A One-day Scientific Conference: Updates on Hepatitis C Treatments along with Consensus on Management of Hepatitis C in Iran

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Treatment of HCV genotype 1 & 4 with DAAs

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Speaking and teaching:	Tibotec, Roche, Novartis, Bayer, BMS, Gilead Sciences, Vertex, Merck, Janssen, AbbVie

The EASL 2015 HCV Treatment Recommendations
Treatment Options

IFN-free regimens	GT
Sofosbuvir + RBV	2, 3
Sofosbuvir/Ledipasvir (± RBV)	1, 4, 5, 6
Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (± RBV)	1
Sofosbuvir + Simeprevir (± RBV)	1, 4
Sofosbuvir + Daclatasvir (± RBV)	All
Ombitasvir/Paritaprevir/Ritonavir (± RBV)	**4**

Pending

Sofosbuvir + Velpatasvir (Epclusa)	All
Grazoprevir + Elbasvir (Zepatier)	1, 4

EASL HCV Treatment Recommendations, J Hepatol 2015

In Vitro Antiviral Activity of NS5A Inhibitors Stable HCV Replicon EC50 (pM)

	GT-1a	GT-1b	GT-2a	GT-2b	GT-3a	GT-4a	GT-5a	GT-6a
ABT-530	2	4	2	2	2	2	1	3
Ombitasvir	14	5	12	4	19	2	3	366
Daclatasvir	22	3	13,000	NA	530	13	5	74
Ledipasvir	31	4	21,000	16,000	168,000	390	150	1100
Velpatasvir	12	15	9	8	12	9	75	6
Elbasvir	4	3	3	3000	20	3	1	3
MK-8408	1	2	1	4	2	2	1	4
ACH-3102	26	5	21	~150	NA	NA	NA	NA

