Future therapies for HCV Genotype 4

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Disclosures

Advisory Board/Speaker Bureau member and investigator for: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and Roche

Current and Future therapies for HCV Genotype 4

Introduction

- **GT4 : medical need**
- **Virus diversity**

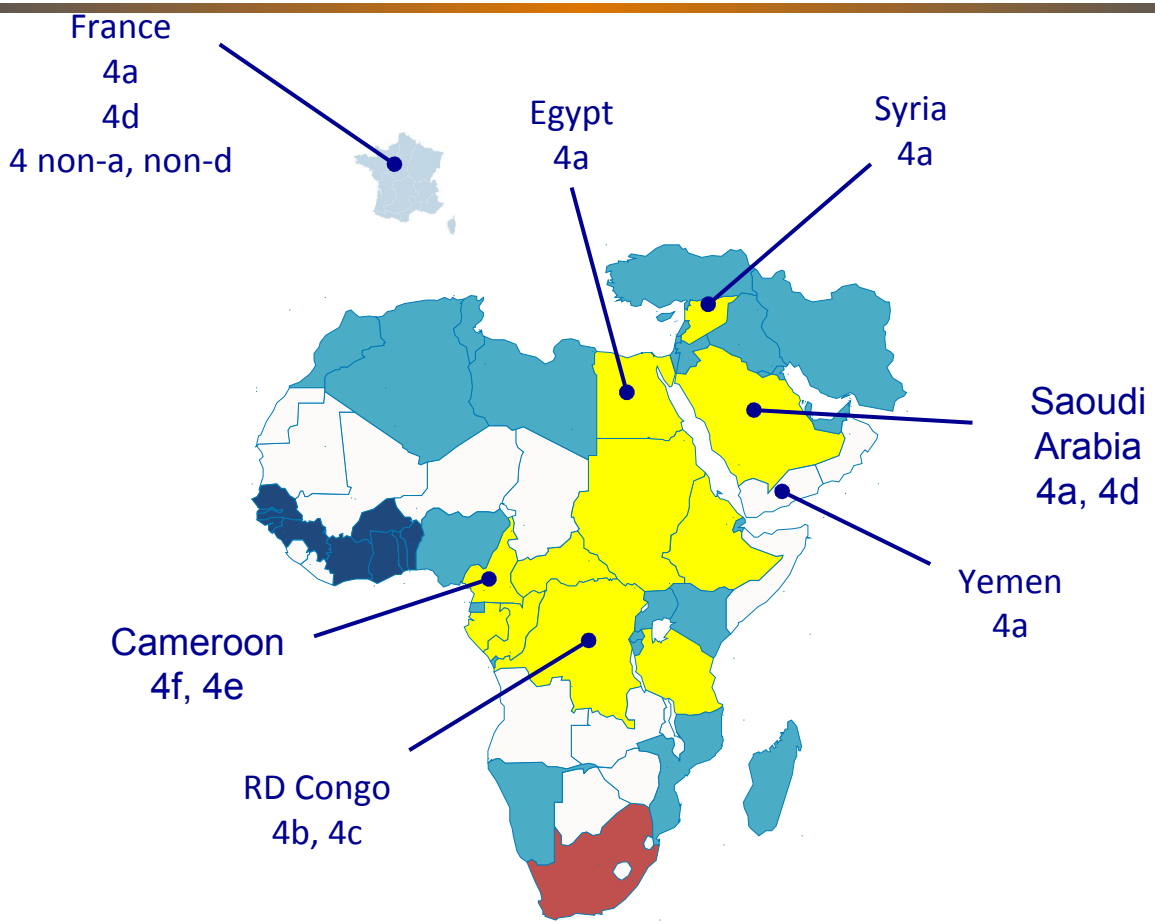
Available Treatments

- With Interferon
- Without interferon

Future Treatments

Conclusion

HCV-GT4 : sub-types



Smith DB. et al. Hepatology. 2014;59:318–27
Gower E., et al. J Hepatol 2014; 61:S45–S57;
Messina J. et al. Hepatology, 2015;61:77–87
Asselah et al. J Hepatol. 2012;56(3):527-32.
Roulot D, et al. J Viral Hepat 2007;14:460–7;

Changing epidemiology of HCV infection: increasing G4 prevalence

- HCV genotype 4 accounts for approximately 20% of all cases of chronic HCV worldwide1
- High prevalence in the Middle East1-3 and Africa4
  - Responsible for >80% of HCV infections
- Prevalence of HCV genotype 4 is increasing in Europe,

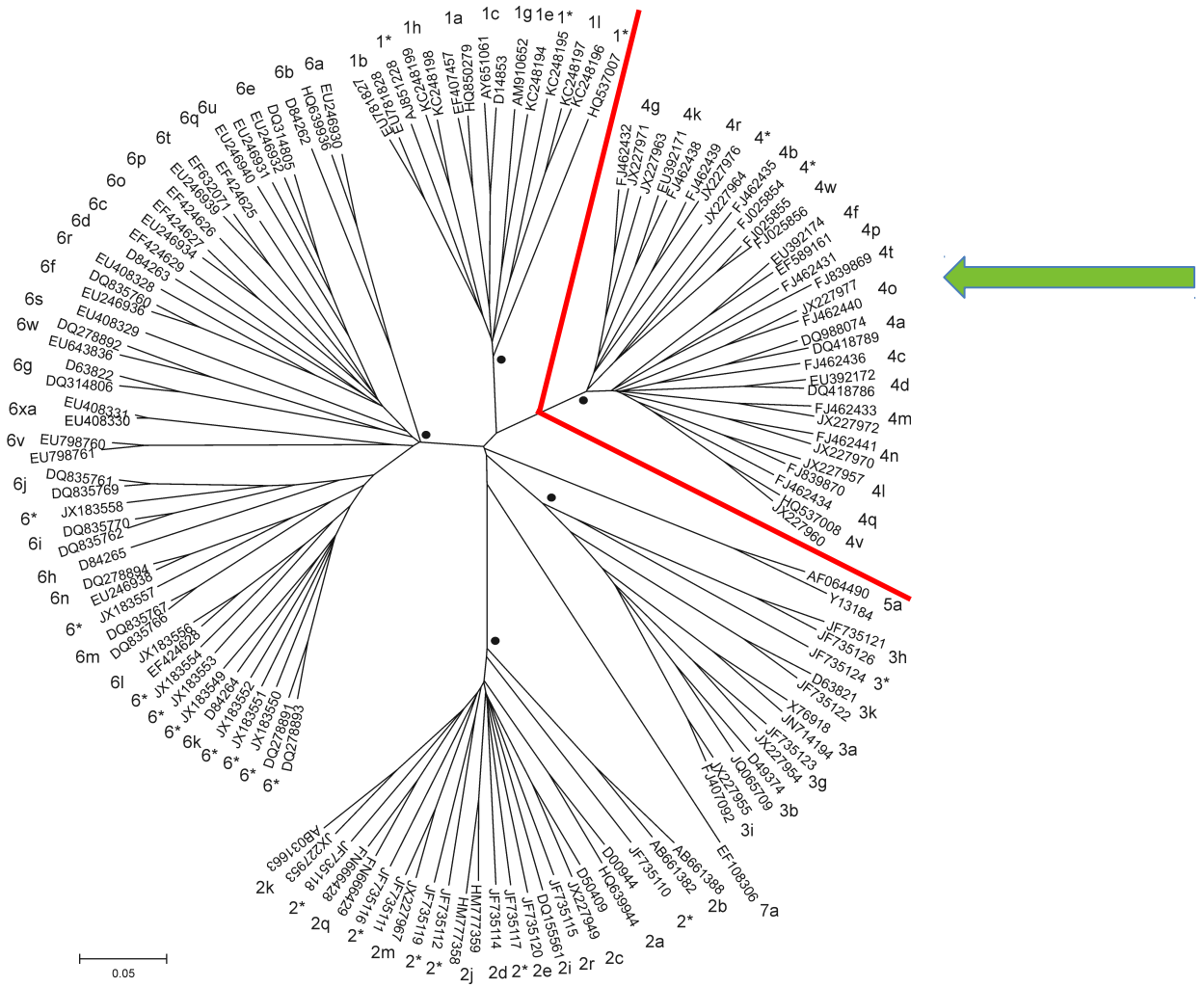
Responsible for ≈ 10 to 20 % of HCV infections in southern Spain5, Italy6, France7.

Also, increased in some regions (Turkey8)

1. Khattab MA, et al. J Hepatol 2011;54:1250-62;
2. Esmat et al. Liver Int. 2013 Feb;33 Suppl 1:41-5.
3. Alfaleh et al. Liver Int. 2013 Jul;33(6):871-83.
4. Njouom et al. PLoS One. 2012;7(8):e42002.
5. Cifuentes C, et al. Enferm Infecc Microbiol Clin 2012;30:452-7.
6. Ciccozzi et al. J Med Virol. 2012 Oct;84(10):1613-9.
7. Asselah et al. J Hepatol. 2012;56(3):527-32.
8. Sariguzel et al. Clin Lab. 2013;59(11-12):1403-8.

HCV diversity: Genotypes and Sub-types

Importance to have studies with all sub-types represented



Smith et al. Hepatology 2014; 59: 318-27.

