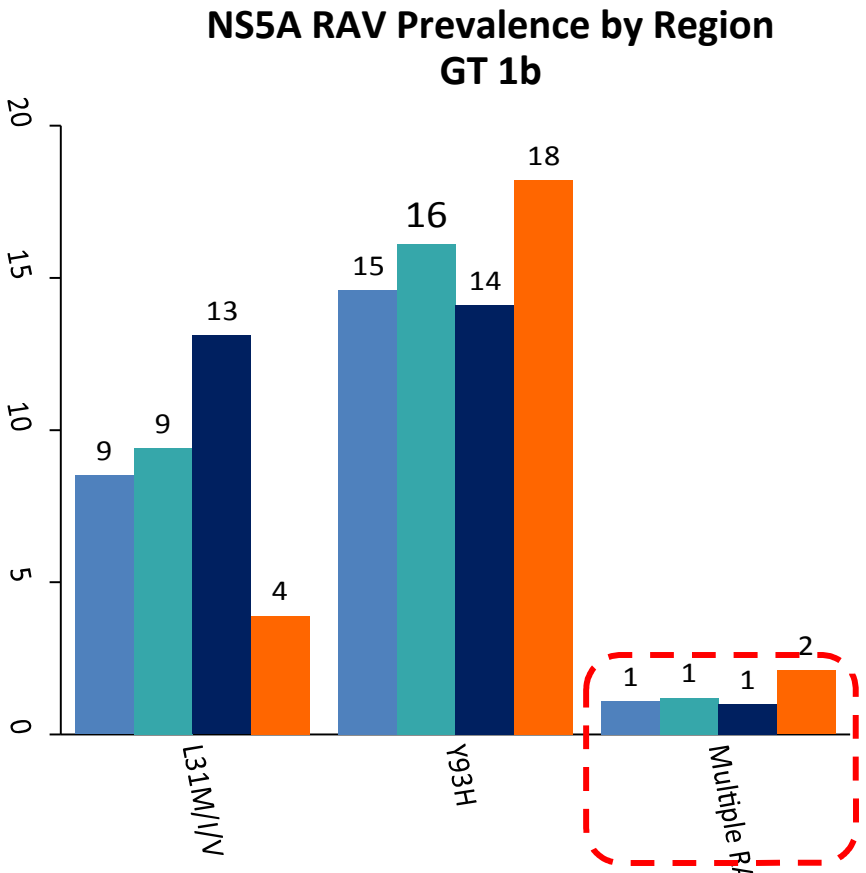


Dvory-Sobol H, et al. EASL 2015. Abstract O059.

Prevalence of Pre-Treatment NS5A RAVs among GT 1 infected

NS5A deep sequencing analysis (1% cut-off) in 5397 patients





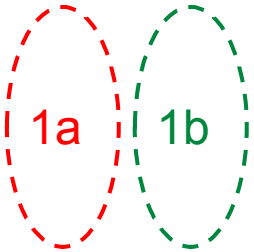
R, L31M and Y93H RAVs confer >100 fold shift to LDV.

GT1a in Asia Pacific not included due to low number of patients (n=27)

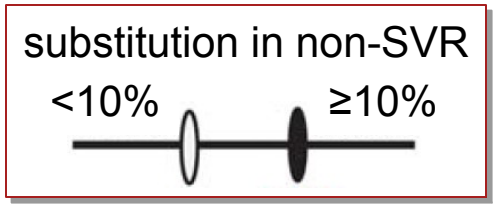
L31M/I/V confer 3-43 fold shift to LDV; Y93H confers >100 fold shift to LDV

