Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

Management dell'Infezione da HCV nel pre- e post-Trapianto

Stefano Fagiuoli
U.S.C. Gastroenterologia Epatologie e Trapiantologia
Ospedale Papa Giovanni XXIII - Bergamo

formAzione

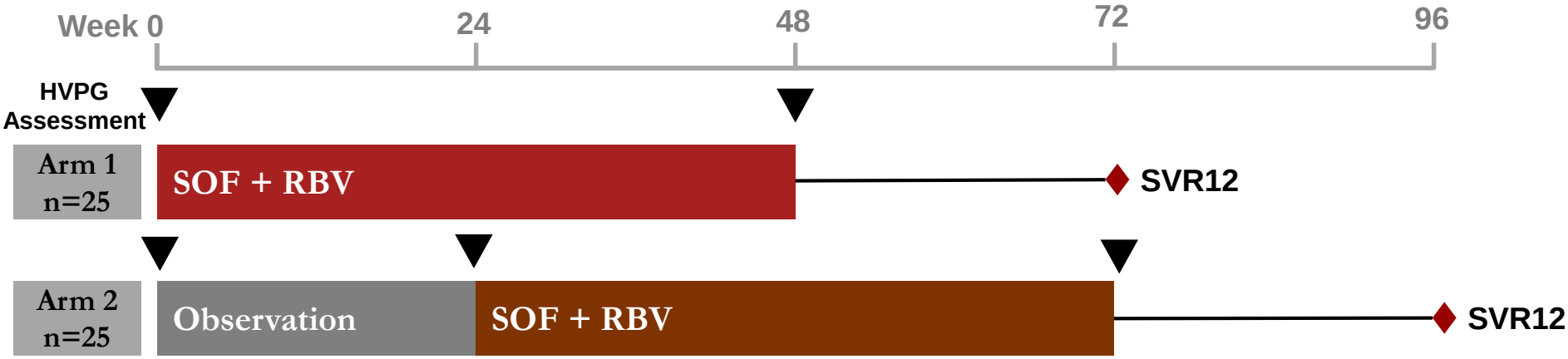
CORSO DI AGGIORNAMENTO
UPDATE SUL TRATTAMENTO DELL'INFEZIONE DA HCV: PROBLEMI CLINICI E GESTIONALI
MILANO, STARHOTEL ECHO - 2 OTTOBRE 2015

Outline

- Decompensated cirrhosis (patient on the waiting list)
- Prevention of post-transplant HCV recurrence
- Treatment of post-transplant HCV recurrence

Effect of SOF+RBV on Hepatic Venous Pressure Gradient

SOF+RBV in Compensated and Decompensated Cirrhotics with Portal Hypertension



RBV 1000–1200 mg

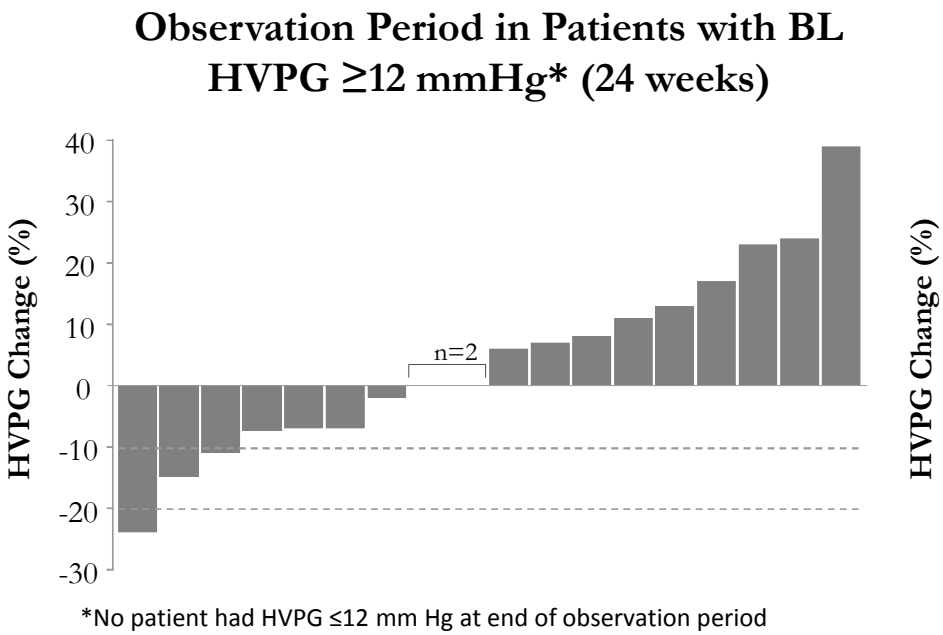
	Arm 1 n=25	Arm 2 n=25	All With Paired HVPG n=37
Male, n (%)	18 (72)	20 (80)	28 (76)
Mean age, y (range)	55 (43–69)	56 (44–69)	55 (44–69)
HCV GT 1, n (%)	19 (76)	15 (60)	25 (68)
HCV GT 2, 3, 4, n (%)	2 (8), 2 (8), 2 (8)	1 (4), 8 (32), 1 (4)	2 (5), 8 (22), 2 (5)
Prior HCV treatment	17 (68)	23 (92)	28 (76)