Poordad F et al. AASLD 2015;Abstract 41

New Oral Treatment of HCV-1&4

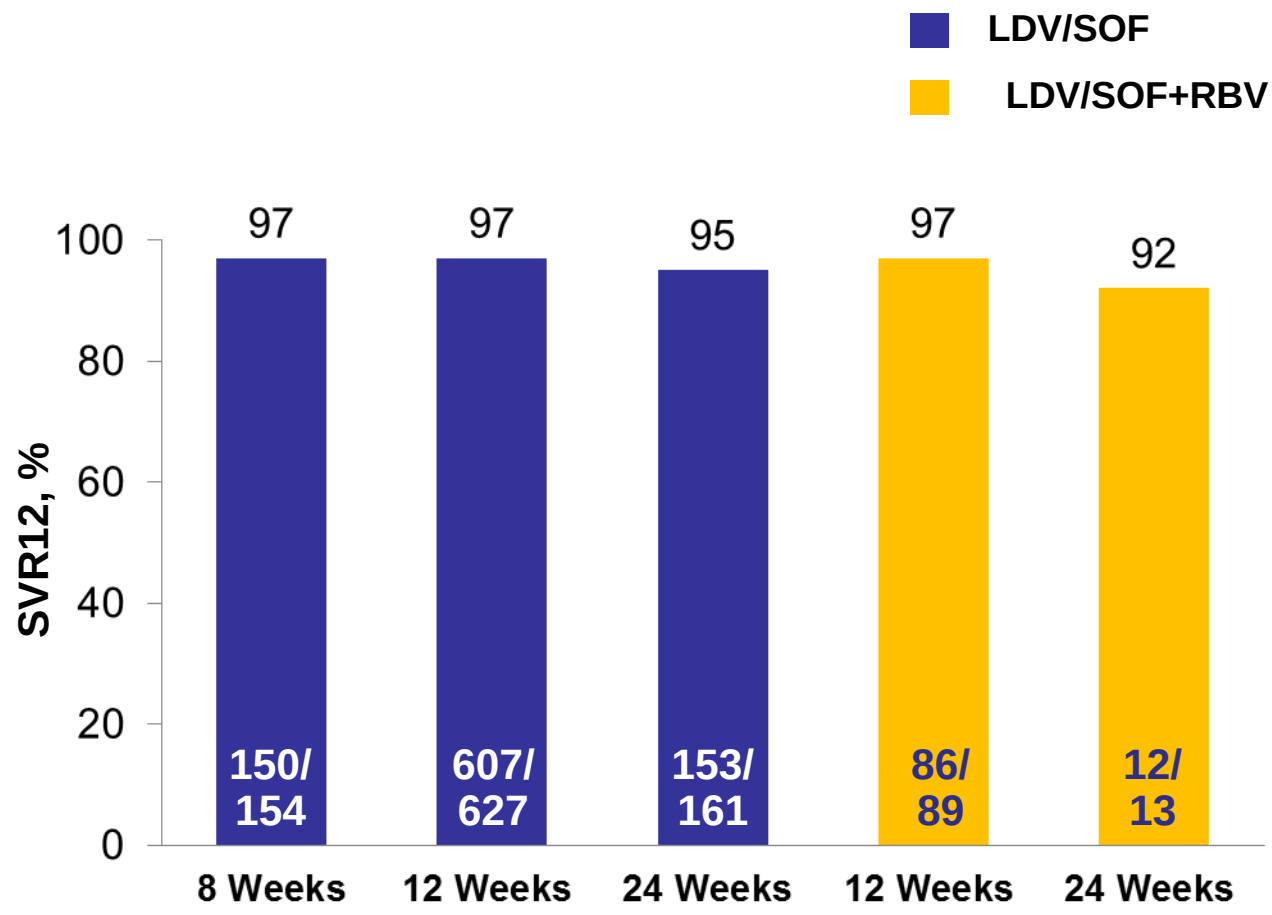
SAFETY AND EFFICACY OF DAAs VALIDATED

BY REAL LIFE STUDIES

HCV-TARGET: SVR with LDV/SOF±RBV in HCV-1 for 8, 12, and 24 Weeks

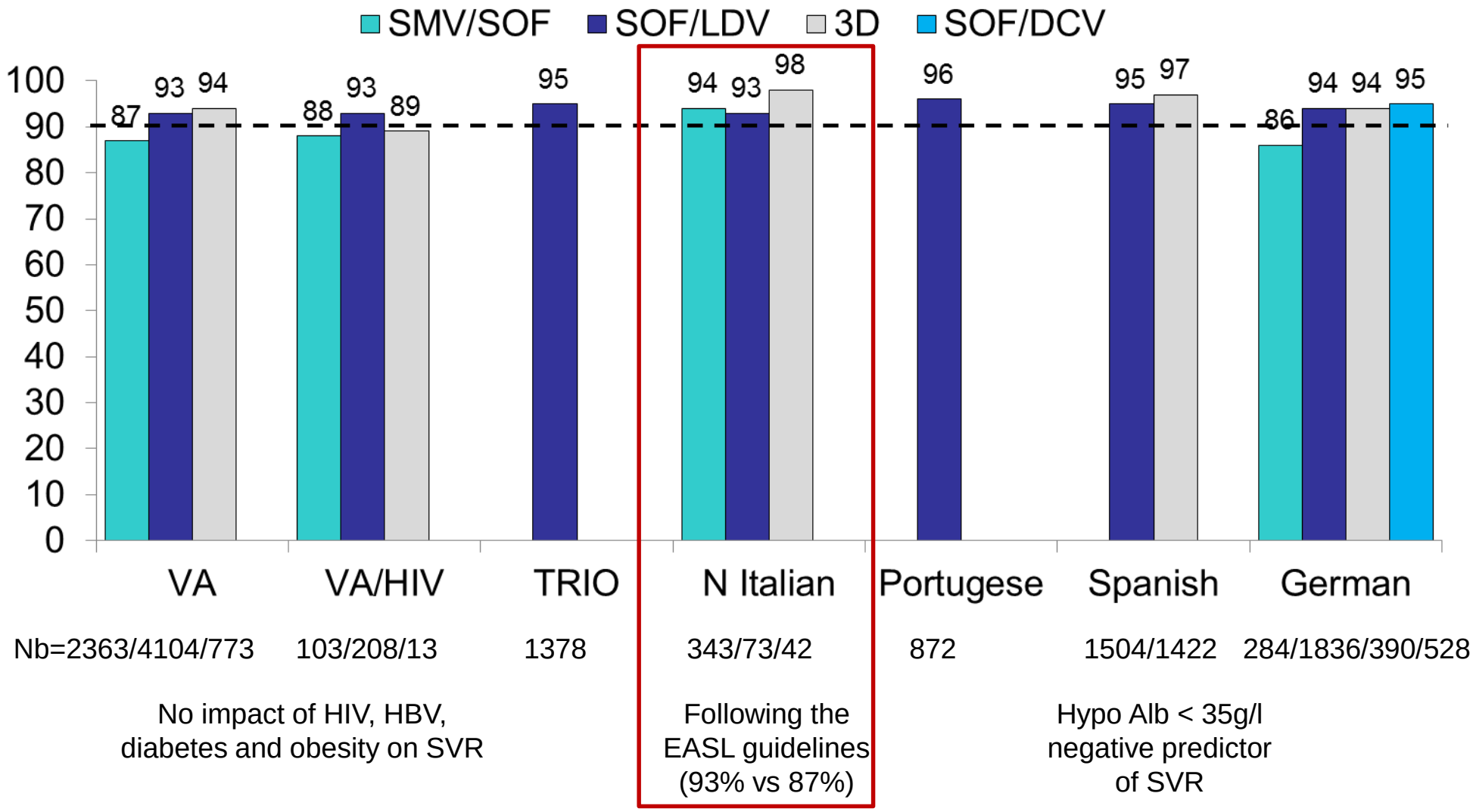
Key baseline demographics

- Age: 60-61 yr
- 73% Caucasian
- 65% HCV-1a; 27% HCV-1b
- 38% compensated cirrhosis
- 13% decompensated cirrhosis
- 53% treatment naive



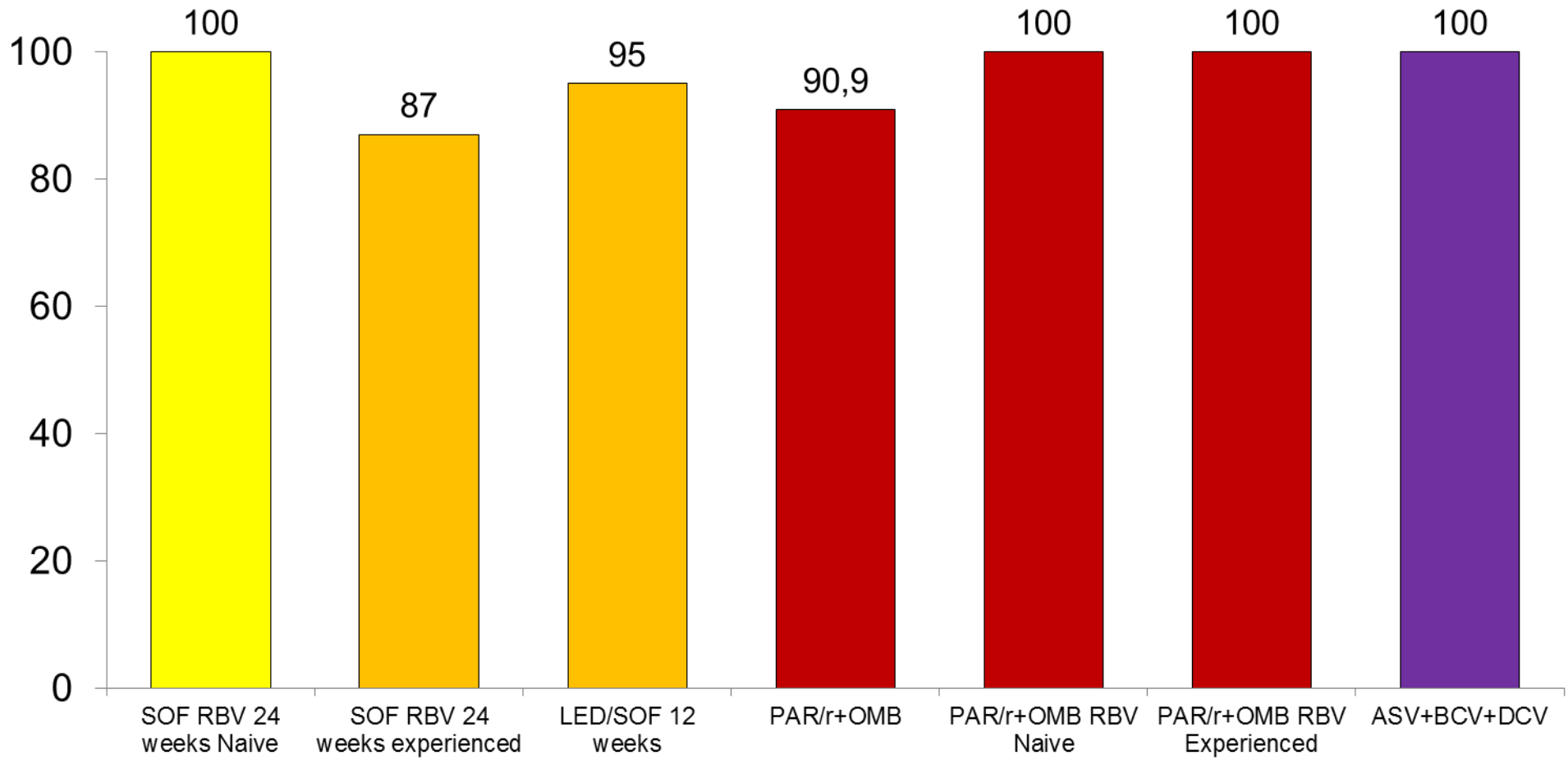
Terrault, AASLD 2015 abs# 94

Large Real-world Data Confirm Clinical Trial Results
16,236 HCV-1 Patients



McCombs et al; McGinnis et al; Afdhal et al; Aghemo et al; Marinho et al; Crespo et al; Calleja et al; Mauss et al, ILC2016 Barcelona

