Transformation of Chronic Hepatitis C Treatment

UVHS, Adana, 22 May 2015

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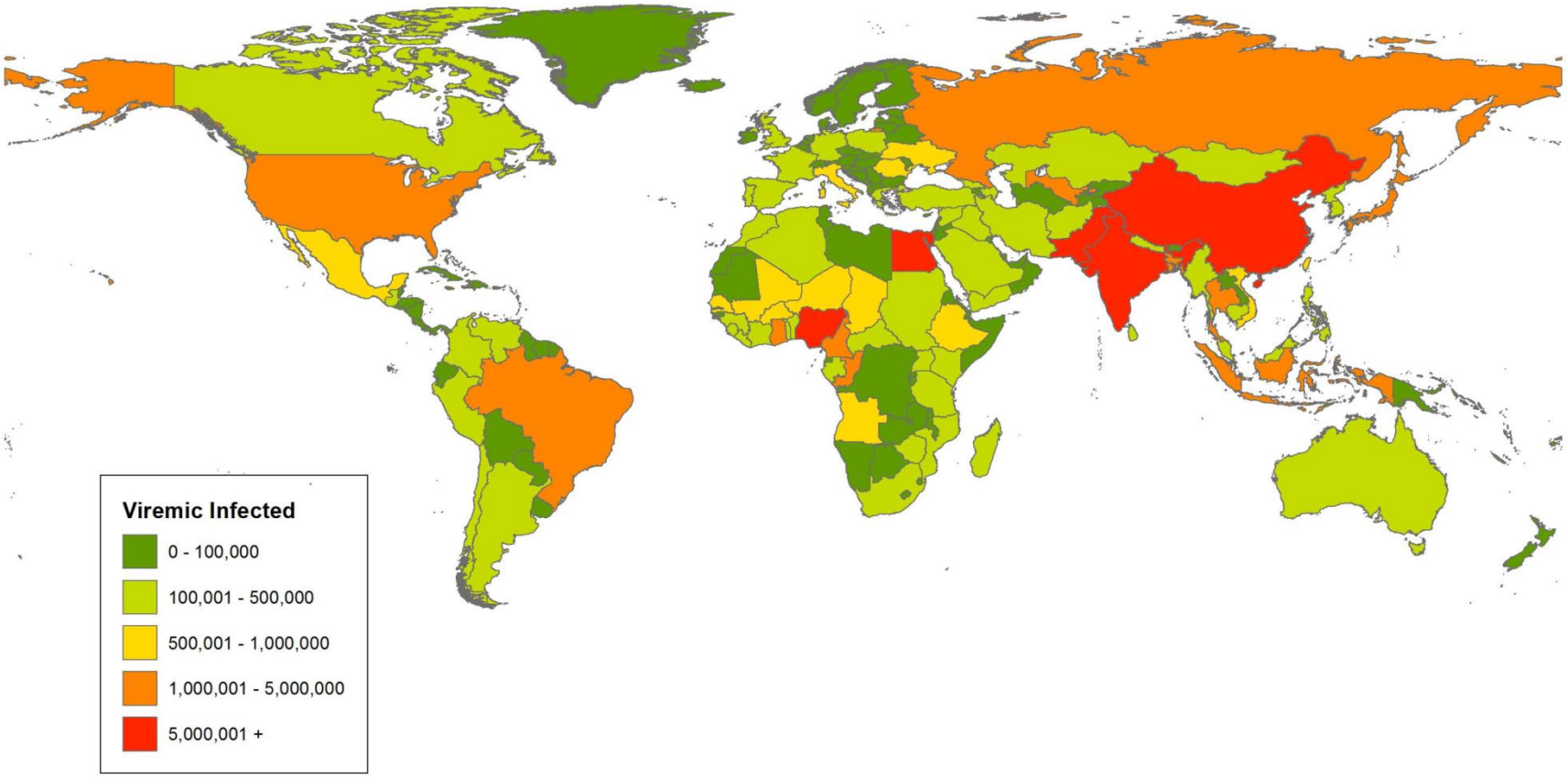
Epidemiology of HCV Infection

Global

Global HCV Prevalence (anti HCV adults 2.0%, all ages 1.6%)

Global viremic patients all ages: 1.1% 80 (64-103) Millionen

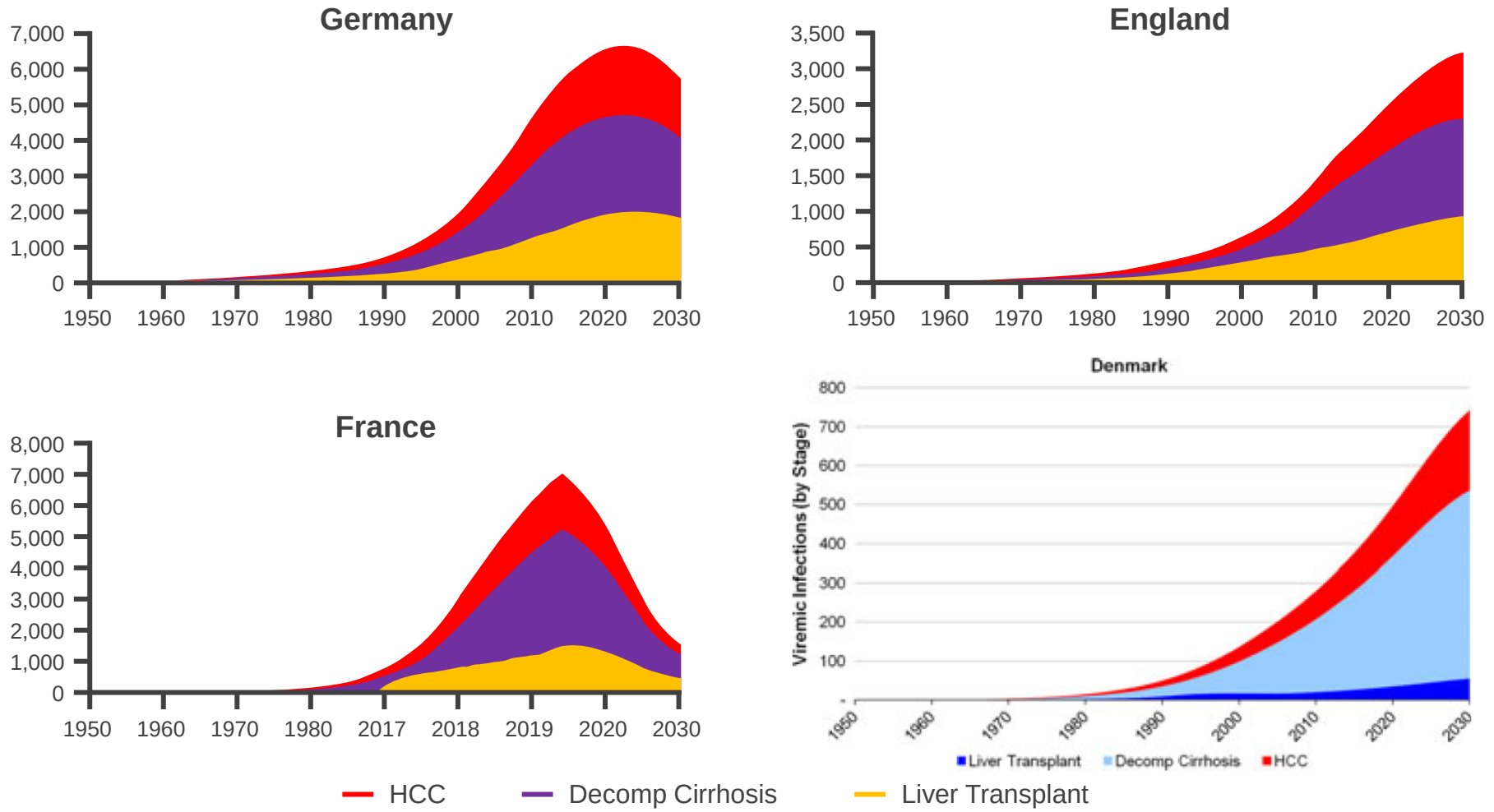


Gower et al., J Hepatol 2014 epub

Burden of disease

Liver cancer, decompensated cirrhosis, liver transplant

Change in the number of liver transplants, decompensated cirrhosis cases and HCC cases over time



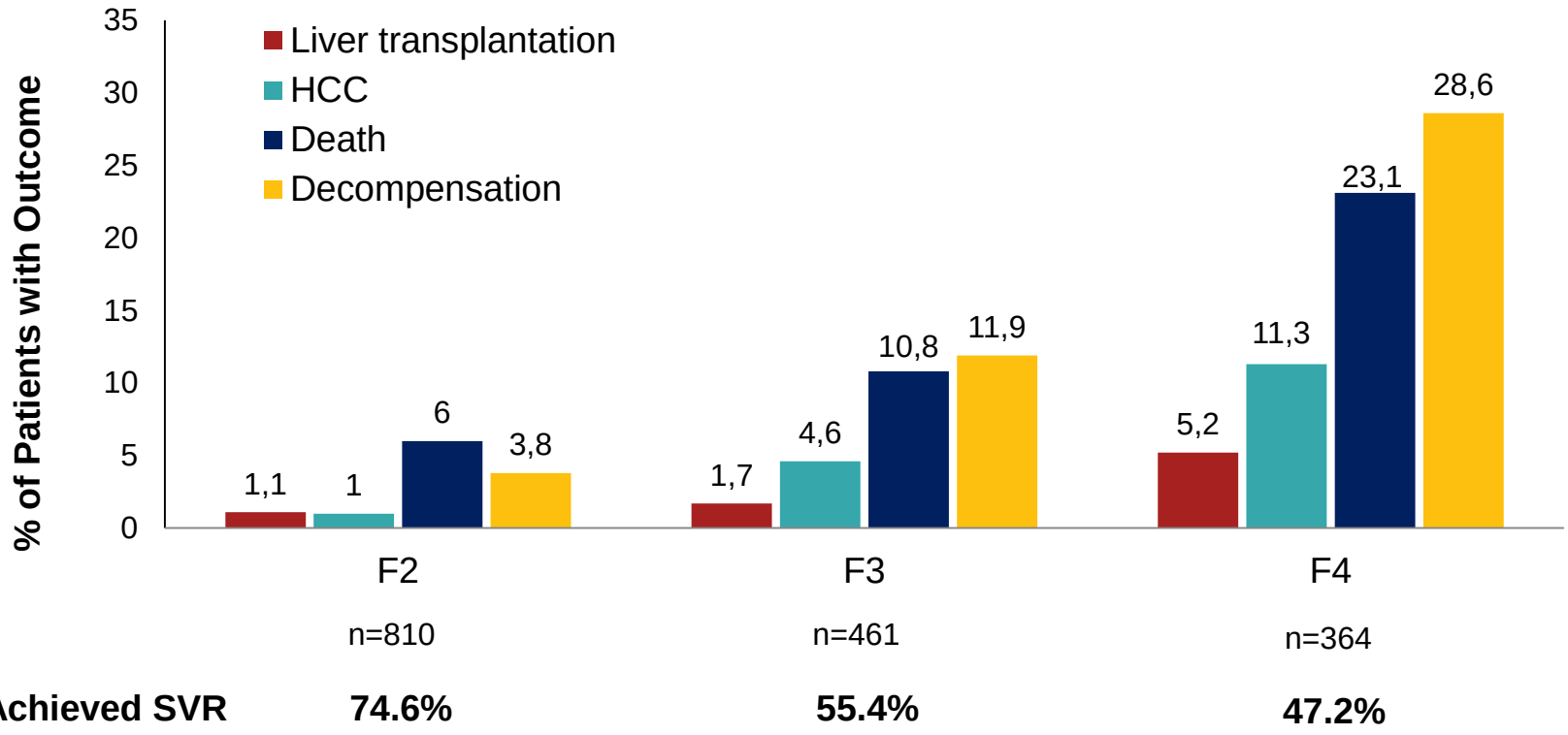
HCC: hepatocellular carcinoma

Razavi, Waked, Sarrazin et al., J Viral Hepatitis 2014; 21:34–59

Sequelae of chronic Hepatitis C

Follow up in 4 US centers before introduction of DAAs
Treatment-naive patients from 2004-2011 with liver biopsy
(2.110 of 14.256 Patienten)
Follow-up 3,7-4,2 years