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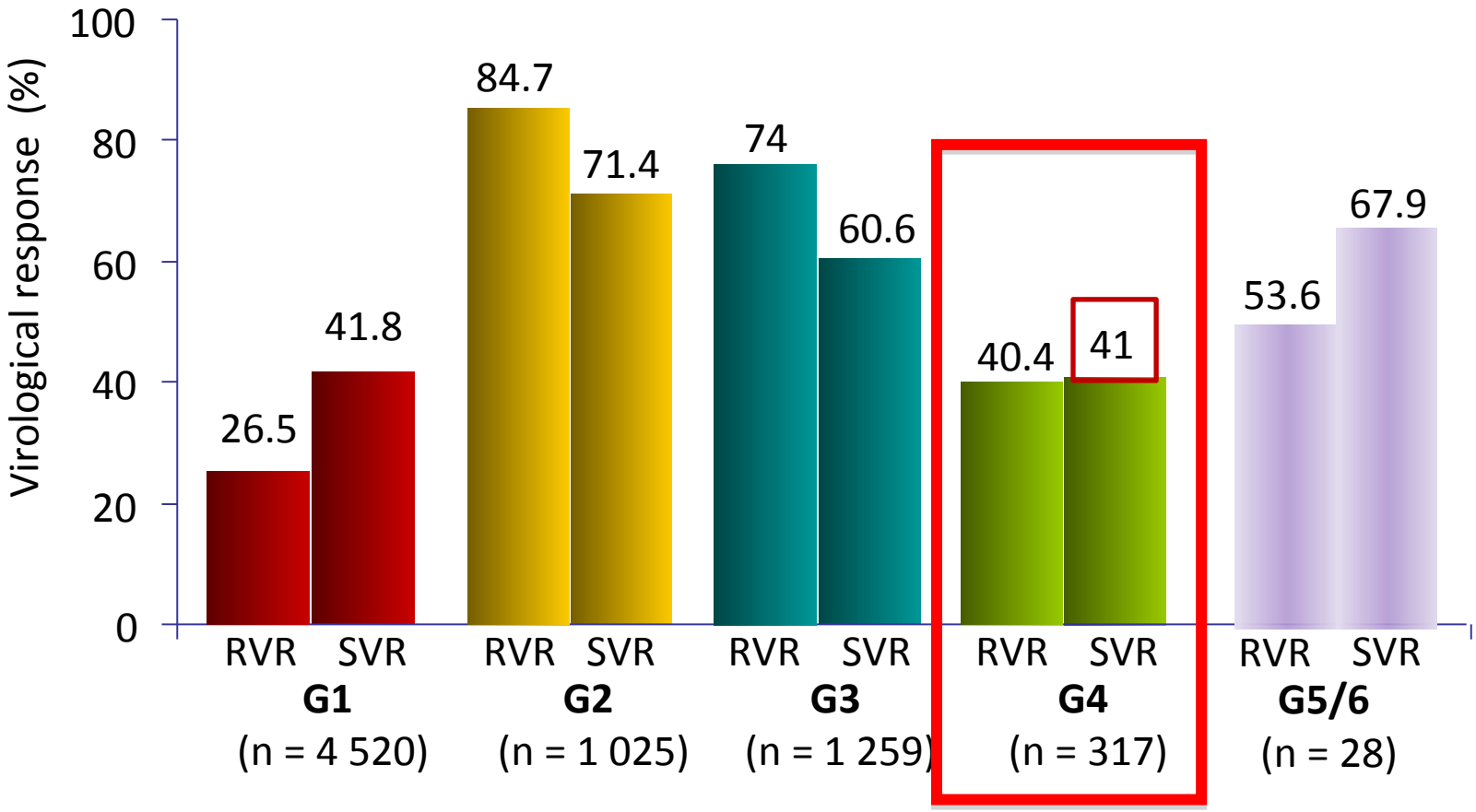
Worldwide experience of SOC among 7163 naive HCV patients: PROPHESYS cohort study

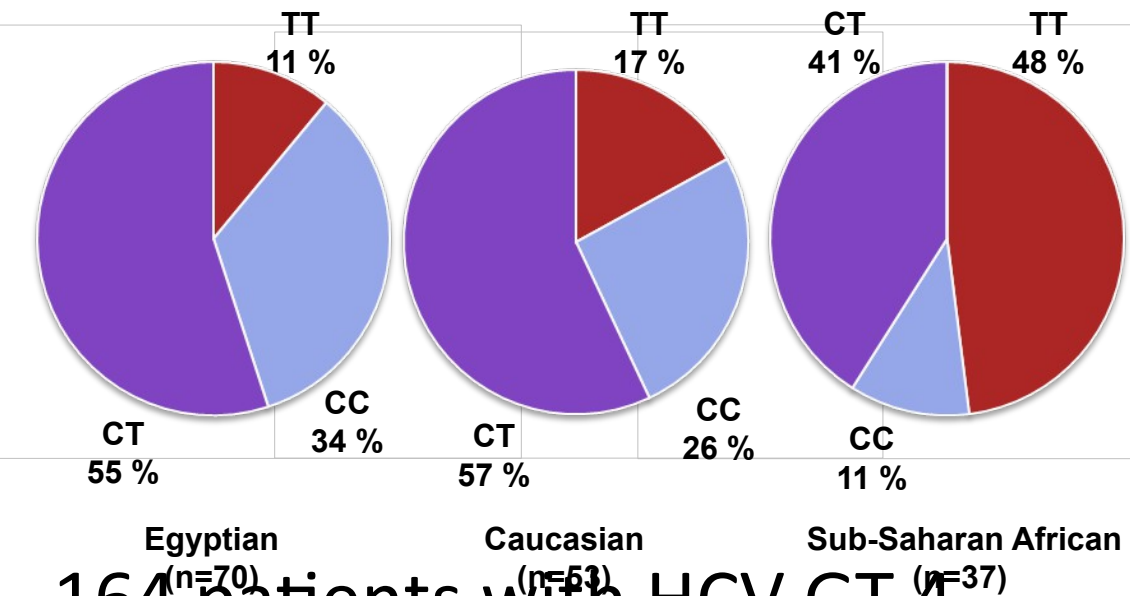
- 63.1 % patients were G1, 28.5 % had advance disease (F3, F4)
- Patients were treated with PEG-IFNα-2a (92.5 %) or α-2b (7.5%) + RBV



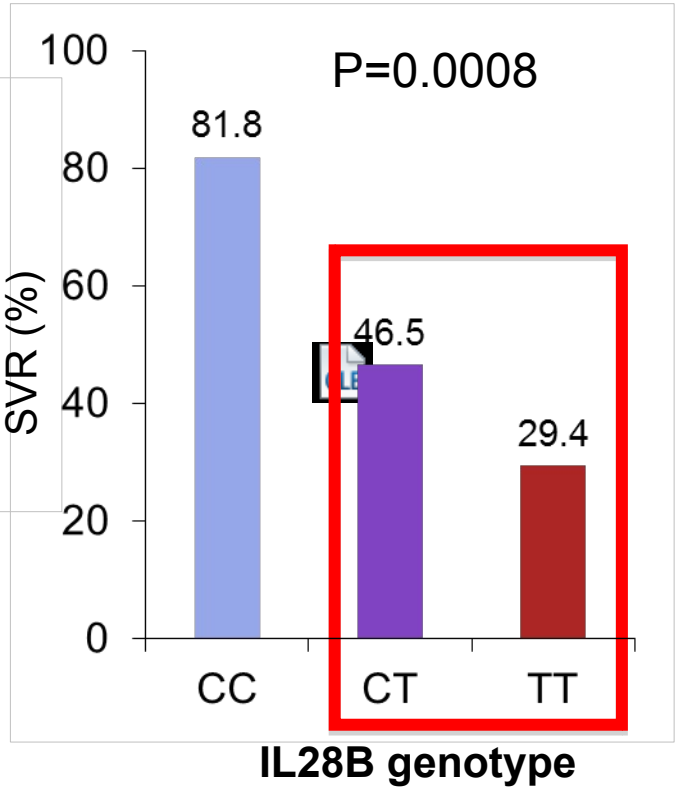
Marcellin et al . Hepatology 2012

IL28B polymorphism and SVR (GT4) with PEG-IFN + RBV treatment

IL28B polymorphism in patients with GT 4, according to ethnicity



SVR according to IL28B polymorphism



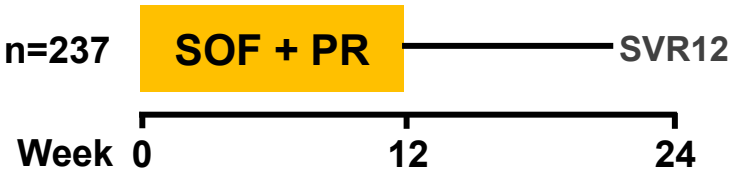
164 patients with HCV GT 4

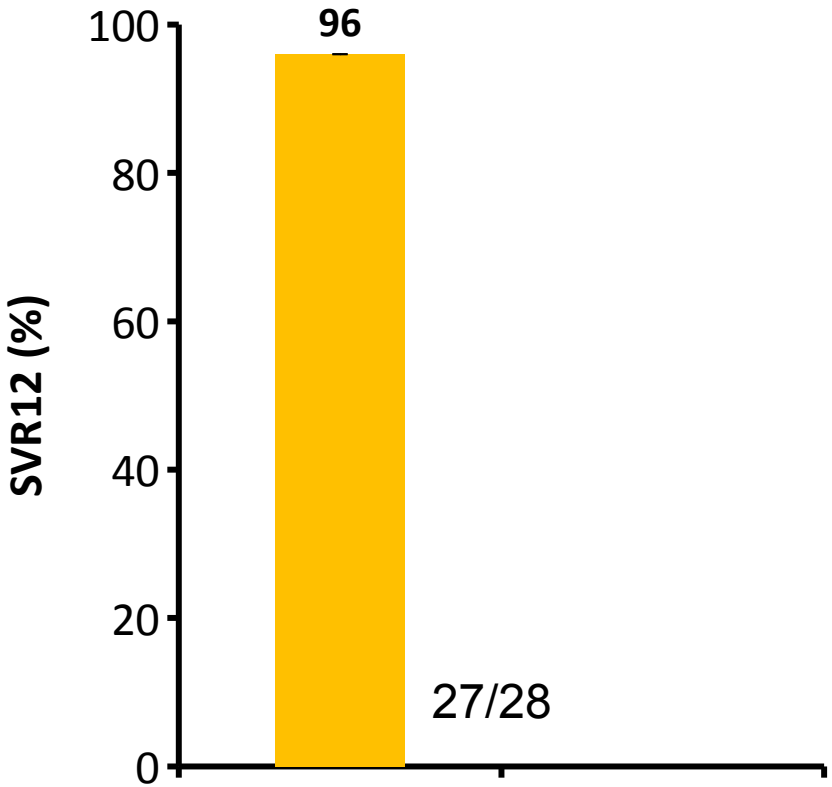
82 treated with standard of care

PEG-IFN: pegylated interferon; RBV: ribavirin;
SVR: sustained virological response