HCV-4. Summary of Interferon-free Therapies

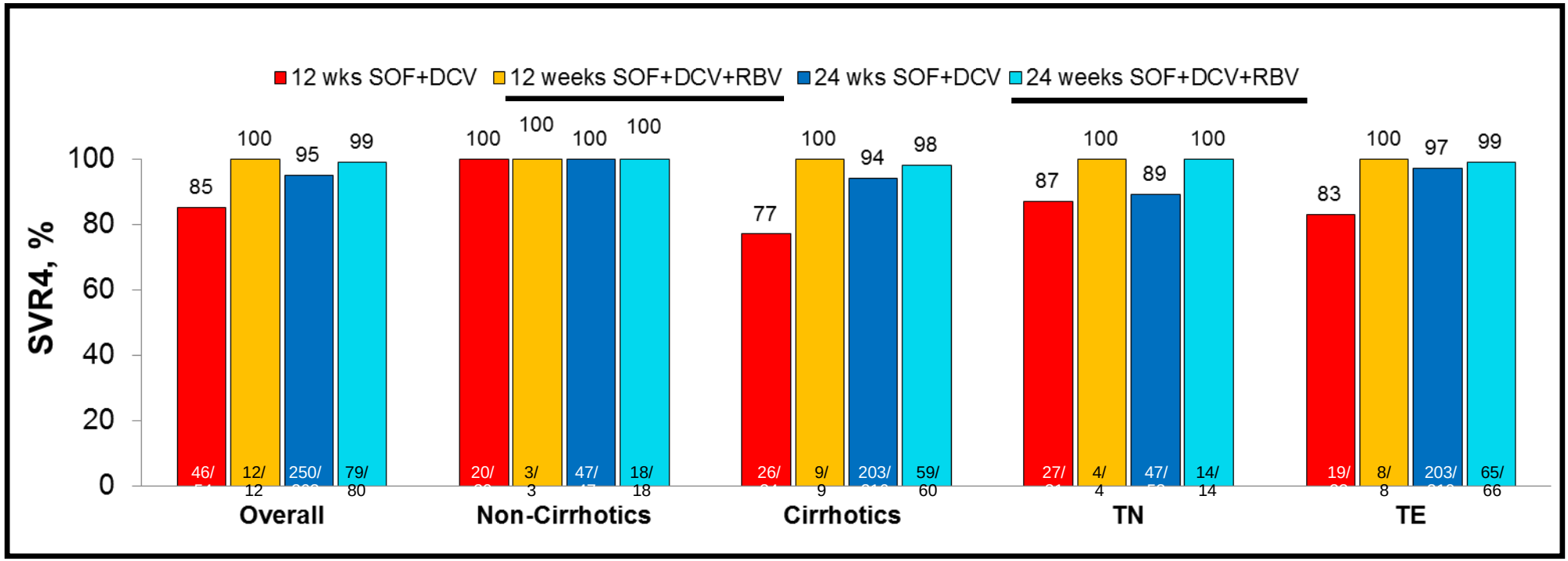


Lawitz et al NEJM 2013. Ruane EASL 2014. Esmat et al AASLD 2014. Kapoor et al AASLD 2014. Pol Hepatology 2014

THE DIFFICULT-TO-TREAT PATIENT: THE IMPORTANCE OF TREATMENT DURATION AND RBV

EAP HEPATHER.SOF+DCV +/- RBV in HCV-1 Patients Advanced Liver Disease .32 French Centers

- F3/4, symptomatic cryoglobulinemic vasculitis, pre-/post-liver or renal transplant
- 319 (78%) GT1 cirrhosis and 307 (75%) TE (56% PI+PR),39 (81%) GT4 cirrhosis and 40 (83%) TE



Cirrhosis strongly associated with treatment failure
RBV and 24 weeks of treatment improved SVR in cirrhotics and TE

Pol et al, EASL Vienna 2015, L03

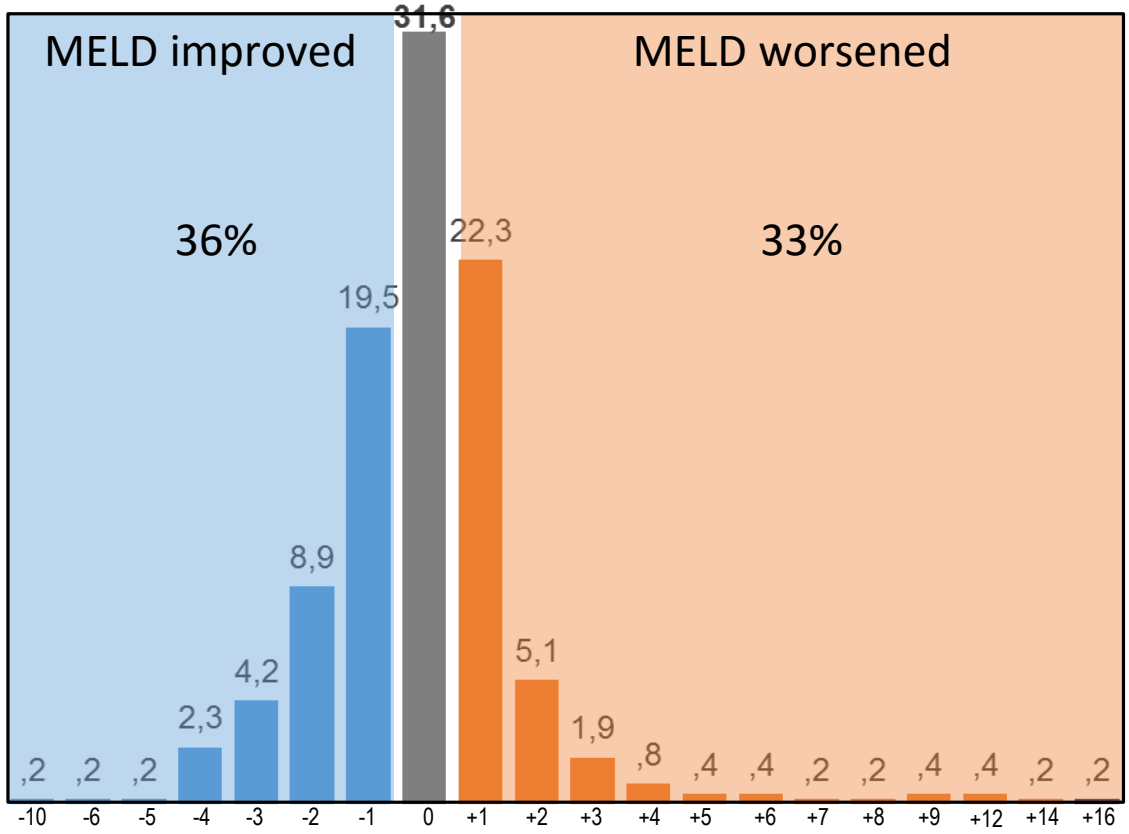
UK EAP.Outcomes a Year after Successful DAA Therapy for Decompensated HCV Cirrhosis