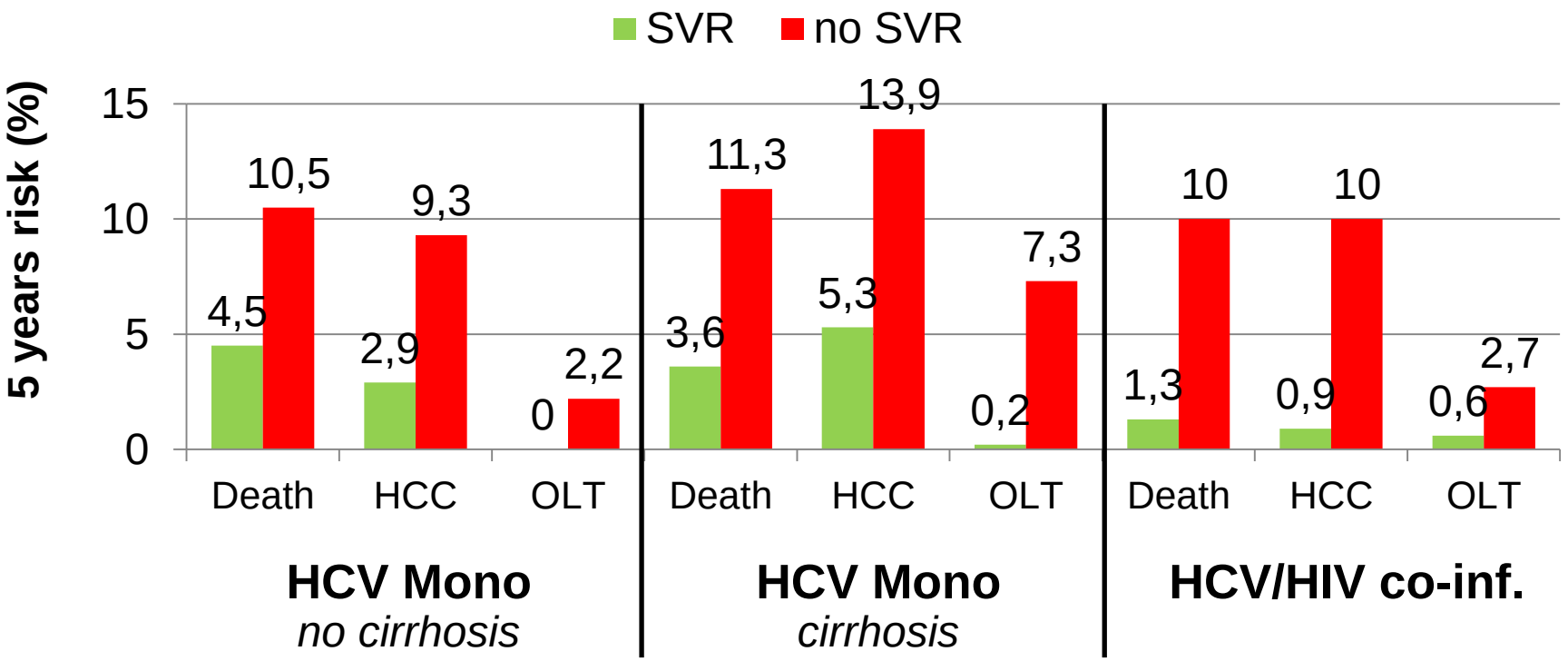
Clinical Outcomes after Baseline Biopsy



Moorman, AASLD, 2014, Oral #174

Surrogate SVR and cure of hepatitis C

Meta-Analysis (PEG-based therapy) n=34.563



Risk-Reduction by viral eradication (SVR)

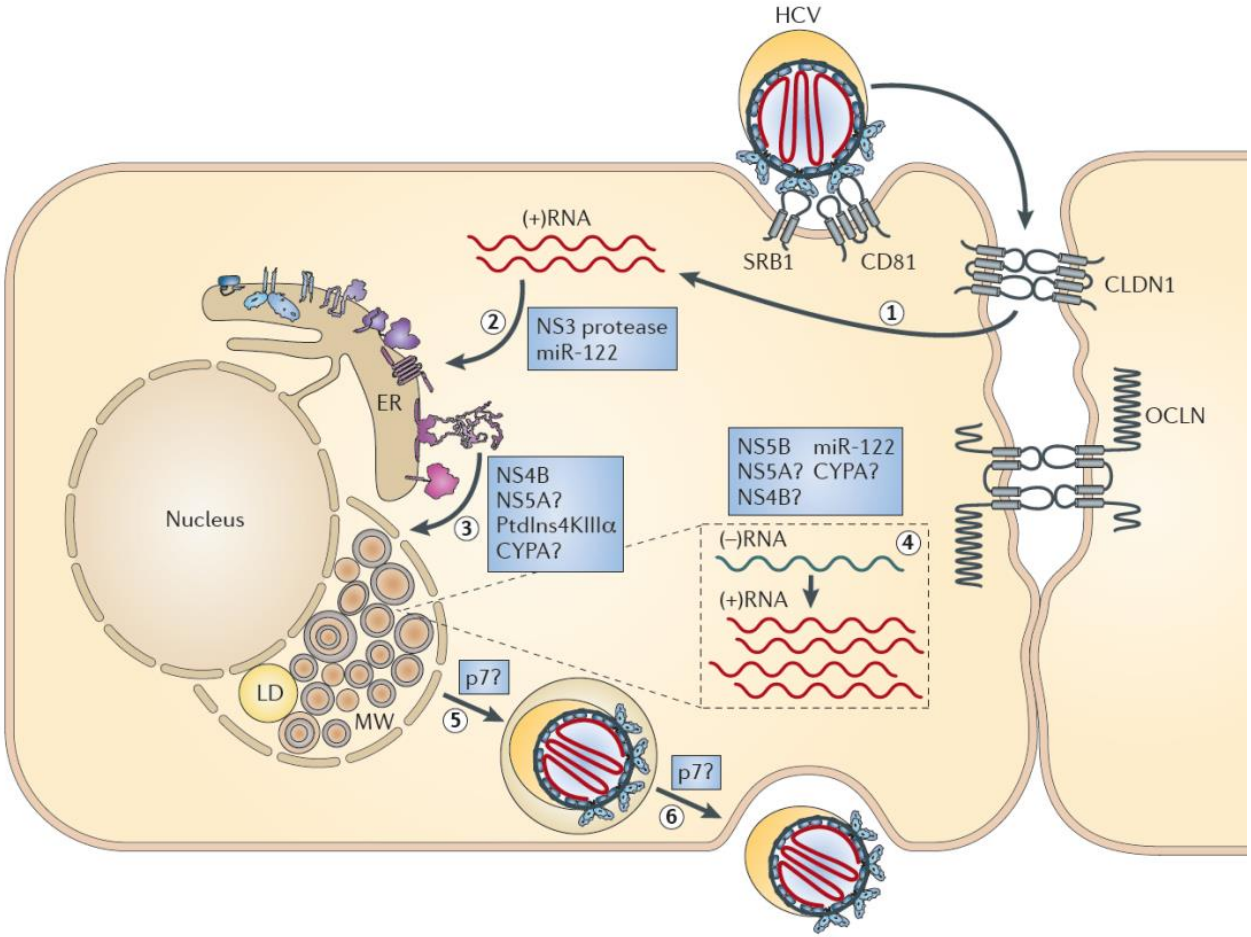
- Mortality	62-84%
- OLT	90%
- HCC	68-79%