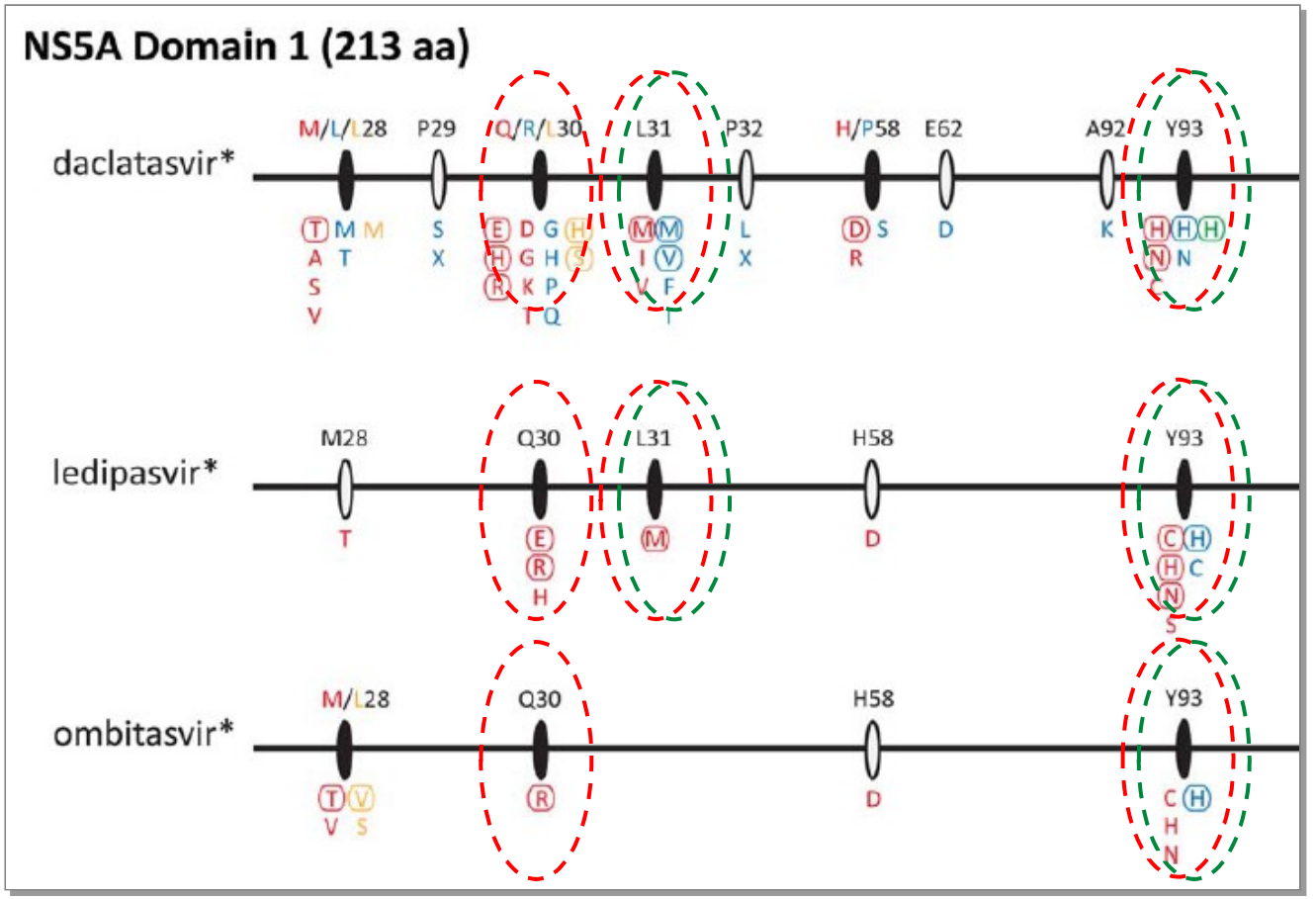
Zeuzem, AASLD, 2015, 91

NS5A resistance associated substitutions observed with treatment



the most frequent substitutions for GT1a and GT1b respectively

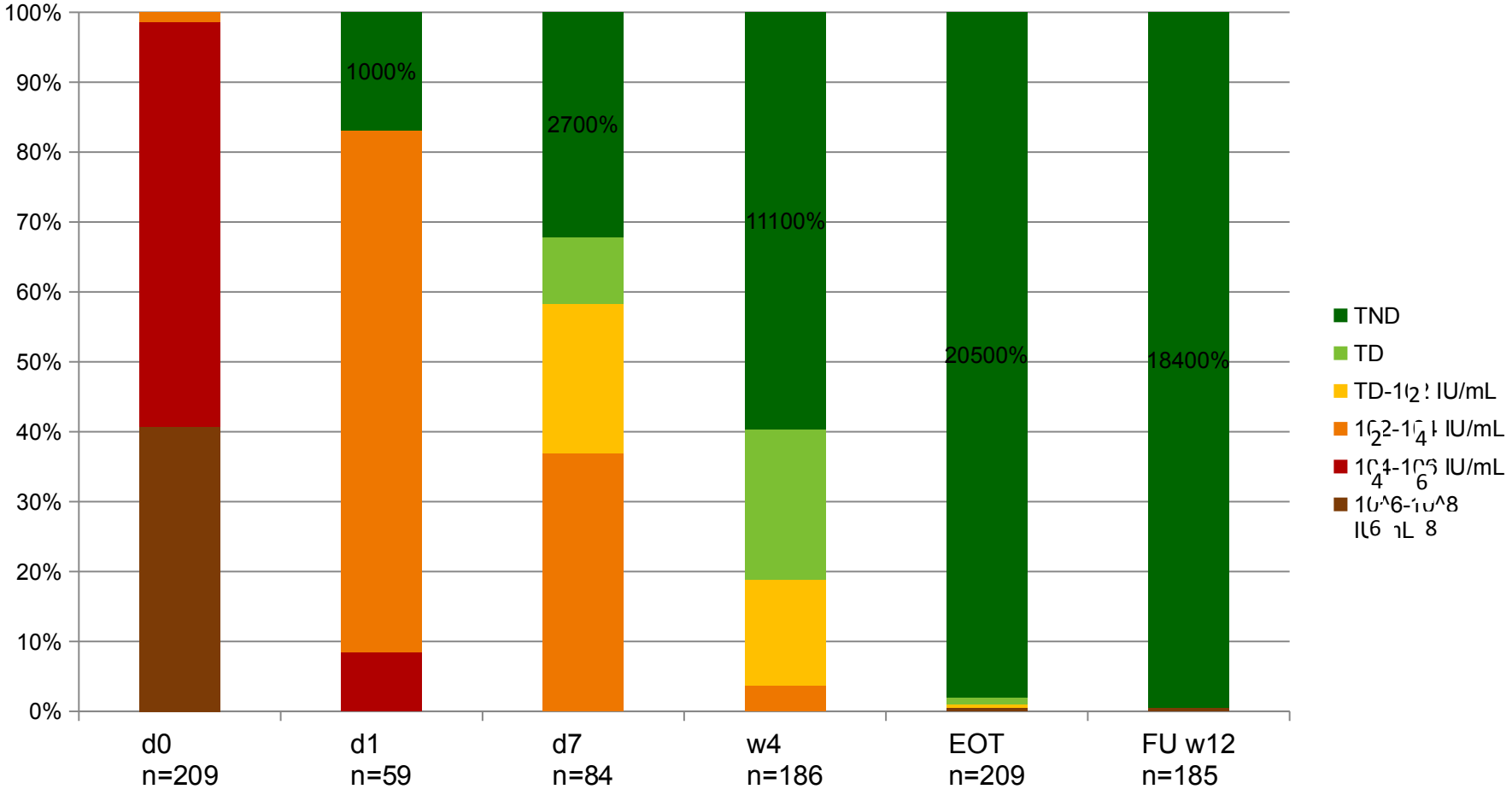




Lontok E, et al. *Hepatology*. 2015; 62(5):1623-1632

Virologic response during OBV/PTV/r ±DSV ±RBV real life AMBER study in GT1/4 (GT1b=84%) population.

treatmnet failures -70% (39% null-resp, 7% triple regimen), cirrhosis – 57%, cirrhosis + null-response – 27%, post-transplant – 10%,



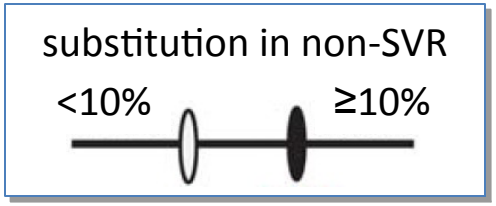
Among 4 viremic at EOT, 3 achieved status TND during the follow-up.

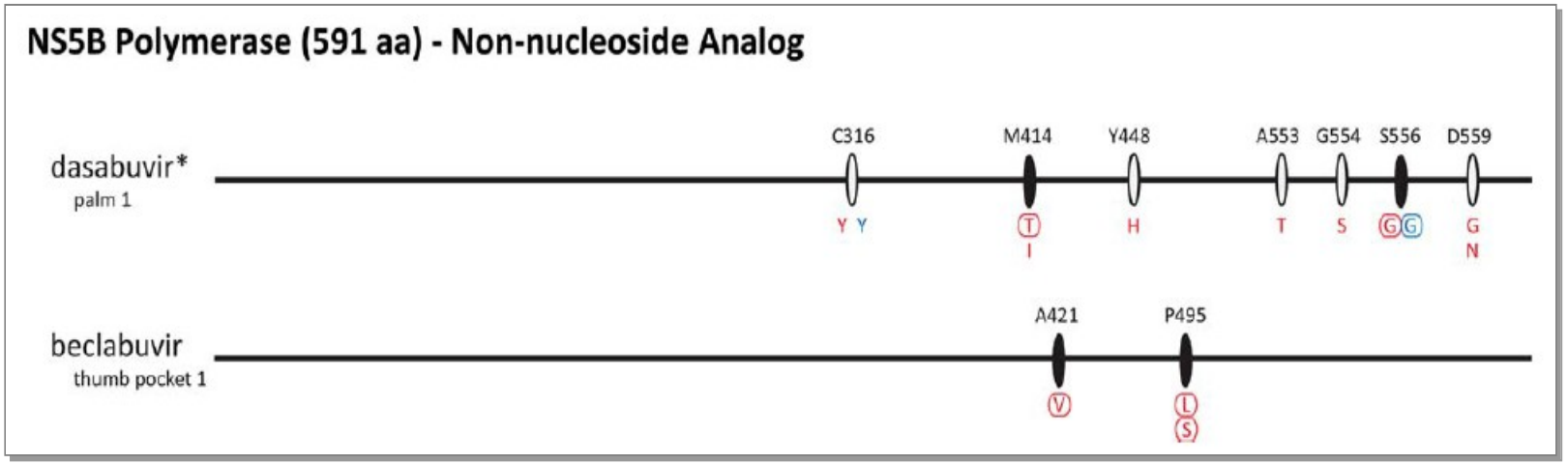
Five patients discontinued therapy (in 3 possibly related to medication), 4 achieved SVR.

