Need to assess HCV resistance to DAAs: is it useful and when?

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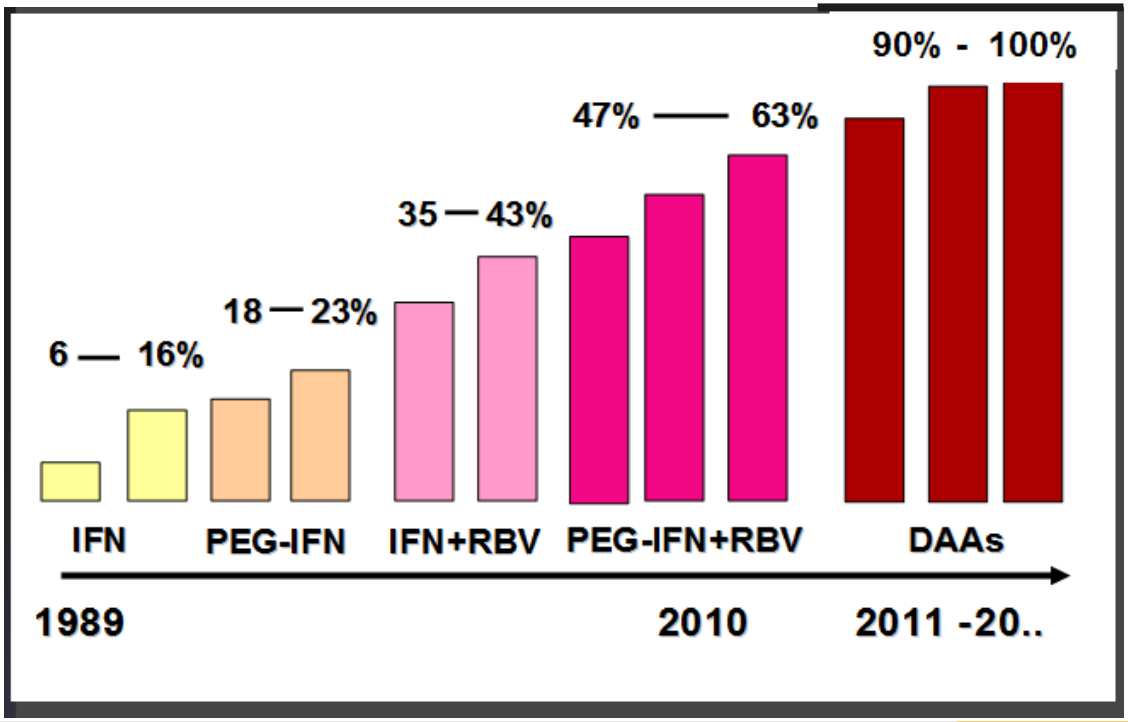
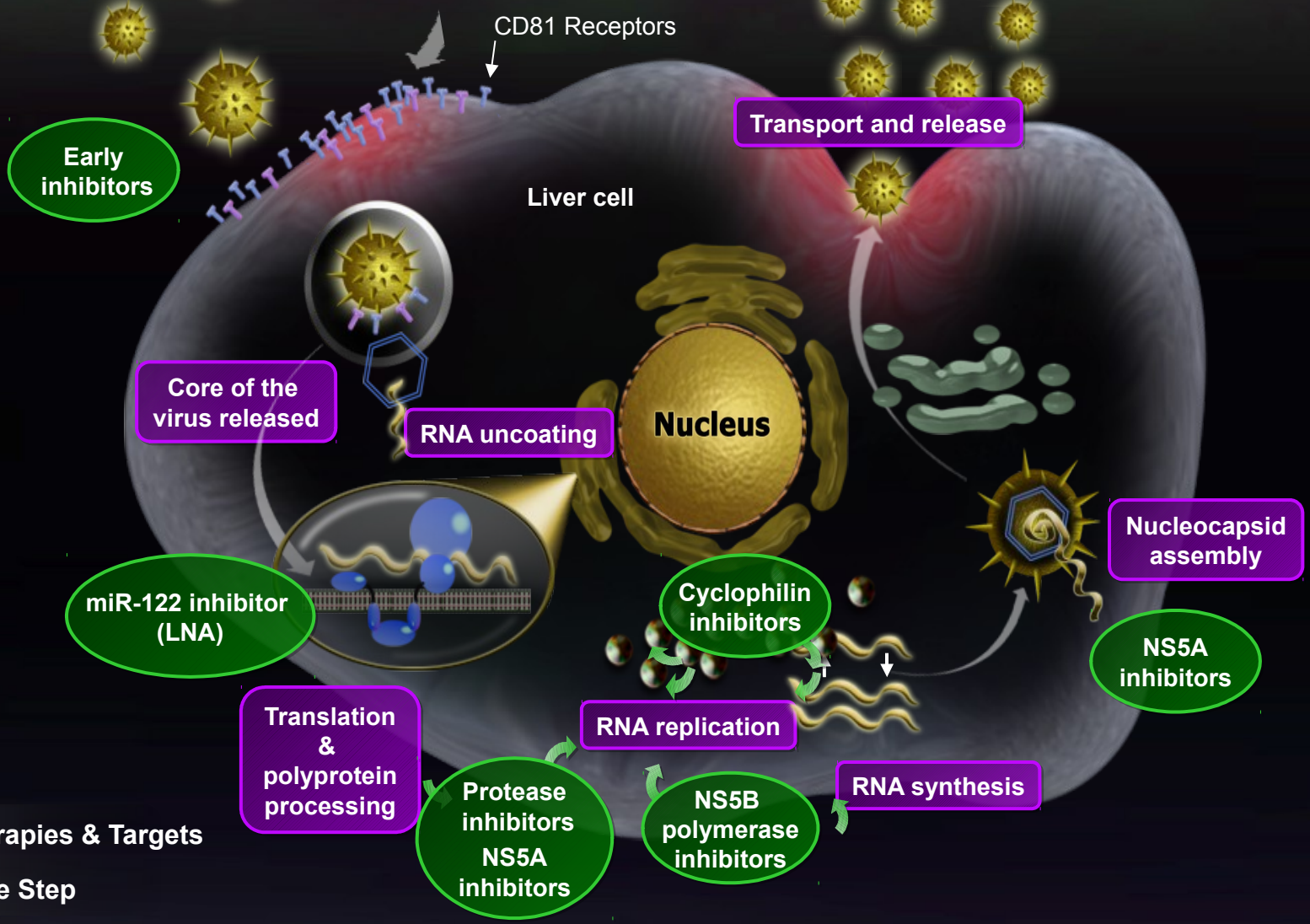
Progress in the Treatment of Hepatitis C



	HBV	HIV	HCV
Genome	DNA	RNA	RNA
Mutation rate	+++	+	+++
Daily viral production	10^{13}	10^{10}	10^{12}
Viral Reservoir	cccDNA	Integrated c DNA	None
Therapeutic strategy	Single	Multiple	Multiple
recovery	No	No	Yes


Mr. IFN

Drug targets in the HCV lifecycle



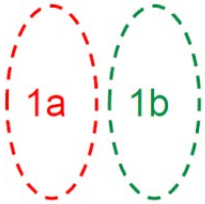
Outcomes Case 1

- You are considering treatment options for a treatment non responder to PEG-IFN cirrhotic patient with genotype 1a HCV infection and an HCV RNA level of 7.4 x 106 IU/mL

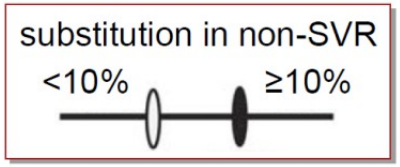
If treating with DAA, which of the following would you recommend?

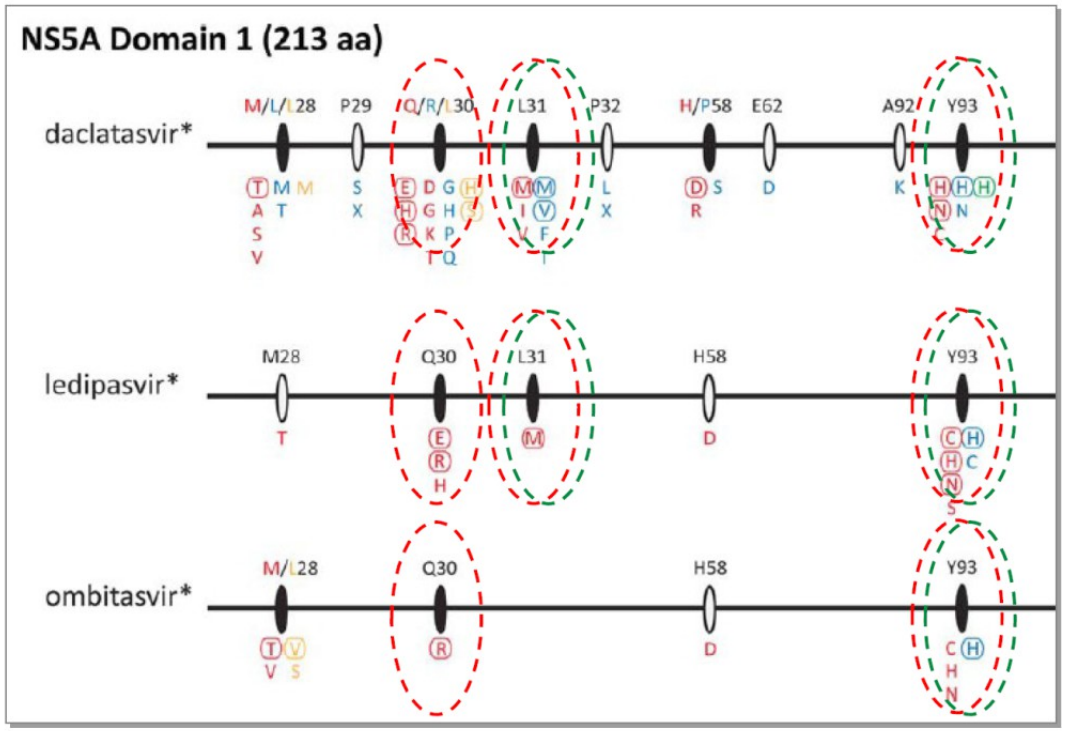
1. Sofosbuvir/ledipasvir for 12 wks + RBV
2. Sofosbuvir/ledipasvir for 24 wks
3. HCV baseline resistance NS5A+ NS5B analysis
4. Grazoprevir+Elbasvir for 16 wks
5. Grazoprevir+Elbasvir for 12 wks with NS5A analysis
6. Paritaprevir/ritonavir, ombitasvir +/- dasabuvir 12w
7. Sofosbuvir+Velpatasvir for 8 weeks
8. SOF + LDV + GS9451 ± GS9669 for 4 weeks

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

NS5A Class RAVs : variants at any position associated with resistance to any NS5A inhibitor

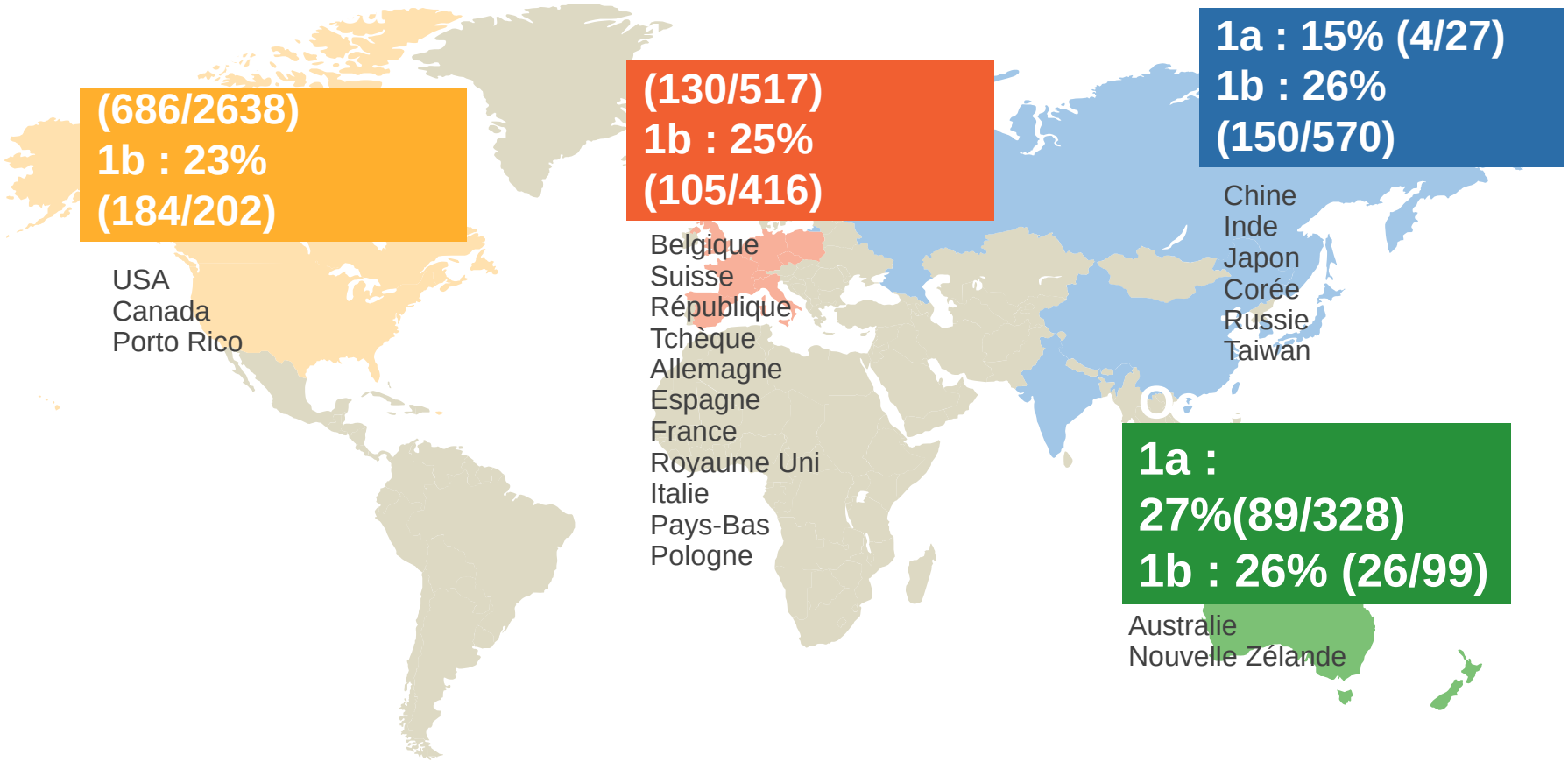
HCV Genotypes	NS5A Amino Acid Position								
	24	28	30	31	32	38	58	92	93
1a	K	I/M	Q	L	P	S	H	A	Y
	→G/N/R	→A/G/T	Q→E/H/R/G/K	L→I/F	P→L/S	S→F	H→D	A→T	Y→C/H/N/S
		M→V	Q→L/T	L→M/V					Y→F
1b	Q	I/L/M	H/Q/R	I/L	P	S	P	A	Y/C/F/S
		L→T	R→H	L→M	P→L/S		P→D	A→K	Y→H
				L→F/V					
2a	T	F/L	K	L	P	S	P	C	Y
	T→A	F→S L→F		L→M/V				C→R	Y→H
3a	S	M	A	L	P	S	P	A	Y
		M→T	A→K	L→F/M/V					Y→H
4a/d	K	L	L	M	P	S	P/T	A	Y
		L→V	L→H/R+/S+/T+/V+	M→V			T→S+		→S
		L→M+/V	→A	M→L+					→H/R/S+/T+
5a	Q	L	Q	L	P	S	P	A	T
		L→I		L→F/V					
6a	Q	F	R	L	P	S	T	A	T
	Q→H			L→M	P→L/S		T→N		
				L→V			T→A/S		

Five main major class NS5A RAVs
NS5A resistance < 10-fold
NS5A resistance 10 - <100-fold
NS5A resistance > 100-fold

+ Resistance observed in combination with other RAVs

Halfon P et al . Hepatology 2016

Baseline prevalence of RAVs NS5A (n = 5397 pts, cut-off 1%)



Zeuzem *et al*. AASLD 2015. Abstract 91.

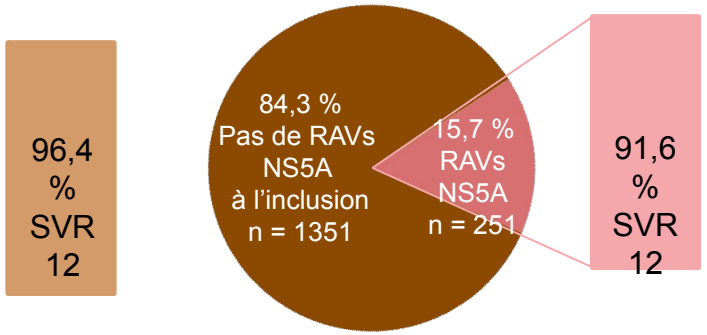
*G1a NS5A RAVs: K24G/N/R, K26E, M28A/G/T/V, Q30C/E/G/H/I/L/K/R/S/T/Y, L31I/F/M/V, P32L, S38F, H58D/L, A92K/T, Y93C/F/H/L/N/R/S/T/W
G1b RAVs: L28M, L31I/F/M/V, P32L, P58D, A92K, Y93C/H/N/S

Baseline and Post-baseline Resistance Analyses of Phase 2/3 Studies of Ledipasvir/Sofosbuvir ± RBV