Hill et al., AASLD 2014, #44

Direct antiviral therapy

Mechanism of action

HCV replication cycle and targets of direct antiviral therapy

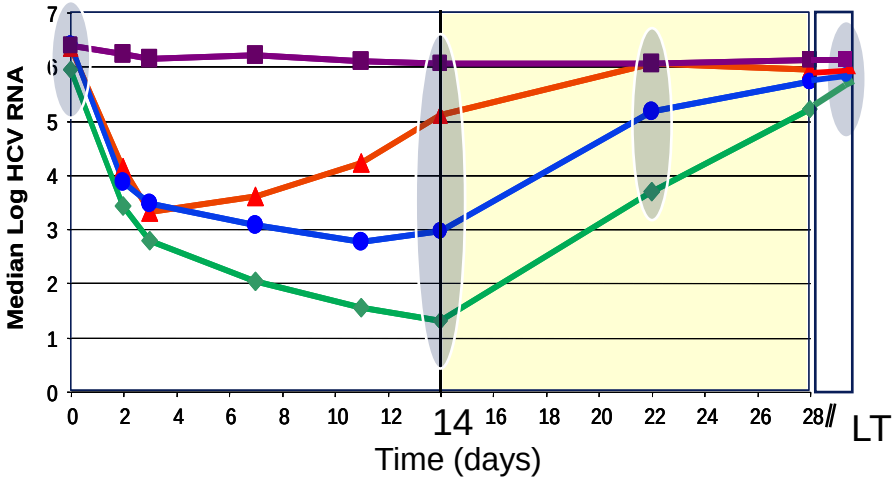


Bartenschlager, Lohman, Penin, Nat Rev Microbiol 2013

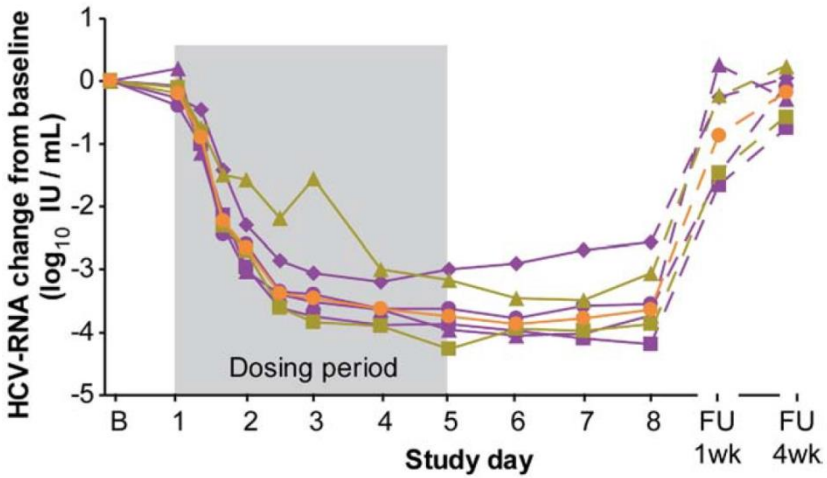
Monotherapies with DAAs

High antiviral activities but low barriers to resistance

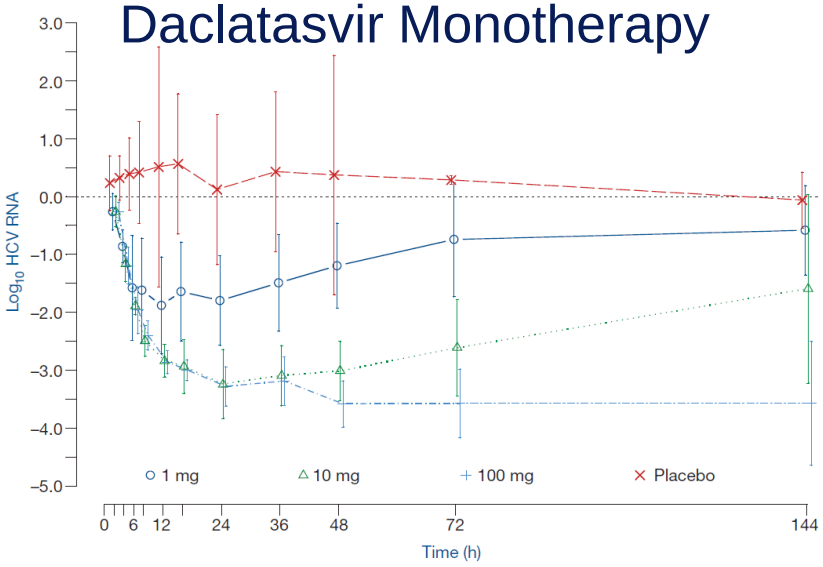
Telaprevir Monotherapy



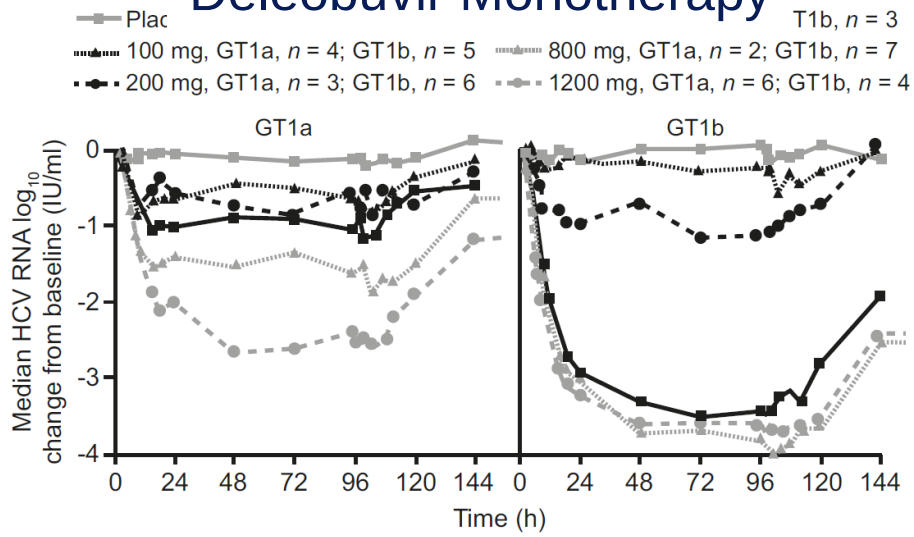
Simeprevir Monotherapy



Daclatasvir Monotherapy



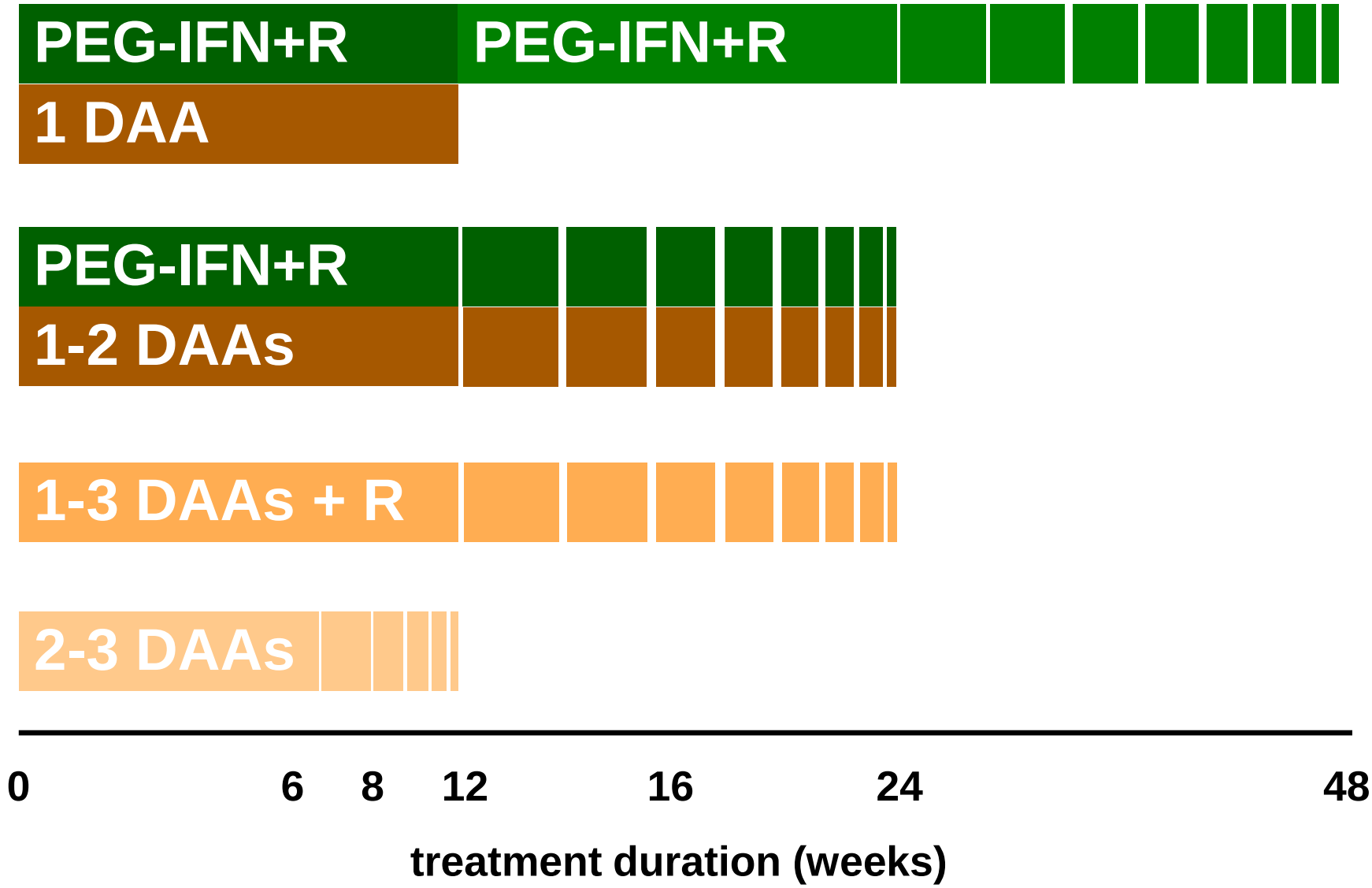
Deleobuvir Monotherapy



Sarrazin et al., Gastro 2007, Reesink et al., Gastro 2010, Gao et al., Nature 2010; Larrey et al., AAC 2013

Possible treatment schedules

IFN-based, IFN-free, IFN+R free



Approved DAAs for IFN-free treatment in Europe
(EMA / EU)

Nukleoside	Prot.-Inh.	NS5A-Inh.	Non-Nucs	unkn.mech.
Jan 2014				
Sofosbuvir				Ribavirin
	May 2014			
Sofosbuvir	Simeprevir			Ribavirin
		August 2014		
Sofosbuvir		Daclatasvir		Ribavirin
		Nov 2014		
Sofosbuvir		Ledipasvir		Ribavirin
		Jan 2015		
	Paritaprevir	Ombitasvir	Dasabuvir	Ribavirin

HCV Clinical Practice Guidelines

EASL and National

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

SUMMARY of

EASL Recommendations on Treatment

of Hepatitis C 2015

February 2015

European Association for the Study of the Liver

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Panel members: Alessio Aghemo (GB)
Geoffrey Dusheiko
Xavier Forns
Massimo Puoti
Christoph Sarrazin