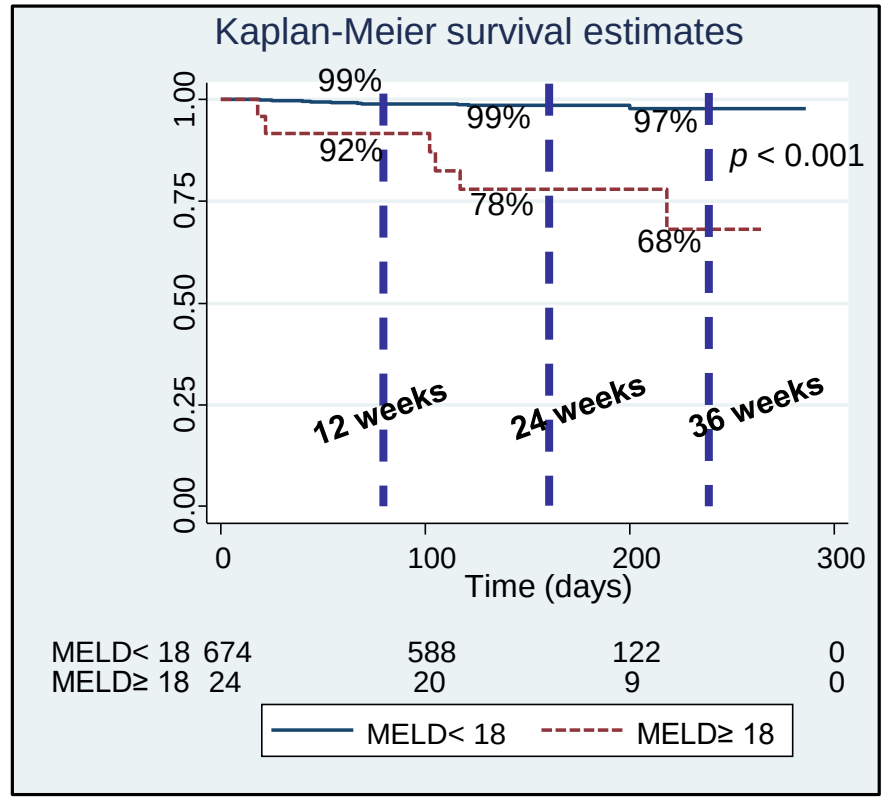
Adverse event	Untreated	All treated N=406			SVR24 N=317			Non SVR24 N=89			Virological failure N=53		
	Month 0-6	Month 0-6	Month 6-15	Overall	Month 0-6	Month 6-15	Overall	Month 0-6	Month 6-15	Overall	Month 0-6	Month 6-15	Overall
Died	13 (5%)	14 (3.4%)	26 (6.4%)	40 (9.9%)	0 (0%)	9 (2.8%)	9 (2.8%)	14 (15.7%)	17 (19.1%)	31 (34.8%)	0 (0%)	3 (5.7%)	3 (5.7%)
HCC	21 (8%)	17 (4.2%)	10 (2.5%)	27 (6.7%)	11 (3.5%)	6 (1.9%)	17 (5.4%)	6 (6.7%)	4 (4.5%)	10 (11.2%)	3 (5.7%)	3 (5.7%)	6 (11.3%)
OLT	10 (3.8%)	29 (7.1%)	17 (4.2%)	46 (11.3%)	27 (8.5%)	12 (3.8%)	39 (12.3%)	2 (2.2%)	5 (5.6%)	7 (7.9%)	1 (1.9%)	5 (9.4%)	6 (11.3%)
Decompensation	73 (28%)	72 (17.7%)	30 (7.4%)	87 (21.4%)	46 (14.5%)	16 (5%)	52 (16.4%)	26 (29.2%)	-	-	-	-	-

Cheung et al, J Hepatol in press

Treatment of Hepatitis C Virus in Patients with Advanced Cirrhosis. The Hepa-C Registry

Deaths 16 (2%), Breakthroughs 9 (1%), Relapses 45 (7%)





Fernàndez-Carrillo, et al. ILC2016 Barcelona

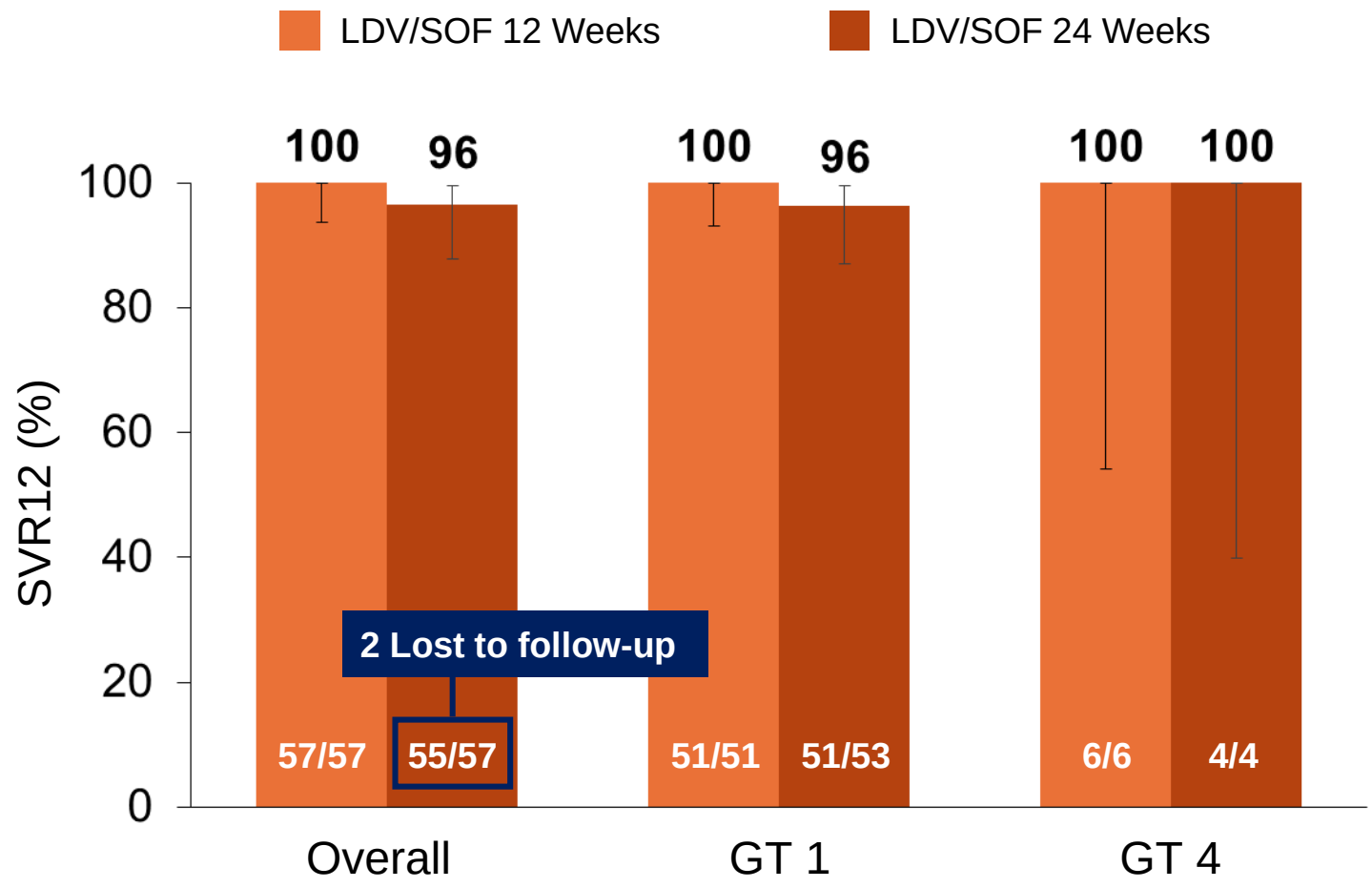
All Oral Therapy of Post Transplant Recurrent HCV-1