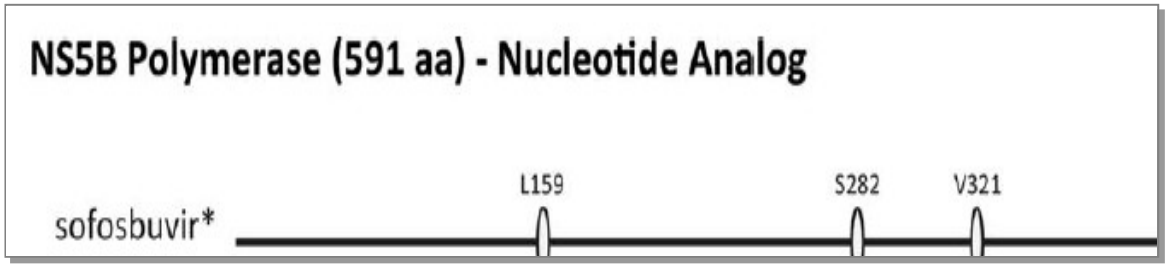
Flisiak R. et al. HepDart 2015: 122

LOD: HCV RNA: <15 IU/mL in 90% patients (others <25 IU/mL)

NS5B resistance associated substitutions observed with treatment





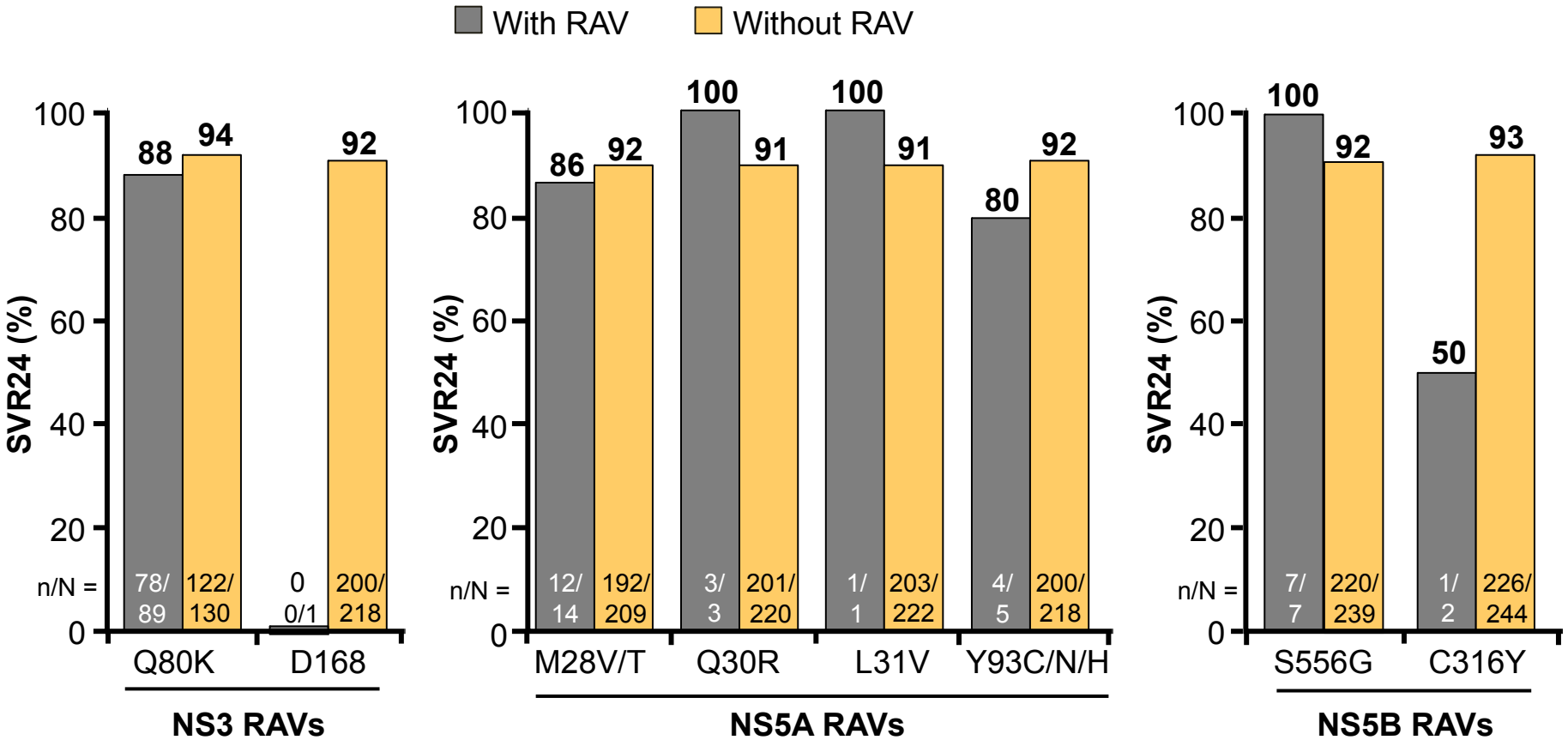


Lontok E, et al. *Hepatology*. 2015; 62(5):1623-1632

Baseline RAVs and currently available medication

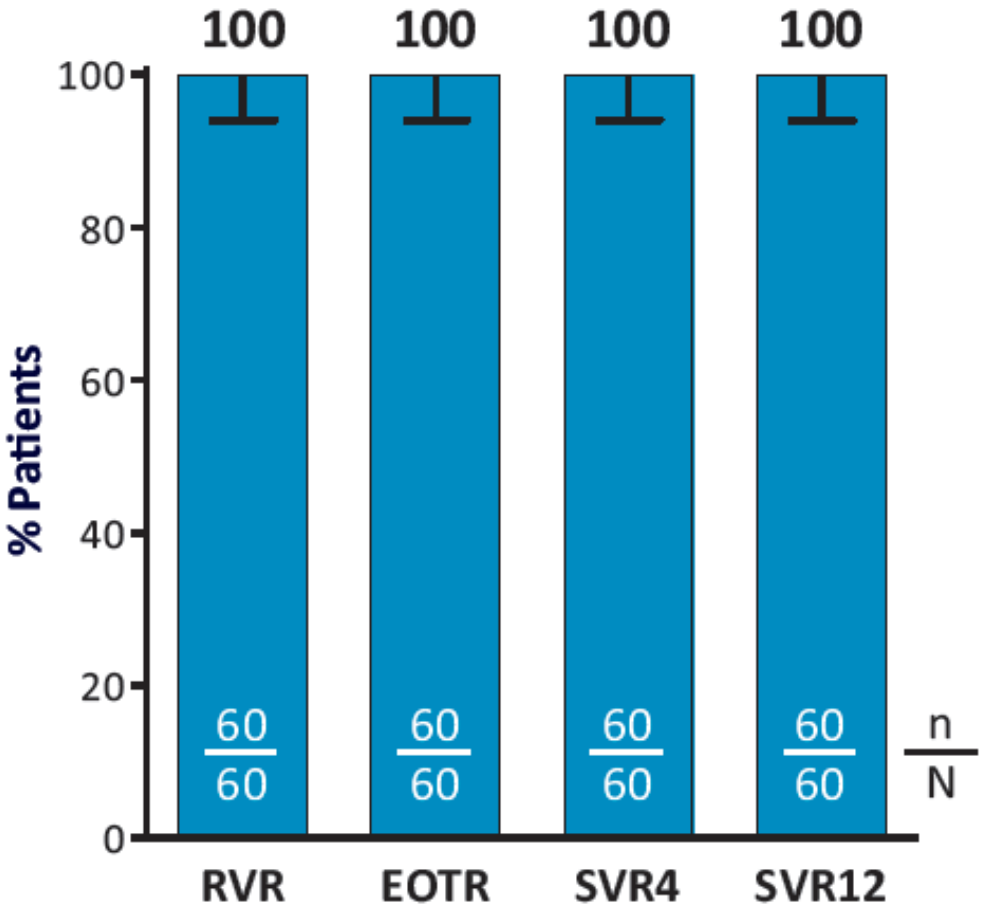
No Impact of baseline RAVs in GT1a patients treated with OBV/PTV/r+DSV in AVIATOR study

- Treatment naive pts or null responders to previous pegIFN/RBV
- All differences in SVR24, with vs without baseline RAVs were non-significant



Krishnan P, et al. Antimicrob Agents Chemother. 2015;59:5445-5454.