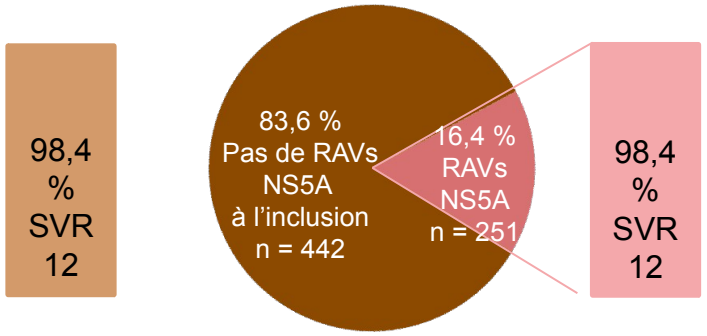
SOF + LDV ± RBV 1

Prevalence and Impact of RAVS NS5A

G 1a

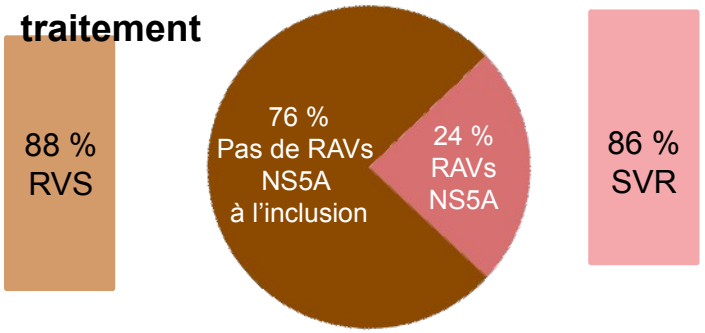


G 1b

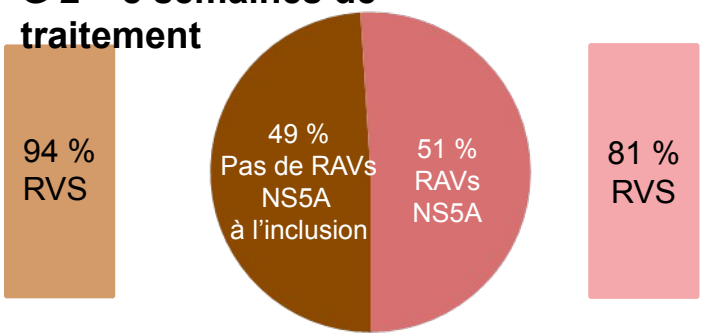


SOF + GS-5816 ± RBV ²

G 1 - 8 semaines de traitement



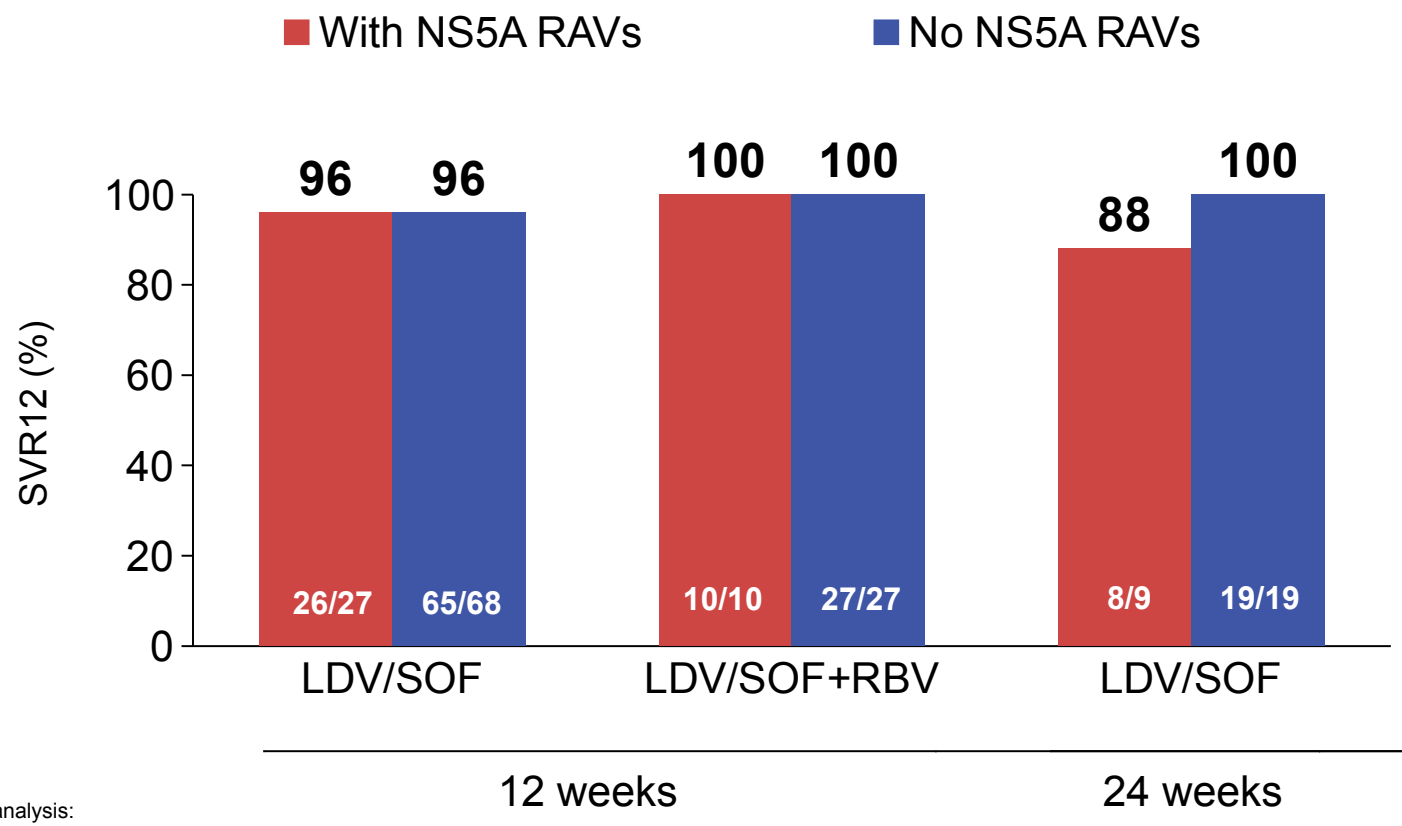
G 2 – 8 semaines de traitement



Baseline RAVs NS5A before SOF/LDV is not predictive of failure 1

1) Sarrazin *et al*. AASLD 2014. Abstract 1926., Gastroenterology 2016.

SVR12 Rates by Treatment Regimen (LDV/SOF) and Duration: TN Patients with Cirrhosis

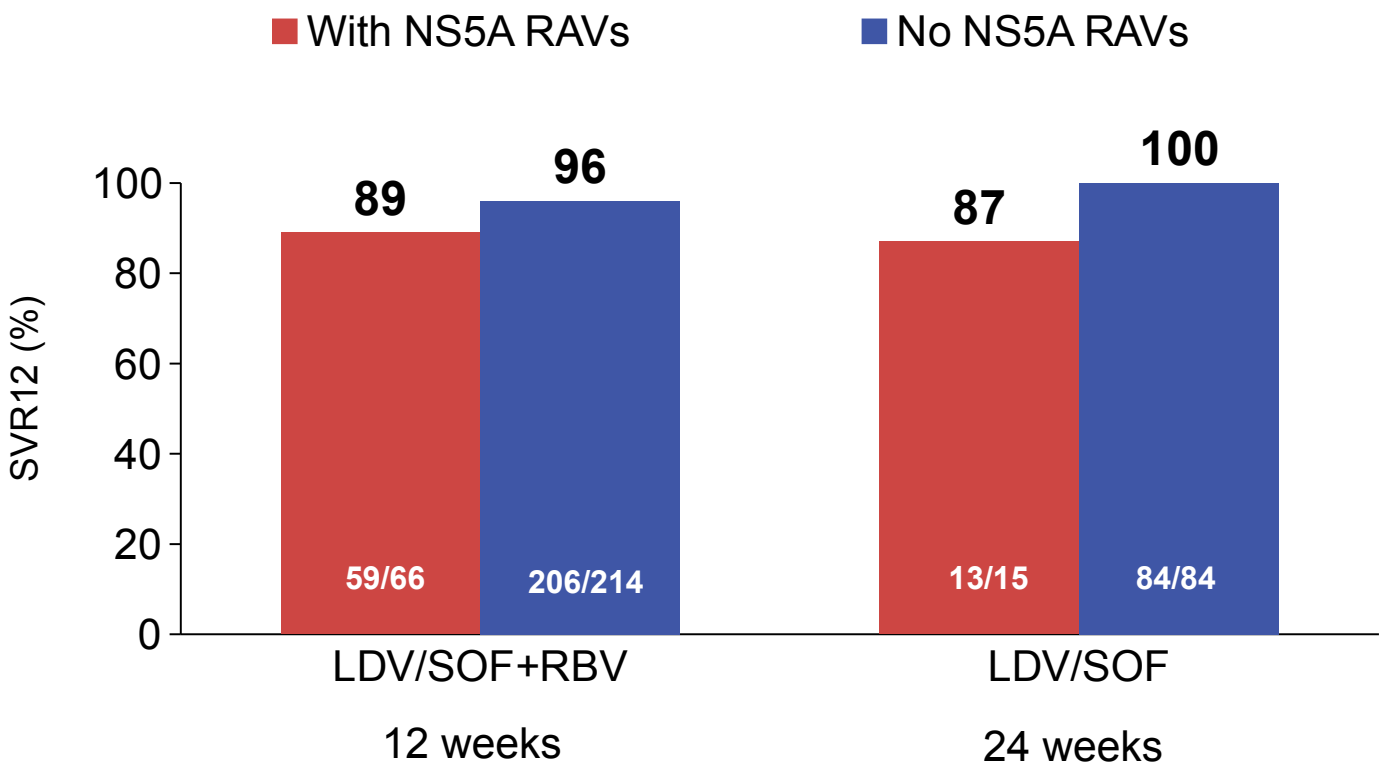


Studies included for analysis:
LDV/SOF 12 Wks: GS-US-334-1274 (Bleeding Disorder), GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0115 (ION-4), GS-US-337-0122 (ELECTRON-2), GS-US-337-0131(China), GS-US-337-1406;
LDV/SOF+RBV 12 Wks: GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0122 (ELECTRON-2); **LDV/SOF 24 Wks**: GS-US-337-0102 (ION-1), GS-US-334-1274 (Bleeding Disorder)

Sensitivity threshold at 1% (deep sequencing)

Zeuzem et al., AASLD 2015

SVR12 Rates by Treatment Regimen and Duration: TE Patients with Cirrhosis

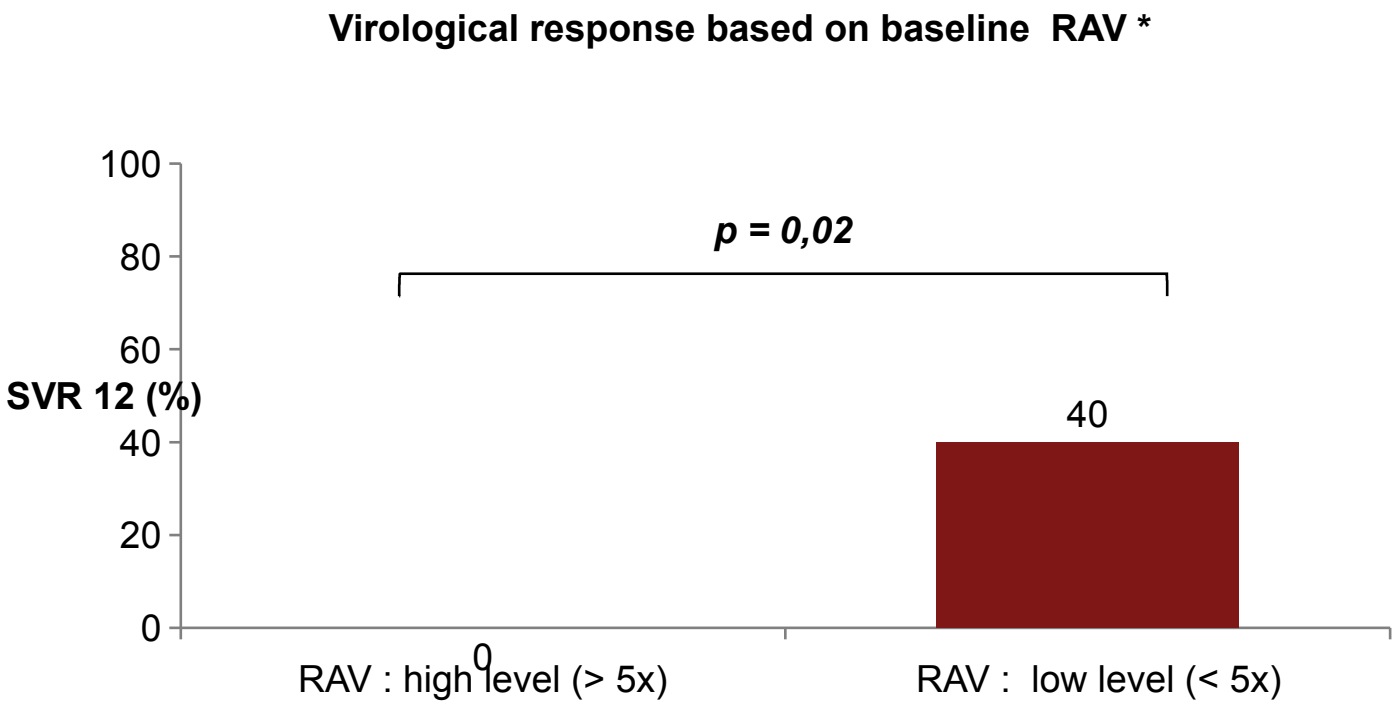


Studies included for analysis:
LDV/SOF+RBV 12 Wks: GS-US-337-0109 (ION-2), GS-US-337-0113 (Japan 1), GS-US-337-0118 (LONESTAR-1), GS-US-337-0122 (ELECTRON-2), GS-US-337-0123 (SOLAR-1), GS-US-337-0124 (SOLAR-2), GS-US-337-1118 (Retreatment), P7977-0523 (ELECTRON); **LDV/SOF 24 Wks**: GS-US-337-0109 (ION-2), GS-US-337-0121 (SIRIUS), GS-US-334-1274 (Bleeding Disorder)

Sensitivity threshold at 1% (deep sequencing)

Zeuzem et al., AASLD 2015

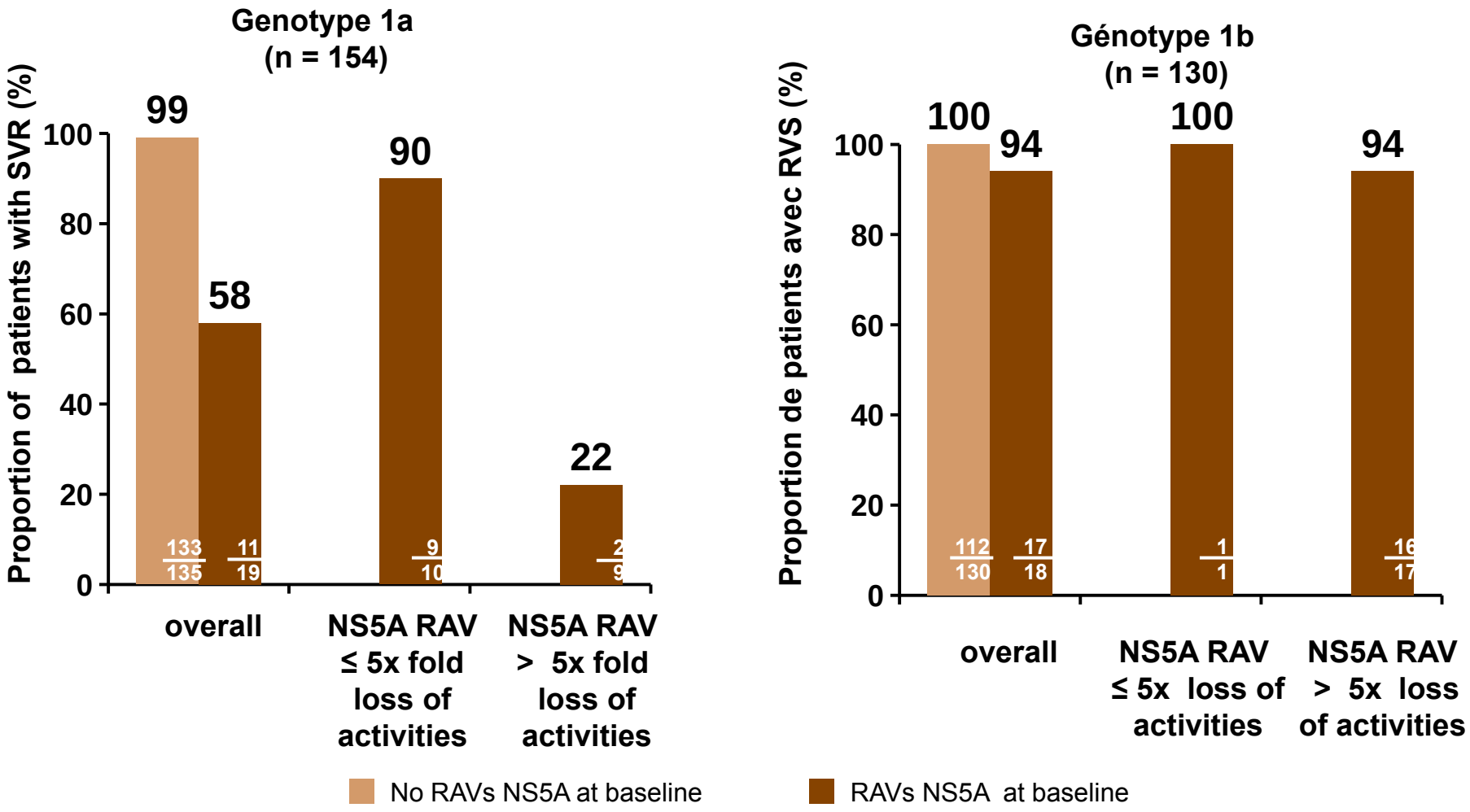
SYNERGY study : SOF + LDV + GS9451 ± GS9669 for 4 weeks



Baseline RAV is a strong negative factor of SVR in case of shorten therapy (4 weeks)

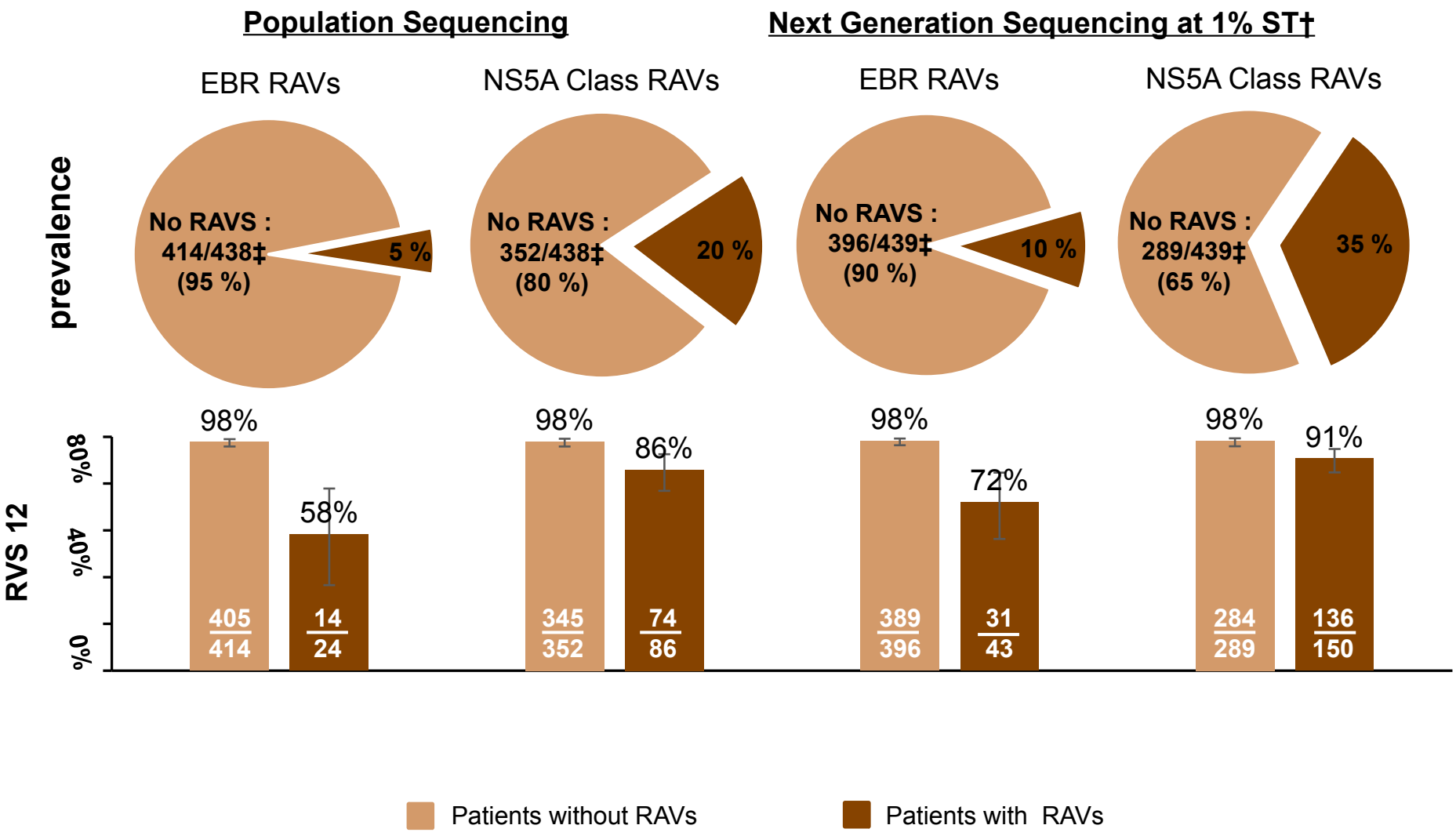
Kattakuzhy *et al*. AASLD 2015. Abstract OP220.