Asselah T, et al. J Hepatol 2012;56:527–32

SOF + PR: NEUTRINO – genotype 4 patients





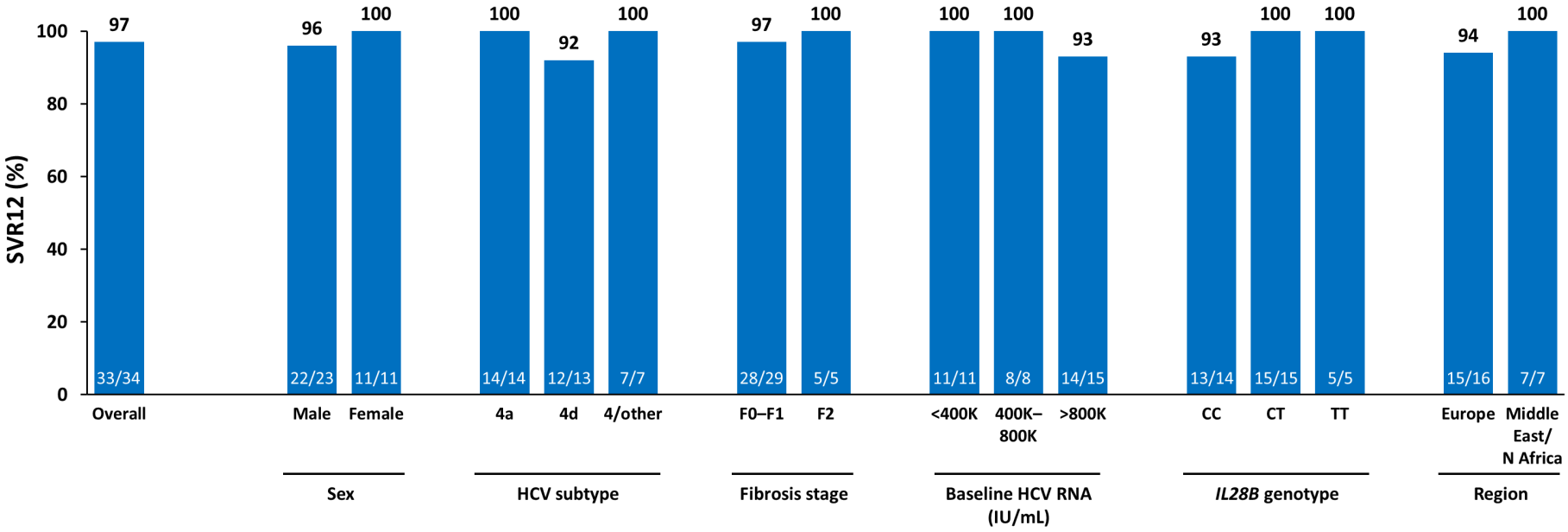
Lawitz E, et al., N Engl J Med 2013;368;20;1878-87

Simeprevir + PEG-IFN + RBV : Response guided therapy : 12 weeks

Reducing HCV treatment duration while maintaining efficacy could benefit patients and reduce clinical burden.

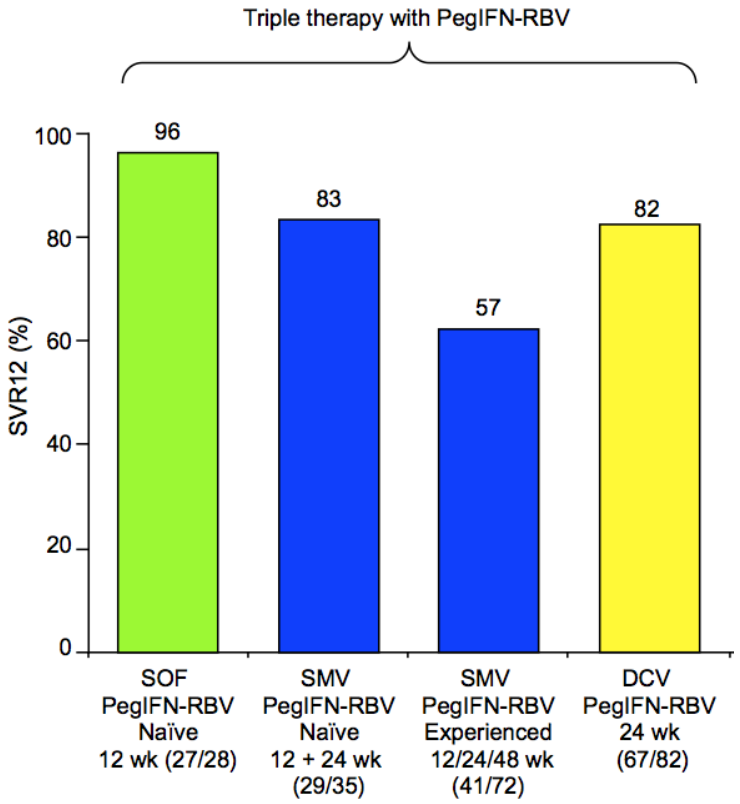
Patients with early virological response :

Week 2 undetectable were treated for 12 weeks



Asselah et al. EASL, Abstract P0792

GT 4: SVR with different DAA (with or without IFN)



ASV: asunaprevir; BCV: boceprevir; DCV: daclatasvir; LDV: ledipasvir; OBV: ombitasvir; PTV: paritaprevir; SMV: simeprevir; SOF: sofosbuvir

Asselah T. J Hepatol 2015;62:996–9

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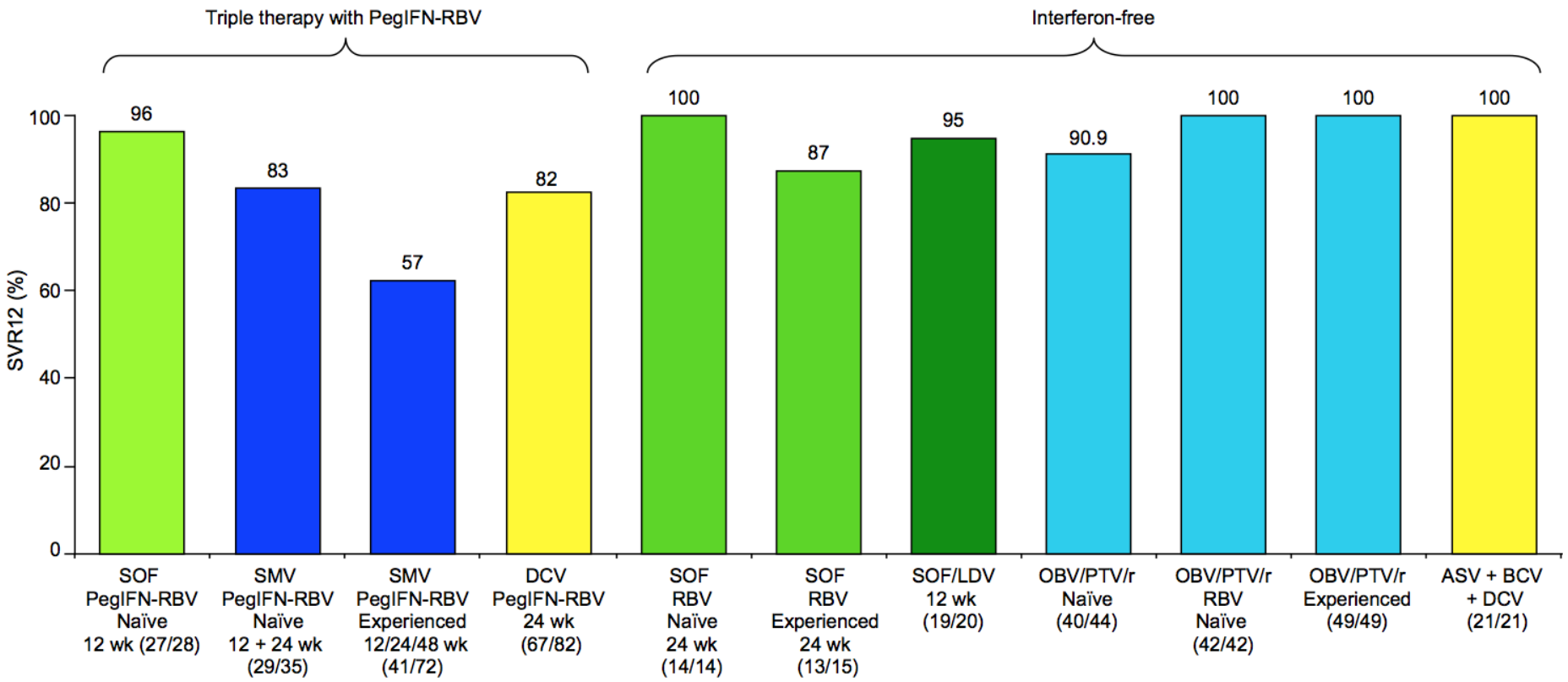