12-week RBV-free regimen of OBV/PRV/r + DSV for patients with HCV GT1b and cirrhosis (TURQUOISE-III study)



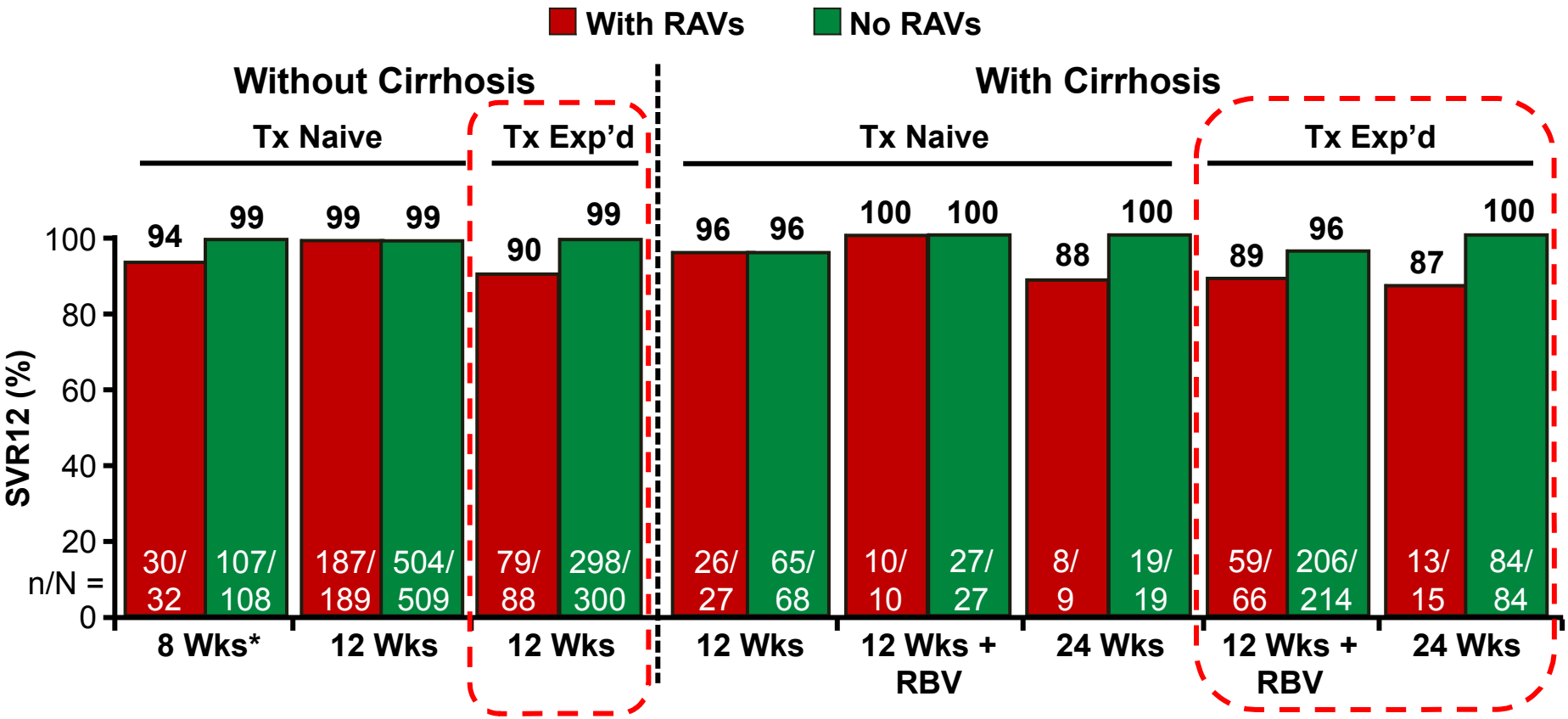
Because of 100% efficacy for GT1b infected patients even with cirrhosis we do not need:

- **RBV**
- **24 weeks regimen**
- **baseline RAVs evaluation**

Poordad F et al. AASLD 2015: 1051

No significant effect of baseline NS5A RAVs on LDV/SOF efficacy in GT1 HCV (except Tx experienced)

Deep sequencing of baseline samples obtained from 1566 pts treated with guideline-based LDV/SOF regimens in clinical trials



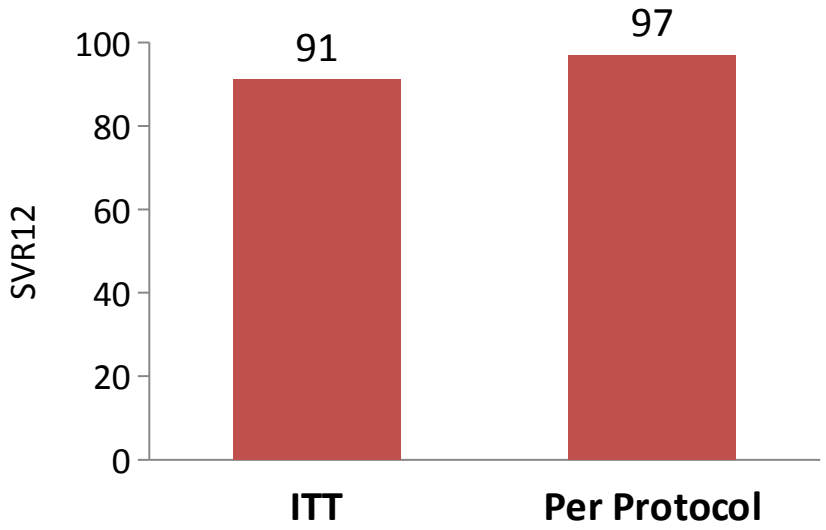
Zeuzem S, et al. AASLD 2015: 91

*HCV RNA < 6 million IU/mL.