Grazoprevir+Elbasvir combination



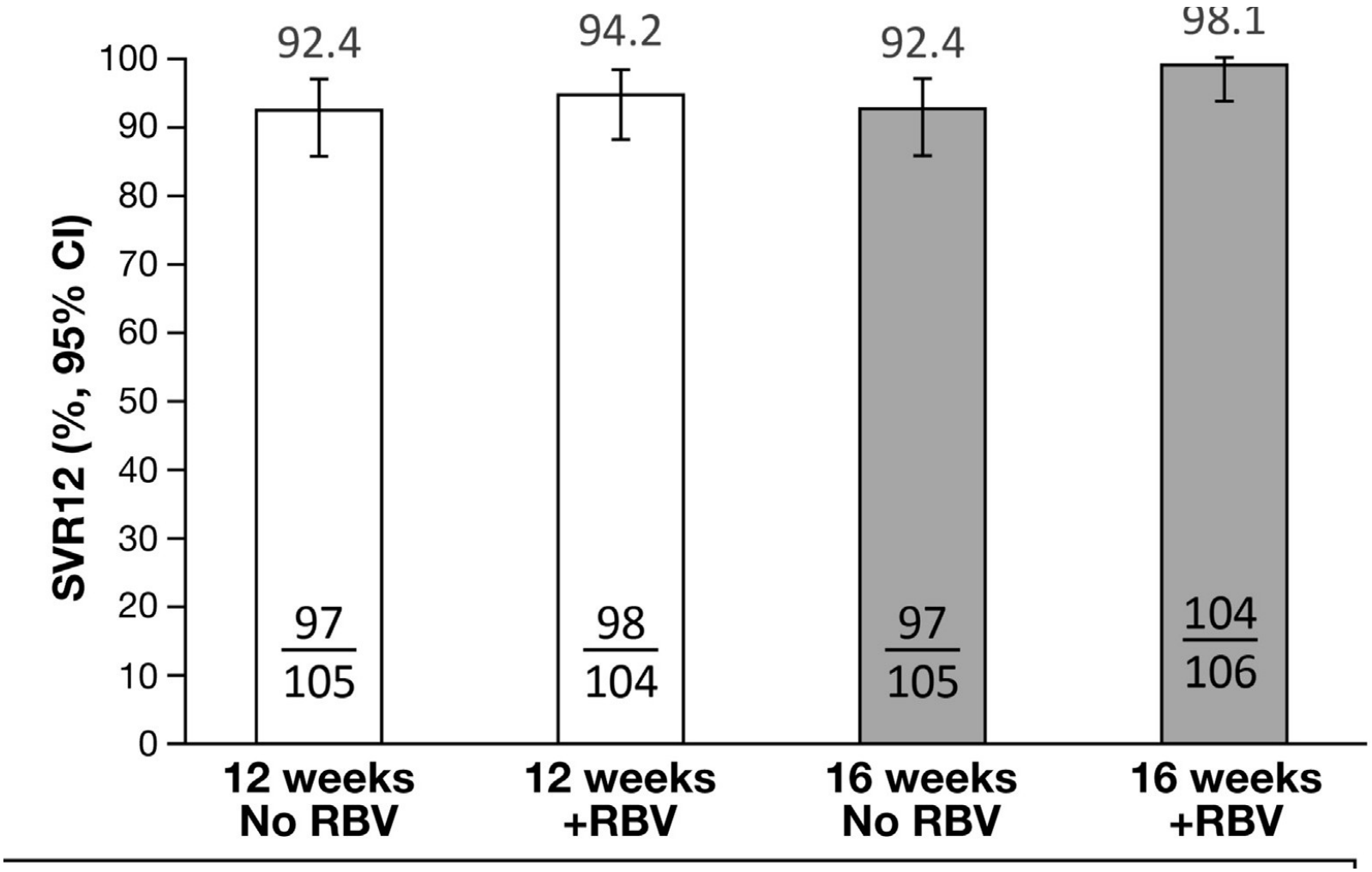
Zeuzem *et al*. *Ann Intern Med*. 2015; 163(1): 1-13.

Grazoprevir+Elbasvir in G1a patients



Kwo P , Gastroenterology 2017.

Grazoprevir+Elbasvir in G1a patients 12 weeks vs 16 weeks



Kwo P , Gastroenterology 2017.

Do we Need to assess Baseline HCV resistance to DAAs: is it useful and when?

1/ First and most important : Methodology for detection of RAVs must standardized (and automated)

2/ Usefulness of RAV testing will be patient population and treatment regimen dependent

- RAV testing most likely not required in patient populations with SVR rates > 99%

- RAV testing most likely be clinical useful and cost-effective in population with suboptimal SVR rates (definition < 95% / < 90% ?) & if population large enough
  - Regimens w/o a very high barrier to resistance drug
  - Treatment-experienced patients (in particular when exposed to DAAs)
  - Patients with cirrhosis
  - When the shortest possible treatment duration is economically important

If treating with DAA, which of the following would you recommend?

1. Sofosbuvir/ledipasvir for 12 wks + RBV
2. Sofosbuvir/ledipasvir for 24 wks
3. HCV baseline resistance NS5A+ NS5B analysis
4. Grazoprevir+Elbasvir for 16 wks
5. Grazoprevir+Elbasvir for 12 wks with NS5A analysis
6. Paritaprevir/ritonavir, ombitasvir +/- dasabuvir 12w
7. Sofosbuvir+Velpatasvir for 8 weeks
8. SOF + LDV + GS9451 ± GS9669 for 4 weeks

Outcomes Case 2

- You are considering treatment options for a treatment non responder to Ledipasvir/sofosbuvir cirrhotic patient with genotype 1a HCV infection and an HCV RNA level of 10 x 106 IU/mL

If retreating with DAA, which of the following would you recommend?

1. HCV baseline resistance NS5A+NS5B analysis
2. Sofosbuvir/ledipasvir for 24 wks+ RBV without HCV resistance analysis
3. Grazoprevir+Elbasvir +Sofosbuvir for 16 wks
4. ABT-493 +ABT-530 for 12 weeks
5. Sofosbuvir+Velpatasvir+Voxilaprevir for 12 weeks
6. Others

How to retreat the subgroup of experienced-patients with relapse or/and resistance to DAA?

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

Guidelines

EASL JOURNAL OF HEPATOLOGY

Recommendations for Testing, Managing, and Treating Hepatitis C

Recommended for Genotype 1 HCV NS5A Inhibitor Treatment-Experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Deferral of treatment is genotype 1, regardless nonstructural protein 5 have reasons for urgen**
  Rating: Class IIb, Level C

- **Testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, and who have compensated cirrhosis,‡ or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.**
  Rating: Class IIb, Level C

- **When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based ribavirin, unless contraindicated, should be added.**
  Rating: Class IIb, Level C

- **If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.**
  Rating: Class IIb, Level C

Recommandations are confusing !

EASL Recommendations on Treatment of Hepatitis C 2016☆

European Association for the Study of the Liver*

Retreatment of patients with DAA treatment failures

Patients who failed on a DAA-containing regimen should be retreated with an IFN-free regimen for 12 weeks with weight-based ribavirin if they have no, mild or moderate fibrosis (METAVIR score F0 to F2), for 24 weeks with ribavirin if they have extensive fibrosis (F3) or cirrhosis, unless otherwise specified below (**B1**).

Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus pegylated IFN-α and ribavirin can be retreated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), sofosbuvir and velpatasvir (all genotypes), ritonavir-boosted paritaprevir and ombitasvir (genotype 4), ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), grazoprevir and elbasvir (genotypes 1 and 4) or simeprevir and daclatasvir (genotypes 1 or 4) for 12 weeks (genotype 1b or 4 patients with METAVIR score F0 to F2) or 24 weeks (genotype 1a or 3 patients with METAVIR score F0 to F2 or genotype 1b and 4 patients with METAVIR score F3 or with compensated cirrhosis) (**B1**).

Patients who failed on a regimen containing sofosbuvir and simeprevir should be retreated with a combination of sofosbuvir with ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir (**B1**).

Patients infected with HCV genotype 1 or 4 who failed on a regimen containing an NS5A inhibitor, such as ledipasvir, velpatasvir, ombitasvir, elbasvir or daclatasvir, should be retreated with a combination of sofosbuvir, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), with a combination of sofosbuvir, ritonavir-boosted paritaprevir and ombitasvir (genotype 4), with a combination of sofosbuvir, grazoprevir and elbasvir (genotypes 1 and 4) or with a combination of sofosbuvir, simeprevir and daclatasvir (genotypes 1 or 4), for 12 weeks (genotype 1b or 4 patients with METAVIR score F0 to F2) or 24 weeks (all patients with genotype 1a; genotype 1b and 4 patients with METAVIR score F3 or with compensated cirrhosis) with ribavirin. Treatment should be administered with caution in patients with extensive fibrosis (METAVIR score F3) or compensated cirrhosis due to a possible risk of severe adverse events of some of these combinations (**B1**).

Patients infected with HCV genotype 2, 3, 5 or 6 who failed on a regimen containing an NS5A inhibitor, such as ledipasvir, velpatasvir or daclatasvir, should be retreated with a combination of sofosbuvir and velpatasvir for 24 weeks with ribavirin (**B1**).

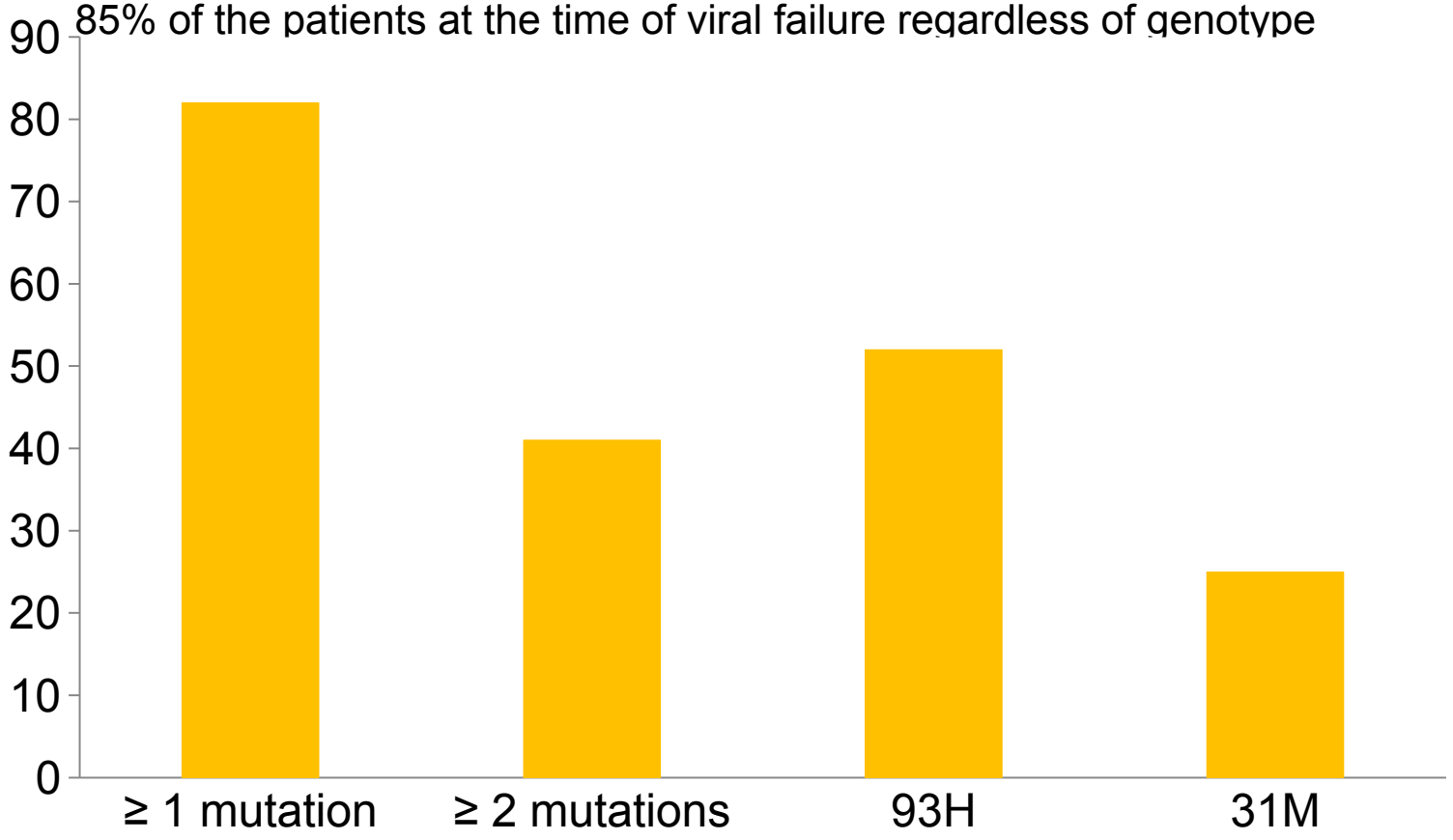
Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available (**A1**).

The utility of HCV resistance testing prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown. If reliable resistance testing is performed, retreatment can be guided by probabilities of response according to the resistance profile observed in the context of an experienced multidisciplinary team (**B2**).

Baseline and post-treatment hepatitis C NS5A resistance analysis in relapsed patients from a multicentric real-life cohort of 2995 patients exposed to NS5A inhibitors

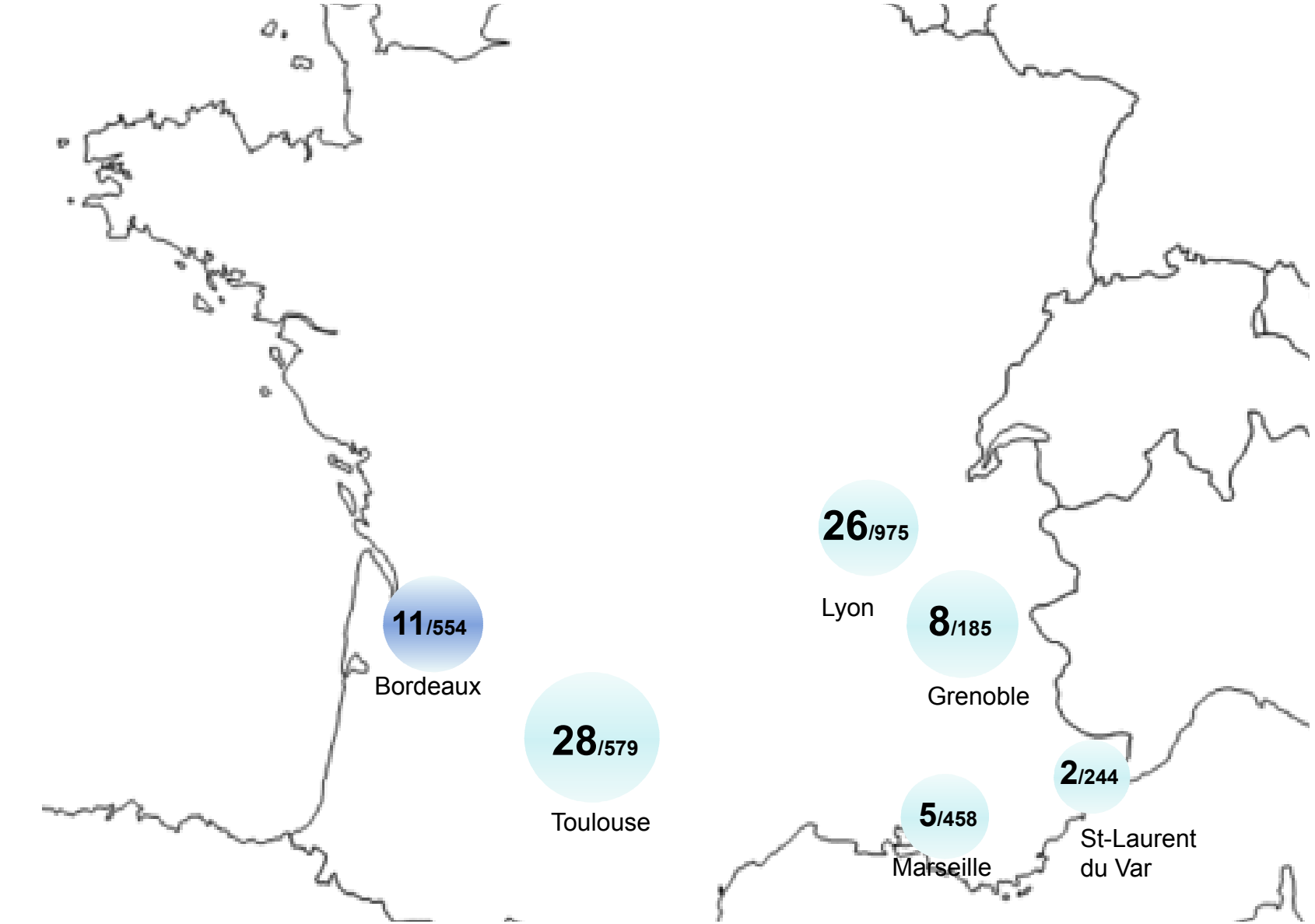
- **Only 81/2295 (2.7%) patients failed**

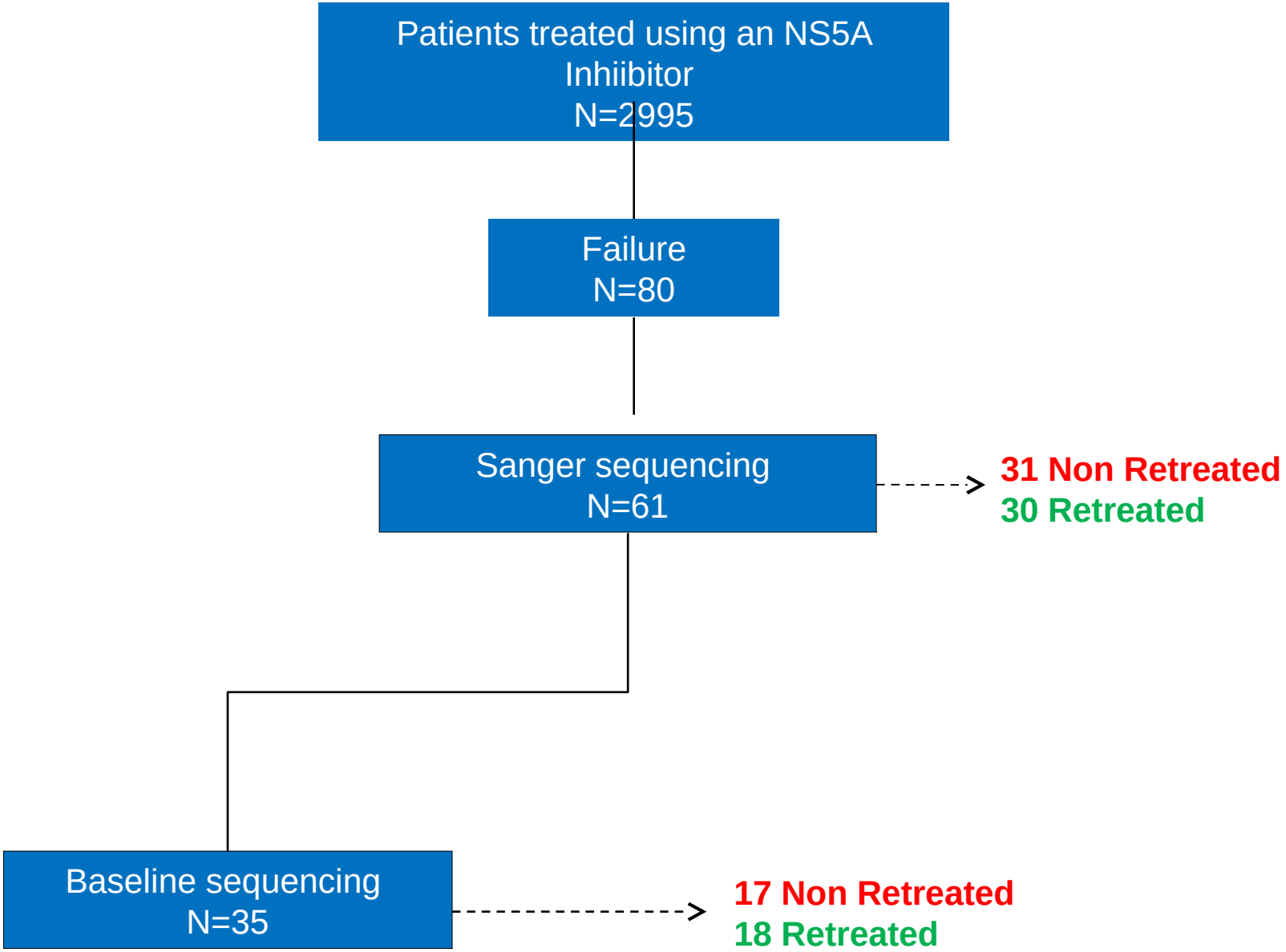
- At the time of failure , Resistance to NS5ANS5A (> 10 fold résistance) was detected in 85% of the patients at the time of viral failure regardless of genotype



Halfon P. et al., AASLD 2016
Trimoulet P. et al. AFEF 2016 (oral presentation)

Geographical distribution of the 80 relapsers among the 2995 HCV-infected patients




Patients treated using an NS5A Inhiibitor
N=2995
Failure
N=80
Sanger sequencing
N=61
31 Non Retreated
30 Retreated
Baseline sequencing
N=35
17 Non Retreated
18 Retreated

Retreatment with Direct Active Antivirals of genotype 1, 3 and 4 chronic hepatitis C patients who previously failed an anti-NS5A-containing regimen in real world

From January 2014 to March 2016, 2995 patients infected with HCV were exposed to NS5A inhibitors in 6 French referent liver centers: 80 (2.7%) patients relapsed.