					SVR	Reference
SOF		+	Ribavirin		70%	Charlton 2015
SOF	Simeprevir	±	Ribavirin		91%	Brown AASLD 2014
SOF	Daclatasvir	±	Ribavirin		96%	Coilly EASL 2015
SOF	Ledipasvir	±	Ribavirin		100%*	Manns EASL 2015
PAR-r	Ombitasvir	Dasabuvir	Ribavirin		97%	Kwo 2014
Daclatasvir	Simeprevir	±	Ribavirin		93%	Forns EASL 2015

** Child Pugh B*

NS5B PI NS5A

HCV-1,4 Kidney Transplanted Patients. A Multinational RCT of 12 vs 24 weeks LDV SOF



New Oral Treatment of HCV-1&4

TREATMENT FAILURES: THE IMPORTANCE OF PRE-EXISTING AND TX -EMERGING RASs

Factors Associated with Virologic Response to IFN-free DAA Regimens in HCV

PI+NUC
(SMV+SOF)

NS5A+NUC
(DCV+SOF, LDV/SOF)

PI+NS5A+nonNUC
(PTVr+OMV+DSV)

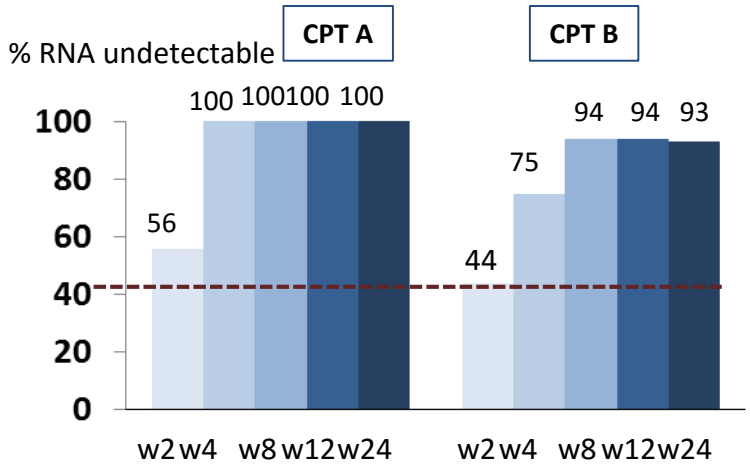
Importance of:

- Liver disease severity
- Addition of ribavirin
- Duration of treatment
- Presence of baseline resistance

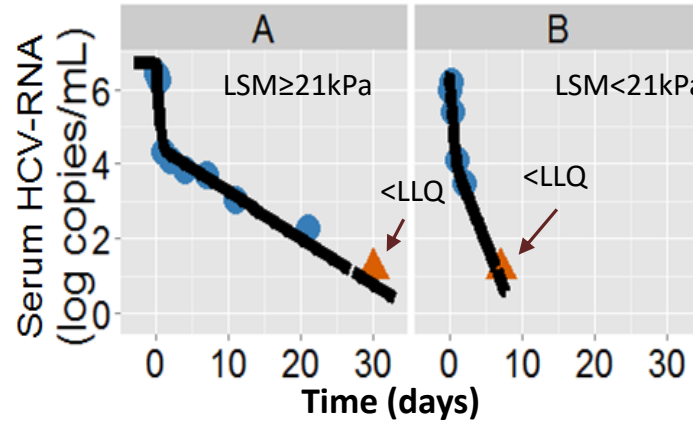
Pearlman et al, Clin Infect Dis 2011;52:889-900

Why is Treatment Failure More Frequent in Advanced Liver Disease?

Virologic response on treatment with SOF+RBV 24w in G1 pts with portal hypertension and/or decompensated liver disease