Retreatment of relapsers after short LDV/SOF+DAA regimen with 12 weeks of LDV/SOF (SYNERGY study)

	LDV/SOF N=34
Baseline RAVs (> 25-fold resistance in NS5A), n (%)	29
Prior regimen, n	
LDV/SOF+GS-9669 for 6 weeks	1
LDV/SOF+GS-9451 for 4 weeks	14
LDV/SOF+GS-9451+GS-9669 for 4 weeks	19

GS-9451=NS3/4A protease inhibitor ; GS-9669=non-nucleoside NS5B inhibitor



- 32/34 (94%) completed therapy with LDV/SOF.
- 2 patients were LTFU after day 0, and later withdrew consent.
- 29 patients (91%) who completed therapy had baseline RAVs

28/29 patients with baseline NS5A RAVs achieved SVR12 (96%)

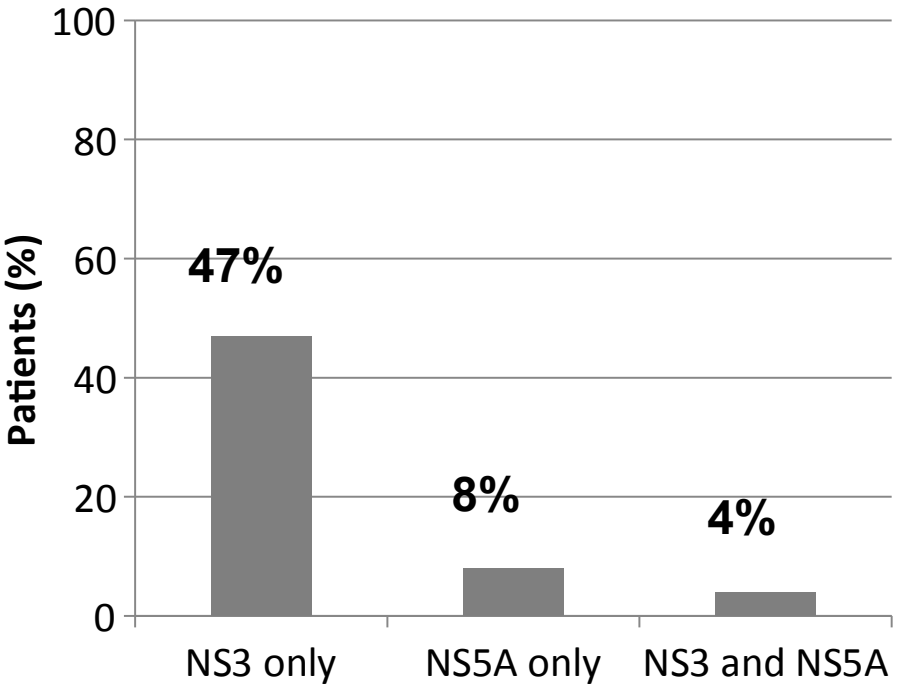
Wilson et al.. AASLD, 2015, 92

Baseline RAVs and next generation medication

SURVEYOR-I part 1 study with (ABT-493 [NS3 inh.] + ABT-530 [NS5A inh.] for 12 wks) in GT1 (1a – 81%) infected patients

- 100% (29/29) treatment-experienced patients achieved SVR12
- 98% (49/50) treatment-naïve patients achieved SVR12

46 (59%) patients had baseline variants in NS3 and/or NS5A



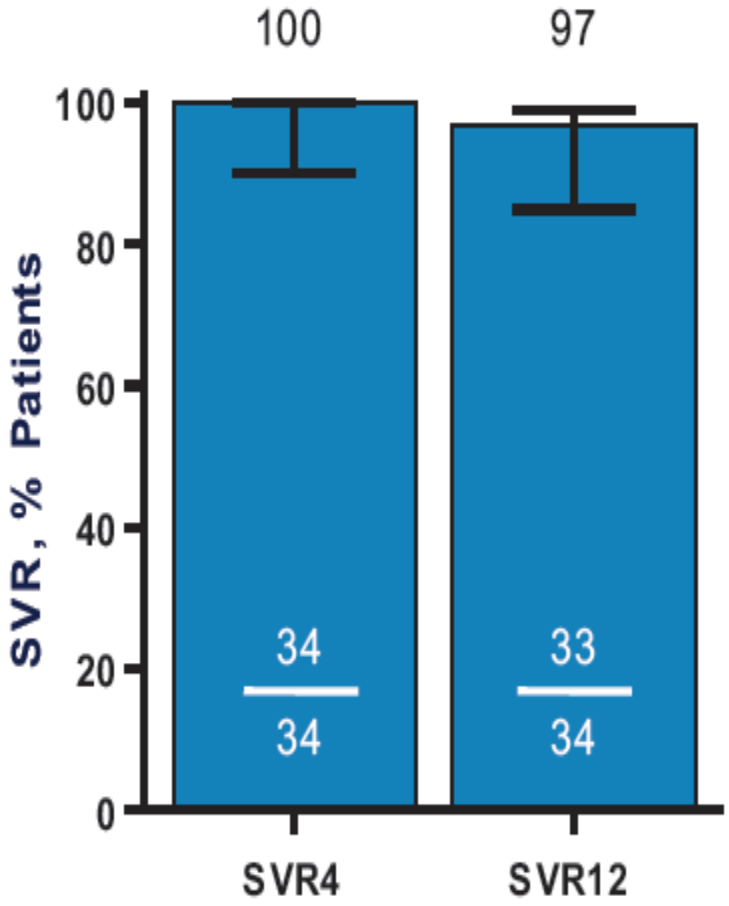
ABT-493 + ABT-530 200 mg + 40 mg 200 mg + 120 mg

aOne treatment-naïve patient with GT1a infection experienced relapse. Identified NS5A RAV at relapse: Q30K + H58D

All patients with baseline NS3 and/or NS5A RAVs achieved SVR12

Poordad F et al. AASLD 2015

SURVEYOR-I part 2 study with (ABT-493 [NS3 inh.] + ABT-530 [NS5A inh.] for 8 wks) in GT1 (1a – 71%) infected patients