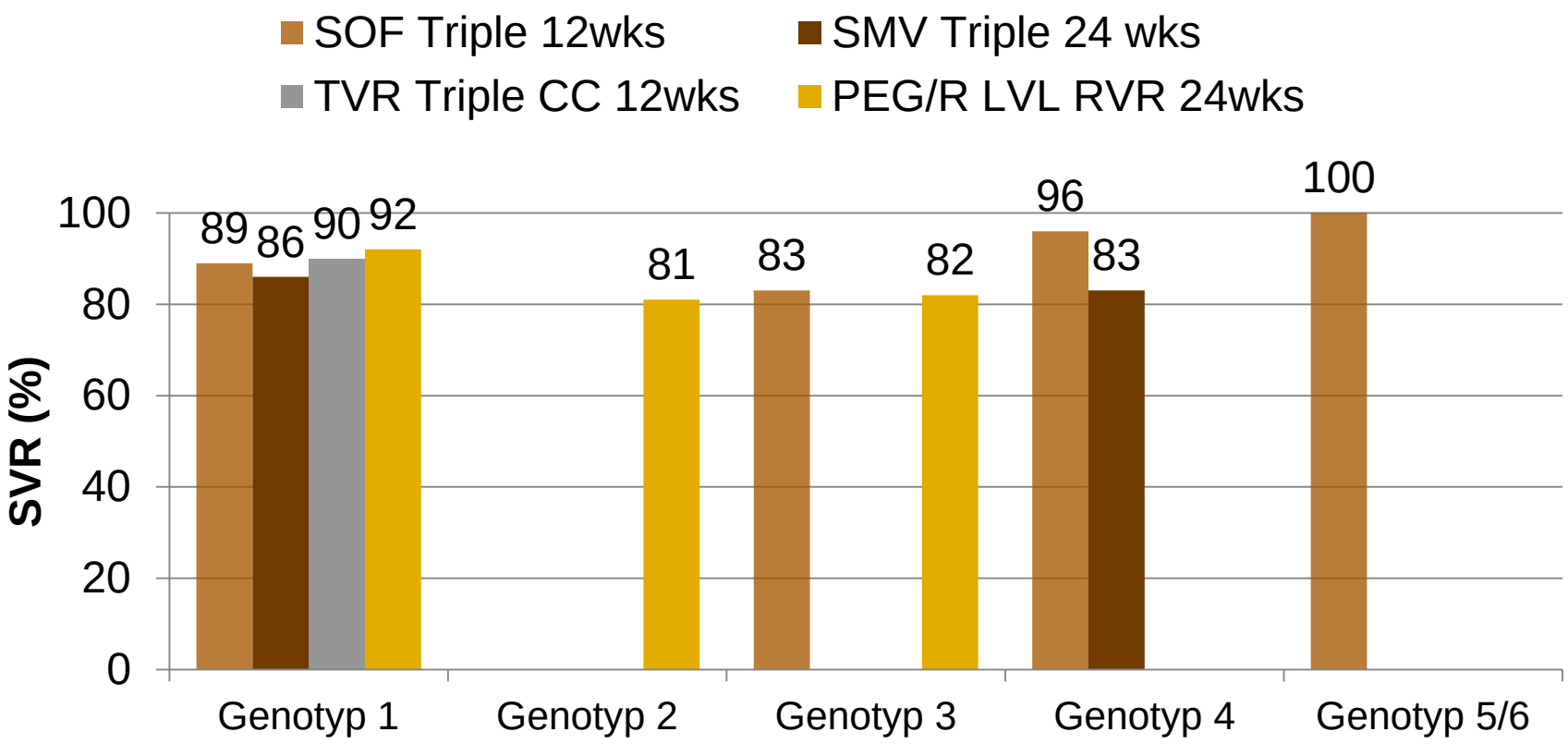
National Guidelines with recommendations according to local reimbursement situation

Sarrazin et al., Z Gastroenterol 2015

Interferon alfa-based triple therapies

High SVR rates in easy to treat patients from phase 3 studies

SOF+PEG/R, SMV+PEG/R, PI(BOC/TVR)+PEG/R, PEG/R

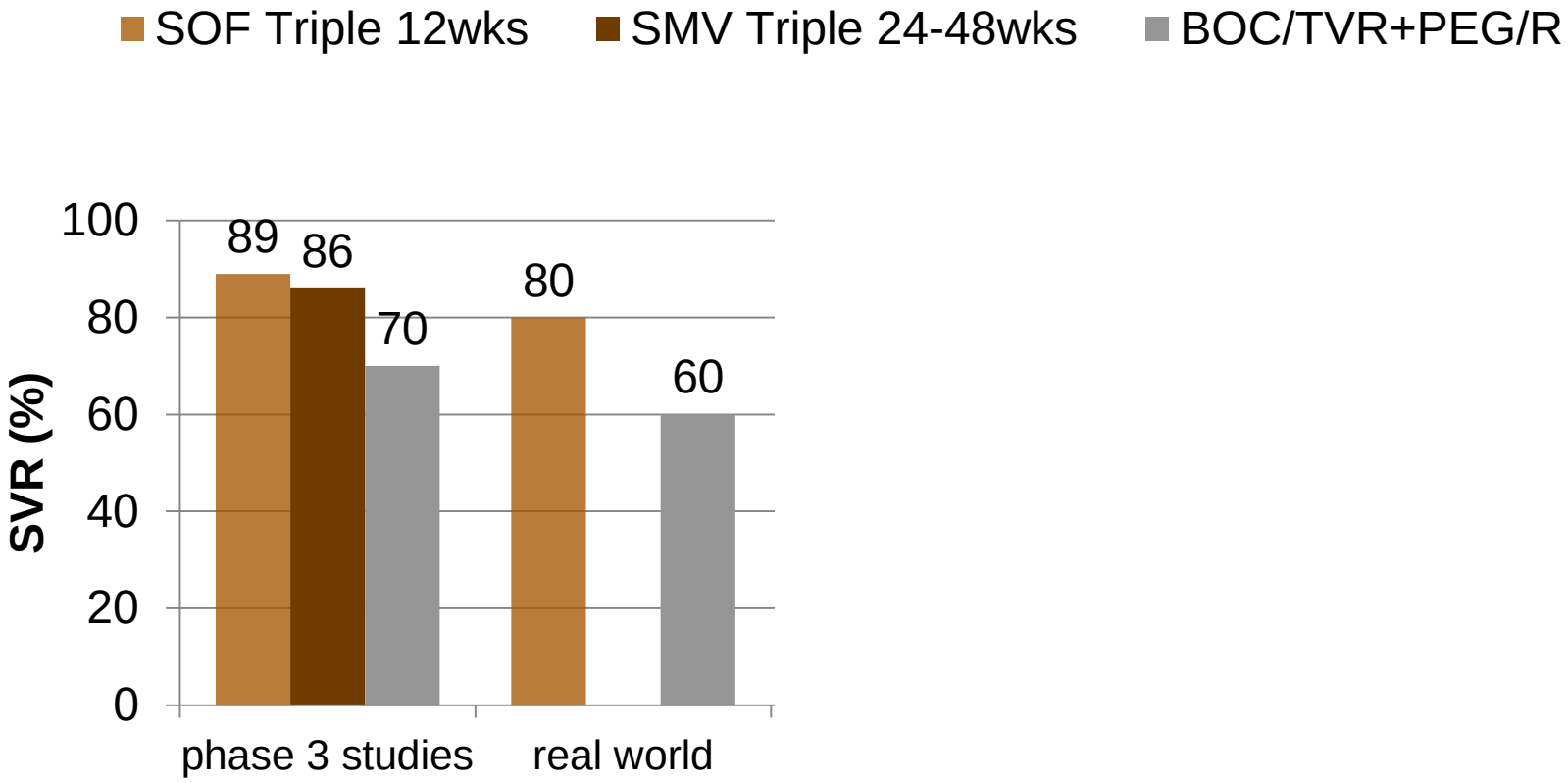


Lawitz et al., NEJM 2013, Jacobson et al., NEJM 2013, Lawitz et al., Lancet 2014, Sarrazin et al., Gastro 2011, Shiffman et al., NEJM 2007; Moreno et al., EASL 2014, #1319

Interferon alfa-based triple therapies

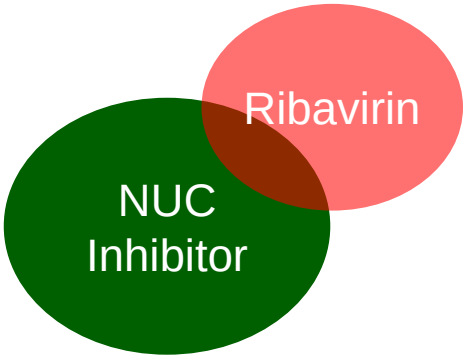
Medium to low SVR rates in real-word / difficult to treat patients

SOF+PEG/R, SMV+PEG/R, PI(BOC/TVR+PEG/R



Lawitz et al., NEJM 2013, Jacobson et al., NEJM 2013, Shiffman et al., NEJM 2007; Moreno et al., EASL 2014, #1319;
Di Bisceglie et al. Hepatology 2013; 227A; Reddy et al., APASL 2013; Manns et al., Lancet 2014

IFN-free DAA combinations in 2014



Sofosbuvir + Ribavirin for Genotype 2 (12 wks) or 3 (24 wks)

≥85%
(TE cirrhosis 72/60%)

Approved treatment options based on large phase 3 development programs

- **Paritaprevir/r + Ombitasvir + Dasabuvir +/- Ribavirin (3D)**
  - Genotype 1 and 4

- **Sofosbuvir + Ledipasvir +/- Ribavirin**
  - Genotype 1 and 4, 5, 6 (3)

German Guidelines - HCV Genotype 1

Treatment regimen	Duration (wks.)	Pat. without cirrhosis			Pat. with comp. cirrhosis		
		TN	TE	BOC/TVR	TN	TE	BOC/TVR
SOF + LDV	8	x[4]					
SOF + LDV	12	x	x	x			
SOF + LDV + RBV	12				x	x	x
SOF + LDV	24				(x)[5]	(x)[5]	(x)[5]
SOF + LDV + RBV	24				(x)[5]	(x)[5]	(x)[5]
PTV/r + OMV + DSV (1b)[6]	12	x[6]	x[6]				
PTV/r + OMV + DSV + RBV	12	x[7]	x[7]		x[8]	x[8]	
PTV/r + OMV + DSV + RBV	24				x[8]	x[8]	
SOF + SMV +/- RBV	12	(x)[9]	(x)[9]		(x)[9]	(x)[9]	
SOF + DCV +/- RBV	12	(x)[10]	(x)[10]	(x)[10]			

TN: treatment-naive
TE: treatment-experienced
BOC/TVR: pre-treatment with boceprevir or telaprevir
SOF, Sofosbuvir; LDV, Ledipasvir; PTV/r, Paritaprevir/r; OMV, Ombitasvir; DSV, Dasabuvir
SMV, Simeprevir; DCV, Daclatasvir

Sarrazin et al., Z Gastroenterol 2015

Sofosbuvir plus Ledipasvir for 8 weeks

"Easy to treat" patients (treatment naive, no cirrhosis)

Relapse and SVR12 Rates by Baseline Viral Load After 8 or 12 Weeks of Treatment (ION-3)

	LDV/SOF				LDV/SOF+RBV	
	8 Weeks n=215		12 Weeks n=216		8 Weeks n=216*	
Patients, n/n (%)	Relapse	SVR	Relapse	SVR	Relapse	SVR
Baseline HCV RNA						
<6 million IU/mL	2/123 (2)	119/123 (97)	2/131 (2)	126/131 (96)	3/137 (2)	133/138 (96)
≥6 million IU/mL	9/92 (10)	83/92 (90)	1/85 (1)	82/85 (96)	6/77 (8)	68/78 (87)

*2 patients were lost to follow-up after their baseline visit and never achieved HCV RNA < lower limit of quantitation on treatment.