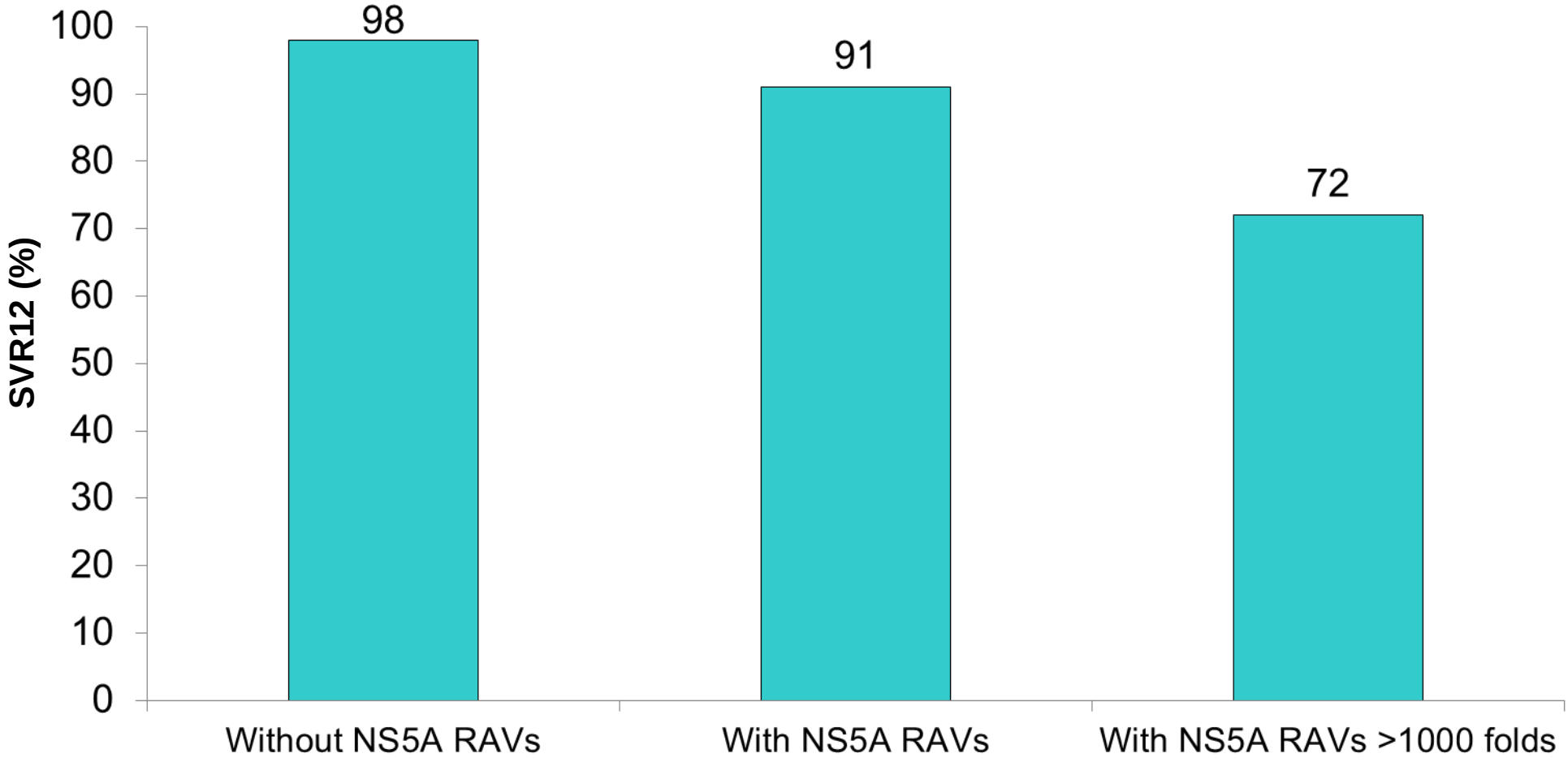
Modeling early HCV kinetics to individualize DAA treatment duration in patients with advanced cirrhosis



Median time to cure was significantly longer in patients with FS≥21 kPa (Fig. A) compared to those with FS<21 kPa (Fig. B)

Afdhal et al, EASL 2014 London; Gambato and Canini et al, EASL 2016 Barcelona (SAT-210)

Pre-treatment NS5A RASs (NGS) and Response to SOF+LDV in HCV-1 Patients



Martin R et al, AASLD 2015 abs 91

HCV Resistance Testing Prior to First-Line DAA Therapy

Available, reliable, Interpretable, understadable*

⇩

Presence of NS5As RASs conferring high-level resistance (pop seq or >15%)

⇩

Add ribavirin and/or increase treatment duration

Not available

⇩

Optimize therapy to avoid treatment failure

⇩

- **Add RBV in TE patients with SOF/LDV, SOF/DCV, SOF/SMV**
- **With 3D, use RBV in GT1a, treat NR cirrhotics 24 weeks**
- **Use GZR/EBR 16 weeks with RBV in GT1a patients**

**recommended for GZR/EBR for US patients with GT1a*

Pawlotsky et al, Gastroenterology 2016

Real-World Data. Resistance-Based HCV Re-treatment After DAA Regimen Failure

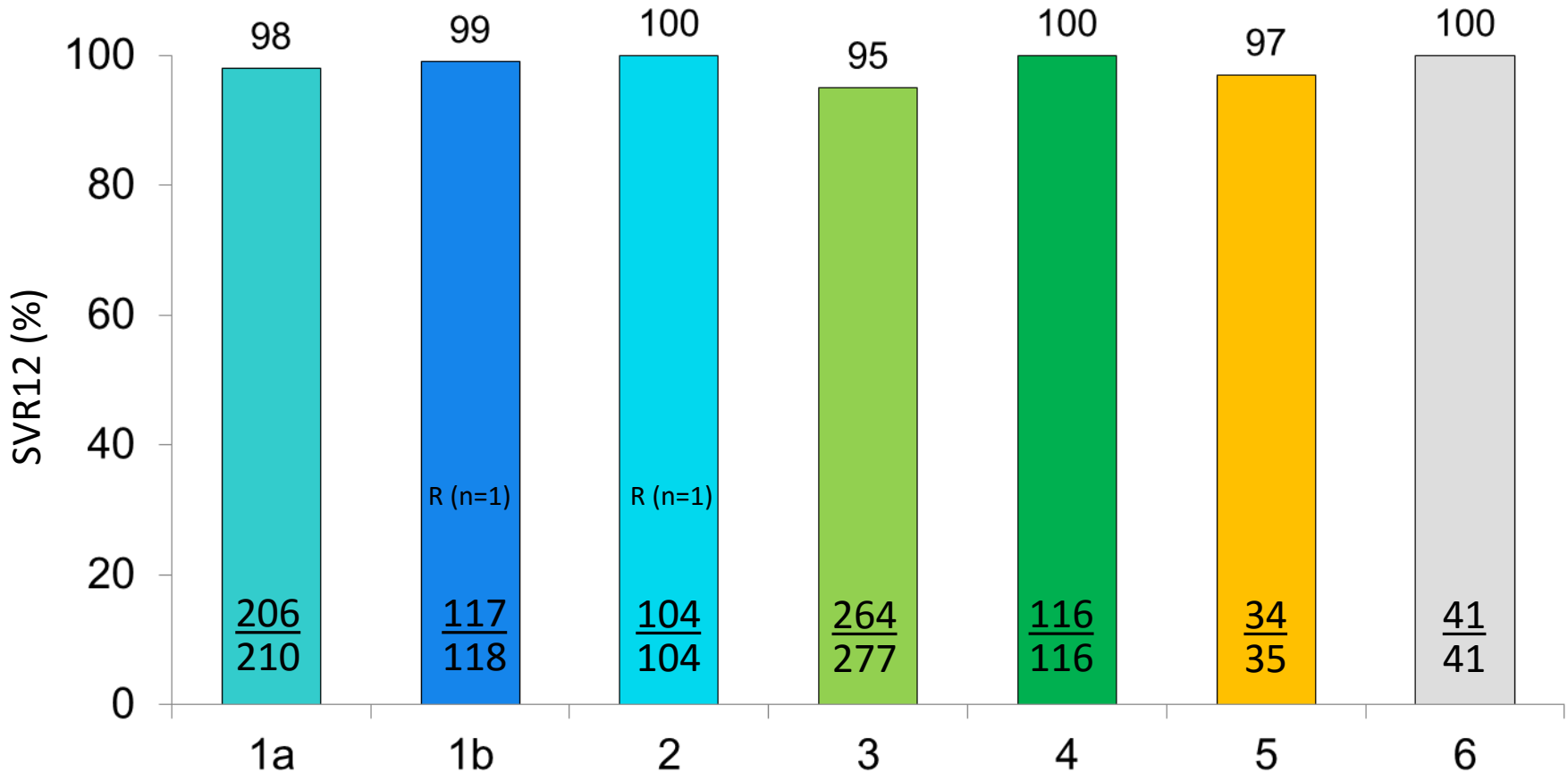
Previous DAA Regimen Failure	Retreatment Regimen	SVR12
GT1: SMV + SOF ± RBV	**NS5A inhibitor–containing regimen**	**91%**
	▪ LDV/SOF ± RBV 12 wks	8/8
	▪ LDV/SOF ± RBV 24 wks	9/10
	▪ OBV/PTV/RTV + DSV ± RBV 12 wks	3/3
	▪ OBV/PTV/RTV + DSV + RBV 24 wks	0/1
GT1: DCV or LDV + SOF ± RBV	**PI-containing regimen**	**86%**
	▪ SMV + SOF ± RBV 12 wks	2/2
	▪ SMV + SOF ± RBV 24 wks	1/1
	▪ OBV/PTV/RTV + DSV ± RBV 12 wks	3/4
GT3: SOF + RBV	**NS5A inhibitor–containing regimen**	**100%**
	▪ DCV + SOF + RBV 12 wks	2/2
	▪ DCV + SOF ± RBV 24 wks	4/4
	▪ LDV/SOF + RBV 24 wks	1/1