ASV: asunaprevir; BCV: boceprevir; DCV: daclatasvir; LDV: ledipasvir;
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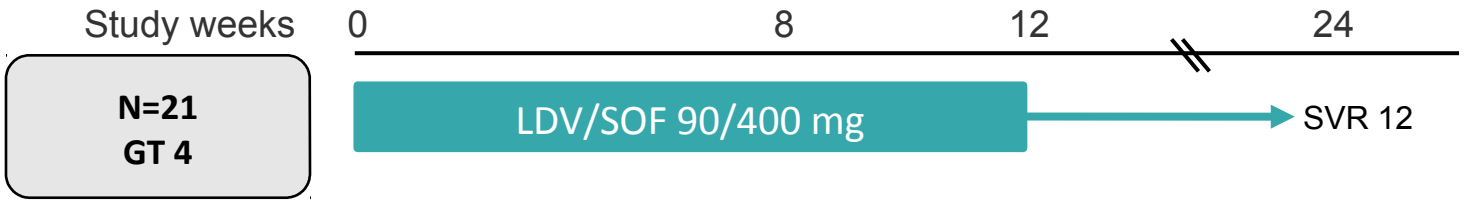
Available Treatments without IFN

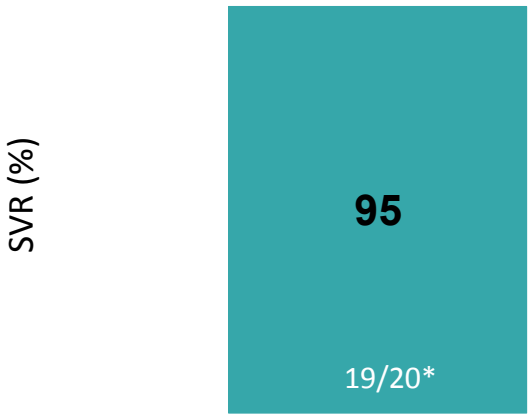
	Duration
Paritaprevir/r/ombitasvir + RBV	12 weeks
Sofosbuvir/ledipasvir	12 weeks
Simeprevir + Sofosbuvir	12 weeks
Daclatasvir + Sofosbuvir	12 weeks

1. Simeprevir EU SmPC;
2. Daclatasvir EU SmPC
3. Sofosbuvir/ledipasivr EU SmPC
4. Paritaprevir/r/ombitasvir and dasabuvir EU SmPC

LDV/SOF for GT 4 for 12 weeks (SYNERGY)

Interim results from a single centre, open-label, Phase 2a trial of LDV/SOF in GT 4





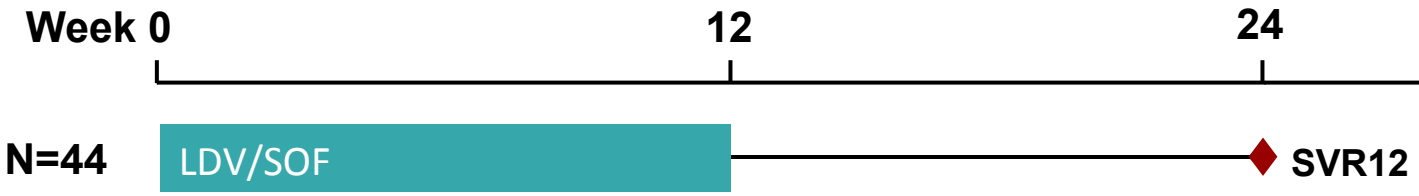
- 95% SVR with LDV/SOF for GT 4 patients – no D/C due to AE

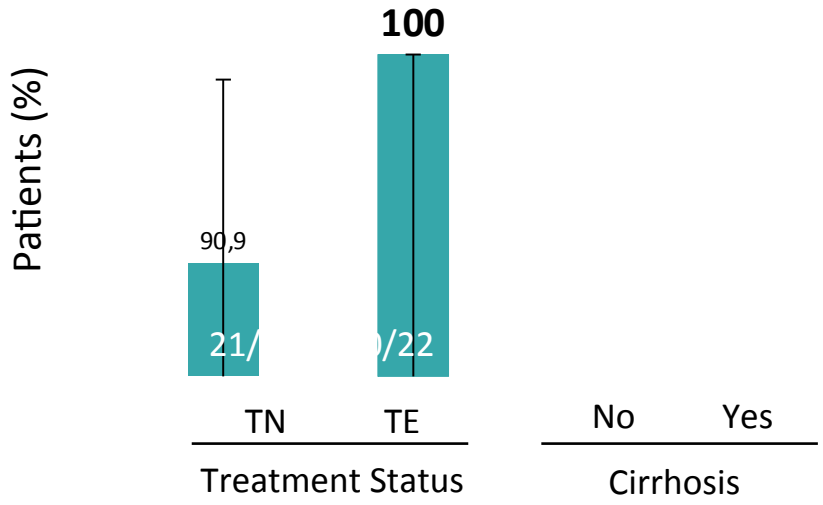
Kohli et al. Lancet Infectious Disease 2015

*One patient had not reached the SVR12 time point at time of presentation;
SD: standard deviation; STR: single tablet regimen

LDV/SOF for 12 weeks for GT 4

Multicentre study in TN/TE GT 4 patients in France





No subjects D/C study due to AE

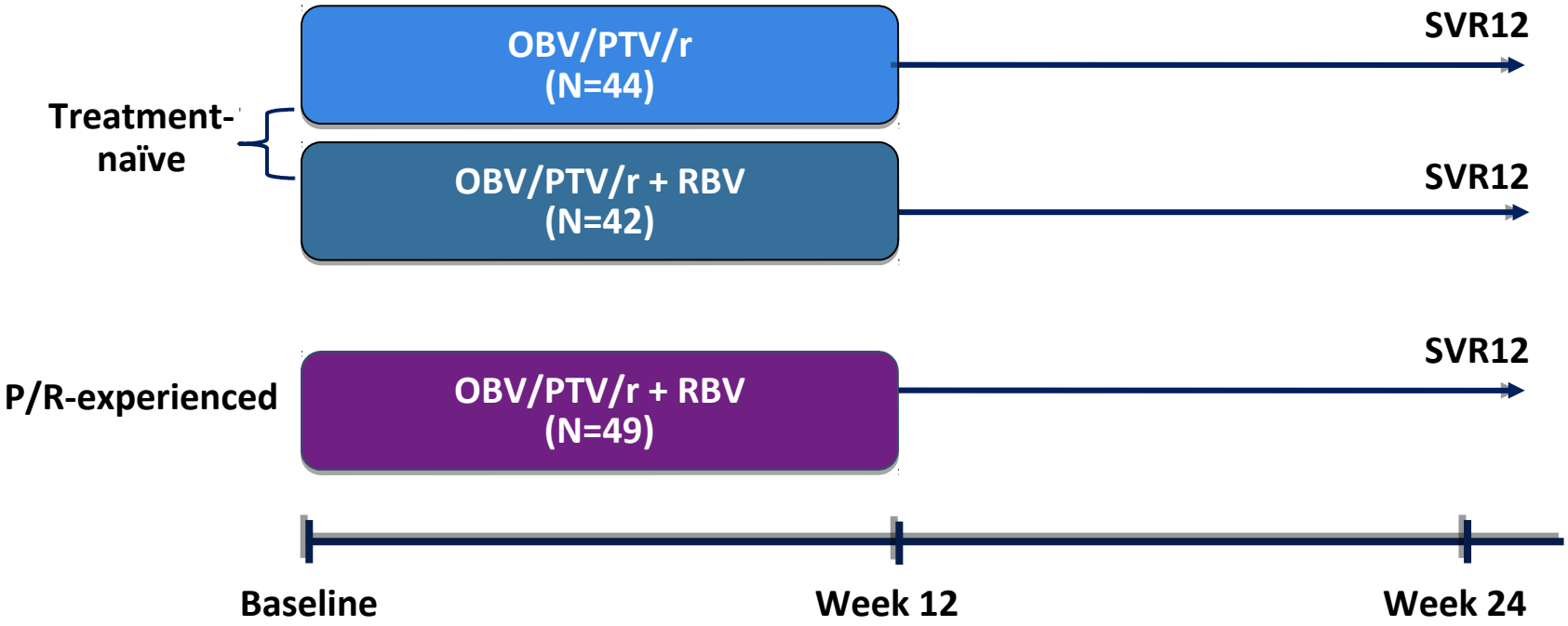
- LDV/SOF for 12 weeks was highly effective and was well tolerated