This “real-world” study included 30 patients among these 80 patients who had failed to achieve SVR on previous NS5A-based therapy.

These patients were retreated with different regimen combination including SOF + Daclatasvir (DAC) ± SIM (19%), SOF + Grazoprevir + Elbasvir (23%), SOF + Ledipasvir (LEDI) (6%), SOF + SIM (16%), SOF + Velpatasvir + GS9857 (20%), Ombitasvir (OBV) + Paritaprevir (PTV) + Ritonavir (RTV) + Dasabuvir (DAS) ± SOF (16%), with or without RBV for all regimens.

Halfon P et al. EASL 2017- Amsterdam

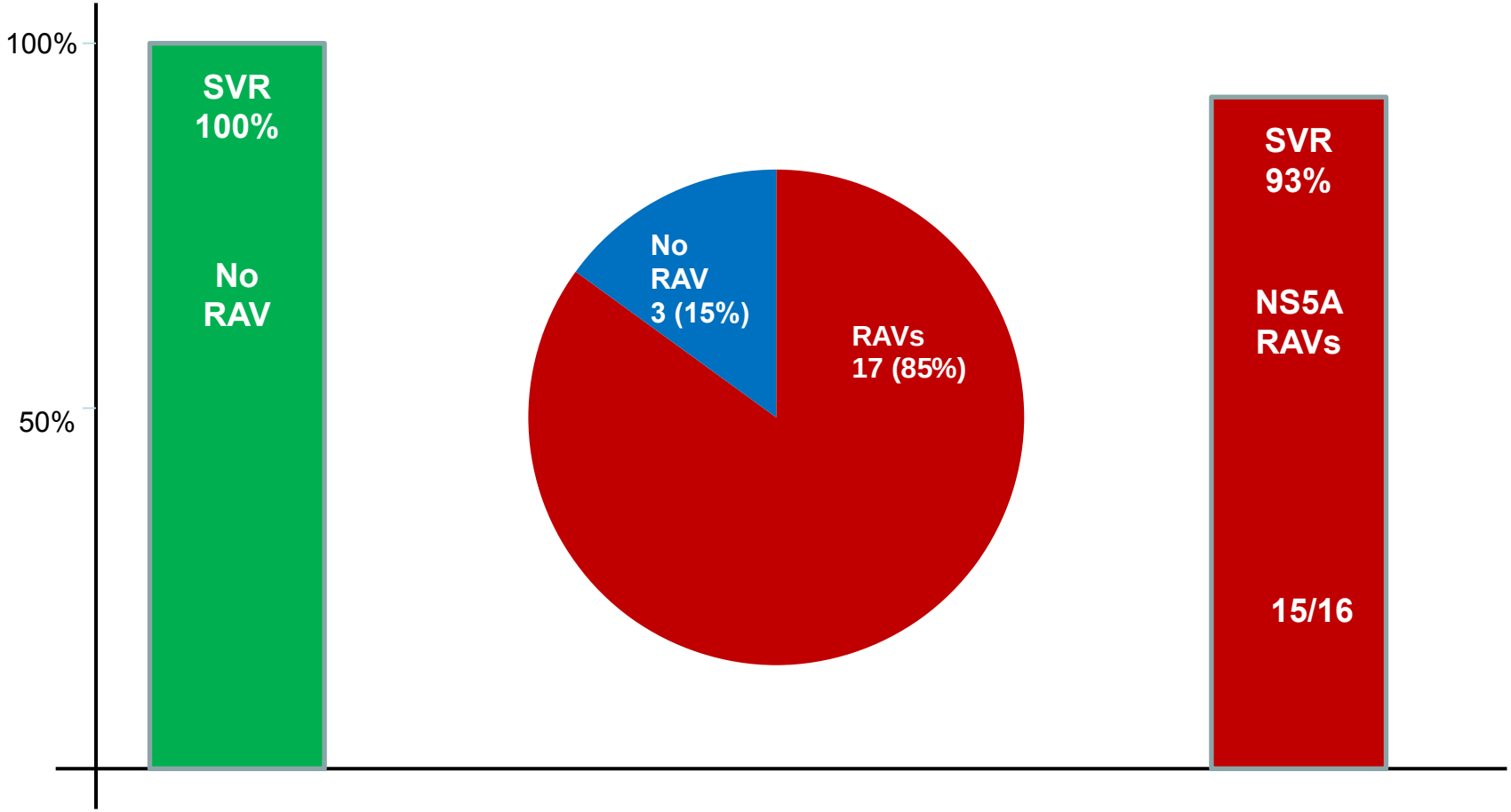
Retreatment with DAA of Hepatitis chronic C genotype 1, 3 and 4 in patients who previously failed a NS5A-containing regimen in real world

First treatment	N	Second Treatment	N	Presence NS5A RAVs
SOF+LDV (12 or 24 Weeks)	6	SOF+DACLA+RBV	1	No
		SOF+DACLA+SIM	1	Yes
		SOF+GRAZO+ELBA±RBV	2	Yes
		SOF+SIM±RBV	6	Yes
SOF+LDV+RBV (12 Weeks)	11	SOF+SIM	1	Yes
		SOF+GRAZO+ELBA±RBV	2	Yes
		SOF+VELPA+GS9857	2	Yes(1)/No(1)
		SOF+OBV+PTV+RTV+DAS+RBV	1	Yes
		SOF+DACLA+SIM	1	Yes
		SOF+LDV+RBV (24 Weeks)	2	No
		VIEKIRAX/EXVIERA+RBV	2	Yes(1)/No(1)
SOF+DACLA (8, 12, or 24 Weeks)	8	SOF+DACLA (24 Weeks)	1	Yes
		SOF+GRAZO+ELBA±RBV	3	Yes
		SOF+VELPA+GS9857	2	Yes
		SOF+OBV+PTV+RTV+DAS+RBV	1	Yes
		VIEKIRAX/EXVIERA+RBV	1	Yes
SOF+DACLA+RBV (12 or 16 Weeks)	2	SOF+DACLA (24 Weeks)	1	Yes
		SOF+VELPA+GS9857	1	Yes
PTV+OBV+RBV (12 Weeks	1	SOF+DACLA +RBV	1	Yes
DACLA+PEG+RBV (12 Weeks	1	SOF+SIM+RBV	1	Yes
ASUNA+DACLA (20 or 24 Weeks)	2	SOF+SIM+RBV	1	Yes
		SOF+VELPA+GS9857	1	Yes

Halfon P et al. EASL 2017- Amsterdam

SVR12 by Baseline Resistance Associated Substitutions (RAS)

Genotype 1

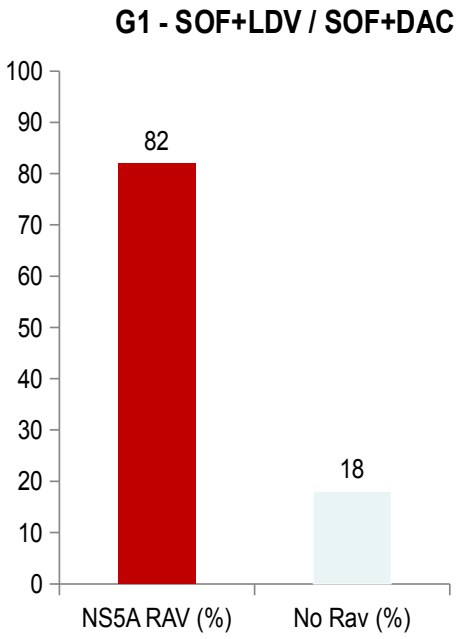


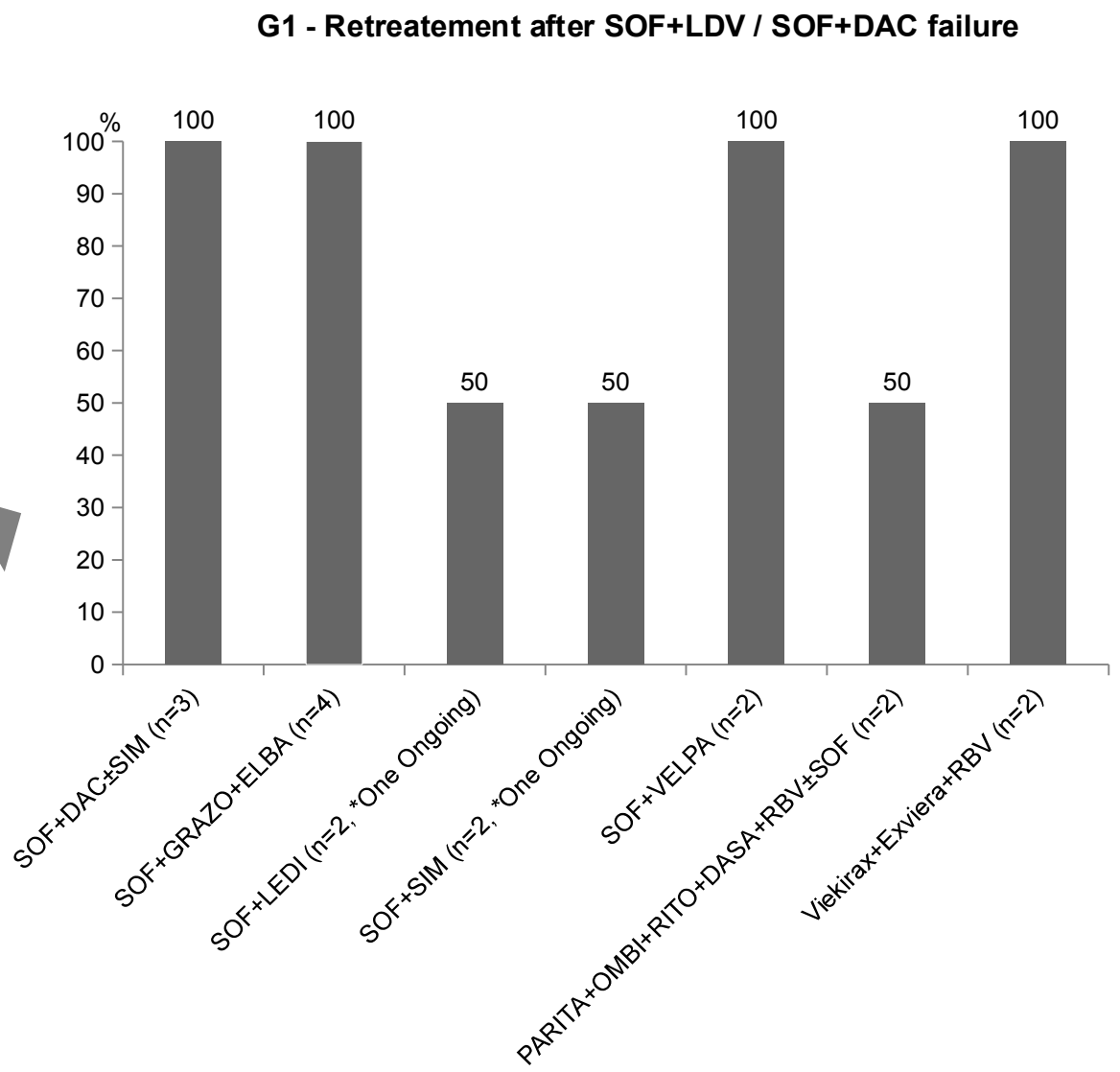
Genotype 1

SVR12 = 94% (n = 15/16)

Failure SOF + LDV (n = 11)

Failure SOF + DAC (n = 6)

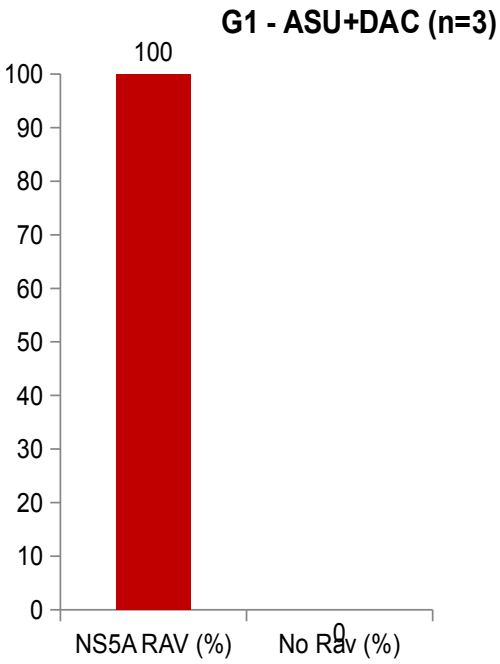


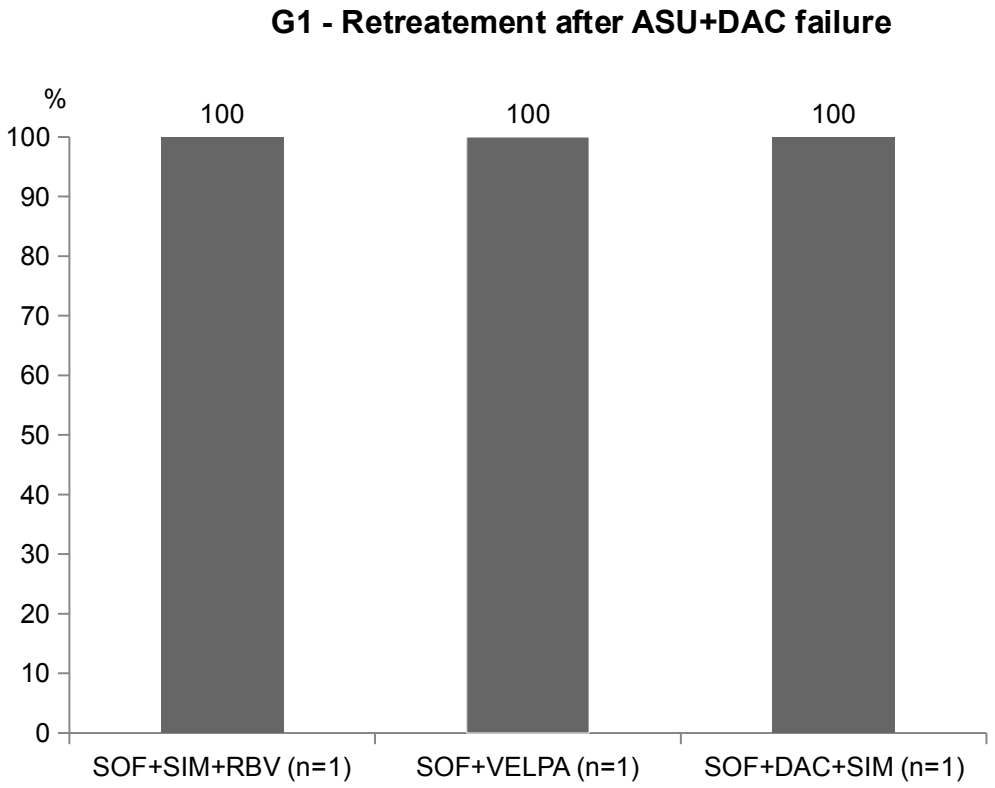


Genotype 1

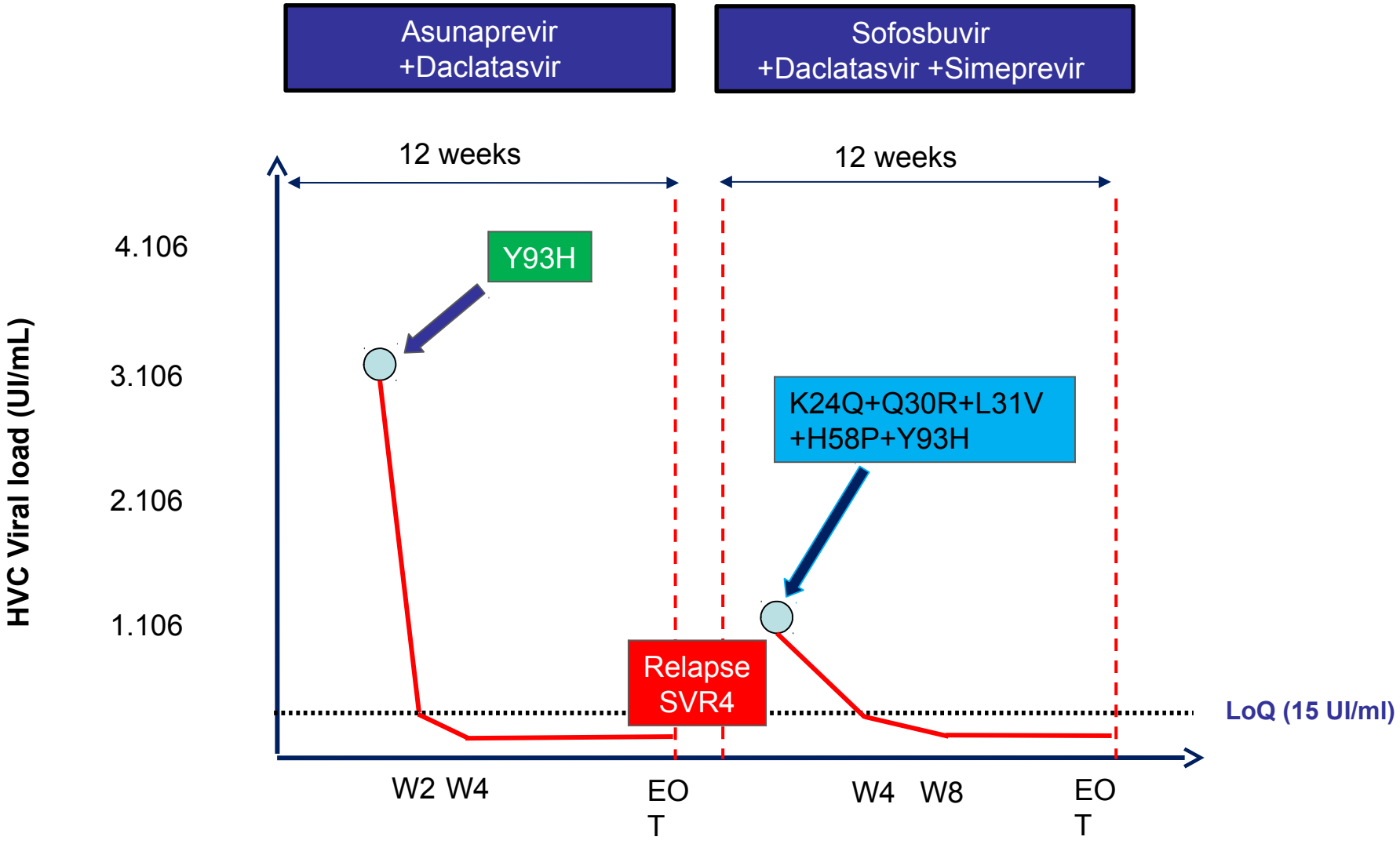
SVR12 = 100% (n = 3/3)