In the ION studies 67% of patients had <6 Mill. IU/ml baseline HCV RNA

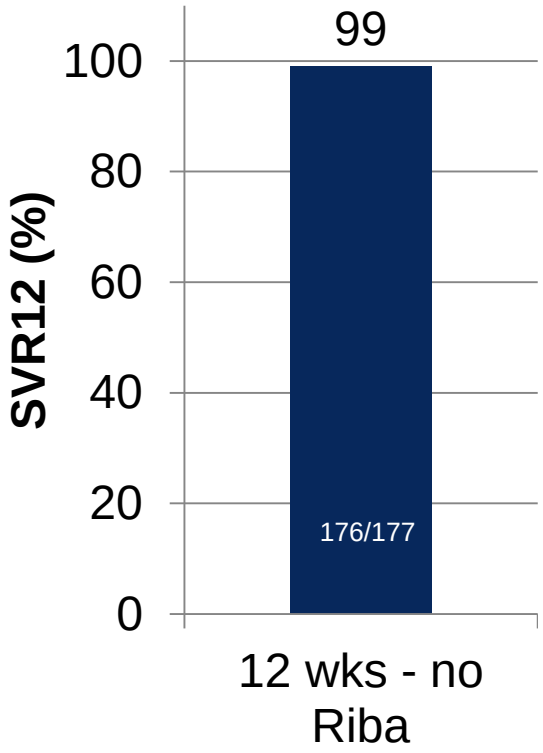
- **Shortening to 8 weeks in treatment-naive patients without cirrhosis and low baseline viremia (< 6 Millionen IU/ml)**

Jacobson et al., AASLD 2014; #1945

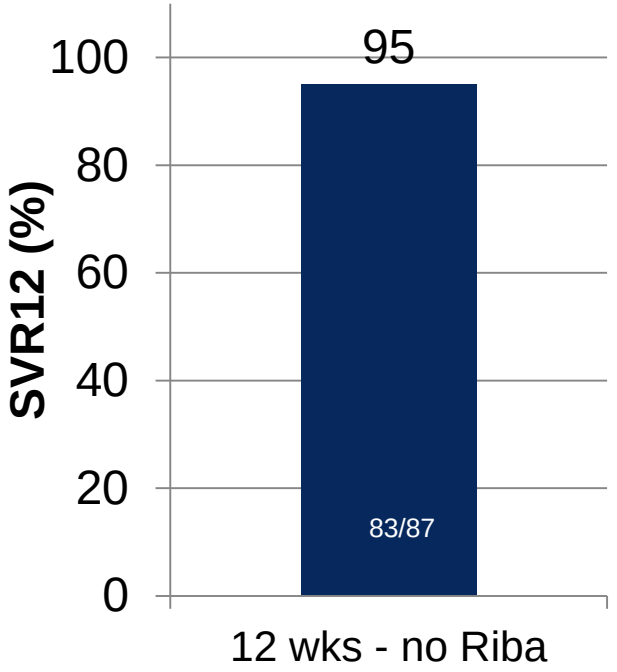
Sofosbuvir + Ledipasvir for 12 weeks

Genotype 1 patients without liver cirrhosis

Treatment naive



Treatment experienced (including BOC/TVR failures)

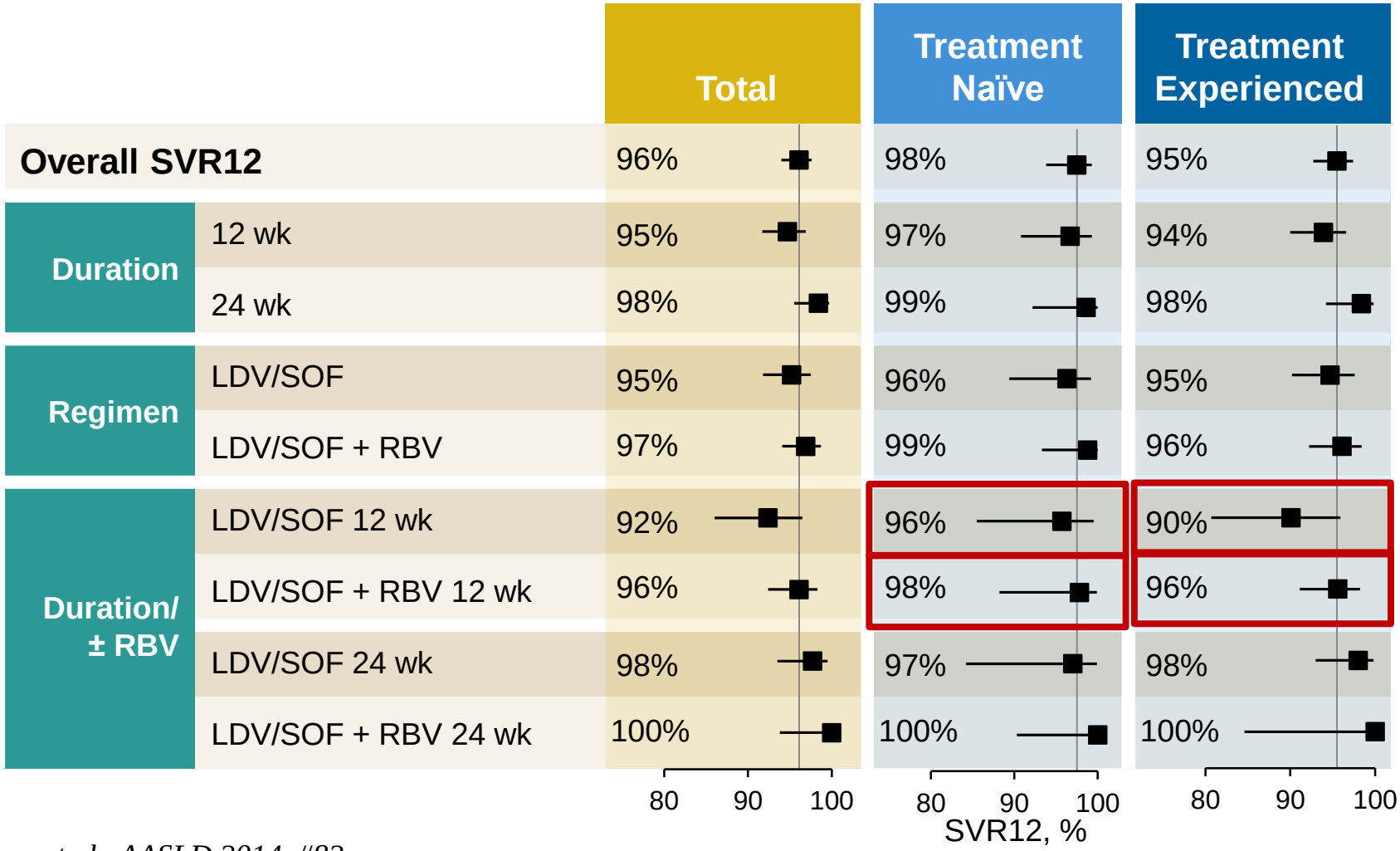


Afdahl et al., NEJM 2014

Sofosbuvir plus Ledipasvir + RBV for 12 weeks

"Difficult to treat" genotype 1 patients: cirrhosis

Analysis of all patients with cirrhosis from phase 2/3 SOF/LDV studies (n=513)



Bourliere et al., AASLD 2014, #82

German Guidelines - HCV Genotype 1

Treatment regimen	Duration (wks.)	Pat. without cirrhosis			Pat. with comp. cirrhosis		
		TN	TE	BOC/TVR	TN	TE	BOC/TVR
SOF + LDV	8	x[4]					
SOF + LDV	12	x	x	x			
SOF + LDV + RBV	12				x	x	x
SOF + LDV	24				(x)[5]	(x)[5]	(x)[5]
SOF + LDV + RBV	24				(x)[5]	(x)[5]	(x)[5]
PTV/r + OMV + DSV (1b)[6]	12	x[6]	x[6]				
PTV/r + OMV + DSV + RBV	12	x[7]	x[7]		x[8]	x[8]	
PTV/r + OMV + DSV + RBV	24				x[8]	x[8]	
SOF + SMV +/- RBV	12	(x)[9]	(x)[9]		(x)[9]	(x)[9]	
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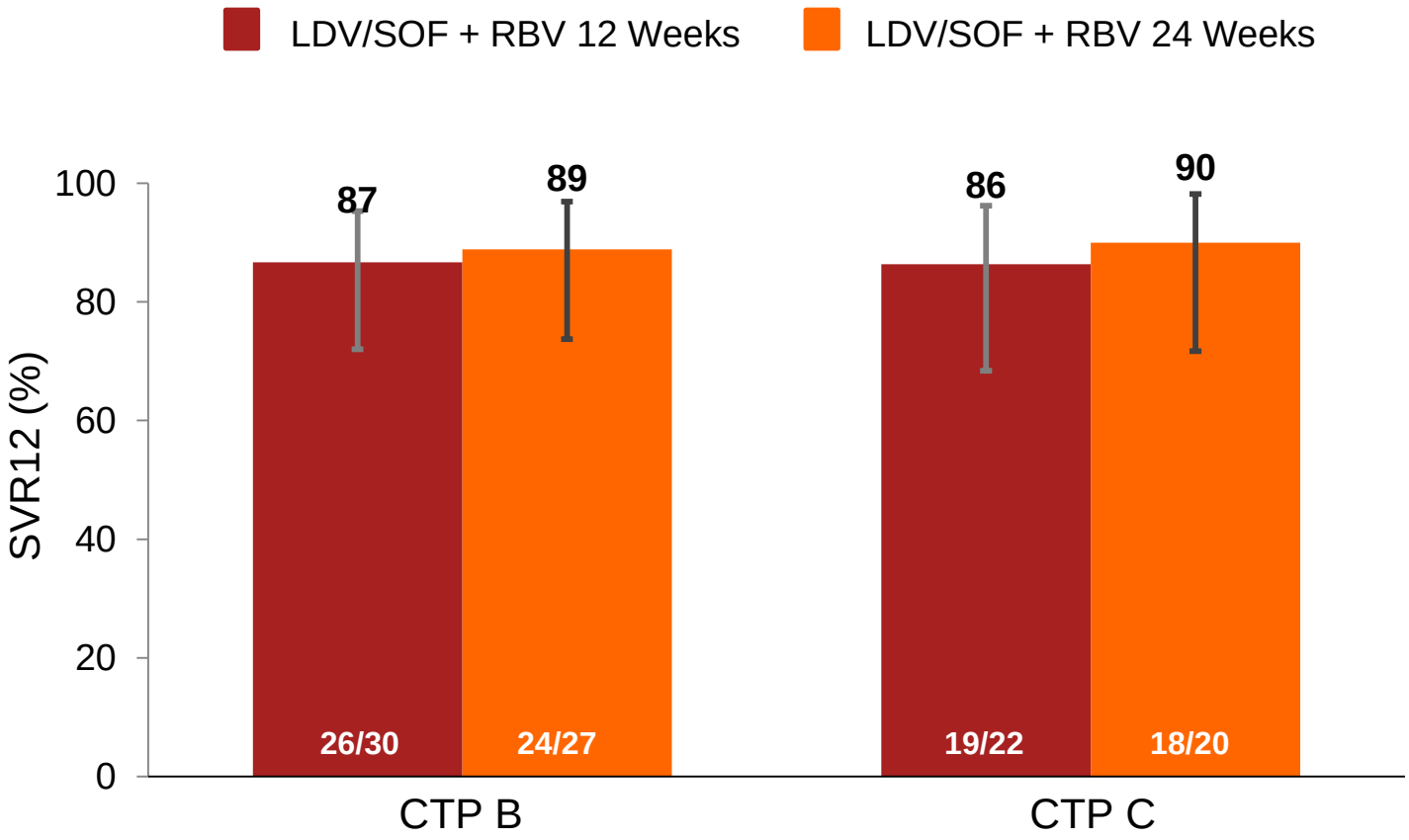
SOF, Sofosbuvir; LDV, Ledipasvir; PTV/r, Paritaprevir/r; OMV, Ombitasvir; DSV, Dasabuvir
SMV, Simeprevir; DCV, Daclatasvir