Abergel, Asselah, Metivier, et al. EASL, 2015, O056

TE: treatment-experienced; TN: treatment-naïve

PEARL-I: GT4 Treatment-Naïve and P/R Treatment-Experienced Patients

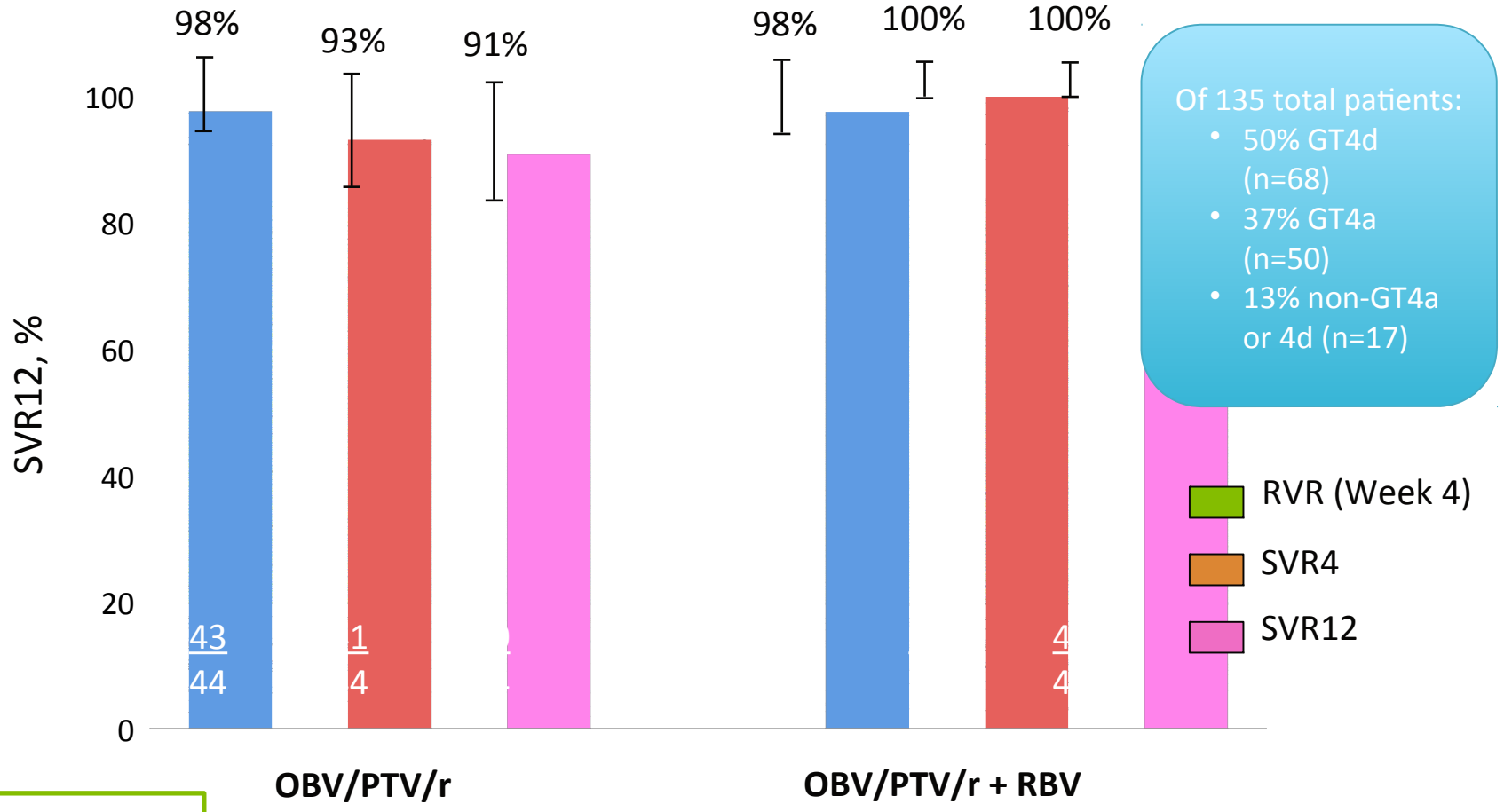
Randomized, global multicenter, open-label trial conducted in **135** adults with GT4 chronic HCV without cirrhosis who were treatment-naïve or did not achieve SVR with prior P/R treatment



NOTE: PEARL-I also includes GT1b treatment arms that will not be covered here.

.Hézode C, Asselah T, Reddy KR, et al. Lancet. 2015;385:2502-2509.

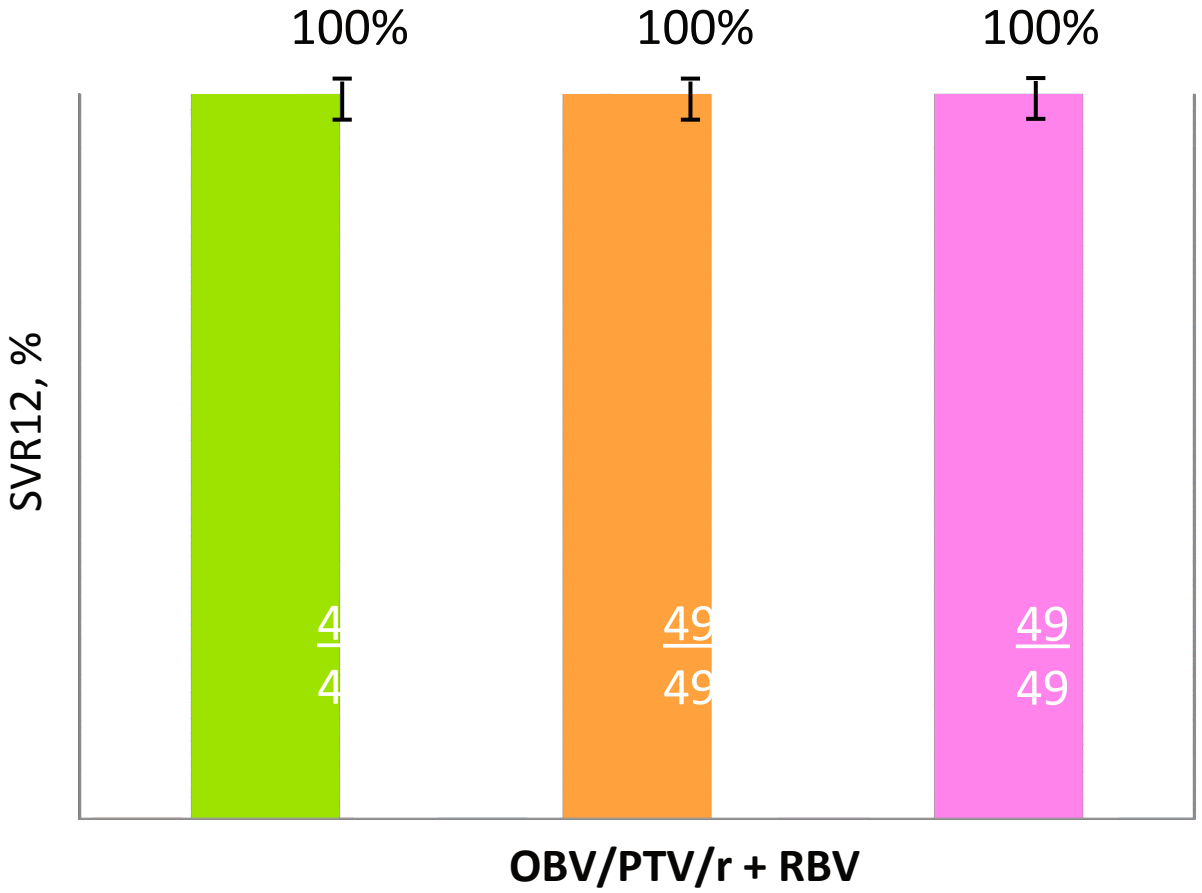
SVR12 Rate in GT4 Treatment-Naïve Patients with OBV/PTV/r + RBV



3 virologic failures (1 breakthrough, 2 relapse): all GT4d
1 patient lost to follow-up

.Hézode C, Asselah T, Reddy KR, et al. Lancet. 2015;385:2502-2509.

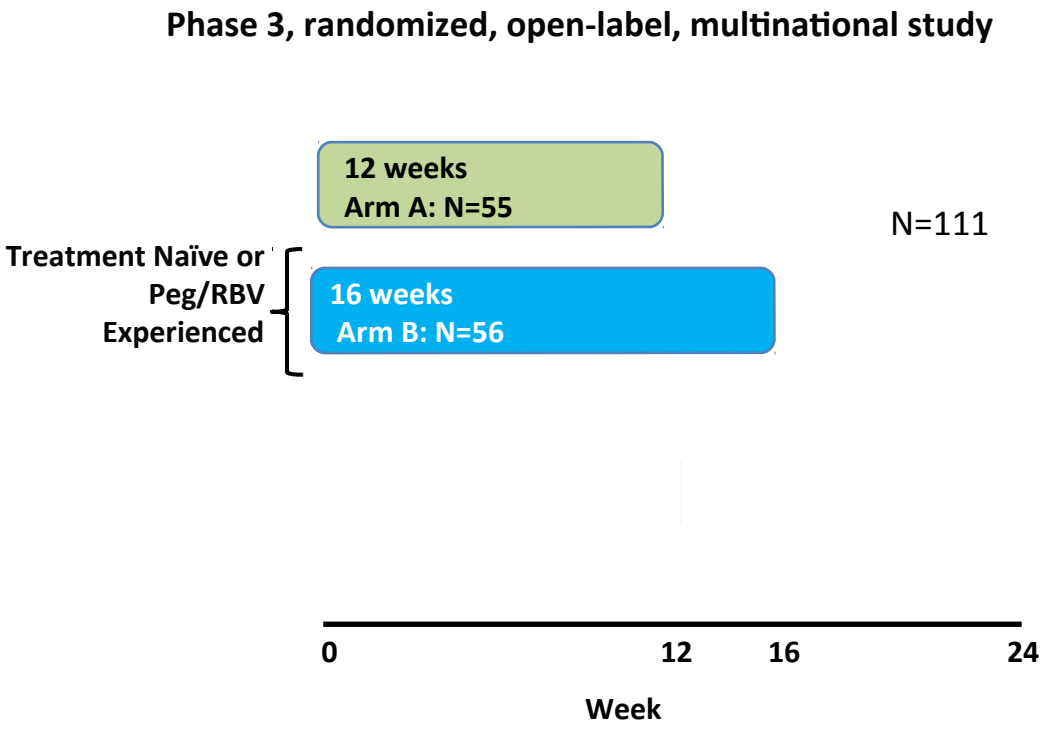
SVR12 Rate in GT4 P/R-Experienced Patients with OBV/PTV/r + RBV



47%
of P/R-experienced patients were difficult-to-treat prior null responders (n=23)