HVPG = hepatic venous pressure gradient

Afdhal, EASL, 2015, LP13

HVPG Change Over Time

SOF+RBV in Compensated and Decompensated Cirrhotics with Portal Hypertension



*No patient had HVPG ≤12 mm Hg at end of observation period

There were clinically meaningful improvements in portal hypertension in addition to improvements in liver biochemistry, CTP and MELD scores

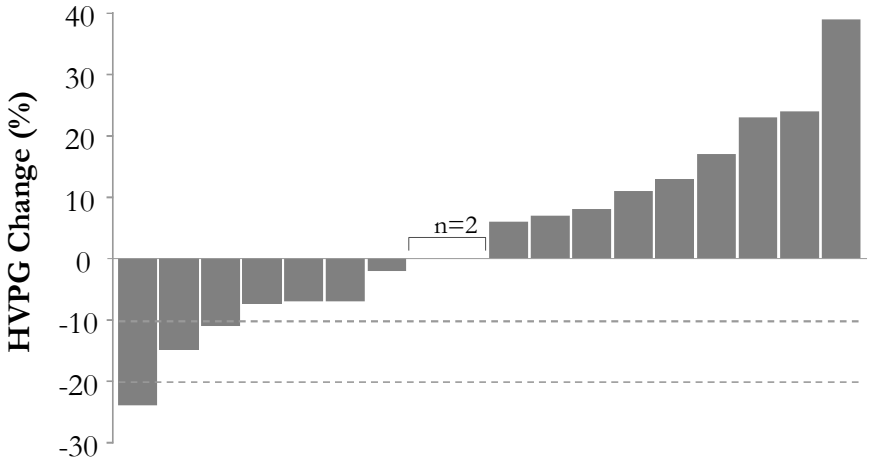
The effect of SVR12 and viral suppression on HVPG is being monitored at 1 year post-treatment

HVPG = hepatic venous pressure gradient
A reduction in HVPG ≥20% or below the 12-mm Hg threshold markedly reduces the risk of variceal bleeding, and varices may decrease in size

HVPG Change Over Time

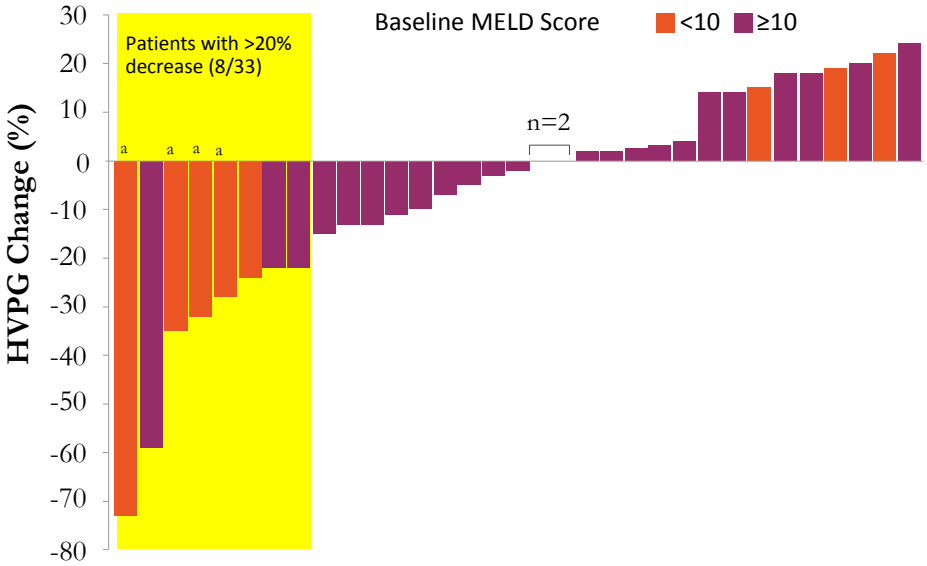
SOF+RBV in Compensated and Decompensated Cirrhotics with Portal Hypertension

Observation Period in Patients with BL HVPG ≥12 mmHg* (24 weeks)



*No patient had HVPG ≤12 mm Hg at end of observation period

Changes After Treatment in Patients with BL HVPG ≥12 mmHg (n=33)



[a]Patients with HVPG ≤12 mm Hg at end of treatment

There were clinically meaningful improvements in portal hypertension in addition to improvements in liver biochemistry, CTP and MELD scores

The effect of SVR12 and viral suppression on HVPG is being monitored at 1 year post-treatment