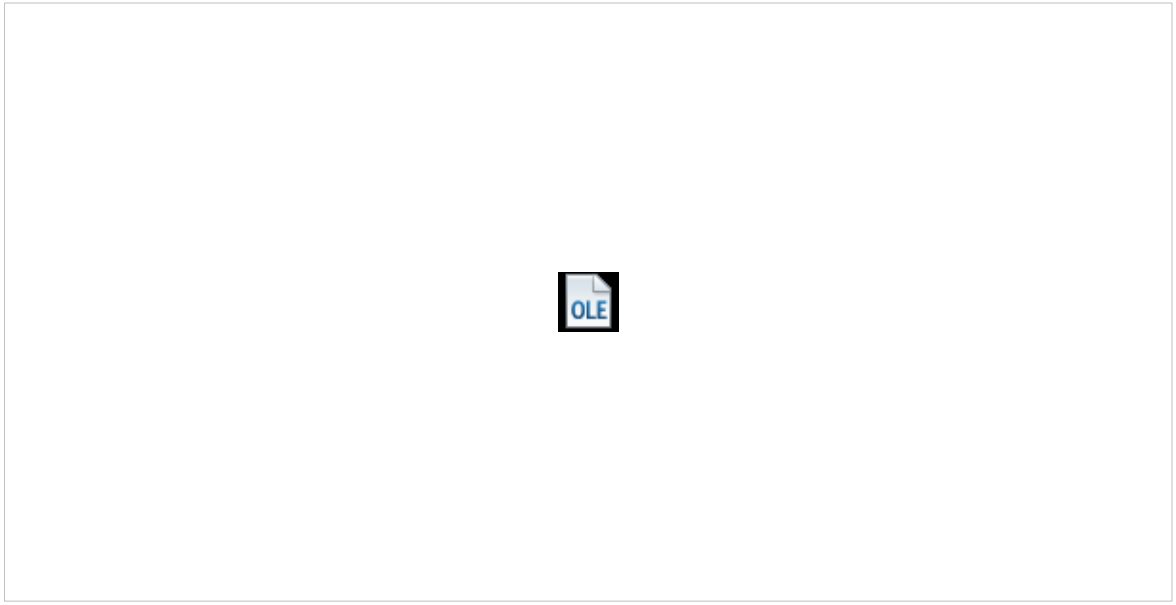


All patients who completed 8 weeks of treatment achieved SVR12, regardless of presence of baseline NS3 and/or NS5A RAVs in 68%.

One patient discontinued treatment at week 4 due to abdominal adenocarcinoma of unknown origin, achieved SVR4 but died before SVR12 evaluation.

Poordad F et al. AASLD 2015: LB-14

SURVEYOR-II study with (ABT-493 [NS3 inh.] + ABT-530 [NS5A inh.]) in GT2 infected patients



ABT-493 + ABT-530	300 mg + 120 mg	200 mg + 120 mg	200 mg + 120 mg + RBV

aOne patient was lost to follow up after treatment week 2.

All patients who completed treatment achieved SVR12, regardless of presence of baseline NS3 or NS5A RAVs in 54%.

Among 74 patients

- NS3 baseline RAVs – 1
- NS5A baseline RAVs – 39 (in 36 - 31M)

Variant positions:

- NS3: 56, 80, 155, 156, and 168
- NS5A: 24, 28, 29, 30, 31, 32, 58, 92, 93

Wyles D et al. AASLD 2015

Only one virologic failure among GT3 infected patients with baseline RAV in SURVEYOR-II (ABT-493+ABT-530)

Baseline RAV	ABT-493 + ABT-530 300 mg + 120 mg (n = 30)	ABT-493 + ABT-530 200 mg + 120 mg (n = 29)	ABT-493 + ABT-530 200 mg + 120 mg + RBV (n = 31)	ABT-493 + ABT-530 200 mg + 40 mg (n = 30)
NS3 only, n	5	3	6	3
NS5A only, n	5	8	2	3
NS3 & NS5A, n	0	1	3	1
Total, n (%)	10 (33%)	12 (41%)	11 (35%)	7 (23%)

Only one virologic failure (relapse) occurred in patients receiving the highest doses (ABT-493 300 mg + ABT-530 120 mg)

- At baseline, no NS3 variants and one NS5A (A30K) variant were identified
- At relapse, a double NS3 variant (Y56H + Q168R) and a double NS5A variant (A30K + Y93H) identified

Kwo P et al. AASLD 2015

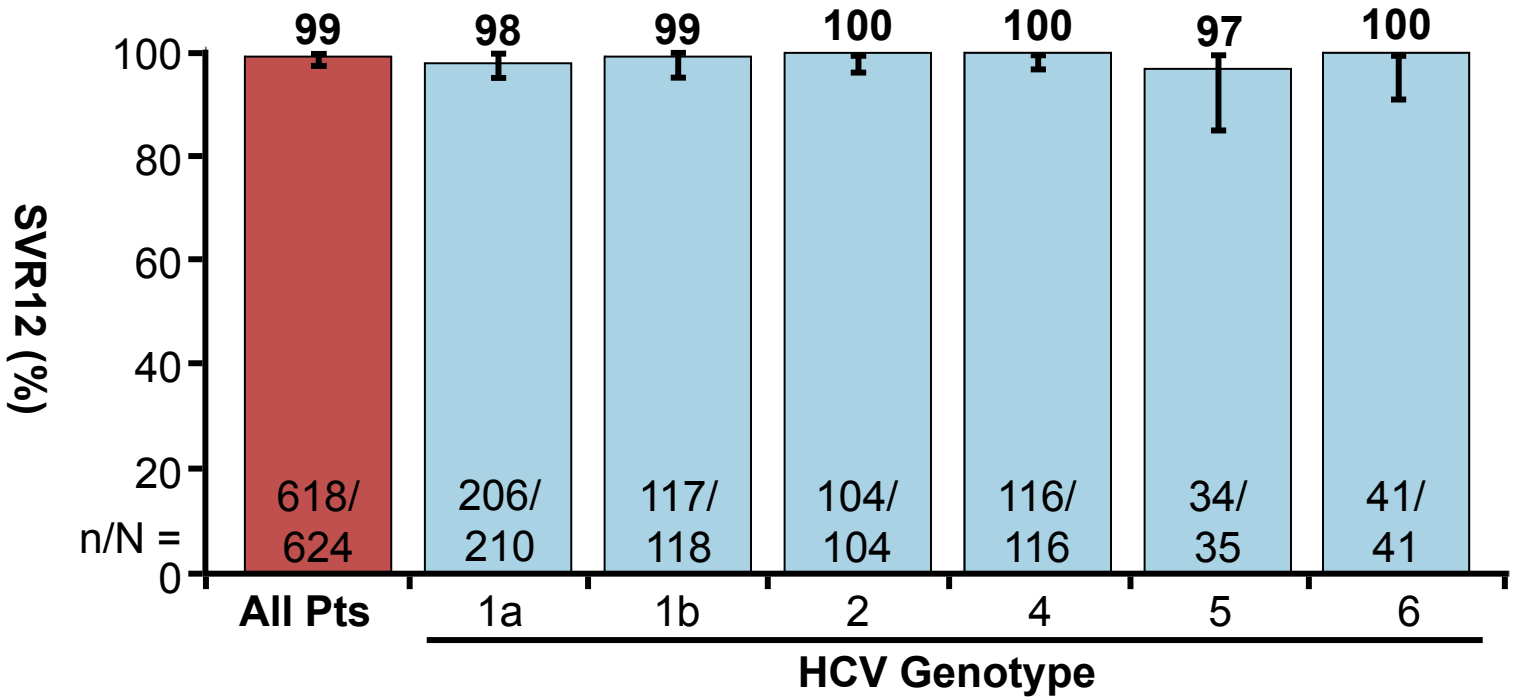
No impact of cirrhosis, treatment experience and baseline NS5A RAVs on SVR