Vermehren J, et al. EASL 2016. Abstract PS103

New Oral Treatment of HCV-1&4

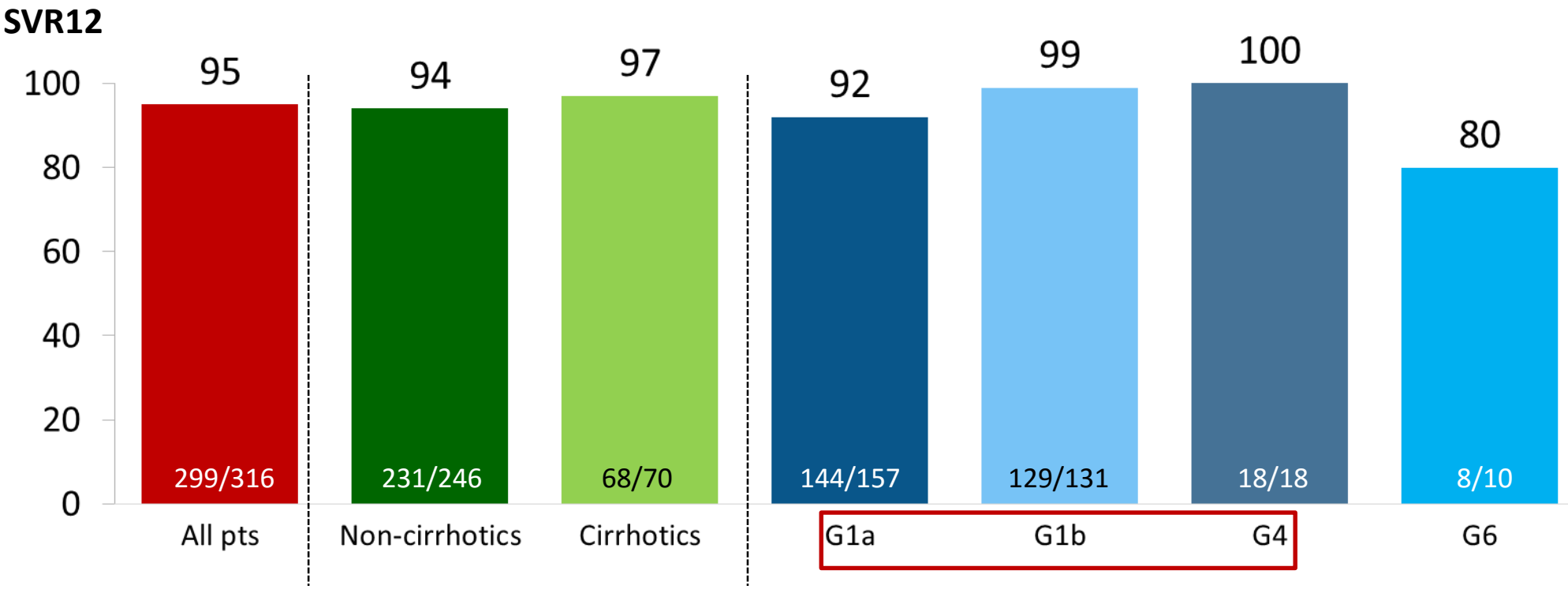
WHAT IS AROUND THE CORNER…

Pooled Analysis of ASTRAL. Twelve Wks SOF+VEL A Pangenotypic Regimen on the Block



Feld JJ, et al. N Engl J Med. 2015. Foster GR, et al. N Engl J Med. 2015

C-EDGE. 12-week Regimen of Grazoprevir + Elbasvir in Treatment-naive HCV-1,4,6



- No drug-related SAE; 2 deaths unrelated to drug
- No concurrent ALT/Bili increase

Non-VF	3	1	0	0
Breakthrough	1	0	0	0
Relapse	9	1	0	2

Zeuzem S, et al., Ann Intern Med 2015

Grazoprevir/Elbasvir (no RBV) Impact of Baseline NS5A RASs in Patients with HCV 1a,b

GT1a-infected

RAV Position	SVR12 Patients with RAVs (NGS 1% ST)	SVR12 Patients with RAVs (PopSeq)
28	61/68 (89.7%)	29/33 (87.9%)
30	14/23 (60.9%)	4/10 (40.0%)
31	15/23 (65.2%)	5/13 (38.5%)
93	9/14 (64.3%)	5/8 (62.5%)