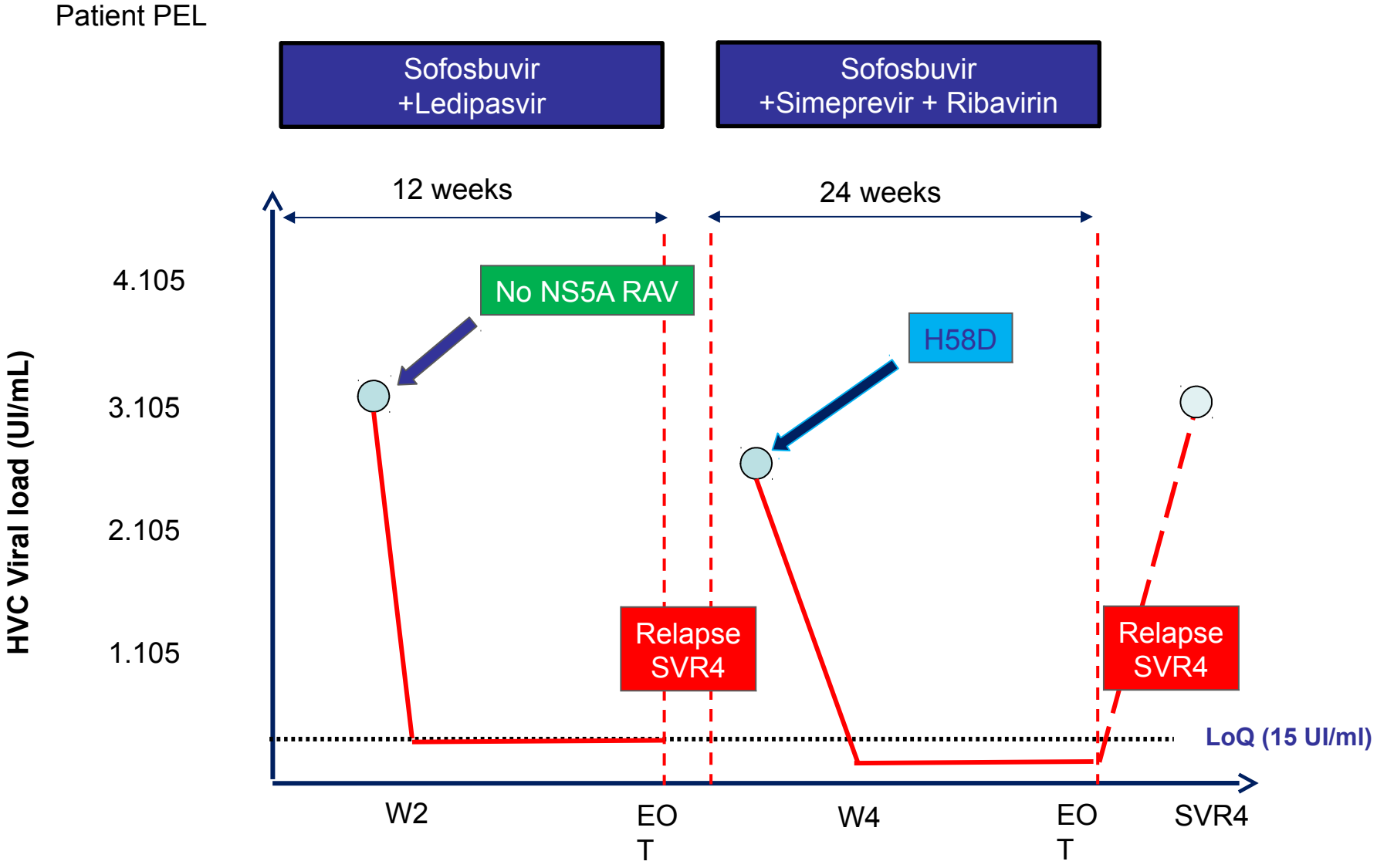
Failure ASU + DAC (n = 3)



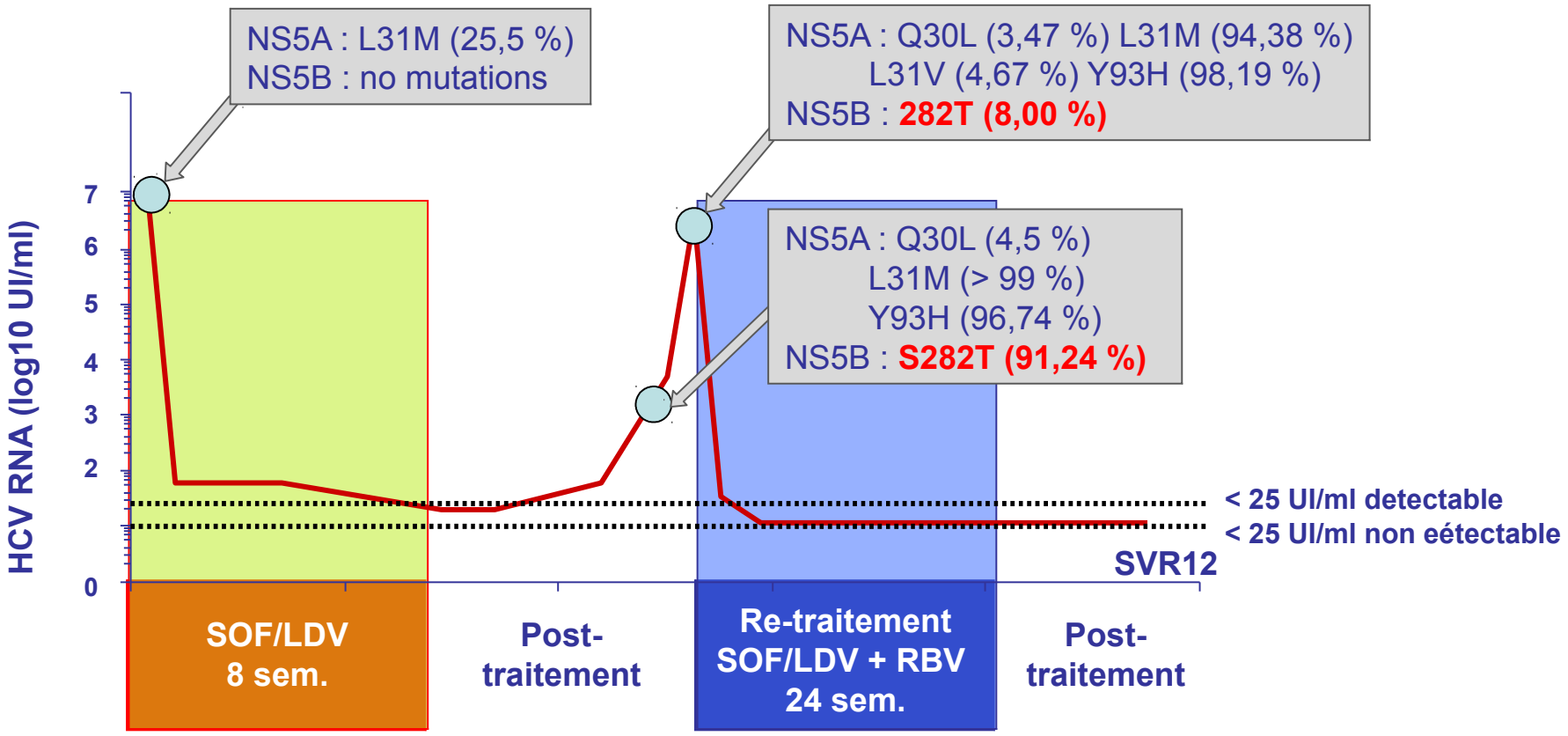


Patient CA


Asunaprevir
+Daclatasvir
Sofosbuvir
+Daclatasvir +Simeprevir
12 weeks
12 weeks
HVC Viral load (UI/mL)
4.106
3.106
2.106
1.106
Y93H
K24Q+Q30R+L31V
+H58P+Y93H
Relapse
SVR4
LoQ (15 UI/ml)
W2 W4
EO
T
W4 W8
EO
T

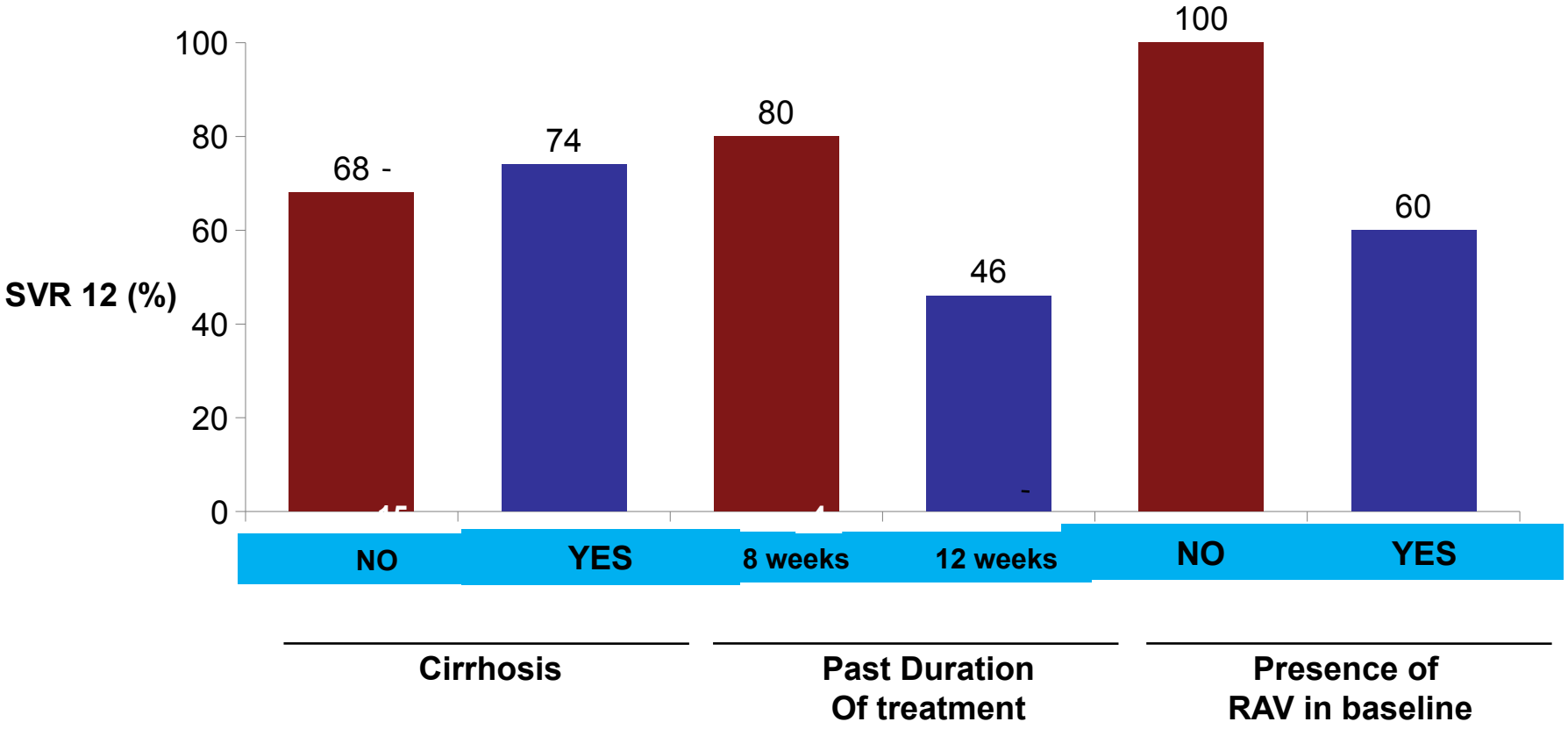

Patient PEL
Sofosbuvir +Ledipasvir
Sofosbuvir +Simeprevir + Ribavirin
12 weeks
24 weeks
HVC Viral load (UI/mL)
4.105
3.105
2.105
1.105
No NS5A RAV
H58D
Relapse SVR4
Relapse SVR4
LoQ (15 UI/ml)
W2
EOT
W4
EOT
SVR4

Re-treatement of patient who relapsed after 8 weeks of sofosbuvir + ledipasvir



Lawitz E ,Etats-Unis, AASLD 2013, Abs. 215/1844,

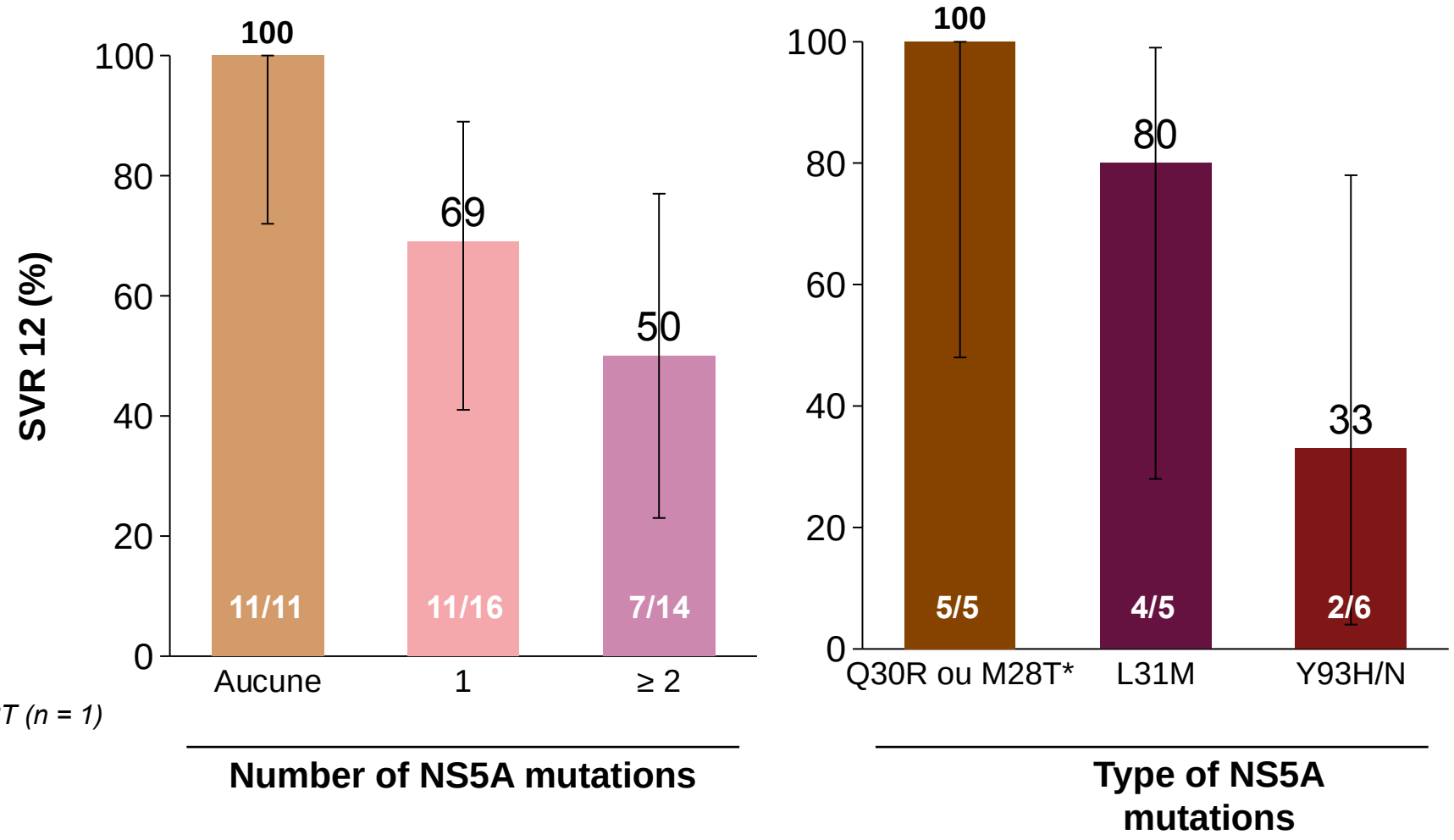
SVR 12 in 41 patients with failure SOF + LDV 8 – 12 weeks , retreated by LDV/SOF during 24 semaines



The chance of succes using the same combination even extended are limited

Lawitz *et al*. EASL 2015. Abstract O005.

SVR 12 in 41 patients with failure SOF + LDV 8 – 12 weeks , retreated by LDV/SOF during 24 semaines

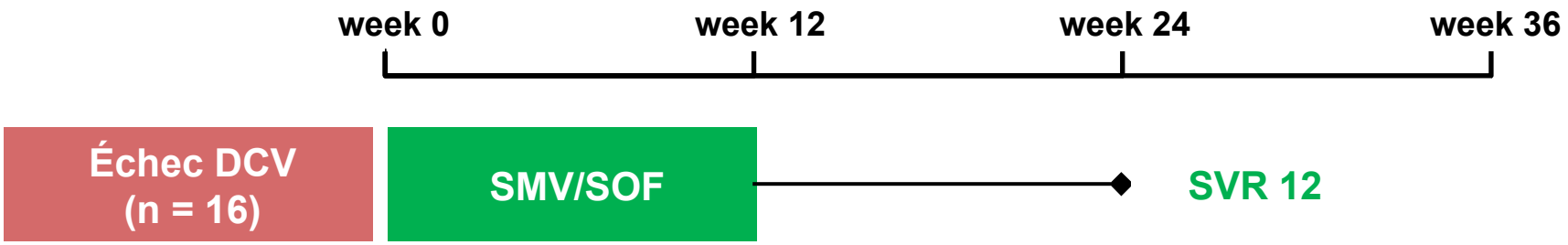


*M28T (n = 1)

The number and type of mutations strongly impact the retreatment

Lawitz *et al*. EASL 2015. Abstract O005.