ASTRAL-1: Sofosbuvir/Velpatasvir for 12 weeks in GT1, 2, 4, 5, 6 HCV

cirrhosis - 19%

treatment experienced - 32%;

baseline NS5A RAVs - 42%



Feld JJ, et al. AASLD 2015. Abstract LB-2.

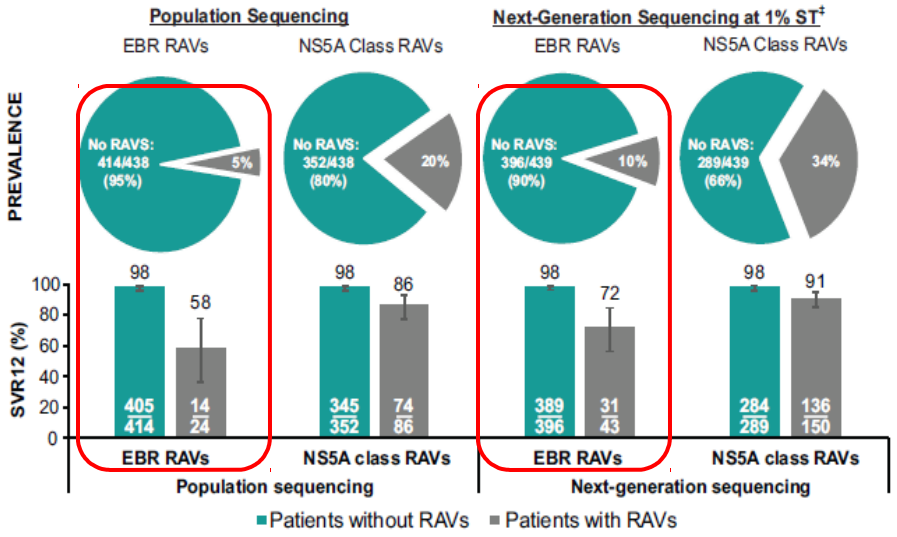
No impact of baseline NS5A RAVs on the efficacy of Elbasvir/Grazoprevir against GT1b, but some in GT1a infected patients from phase 2/3 studies

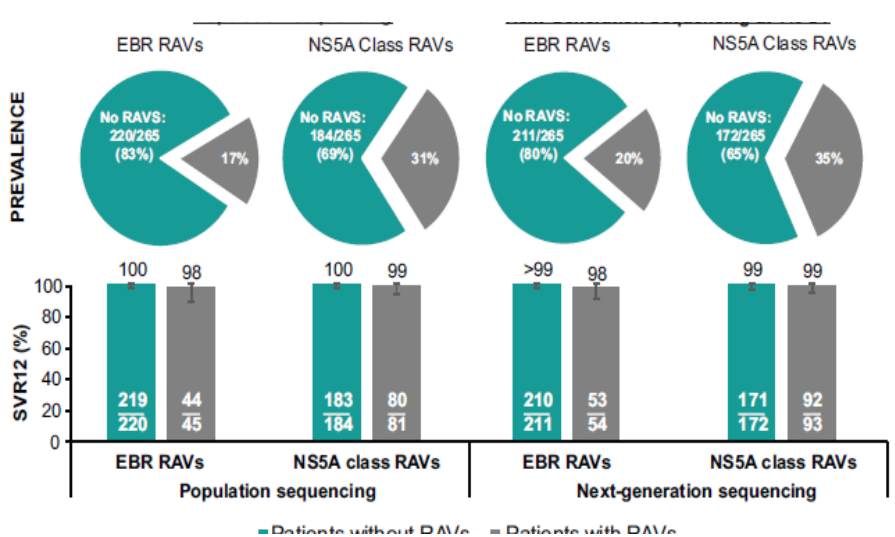
treatment naive or relapse GT1a

SVR12 lower with EBR RAVs (58%) than NS5A class RAVs (86%) and no RAVs (98%)