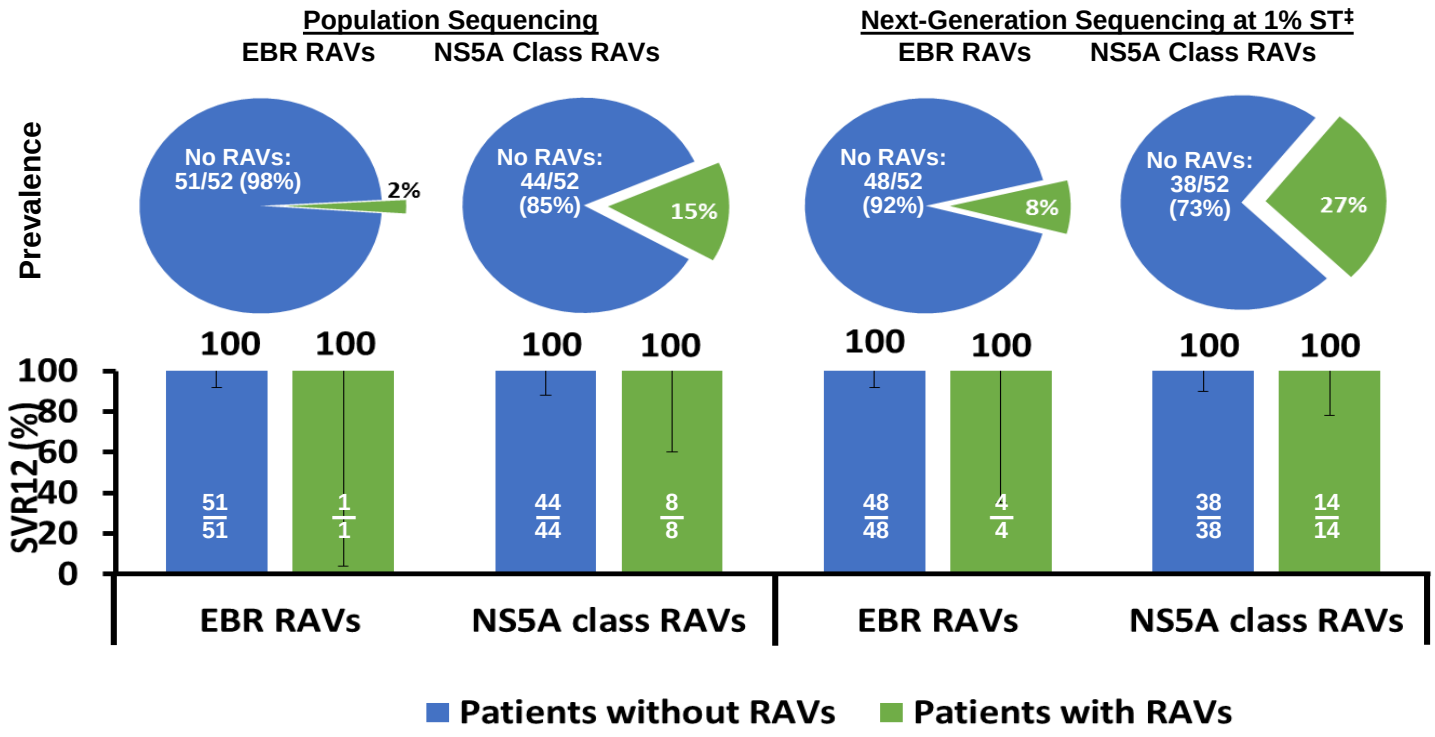
GT1b-infected

RAV Position	SVR12 Patients with RAVs (PopSeq)
28	4/4 (100.0%)
30	16/16 (100.0%)
31	17/19 (89.5%)†
93	21/22 (95.5%)‡

Jacobson I, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. LB-22

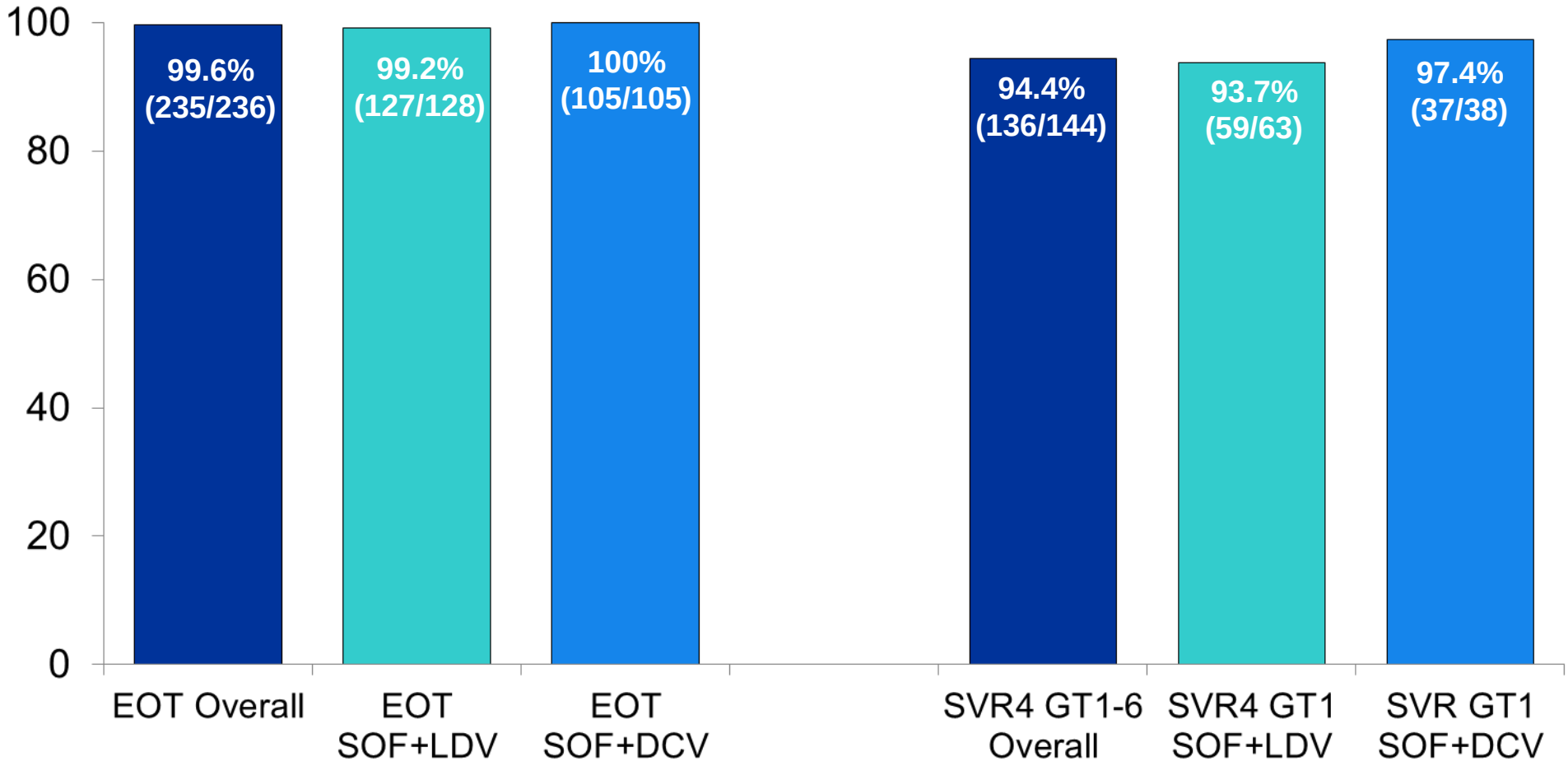
GZV/EBR. 16 Weeks+RBV Lead to High SVR Rate in HCV-1a with Baseline NS5A RASs (aa 28, 30, 31 and 93)

PR Non-responders with Baseline NS5A RAVs†



Jacobson I, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. LB-22.

Generic DAA Treatment for HCV Imported into Australia from China, India and Bangladesh. Redemption



Freeman et al, EASL 2016 LB-4611

Where Do You Set the Bar in 2016 for Anti-HCV Therapy?

- **>90% SVR Rates**
- **12 weeks or less of treatment duration**
- **No need for Ribavirin**
- **No or minimal DDIs**
- **Lack of significant AEs**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