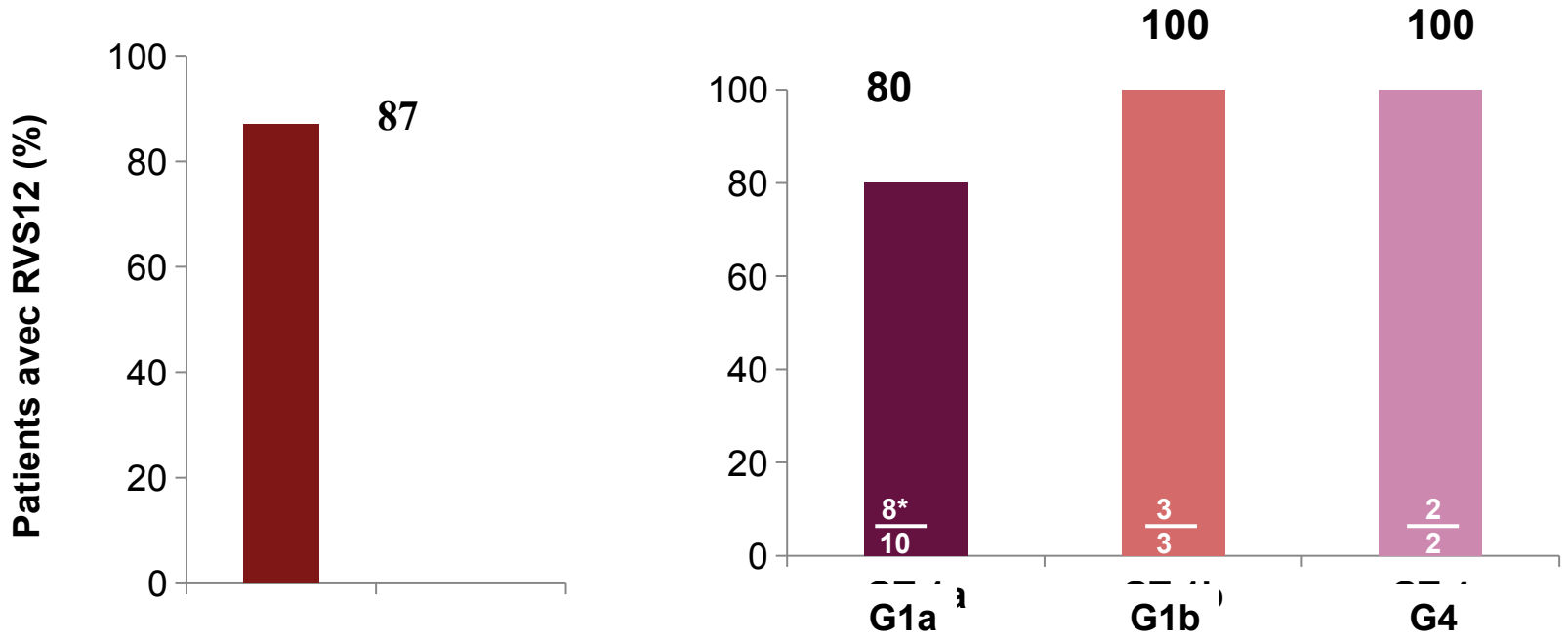
Retraitement of patients failed to NS5A Inhibitors



- HCV Abbott Real *Time* Assay
  (LOQ: 12 UI/ml)
- NS3, NS5A et NS5B sanger sequencing
  before retreatment using SOF/SMV

Hézode *et al*. AFEF 2015..

Retraitement of patients failed to NS5A Inhibitors



Genotype 1a patients are more impacted by previous NS5A failure

Hézode *et al*. AFEF 2015..

POLARIS Phase 3 Program

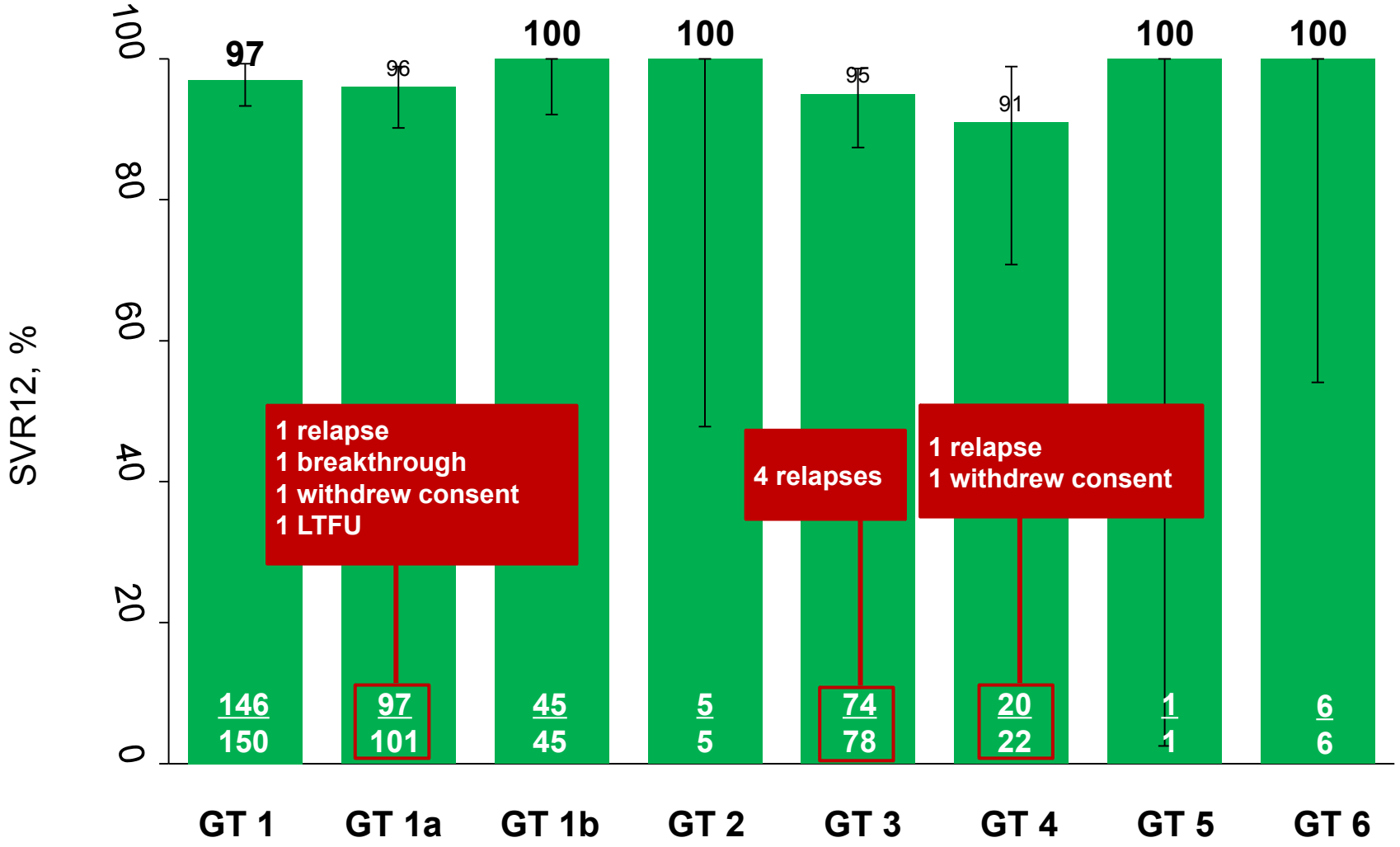
‡

DAA-Experienced		DAA-Naïve	
POLARIS-1	**POLARIS-4**	**POLARIS-2**	**POLARIS-3**
 N = 415 NS5A-experienced ± cirrhosis	 N = 333 Non-NS5A-experienced ± cirrhosis	 N = 941 ± cirrhosis	 N = 219 Cirrhosis
GT 1 2 3 4 5 6	GT 1 2 3 4 5 6	GT 1 2 3 4 5 6	GT 3
SOF/VEL/VOX 12 weeks (n=263)	SOF/VEL/VOX 12 weeks (n=182)	SOF/VEL/VOX 8 weeks (n=501)	SOF/VEL/VOX 8 weeks (n=110)
Placebo (n=152)	SOF/VEL 12 weeks (n=151)	SOF/VEL 12 weeks (n=440)	SOF/VEL 12 weeks (n=109)

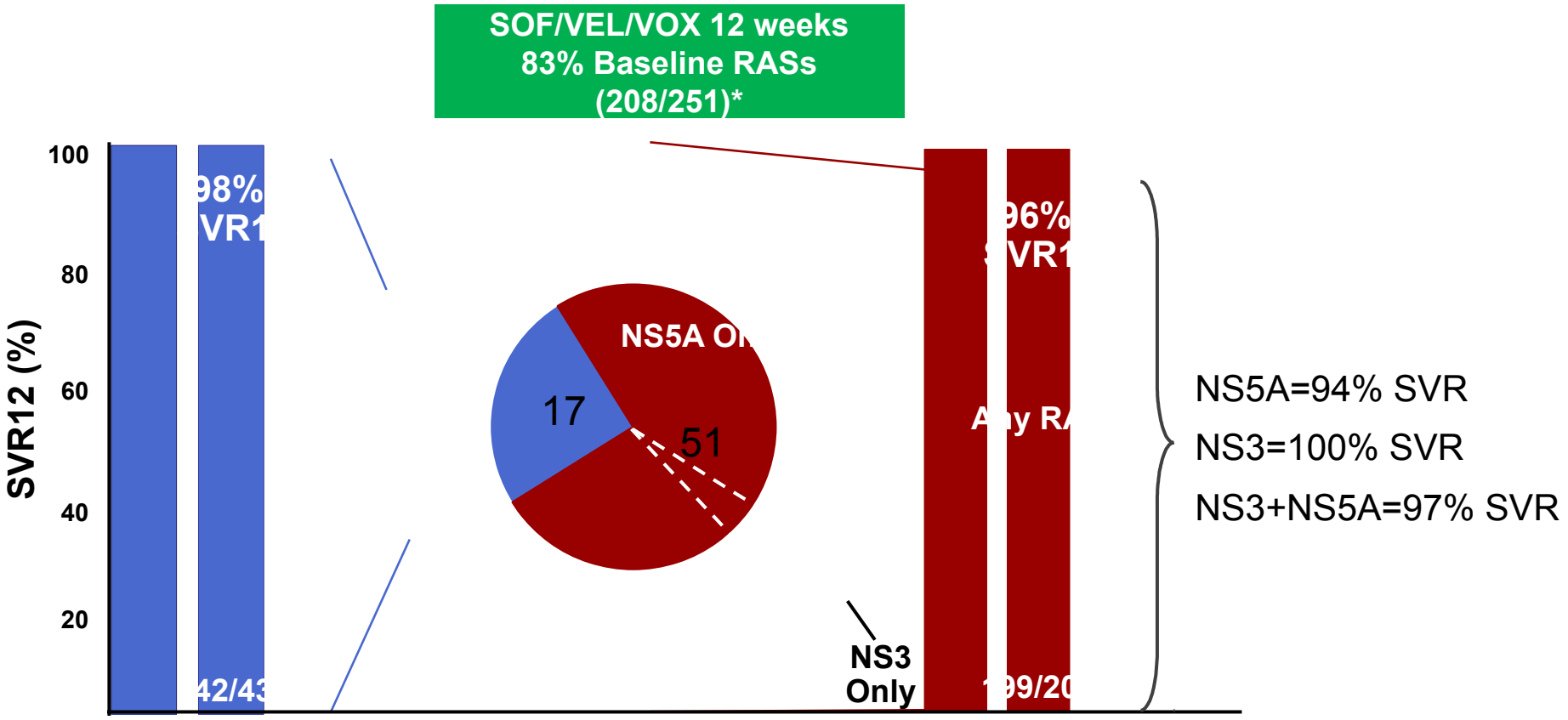
Bourliere M, AASLD 2016, Oral 194. Zeuzem S, AASLD 2016, Oral 109. Jacobson IM, AASLD 2016, Oral LB-12. Foster GR, AASLD 2016, Oral 258

‡

SVR12 Results by Genotype



SVR12 by Baseline Resistance Associated Substitutions (RAS)



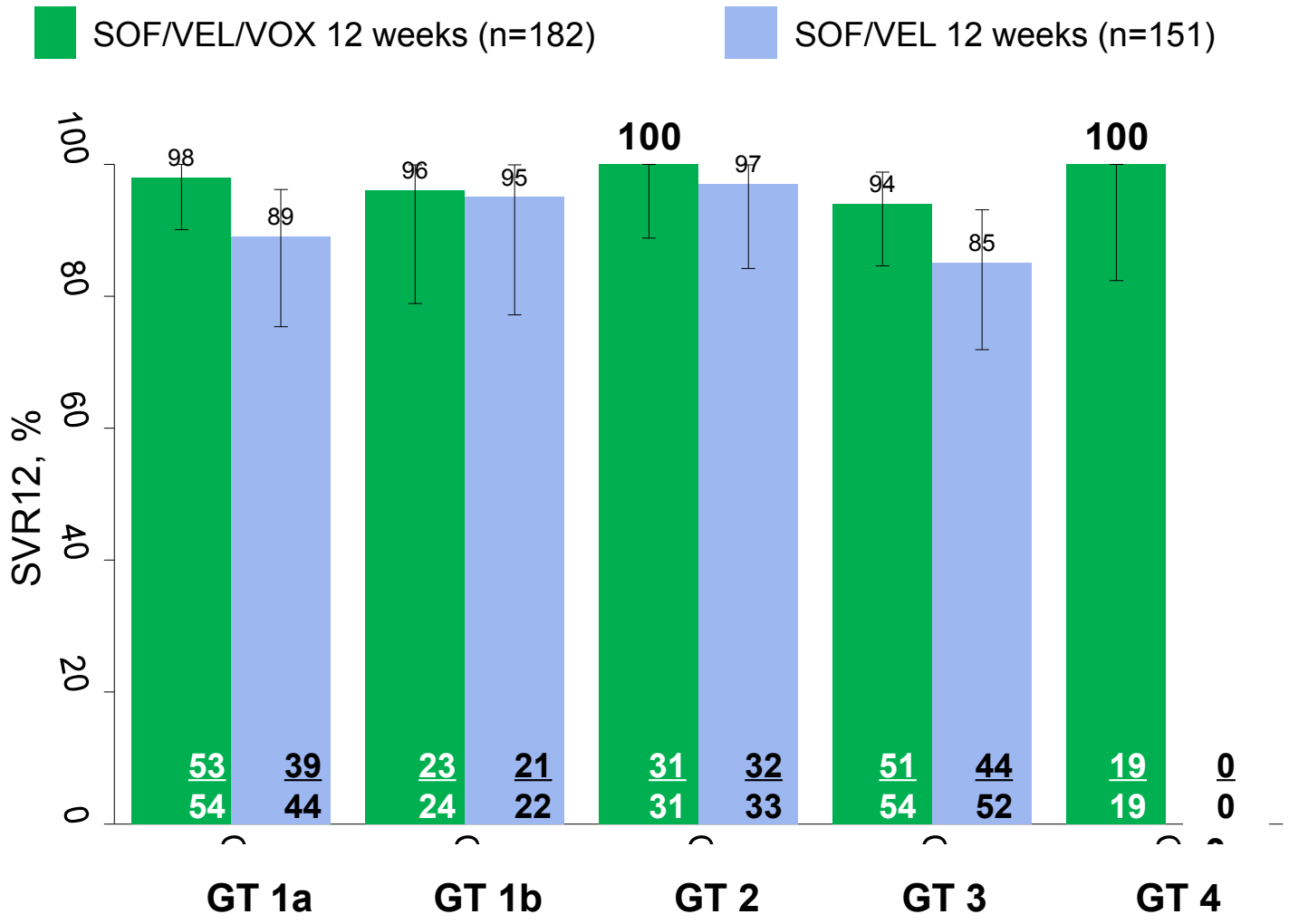
Two patients had S282T at baseline, both achieved SVR12

*12 patients were excluded due to incomplete RAS data; RASs were analyzed using a 15% cut off

Bourliere M, AASLD 2016, Oral 194

POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4

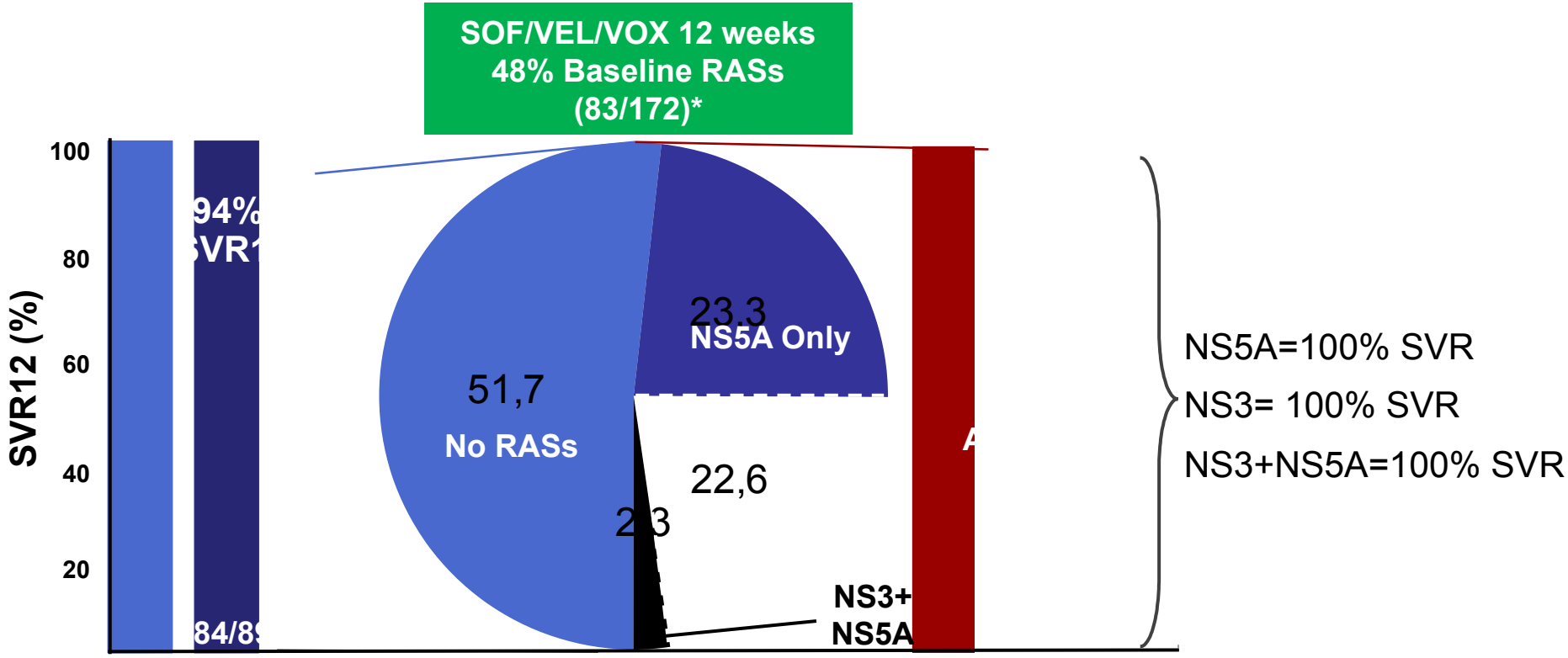
SVR12 Results by Genotype



Zeuzem S, AASLD 2016, Oral 109.

POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4 ‡

SVR12 by Baseline Resistance Associated Substitutions (RAS)



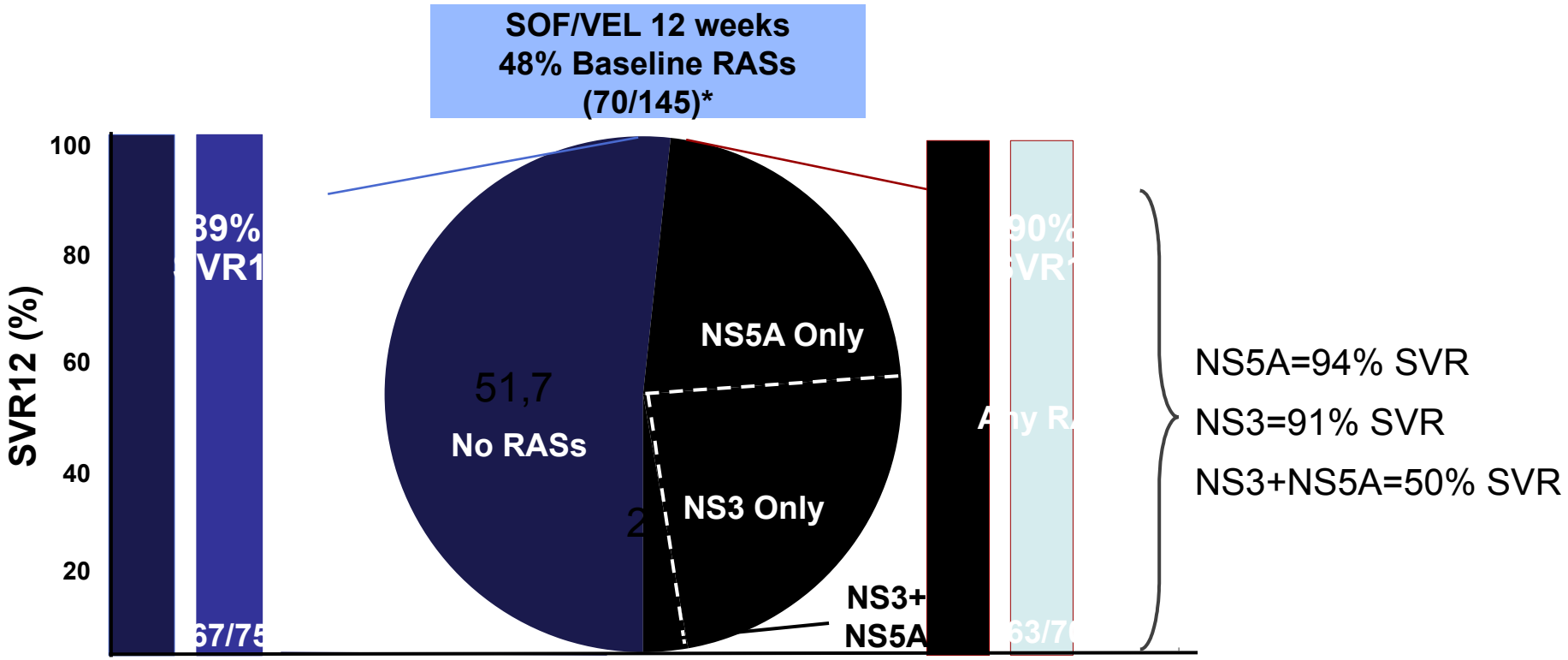
All 22 patients with BL NS5B RAS achieved SVR12
No treatment-emergent RASs were observed in the patient who relapsed following SOF/VEL/VOX

*10 patients were excluded due to unavailable RAS data; RASs were analyzed using a 15% cut off;

Zeuzem S, AASLD 2016, Oral 109.

POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4 ‡

SVR12 by Baseline Resistance Associated Substitutions (RAS)



All 8 patients with BL NS5B RAS achieved SVR12

*6 patients were excluded due to unavailable RAS data; RASs were analyzed using a 15% cut off

Zeuzem S, AASLD 2016, Oral 109.

‡

POLARIS-1 and POLARIS-4

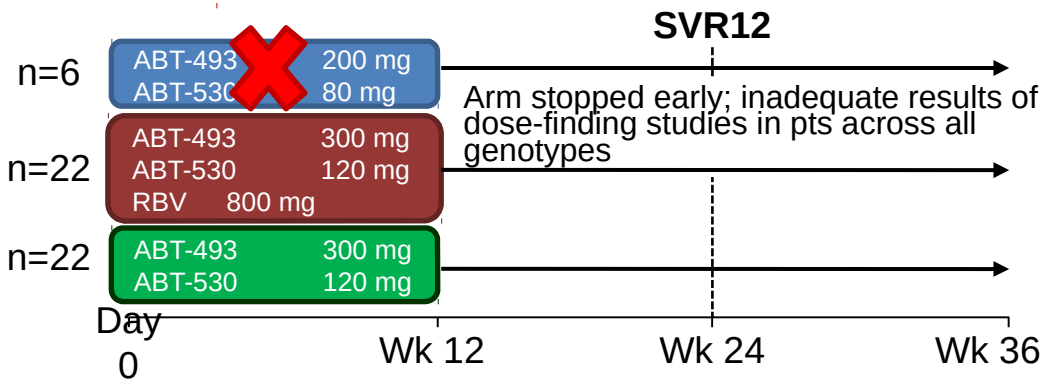
In a wide variety of DAA-experienced patients across all genotypes SOF/VEL/VOX for 12 weeks resulted in:

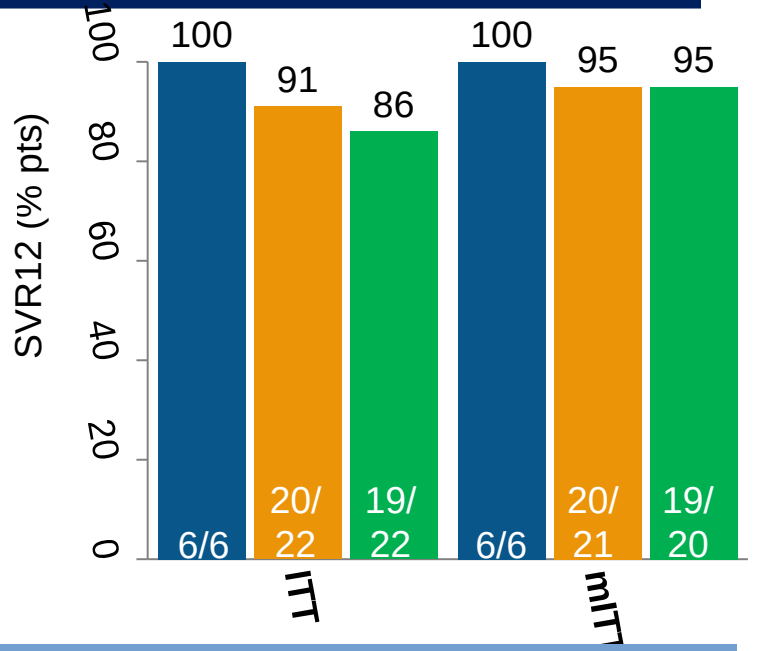
- **96% SVR in NS5A experienced patients**
- **97% in DAA-experienced patients**
- **Including patients with multiple unfavorable characteristics including multiple RASs across NS5A and NS3/4A**
- **Baseline RASs did not impact treatment outcome for SOF/VEL/VOX with SVR rates of 94-100%**
- **No treatment-emergent RASs were observed among patients who relapsed with SOF/VEL/VOX**

SOF/VEL/VOX for 12 weeks provides a simple, well tolerated, and effective single tablet, once daily, RBV-free treatment for DAA-experienced patients, including NS5A and non-NS5A failures

Zeuzem S, AASLD 2016, Oral 109; Bourliere M, AASLD 2016, Oral 194

ABT-493 and ABT-530 in G1 patients who have failed DAA-containing regimens: The MAGELLAN-I study





ABT-493 dose ABT-530 dose RBV dose	200 mg 80 mg - (n=6)	300 mg 120 mg 800 mg (n=22)	300 mg 120 mg - (n=22)
Male, n (%)	3 (50)	20 (91)	18 (82)
Black race, n (%)	2 (33)	5 (23)	10 (45)
Hispanic/Latino, n (%)	1 (17)	1 (5)	2 (9)
Age, median years (range)	59 (39–61)	56 (39–64)	59 (46–70)
BMI, median kg/m2 (range)	27 (25–37)	28 (22–34)	28 (19–37)
HCV RNA, median log10 IU/mL (range)	6.1 (5.5–6.7)	6.7 (5.0–7.3)	6.6 (5.5–7.2)
HCV G1a, n (%)	4 (67)	20 (91)	18 (82)
Fibrosis stage			
F0–F1	4 (67)	17 (77)	11 (50)
F2	1 (17)	0	6 (27)
F3	1 (17)	5 (23)	5 (23)

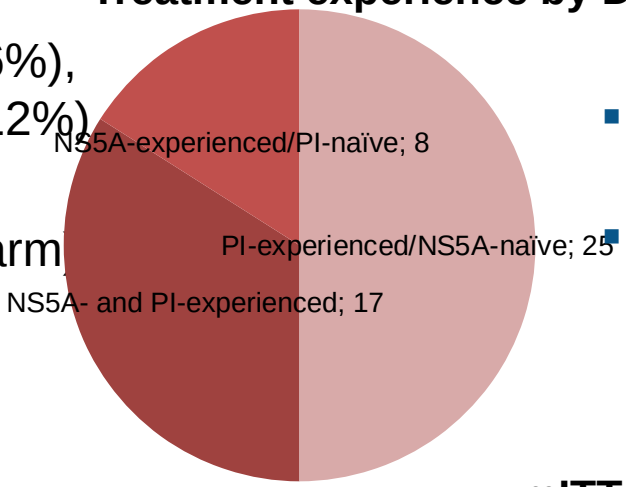
BT	**0**	**0**	**1**	**0**	**0**	**1**
Relapse	**0**	**1**	**0**	**0**	**1**	**0**
LTFU	**0**	**1**	**2**	**0**	**1**	**2**

- 1 LTFU after Week 6 with HCV RNA undetectable
- 2 patients LTFU after completing treatment (1 death); both achieved SVR8

ABT-493 and ABT-530 in G1 patients who have failed DAA-containing regimens: The MAGELLAN-I study

- **Safety**
  - AEs: HA (28%), fatigue (26%), nausea (20%), insomnia (12%)
  - No grade ≥2 ALT elevation
- Grade 2 ↑ bili in 3 pts (RBV arm)
- No early d/c
- No SAE

Treatment experience by DAA class:



- 25 (50%) NS5A-experienced
- 42 (84%) PI-experienced

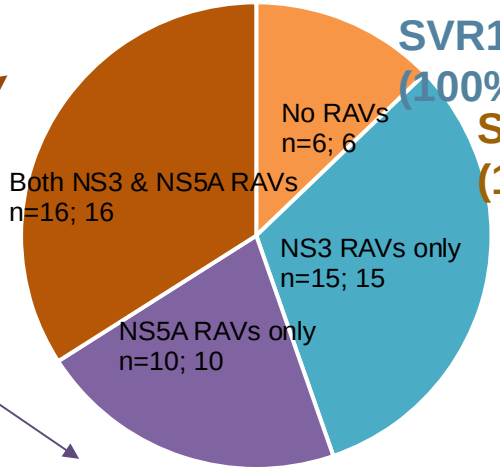
ABT-493 + ABT-530 achieved high SVR in G1 DAA-experienced pts
BL RAVs had no impact on outcome, await data in cirrhosis (part 2)
RBV did not enhance SVR

mITT SVR12 rates in pts w/ BL RAVs

SVR12 15/16 (94%)
1a; 3D+RBV failure
Breakthrough
NS3: Y56H, D168A/T
NS5A: M28V, Q30L/R

1a; DCV, TVR, PR failure
Relapse
NS5A: L31M, H58D

SVR12 9/10 (90%)



SVR12 6/6 (100%)*

SVR12 15/15 (100%)

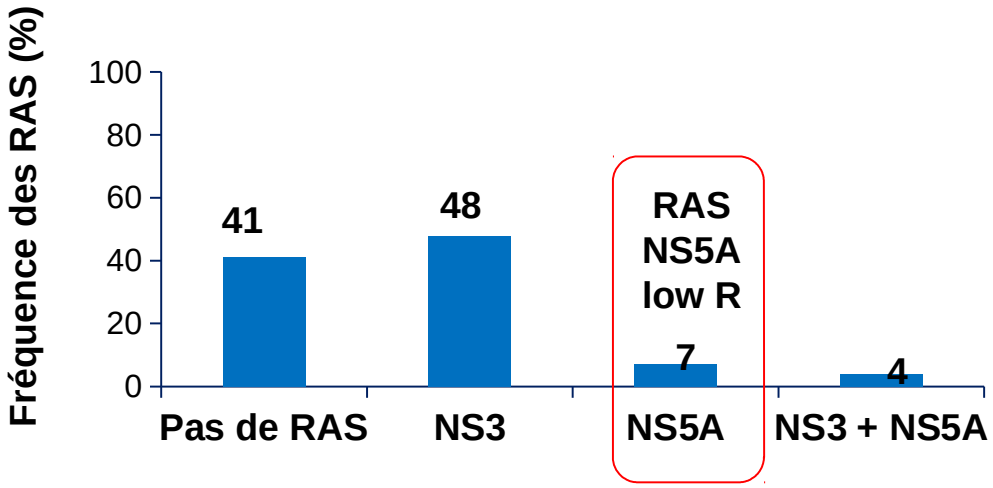
- 100% SVR12 in 10 pts with Y93 NS5A RAVs
- 100% SVR12 in 26 pts w Q80 or R155 NS3 RAVs
- 100% SVR12 in 17 pts w prior failure of a SOF-containing regimen

* 3 pts with no BL RAVs were LTFU (excluded from the mITT analysis). BL RAVs based on deep sequencing **1% threshold**.

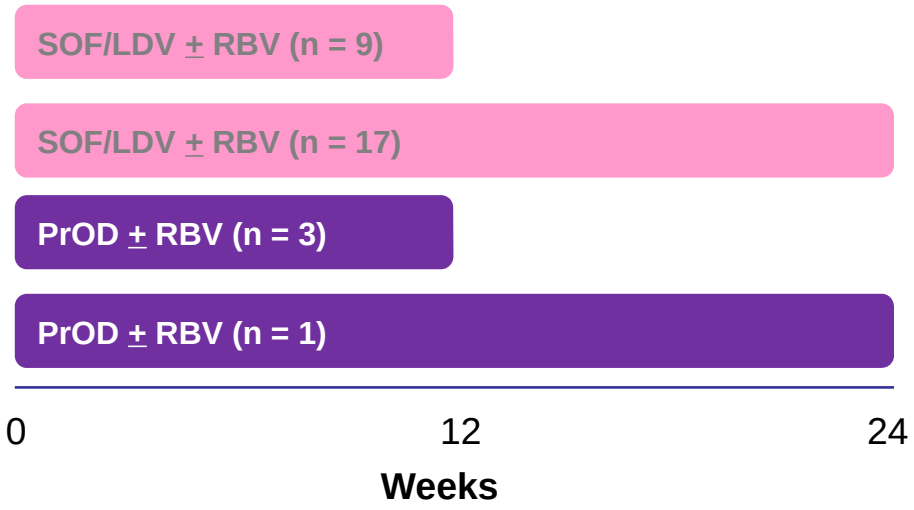
HCV genotype 1 German resistance surveys *(1)*

Genotype 1

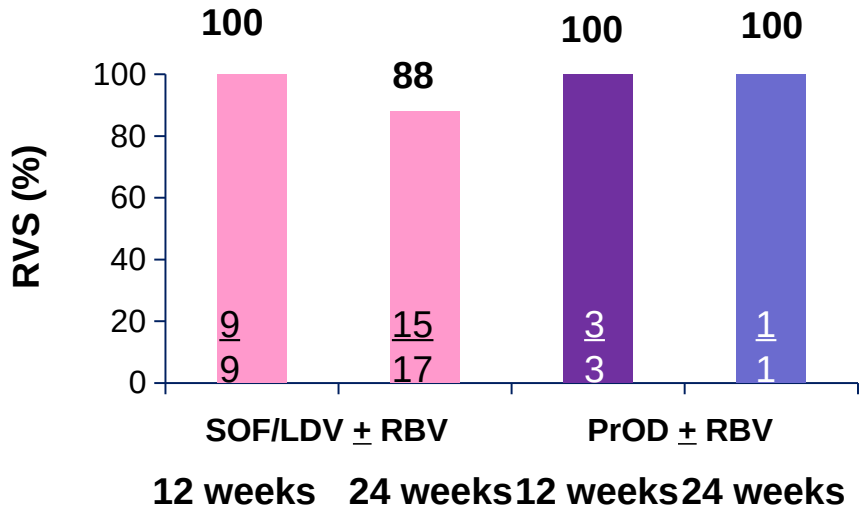
Failure : SOF + SMV (n = 31)



Retreatment with a strategy including a NS5A Inhibibitor Regimen



Intermediate Study
SVR 12 = 93,5 % (n = 28/30)



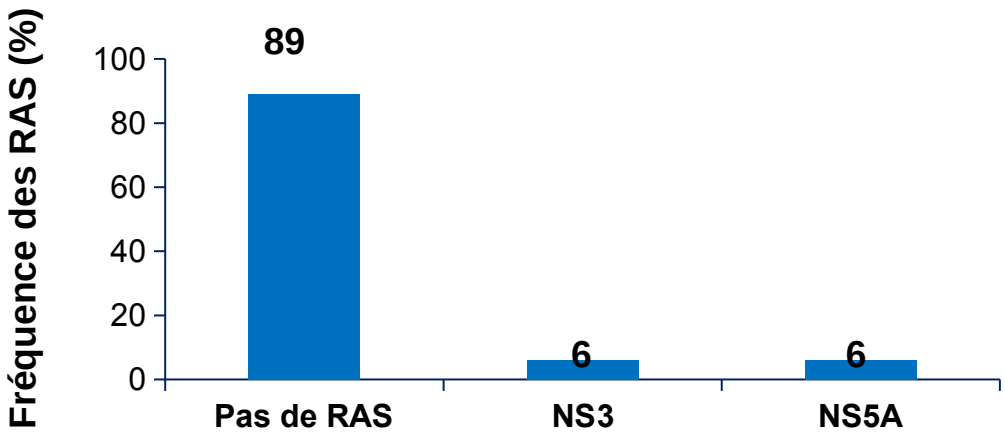
Vermehren J, Allemagne, AASLD 2016, Abs. 89

Genotype 3 German HCV resistance surveys *(4)*

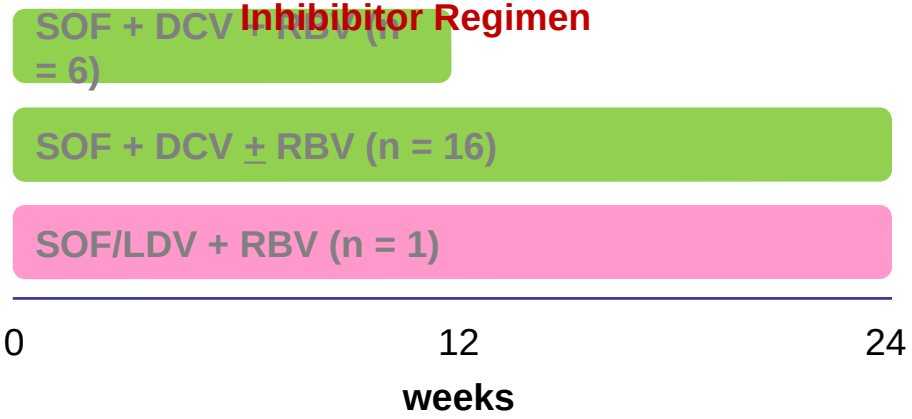
Genotype 3

Failure SOF + RBV (n = 20)

Failure SOF + DCV (n = 4)