treatment naive or relapse GT1b

High SVR12 rates (98% to 100%) regardless of EBR or NS5A class RAVs

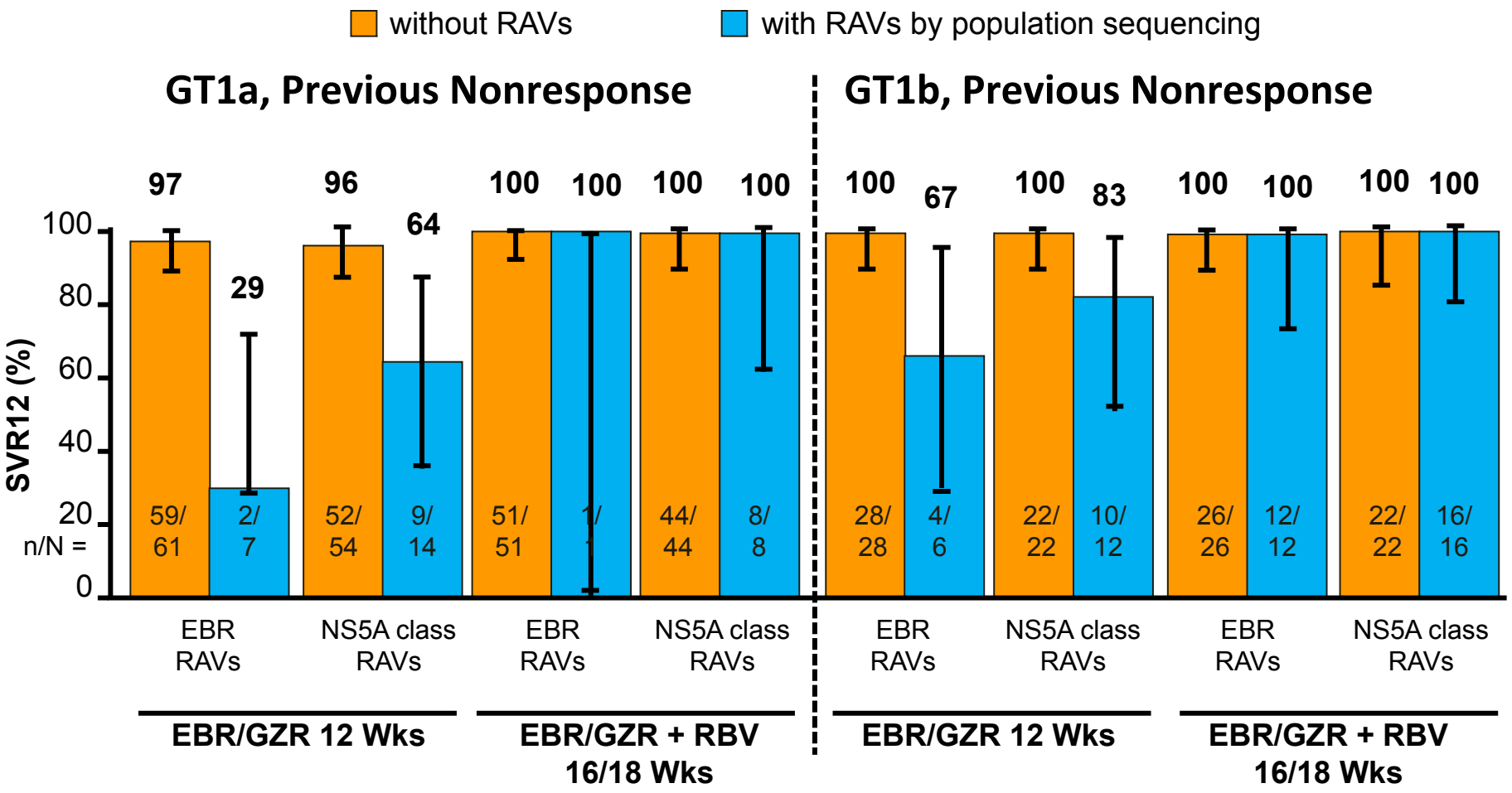




- **Population Sequencing -** the limit of minority variant detection in the population was >25% of the viral population.
- **Next-Generation Sequencing -** amplification using Nextera XT, and sequencing of the NS5A gene (Illumina, MiSeq); sensitivity for variant detection, ranging from a 1% to a 20%.

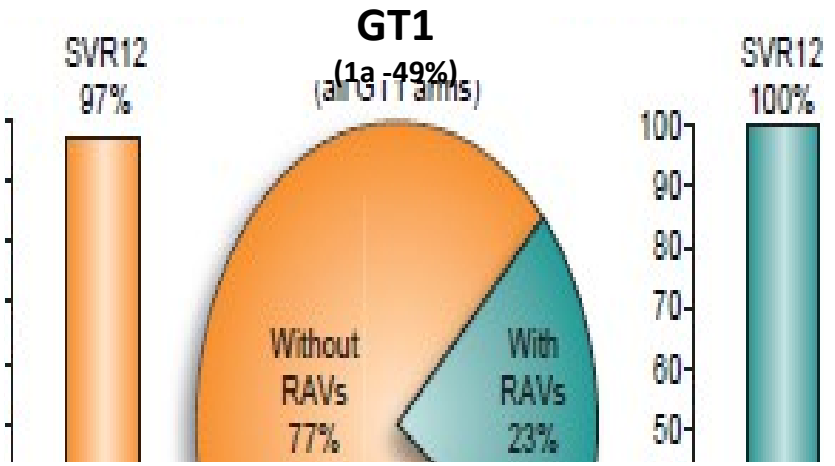
Jacobson IM et al. AASLD 2015: LB-22

Addition of RBV and extension of treatment with Elbasvir/Grazoprevir improve SVR even in GT1a HCV previous nonresponders with baseline NS5A RAVs

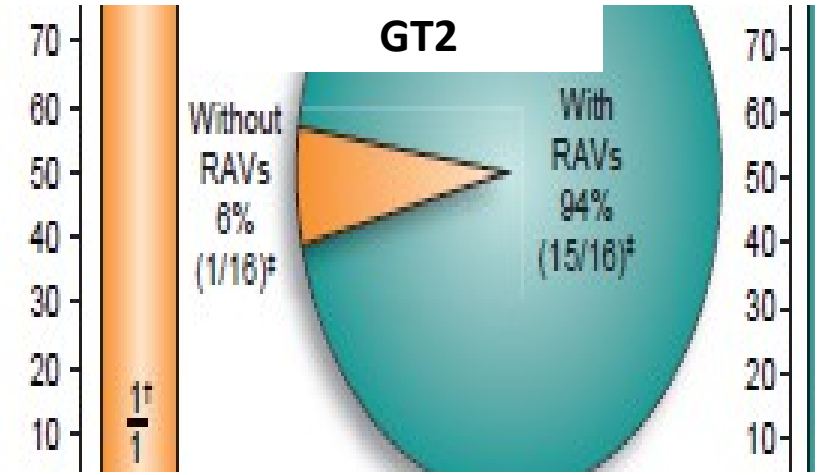


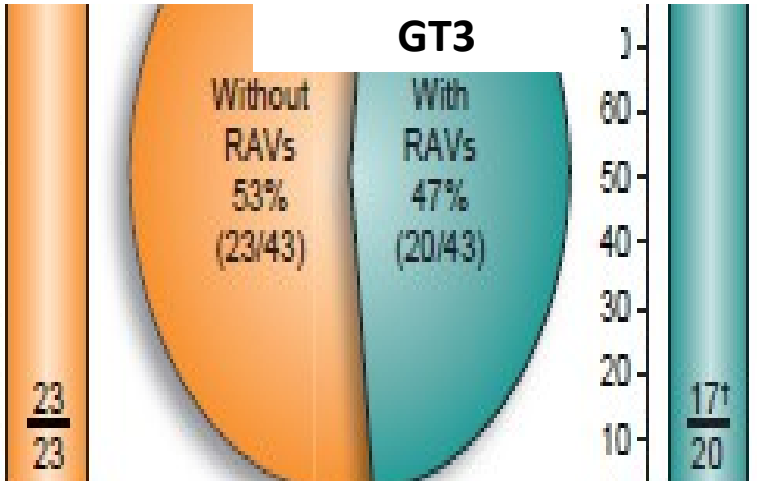
Jacobson IM et al. AASLD 2015: LB-22

No effect of baseline NS5A RAVs on SVR in triple DAA therapy with GZR + MK-3682 (NS5B inh.) + EBR or MK-8408 (NS5A inh.) in patients with HCV GT1, GT2 or GT3 infection (Part A, C-CREST 1 and 2)



SVR12
GT1a: 45/46 (98%)
GT1b: 46/47 (98%)





Gane E et al. AASLD 2015: LB-15

Personal recommendations for resistance testing

- ✓ No need of baseline RAVs testing in patients never treated with IFN-free regimen.
- ✓ Test F3/F4 patients infected with non-GT1b after failure of regimen with any NS5A inhibitor for urgent retreatment; <F3 patients should wait for the second wave therapeutic options.
- ✓ GT1b patients should be tested if completed and failed treatment with 3-4 DAA.