RVR (Week 4)
SVR4
SVR12

AGATE-I: GT4 Cirrhotic Patients Treated With OBV/PTV/r+RBV -

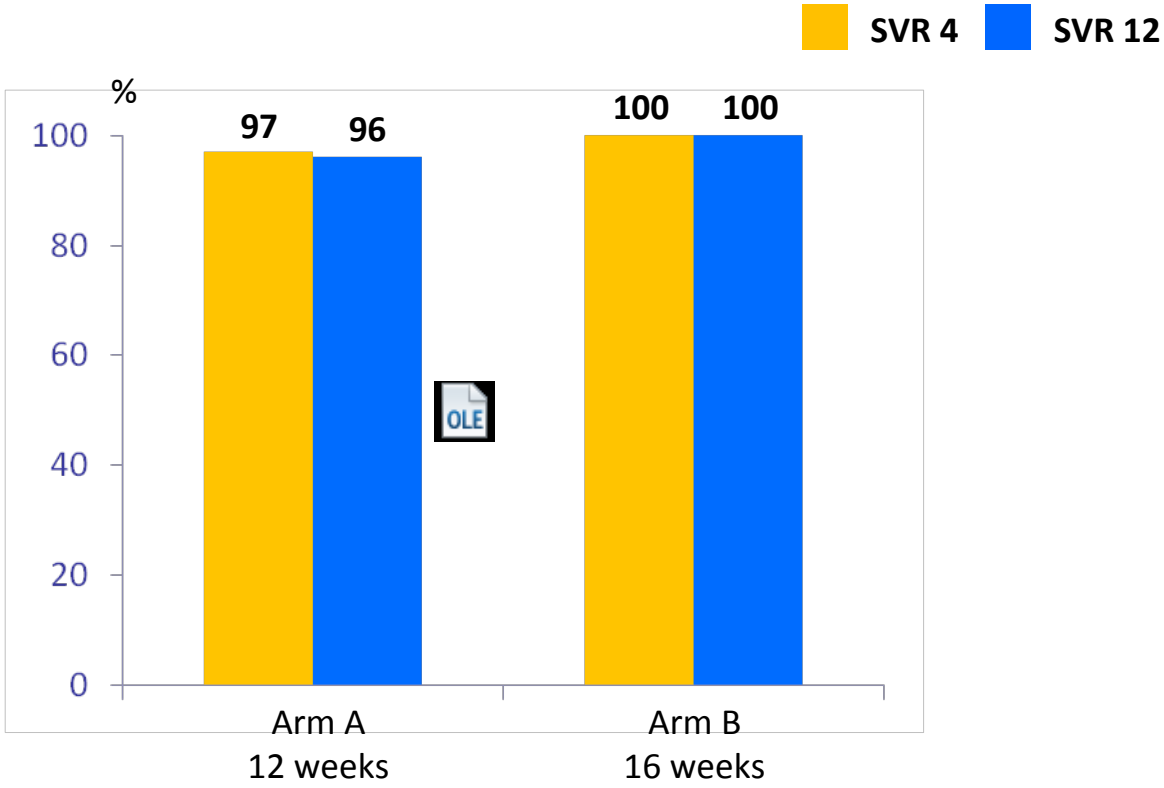


Asselah et al., AASLD 2015, Abs. 714

Ombitasvir/paritaprevir/ritonavir + ribavirine G4 with cirrhosis

- AGATE-I (international)

SVR AGATE-I

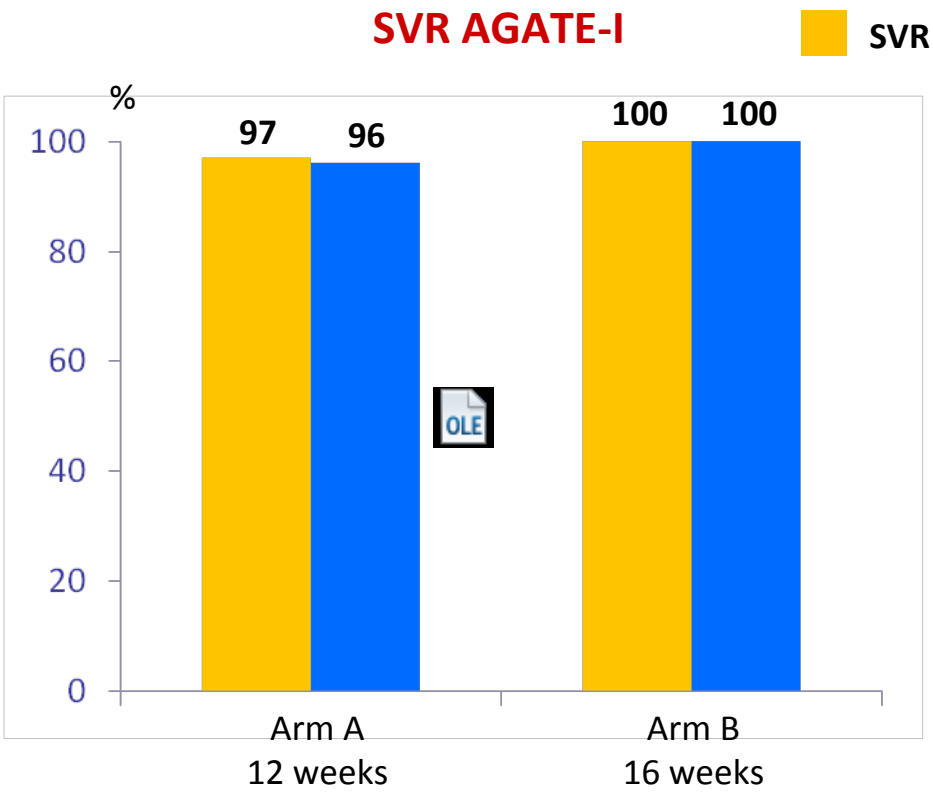


	Arm A 12 weeks	Arm B 16 weeks
Breakthrough :	1/54	0/49
Relapse :	0/52	0/49

Asselah et al., AASLD 2015, Abs. 714

Ombitasvir/paritaprevir/ritonavir + ribavirine G4 with cirrhosis

- AGATE-I (international)



	Arm A 12 weeks	Arm B 16 weeks
Breakthrough :	1/54	0/49
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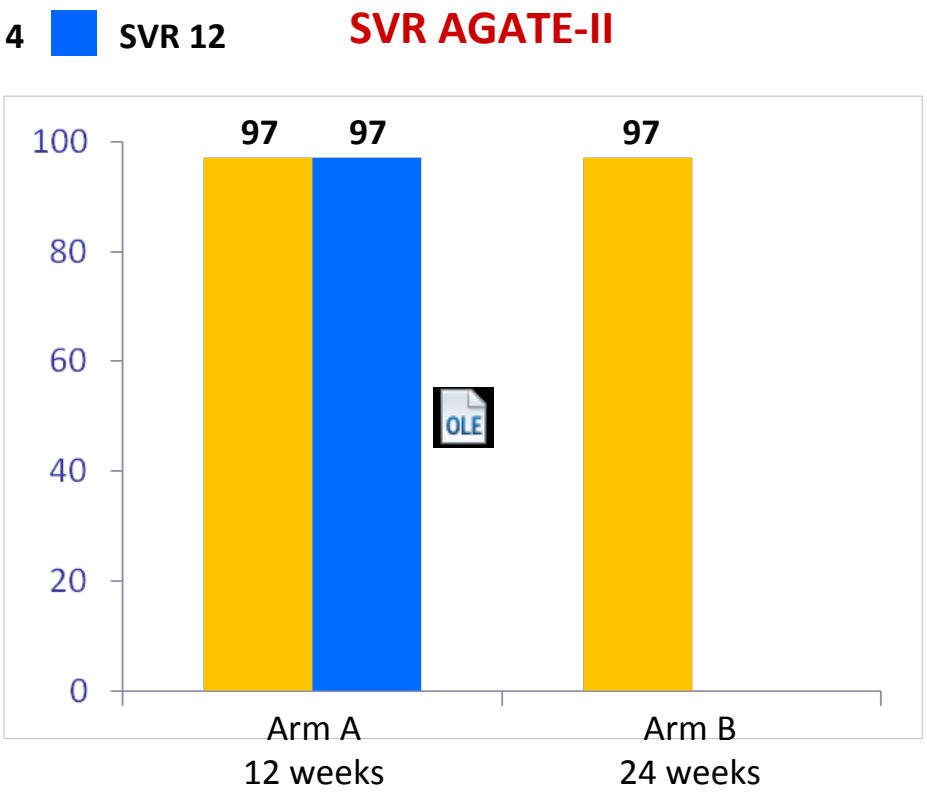
Asselah et al., AASLD 2015, Abs. 714