Retreatment with a strategy including a NS5A Inhibitor Regimen

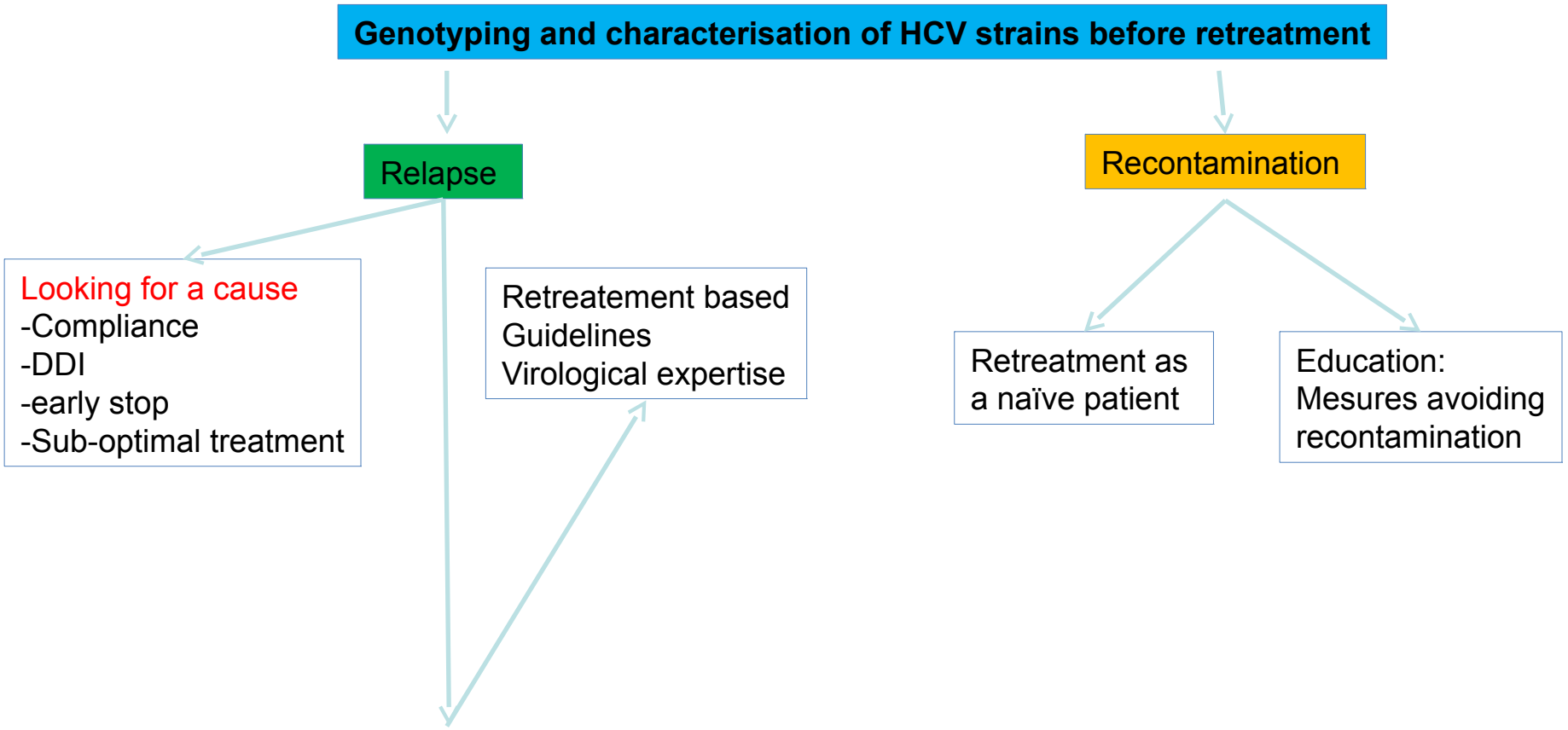


Intermediate analysis: RVS12 = 100 % (n = 7/7)

➔ **Failure SOF + DCV : 50 % of SVR (2/4)**

Vermehren J, Allemagne, AASLD 2016, Abs. 894, actualis

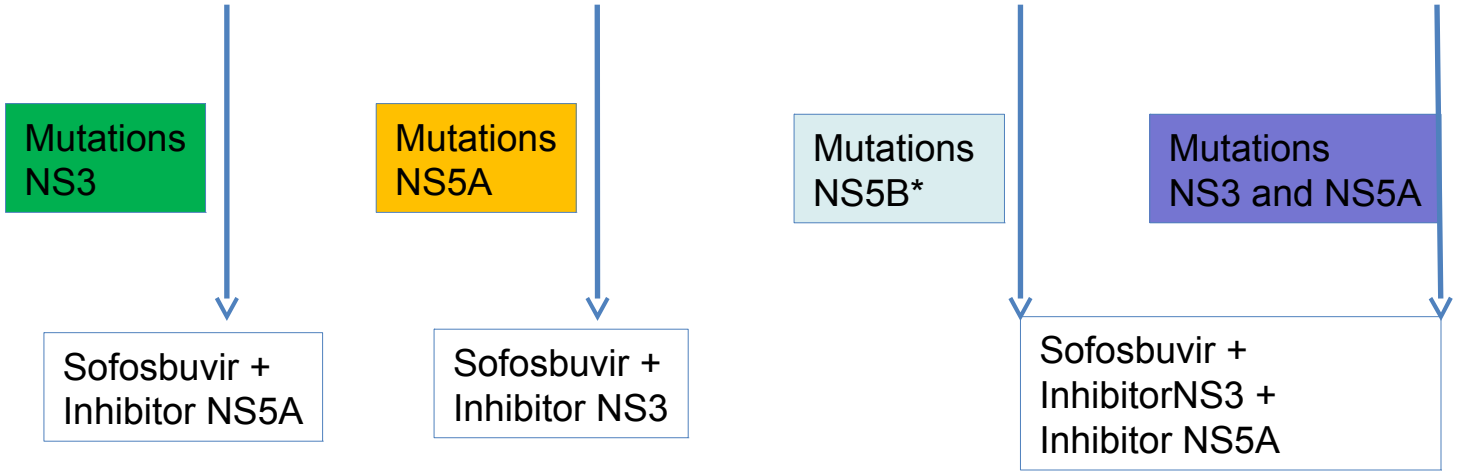
Do we Need to assess HCV resistance to DAAs: is it useful and when?



HCV resistance assessement as close as possible to the initiation of 2°Retreatment

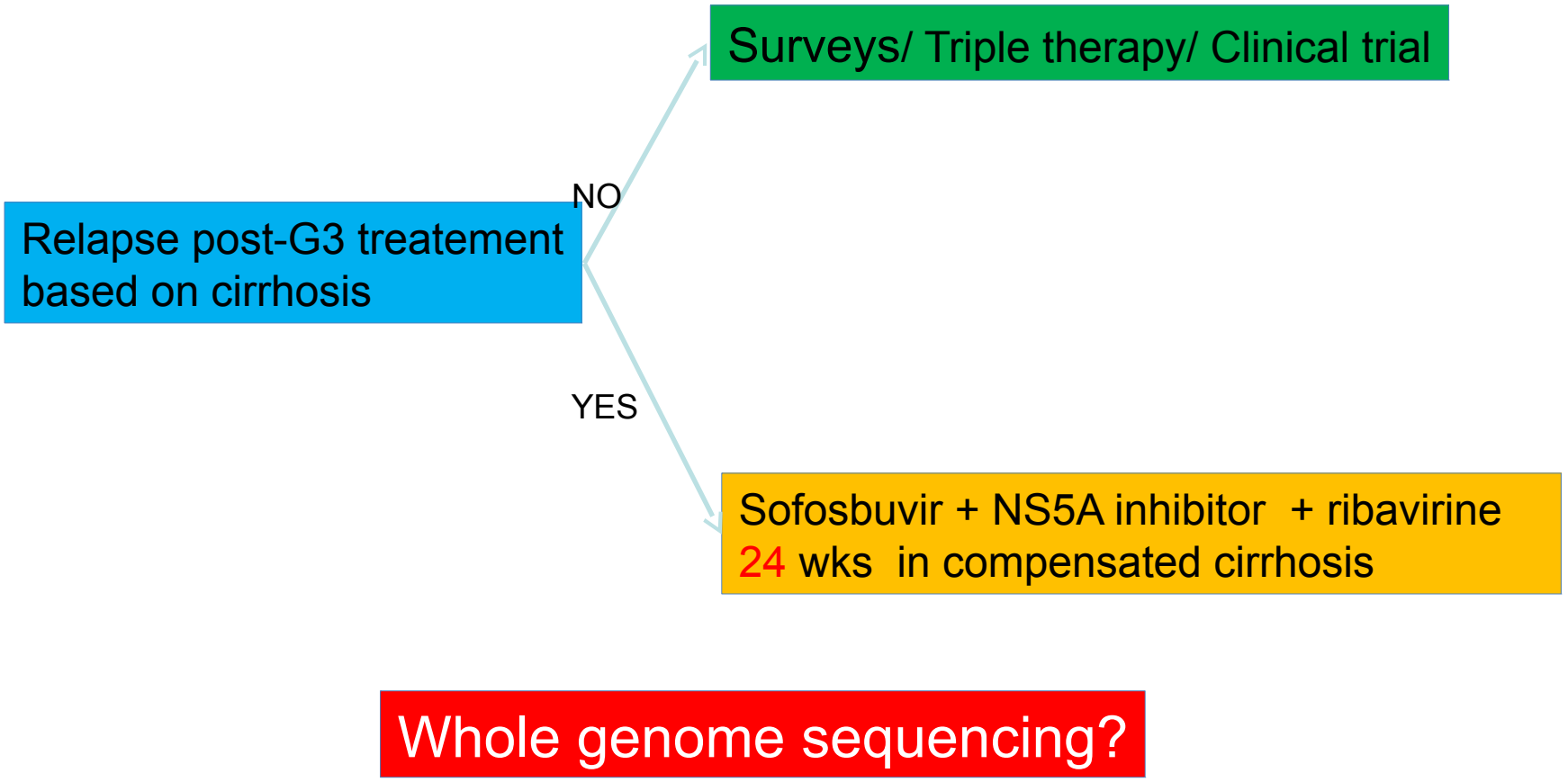
Treatment based on RAVs in Genotype non-3

Retreatment of non-3 patients
Treatment duration of 24 weeks+ RBV+ 2 or 3 DAA depends on the types of mutations



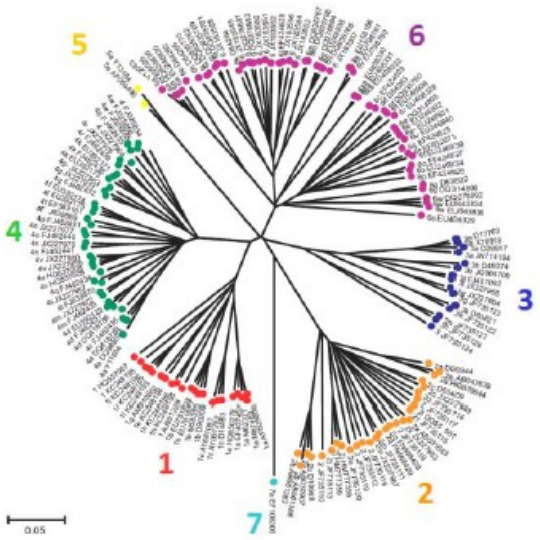
Don’t use paritaprevir/ritonavir, ombitasvir +/- dasabuvir in patients with cirrhosis

Genotype 3 with baseline RAVs

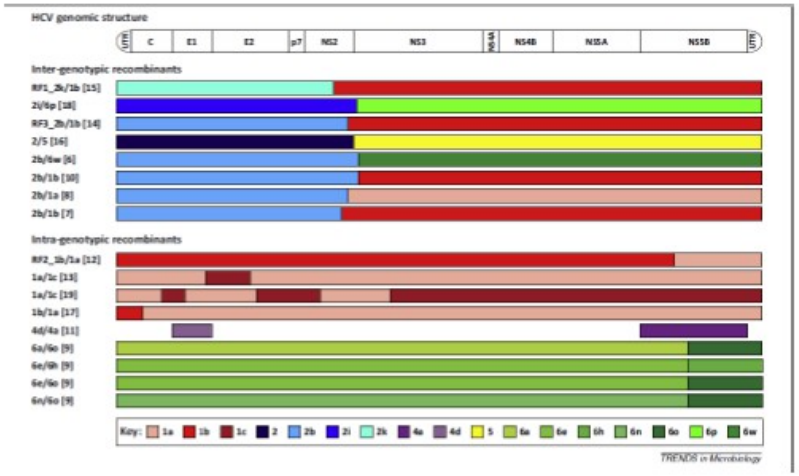


Whole genome sequencing?

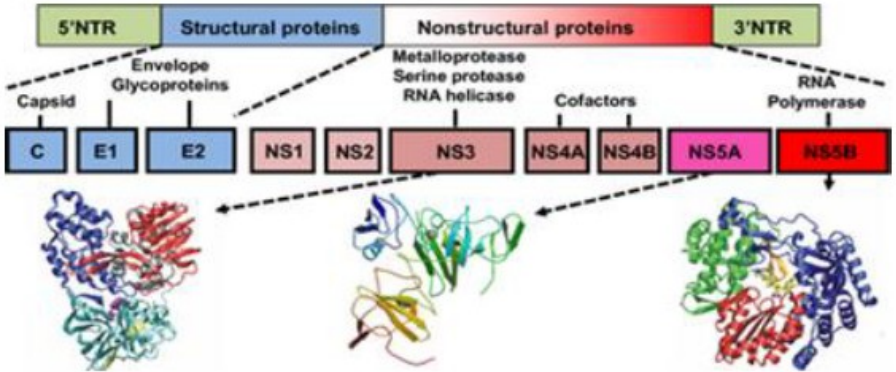
HCV whole genome analysis

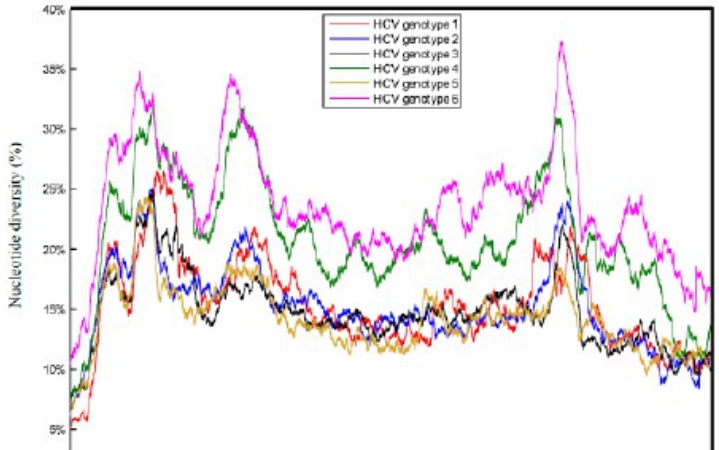


1-Typage précis
+ description
nouvelles souches



2-Détection des mutations de résistance en 1 seule analyse + mut compensatoires





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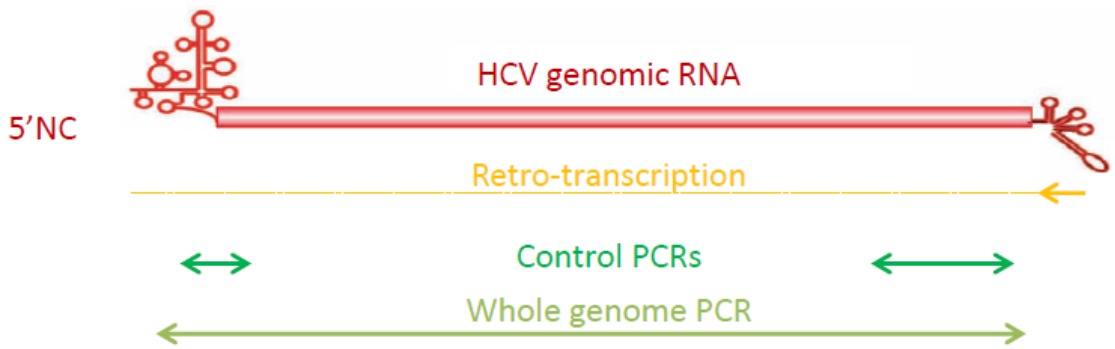
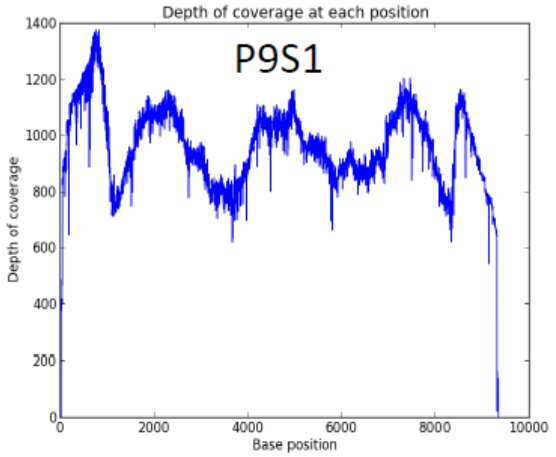
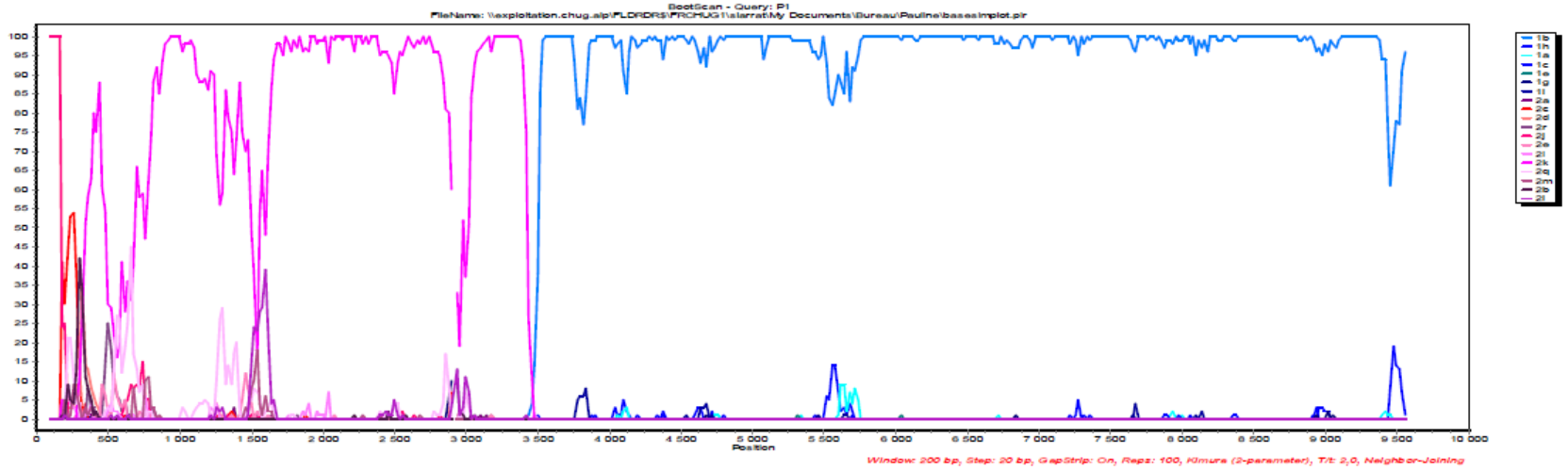
HCV whole genome analysis







↳802 unique genomic sequences covering the recombination breakpoint with at least 30 2k-upstream and 30 1b-downstream nucleotides

How to retreat the subgroup of experienced-patients with relapse or/and resistance to DAA?

- HCV resistance have to be done as close as possible to the initiation of 2°Retreatment
- Don’t use the same class regimen even for 24 weeks to retreat these patients
- The benefice of extension to 24 weeks +RBV have to be extensively studied
- Triple therapy seems very effective in retreatment regardless the presence of RAVs
- Clinical trials combination with new drugs are mandatory

Merci pour votre attention