Sarrazin et al., Z Gastroenterol 2015

Sofosbuvir plus Ledipasvir + RBV for 12 weeks

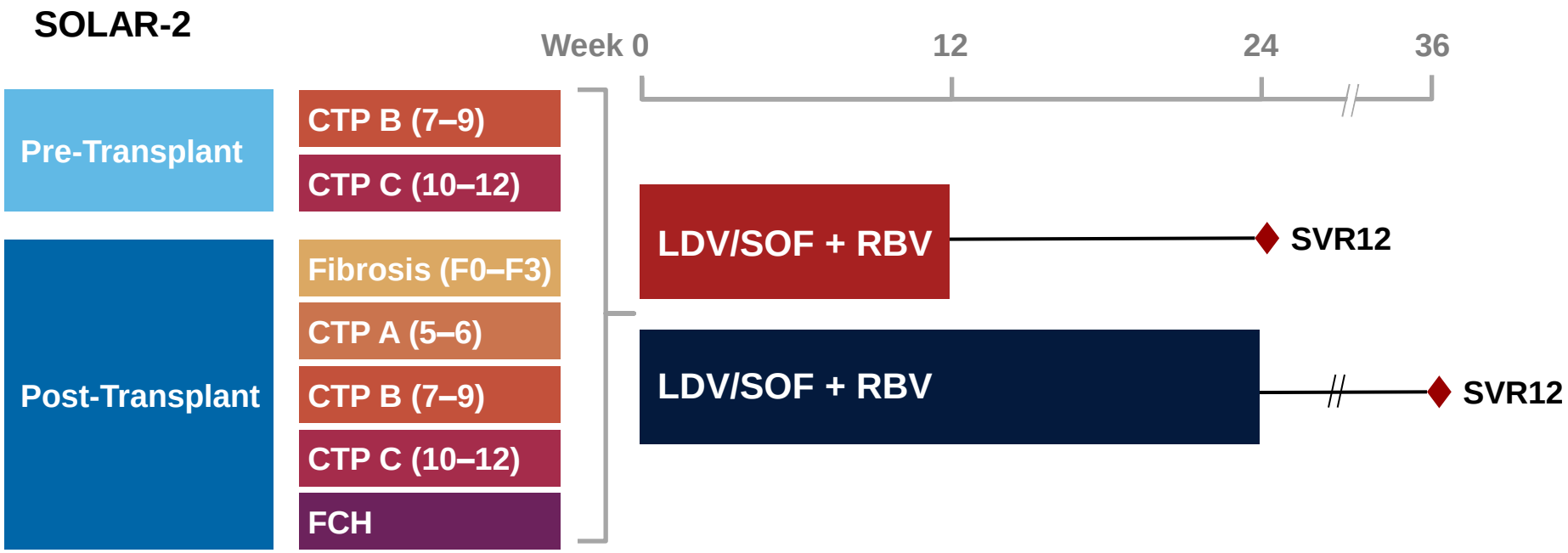
Decompensated liver cirrhosis

Solar 1 Study: Child B and C patients (n=108)



Flamm, AASLD 2014, #239

LDV/SOF+RBV for 12 or 24 Weeks in Decompensated and Post-Liver Transplant HCV GT 1 and GT 4 Patients

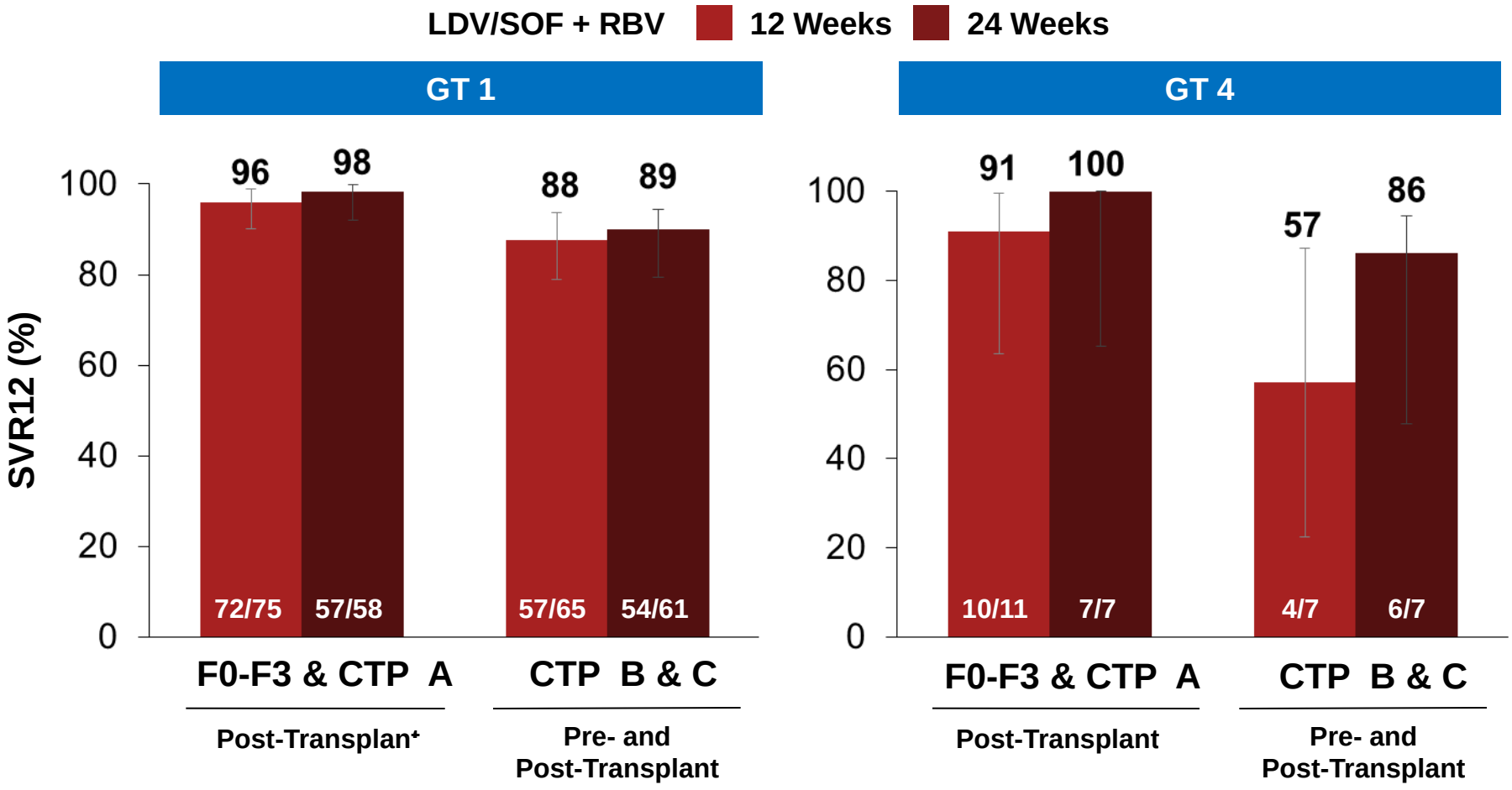


- **Broad inclusion criteria:**
  - **No hepatocellular carcinoma (HCC)**
  - **Total bilirubin ≤ 10 mg/dL, Hemoglobin ≥ 10 g/dL**
  - **CrCl ≥ 40 mL/min, Platelets > 30,000/mL**
- **RBV dosing**
  - **F0–F3 and CTP A cirrhosis: weight-based (< 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)**
  - **CTP B and C cirrhosis: dose escalation, 600–1200 mg/d**

Manns, EASL, 2015, GO2

SOLAR-2: LDV/SOF + RBV in Decompensated and Post-Liver Transplant Patients

SVR12 by Genotype



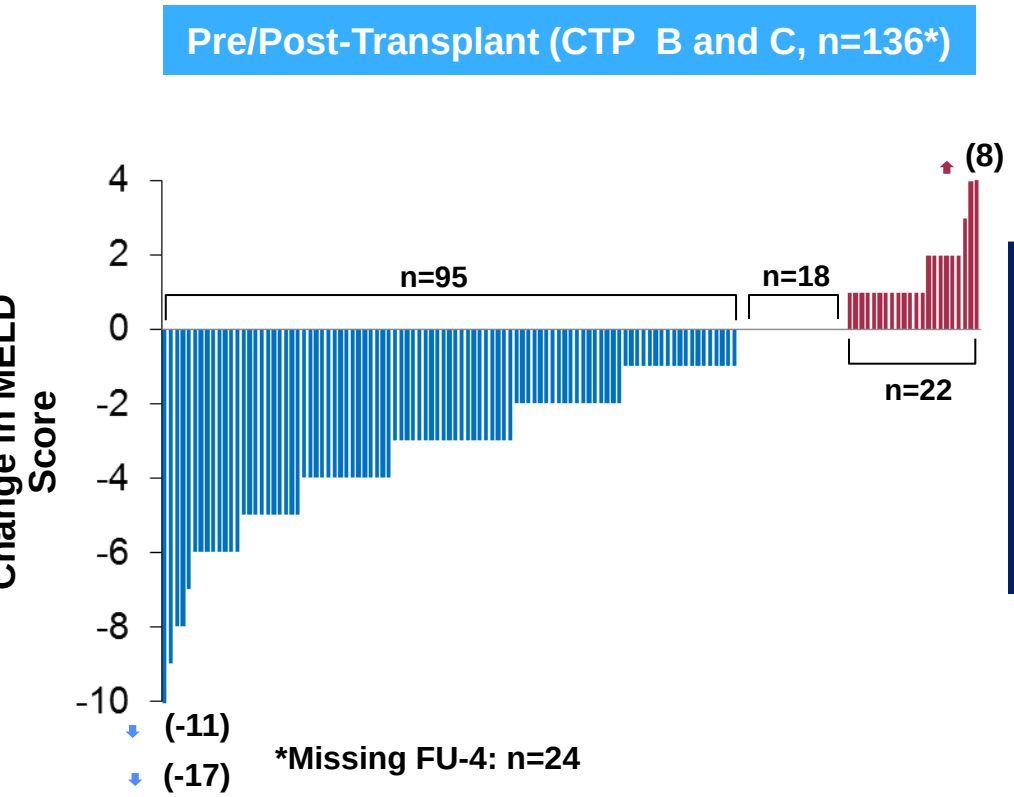
27 subjects in the 24 week arm have not reached SVR12; 7 subjects who were transplanted and 3 subjects did not meet inclusion criteria are excluded.
Error bars represent 2-sided exact 90% confidence intervals.