AGATE-II (Egypte) : phase IIIb

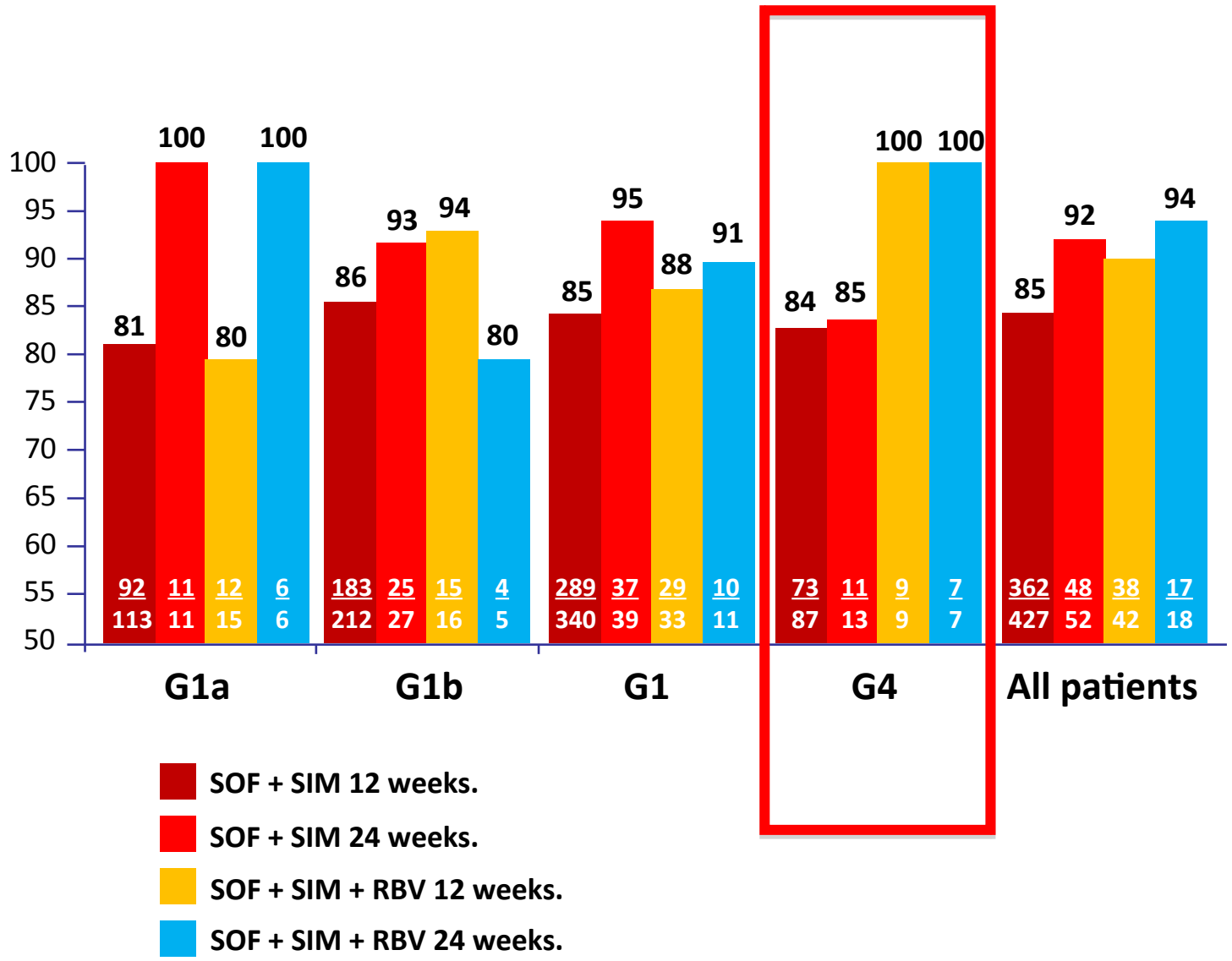


	Arm A 12 weeks	Arm B 24 weeks
Breakthroughs :	1/32	1/29
Relapse :	0/31	

Esmat et al. AASLD 2015, Abs. 708

(ANRS CO22 HEPATHER)

SOF + SMV +/- RBV or SOF + DCV +/- RBV
HCV – GT4(SVR12)



ANRS/AFEF HEPATHER CO22, France, AASLD 2015, Abs. 1073, actualisé

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Introduction

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- Virus diversity

Available Treatments

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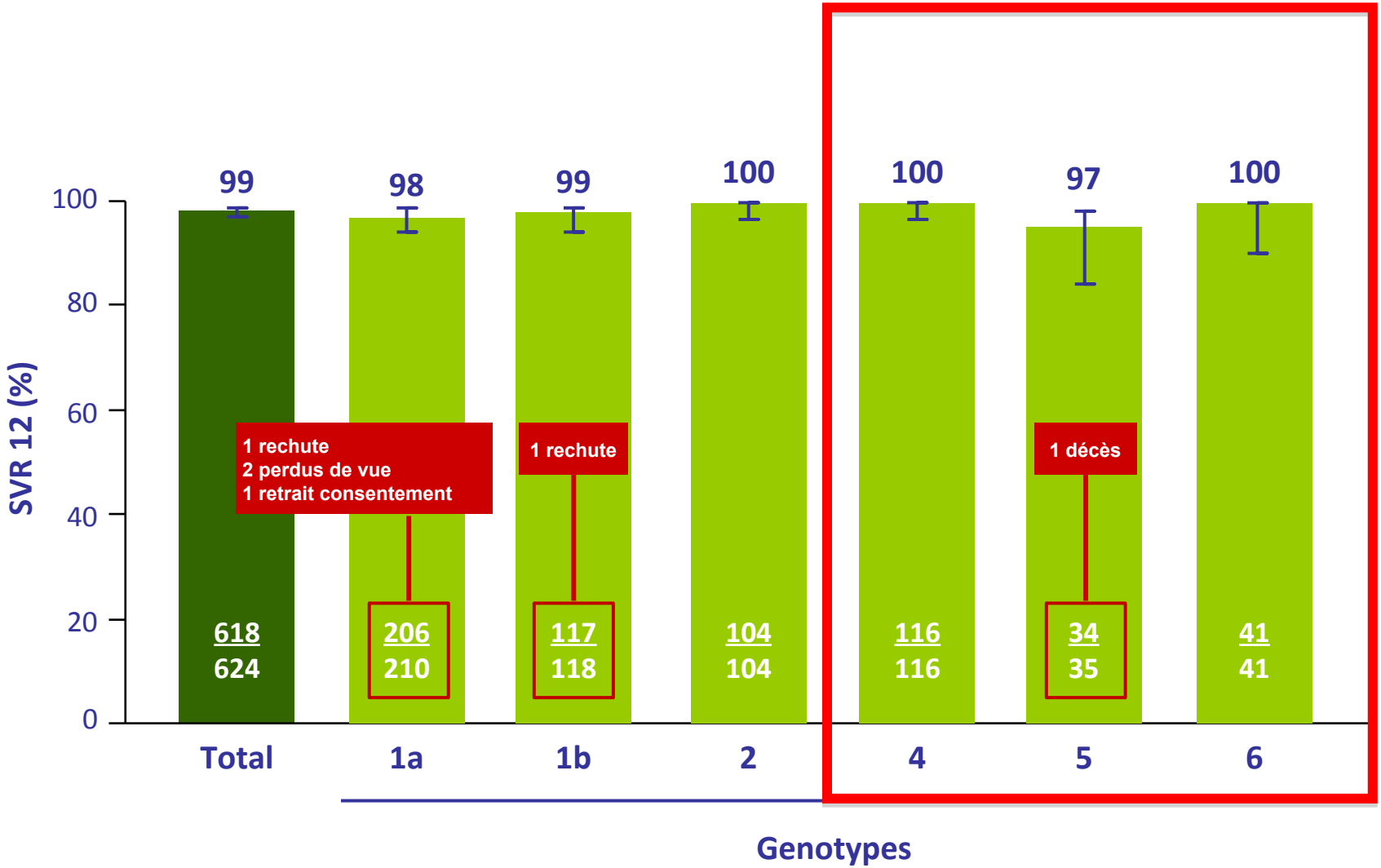
Future Treatments

Conclusion

SOF/Velpatasvir (GS-5816) (Astral 1)

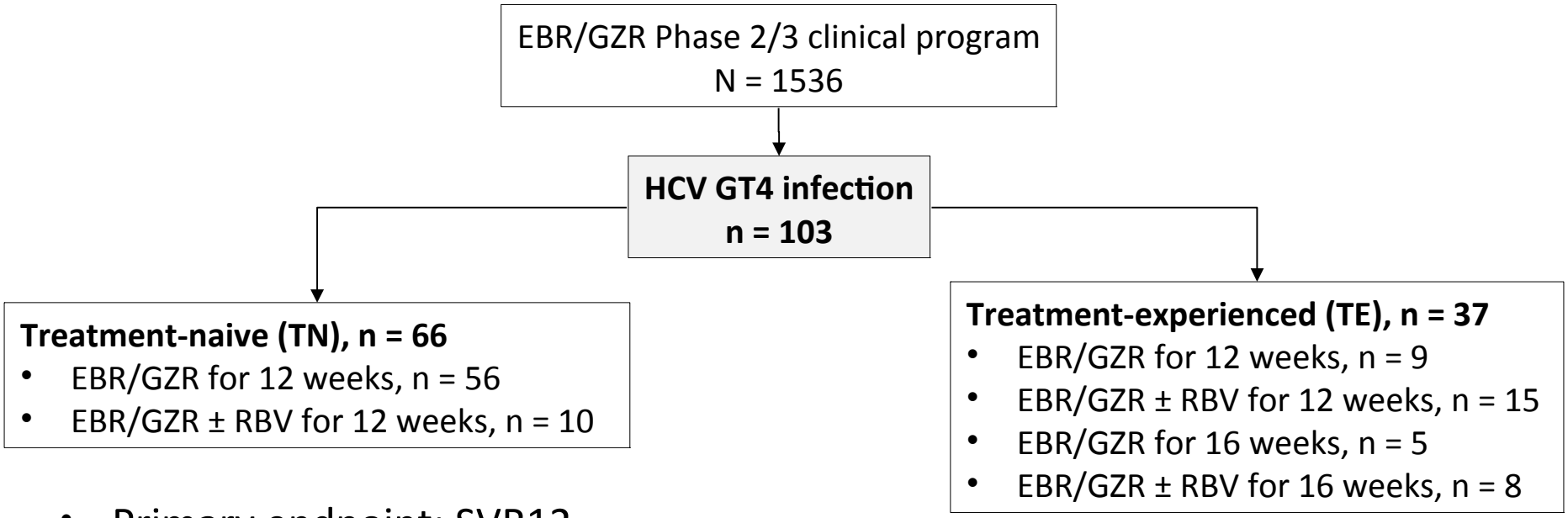


Feld et al. NEJM 2015

ELBASVIR AND GRAZOPREVIR : SVR12: Full analysis set†

Elbasvir (50 mg) Grazoprevir (100 mg)