Manns, EASL, 2015, GO2

SOLAR-2: LDV/SOF + RBV in Decompensated and Post-Liver Transplant Patients

Liver Function Change from Baseline to Follow-Up Wk. 4

MELD Score Change



Change in CTP Class

		Baseline CTP		
		A (5–6) n=73	B (7–9) n=100	C (10–12) n=54
Follow-up Week 4 CTP	A (5–6)	67 (96)	31 (35)	2 (5)
	B (7–9)	3 (4)	57 (65)	20 (48)
	C (10–12)	0	0	20 (48)

no assessment: CTP A, n=3; CTP B, n=12; CTP C, n=12

Majority of patients showed improvements in MELD and CTP scores

Manns, EASL, 2015, GO2

German Guidelines - HCV Genotype 1

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SOF + LDV	12	x	x	x			
SOF + LDV + RBV	12				x	x	x
SOF + LDV	24				(x)[5]	(x)[5]	(x)[5]
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PTV/r + OMV + DSV (1b)[6]	12	x[6]	x[6]				
PTV/r + OMV + DSV + RBV	12	x[7]	x[7]		x[8]	x[8]	
PTV/r + OMV + DSV + RBV	24				x[8]	x[8]	
SOF + SMV +/- RBV	12	(x)[9]	(x)[9]		(x)[9]	(x)[9]	
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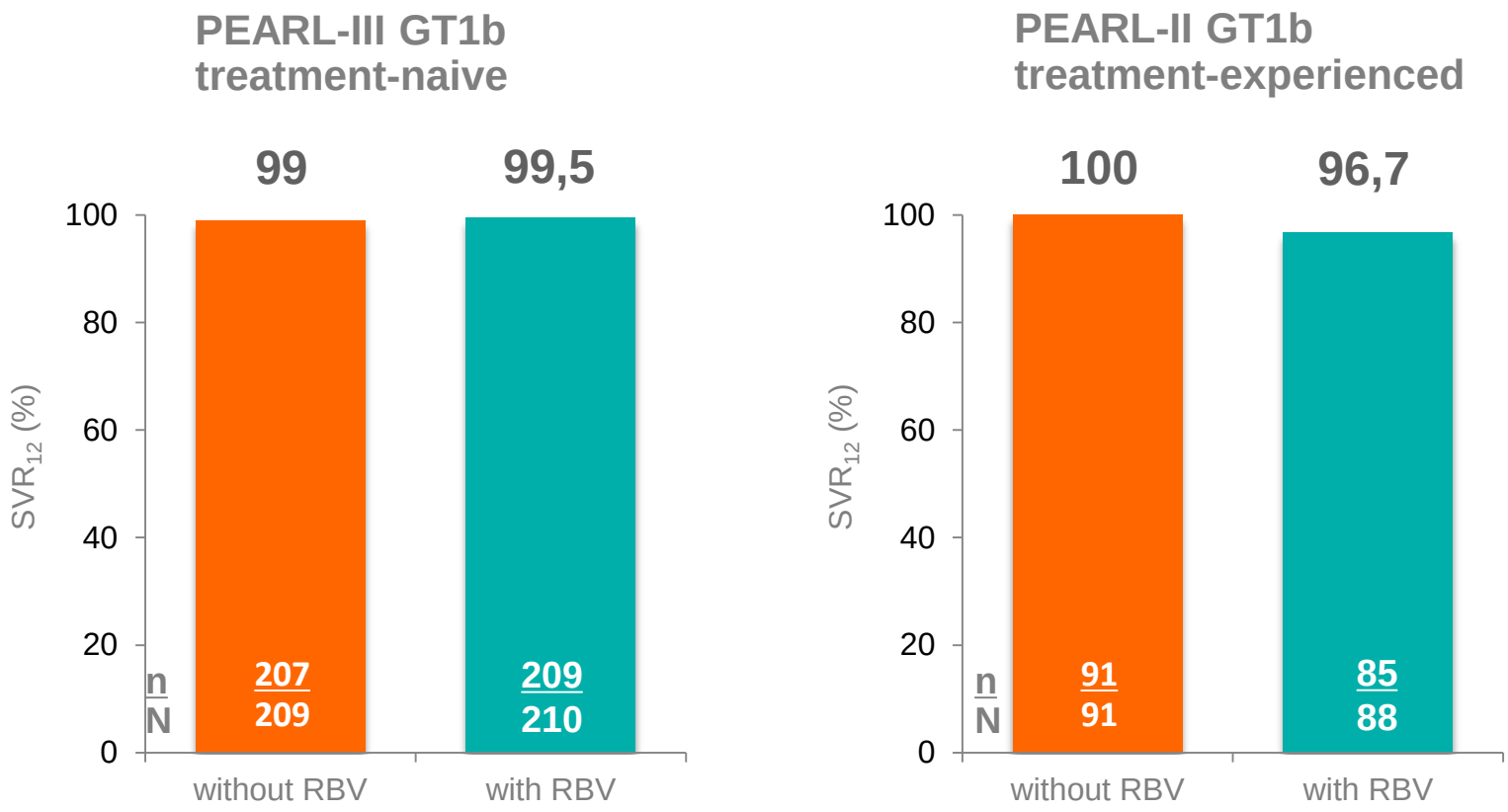
SMV, Simeprevir; DCV, Daclatasvir

Sarrazin et al., Z Gastroenterol 2015

Paritaprevir/r + Ombitasvir + Dasabuvir

Patienten without liver cirrhosis - Genotype 1b

OBV/PTV/r + DSV +/- RBV, 12 weeks



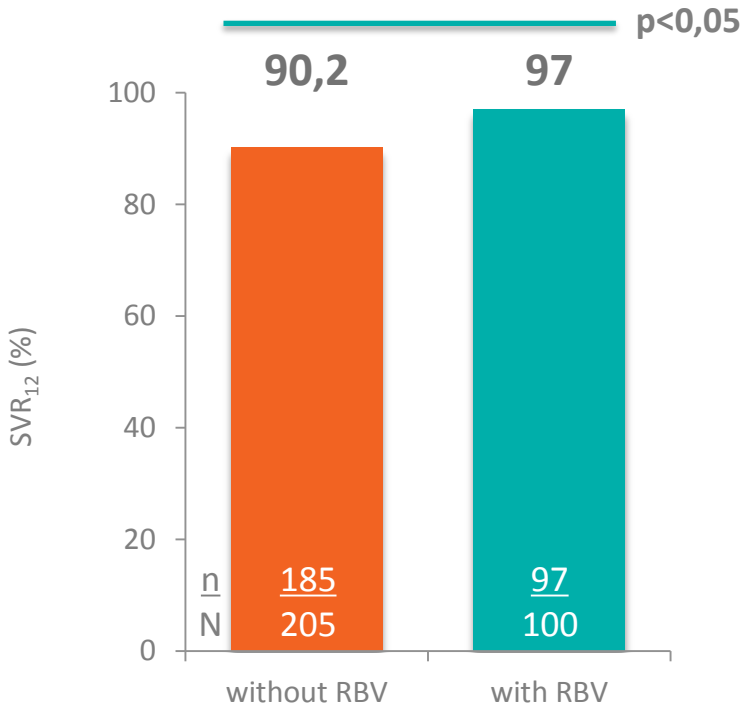
Ferenci P et al. N Engl J Med 2014; 370(21): 1983–92
Andreone P et al. Gastroenterology 2014; 146(5): S–159

Paritaprevir/r + Ombitasvir + Dasabuvir + RBV

Patienten without liver cirrhosis - Genotype 1a

OBV/PTV/r + DSV +/- RBV, 12 weeks

PEARL-IV GT1a treatment-naive



GT1a treatment-experienced

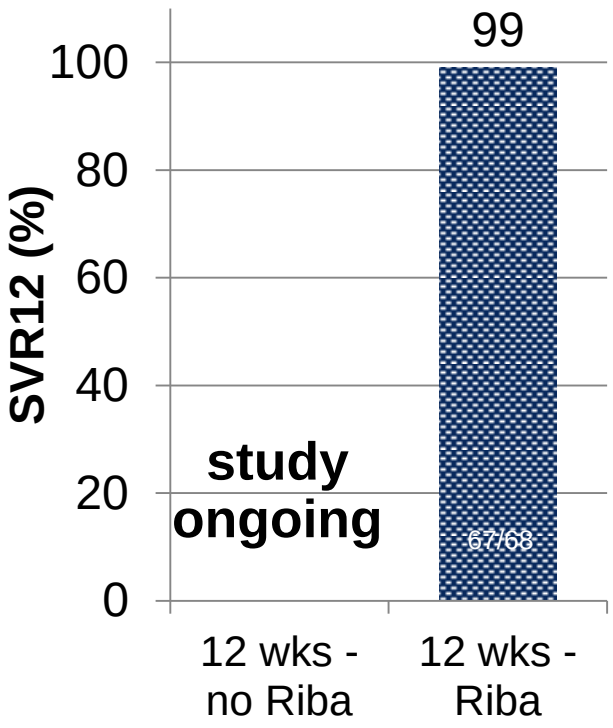
no data

PEARL-II: Andreone P et al., Gastroenterology 2014; 147: 359-365
PEARL-III+IV: Ferenci P et al., N Engl J Med 2014; 370: 1983-1992

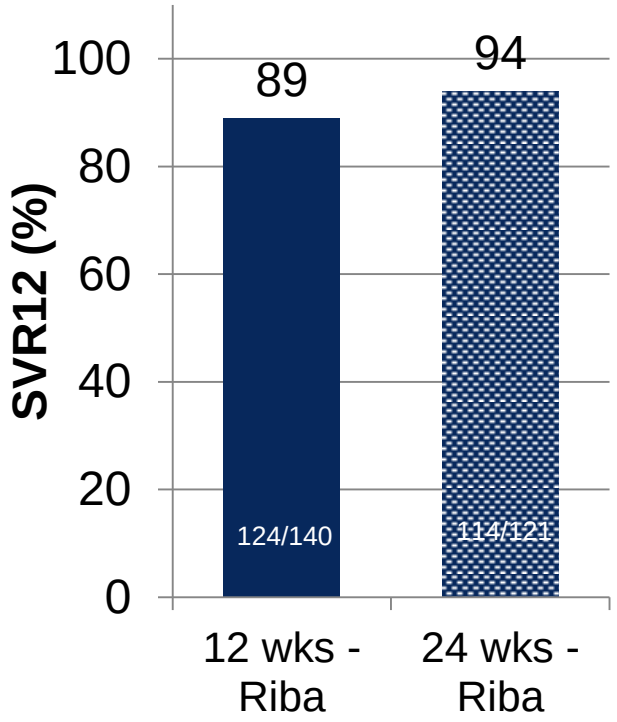
Paritaprevir/r + Ombitasvir + Dasabuvir + RBV