GT4 PATIENTS

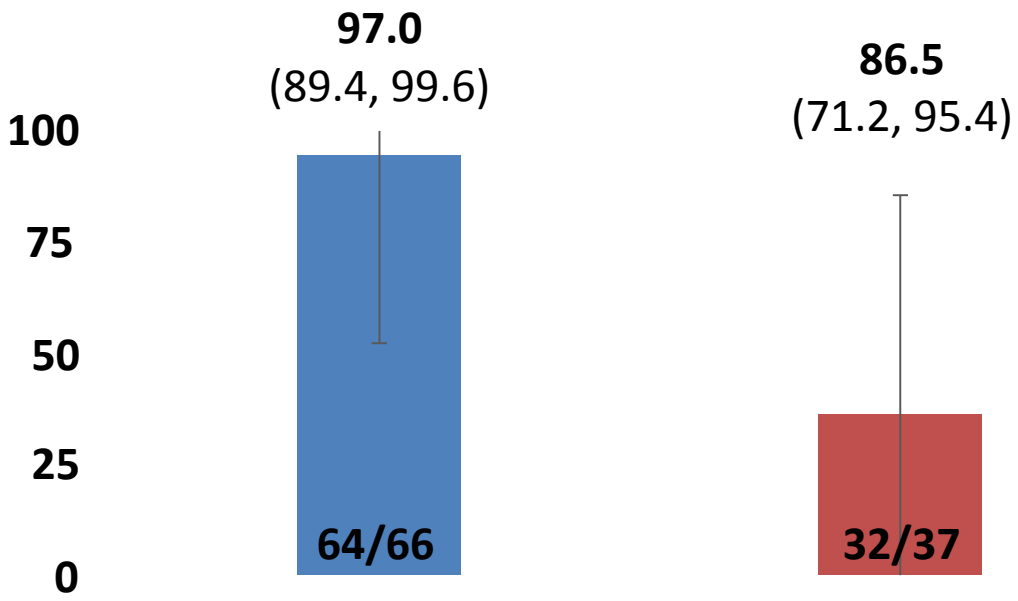


- Primary endpoint: SVR12
  - HCV RNA <assay-specified lower limit of quantitation 12 weeks after completion of study therapy
- Analysis populations
  - Full analysis set (FAS): all patients who received ≥1 dose of study medication
  - Modified full analysis set (mFAS): all patients in the FAS, excluding patients who discontinued treatment for reasons unrelated to study medication

ELBASVIR AND GRAZOPREVIR : SVR12: Full analysis set†

Elbasvir (50 mg) Grazoprevir (100 mg)

GT4 PATIENTS



Relapse	**1**	**2**
On-treatment failure	**0**	**2**
Discontinued due to AE	**0**	**1***
Lost to follow-up	**1‡**	**0**

TN: EBR/GZR ± RBV for 12 weeks.
TE: EBR/GZR ± RBV for 12 or 16 weeks.
*One cirrhotic patient discontinued treatment due to an AE of lymphoma considered unrelated to study medication
†Full analysis set includes all patients who received ≥1 dose of study drug.
‡Achieved SVR4 then lost to follow-up

Asselah et al. AASLD 2015,

RAVS: GT4 virologic failures

Elbasvir (50 mg) Grazoprevir (100 mg)

GT4 PATIENTS

Subject	Baseline HCV RNA (IU/mL)	Cirrhosis	Treatment	VF category	NS3 RAVS		NS5 RAVs	
					Baseline	VF	Baseline	VF
TN GT4d	4.47 × 106	No	EBR/GZR × 12w	Relapse	WT	WT	WT	L28S
Prior OTF GT4d	5.12 × 106	Yes	EBR/GZR + RBV x 12w	Relapse	WT	WT	P58T	M31V, P58T, Y93H
Prior OTF GT4d	2.64 × 106	Yes	EBR/GZR × 12w	Relapse	WT	WT	WT	L28S, M31I
Prior OTF GT4a	1.95 × 106	Yes	EBR/GZR × 16w	OTF	WT	A156M/T/V, D168A/G, V170I	L28M, P58Y	L28M, P58D
Prior OTF GT4a	6.41 × 106	No	EBR/GZR × 16w	OTF	WT	A156M	L28M, Y93H	L28T, Y93H

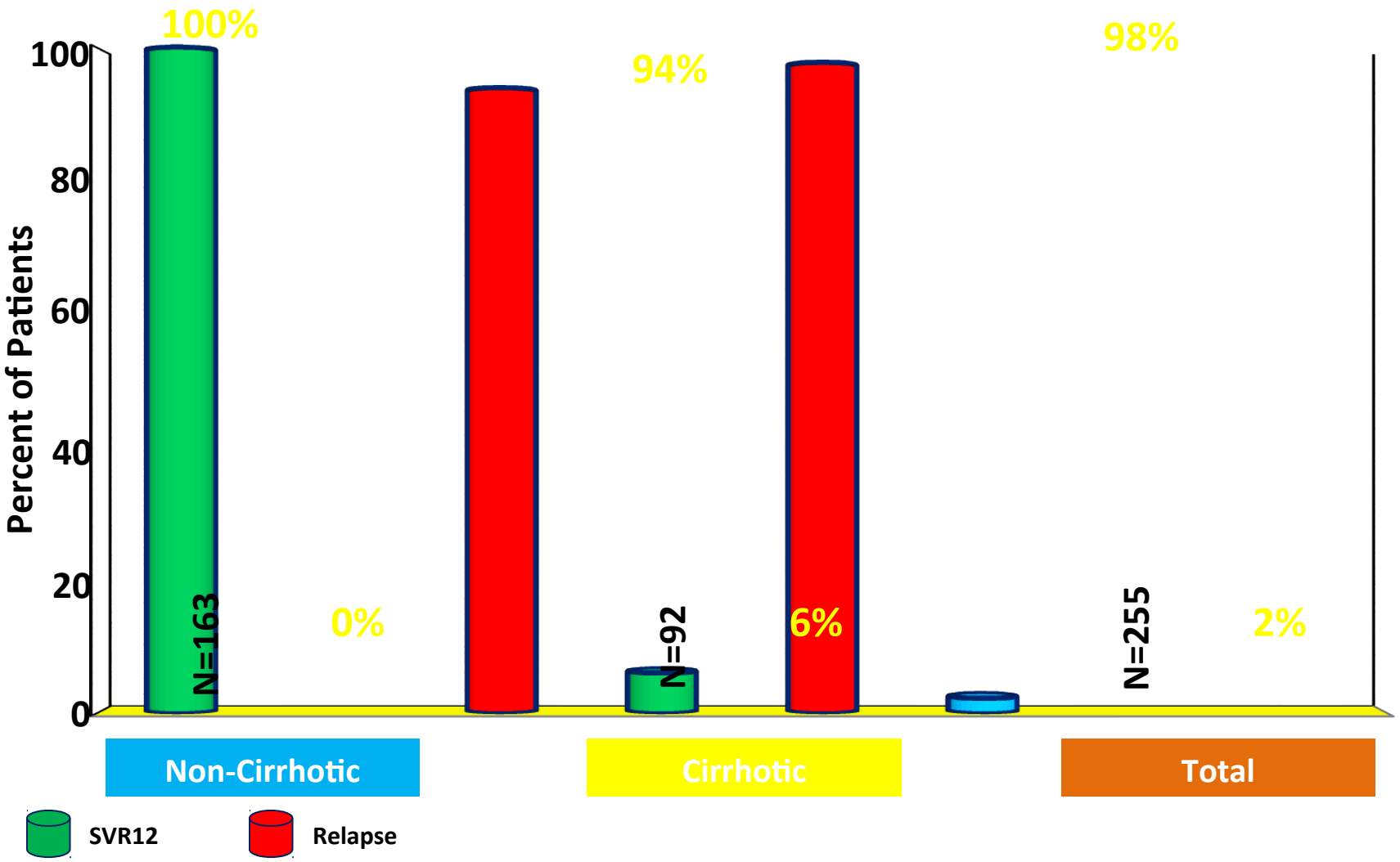
In the overall GT4 population:

- Mean baseline viral load was 2.08 × 106 IU/mL and 2.95 × 106 IU/mL in TN and TE patients, respectively.
- 9% of TN patients and 46% of TE patients had cirrhosis
- 39% of TN patients and 44% of TE patients had baseline NS5A RAVs

RAVs present at baseline and at time of virologic failure are shown in red

OTF = on-treatment failure; TN = treatment-naïve; TE = treatment experienced; VF = virologic failure; WT = wild-type.

Ravidasvir (PPI-668) and Sofosbuvir
Summary of Patient Outcomes (Per Protocol)



- Includes all treatment failures
- Excludes five early discontinuations not related to efficacy or safety

Gesmat et al. AASLD 2015,

Conclusion

- GT 4 : important medical need
- Changing epidemiology: G4 is increasing worldwide
- High proportion of New infection (acute HCV) with HCV G4.
- HCV G1 patient's population decreased : more patients treated and cured.
- Several IFN-free regimens have been shown to have high efficacy (> 90%) and good tolerability in GT 4
- GT4, 5, 6: Few clinical trials with limited number of patients.
- Few data in sub-populations (cirrhosis, CKD, etc…)
- Pan-genotypic treatment are coming soon
- Real life data are important.
- Improving screening and access to treatment