Patients with compensated liver cirrhosis

Treatment-naive/experienced
Genotype 1b



Treatment-naive/experienced
Genotype 1a



AFP <20ng/ml, Thromboc. ≥90/nl, Albumin ≥ 35g/l

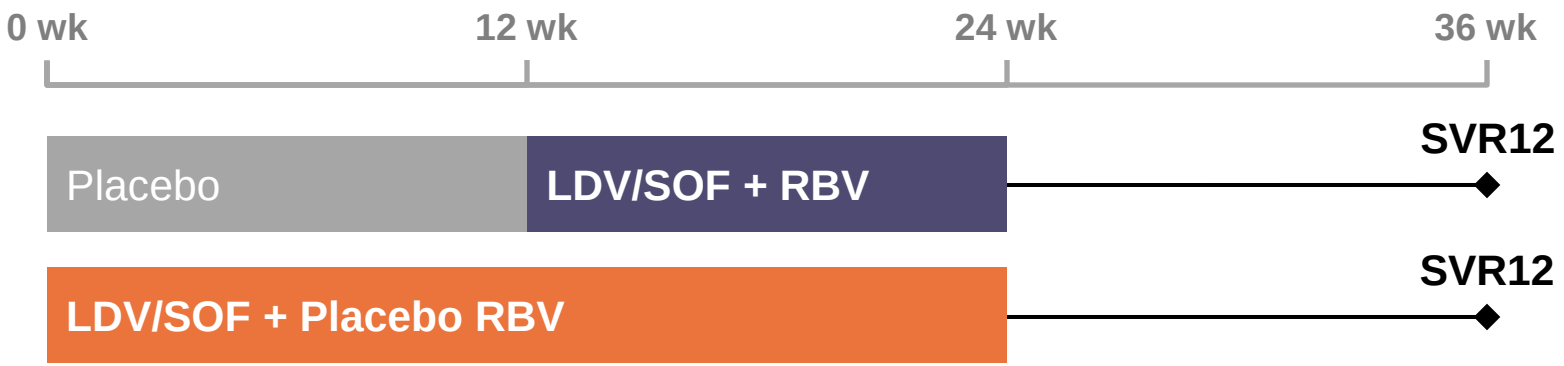
Relapse	12 wks.	24 wks.
Yes	1%	0%
No	21%	2%

Poordad et al., NEJM 2014
and precribing information

Sofosbuvir plus Ledipasvir

Adverse event profile

Sirius Study



- Double-blinded
- Treatment-experienced patients with compensated cirrhosis who did not achieve SVR following sequential PEG + RBV and PI + PEG + RBV regimens
- Stratified
  - HCV genotype (1a, 1b; mixed or other GT 1 results stratified as GT 1a)
  - Prior HCV therapy treatment response (never achieved HCV RNA <LLOQ, achieved HCV RNA <LLOQ)

Bourliere et al., AASLD 2014, LB6

Sofosbuvir plus Ledipasvir

Adverse event profile

	Patients, n (%)	Placebo 12 Weeks → LDV/SOF + RBV 12 Wk			LDV/SOF 24 Wk	
		Placebo 12 Wk n=77	LDV/SOF+RBV 12 Wk n=76	Overall Period n=77	First 12 Wk n=78	Overall Period n=78
Overall Safety	AEs	63 (82)	66 (87)	74 (96)	66 (85)	68 (87)
	Grade 3-4 AEs	1 (1)	5 (7)	6 (8)	2 (3)	10 (13)
	SAEs	1 (1)	3 (4)	4 (5)	3 (4)	8 (10)
	Treatment Related SAEs	0	1 (1)	1 (1)	0	0
	Treatment D/C due to AEs	1 (1)	0	1 (1)	0	0
	Death	0	0	0	0	0
	Grade 3-4 lab abnormalities	18 (23)	8 (11)	24 (31)	15 (19)	11 (14)
	Hb <10 g/dL	1 (1)	1 (1)	2 (3)	0	1 (1)
	Hb <8.5 g/dL	1 (1)	1 (1)	2 (3)	0	0

- Related event was anemia attributed to study treatment
- Treatment D/C due to AEs: bacterial arthritis; decompensated cirrhosis (placebo period)

Bourliere et al., AASLD 2014, LB6

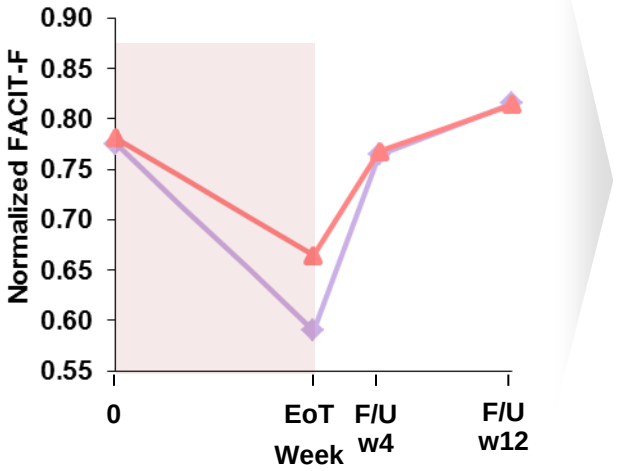
Sofosbuvir plus Ledipasvir

Adverse events and quality of life

Patient related outcome (PRO)

Functional assessment of chronic illness therapy-fatigue (FACIT-F)

PRO with PegIFN/RBV: SOF+PR



➢ **Improvement of quality of life already during treatment**

Younossi et al., AASLD 2014, #77

Side effect profile and drug-drug interactions

Direct antiviral agents	Adverse events	Potential for DDI
Boceprevir (PI)	Anemia, Disgeusea …	Medium
Telaprevir (PI)	Anemia, Rash, Pruritus, …	High
Simeprevir (PI)	Photosensitivity, rash, bilirubin	Medium
Paritaprevir/Ritonavir (PI)	Increase in Bilirubin	Very high
Daclatasvir (NS5A)	No specific so far	Low
Ledipasvir (NS5A)	No specific so far	Low
Ombitasvir (NS5A)	No specific so far	Low
Sofosbuvir (NUC NS5B)	No specific so far	Low
Dasabuvir (Non-NUC NS5B)	No specific so far	Low

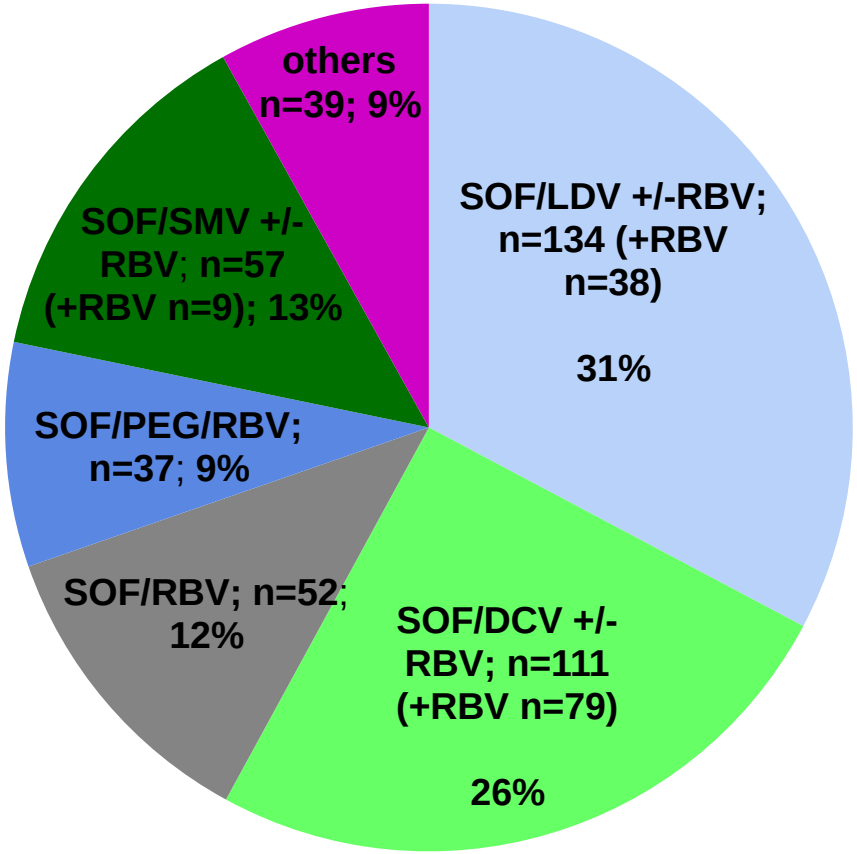
Pill burden

Treatment regimen	DAA	Ribavirin
PEG-IFN s.c. 1/wk + RBV 200mg	n.a.	2/3-0-3
TVR + PEG-IFN + RBV 200mg	2-2-2	2/3-0-3
BOC + PEG-IFN + RBV 200mg	4-4-4	2/3-0-3
PTVr + OMV (FDC) + DSV +/- RBV	3-0-1	2/3-0-3
SOF + LDV (FDC) +/- RBV	1-0-0	2/3-0-3

DAA-based therapies Jan 14 to Mar 15

Frankfurt experience

All patients Frankfurt, Germany, n=430



DAA-based therapies Jan 14 to Mar 15

Frankfurt experience

Genotype 1

Final treatment outcome (at least SVR FU4)

Therapy	n	SVR	SVR %	Relapse	LTFU / AE / death etc.
SOF/PEG/RBV	18	15/18	83%		N=3
SOF/RBV	6	3/6	50%	N=2	N=1
SOF/SMV+/-R	50	42/50	84%	N=5	N=3
SOF/DCV+/-R	52	47/52	90%	N=2	N=3
SOF/LDV+/-R	18	18/18	100%		

Summary

- **High burden of disease with increasing no of patients with complications (cirrhosis, HCC, …)**

- **Interferon based antiviral therapies**
  - (SOF)/PEG/R with high efficacy in easy to treat patients
  - Limited efficacy in Non-Responders/cirrhotics
  - Side effects of Interferon alfa, first generation DAAs …
  - Durations between 12 and 48 weeks, high pill burden

- **Interferon free treatment options**
  - Combinations for all patients with high efficacy
  - Reduced pill burden, improved side effect profile
  - Short durations with 8 or 12 (24) weeks
  - Drug-drug interactions depending on substance class