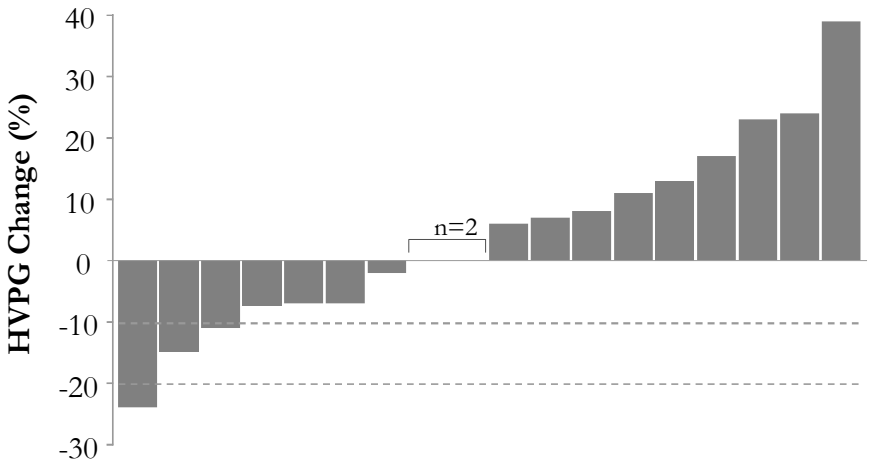
HVPG = hepatic venous pressure gradient
A reduction in HVPG ≥20% or below the 12-mm Hg threshold markedly reduces the risk of variceal bleeding, and varices may decrease in size

Afdhal, EASL, 2015, LP13

HVPG Change Over Time

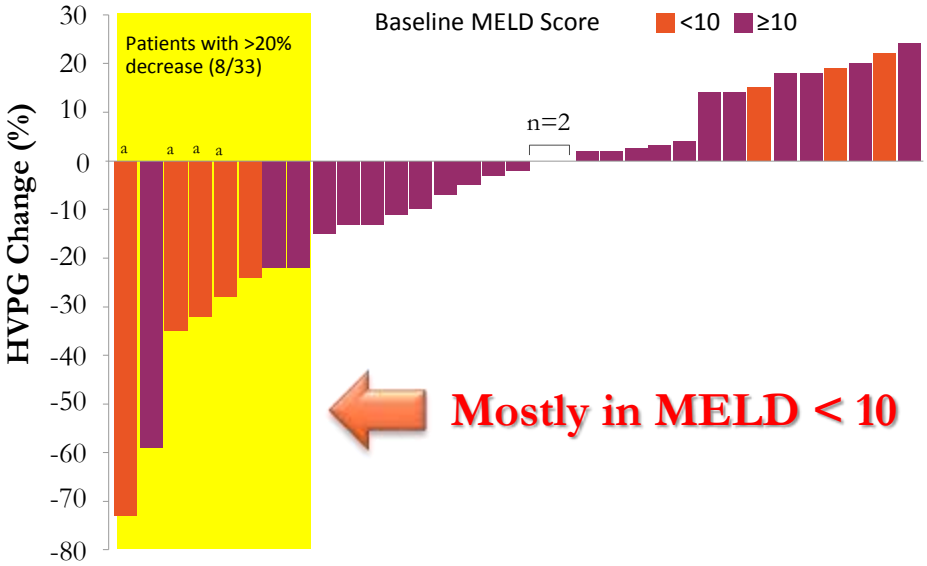
SOF+RBV in Compensated and Decompensated Cirrhotics with Portal Hypertension

Observation Period in Patients with BL HVPG ≥12 mmHg* (24 weeks)



*No patient had HVPG ≤12 mm Hg at end of observation period

Changes After Treatment in Patients with BL HVPG ≥12 mmHg (n=33)



[a]Patients with HVPG ≤12 mm Hg at end of treatment

There were clinically meaningful improvements in portal hypertension in addition to improvements in liver biochemistry, CTP and MELD scores

The effect of SVR12 and viral suppression on HVPG is being monitored at 1 year post-treatment

HVPG = hepatic venous pressure gradient
A reduction in HVPG ≥20% or below the 12-mm Hg threshold markedly reduces the risk of variceal bleeding, and varices may decrease in size

DECOMPENSATED CIRRHOSIS
HCV PATIENT ON THE WAITING LIST

LDV/SOF + RBV FOR HCV PATIENTS WITH DECOMPENSATED CIRRHOSIS (SOLAR-1)

Prospective, multicenter study of 12 or 24 weeks of LDV/SOF + RBV in TN and TE HCV GT 1 and 4 patients with CTP B (N=59) or **CTP C (N=49) clinically decompensated cirrhosis**

- 108 patients randomized 1:1 to 12 or 24 weeks of treatment
- Stratified by CTP class B [7-9] or C [score 10–12]*
- Broad inclusion criteria:
  - No history of major organ transplant, including liver
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤10 mg/dL, Hemoglobin ≥ 10 g/dL
  - CrCl≥ 40 mL/min, Platelets > 30,000
- RBV dosing: dose escalation, 600–1200 mg/d

*Patients with CTP scores 13-15 were excluded

Flamm, AASLD 2014/ Manns EASL 2015/Charlton Gastroenterology 2015

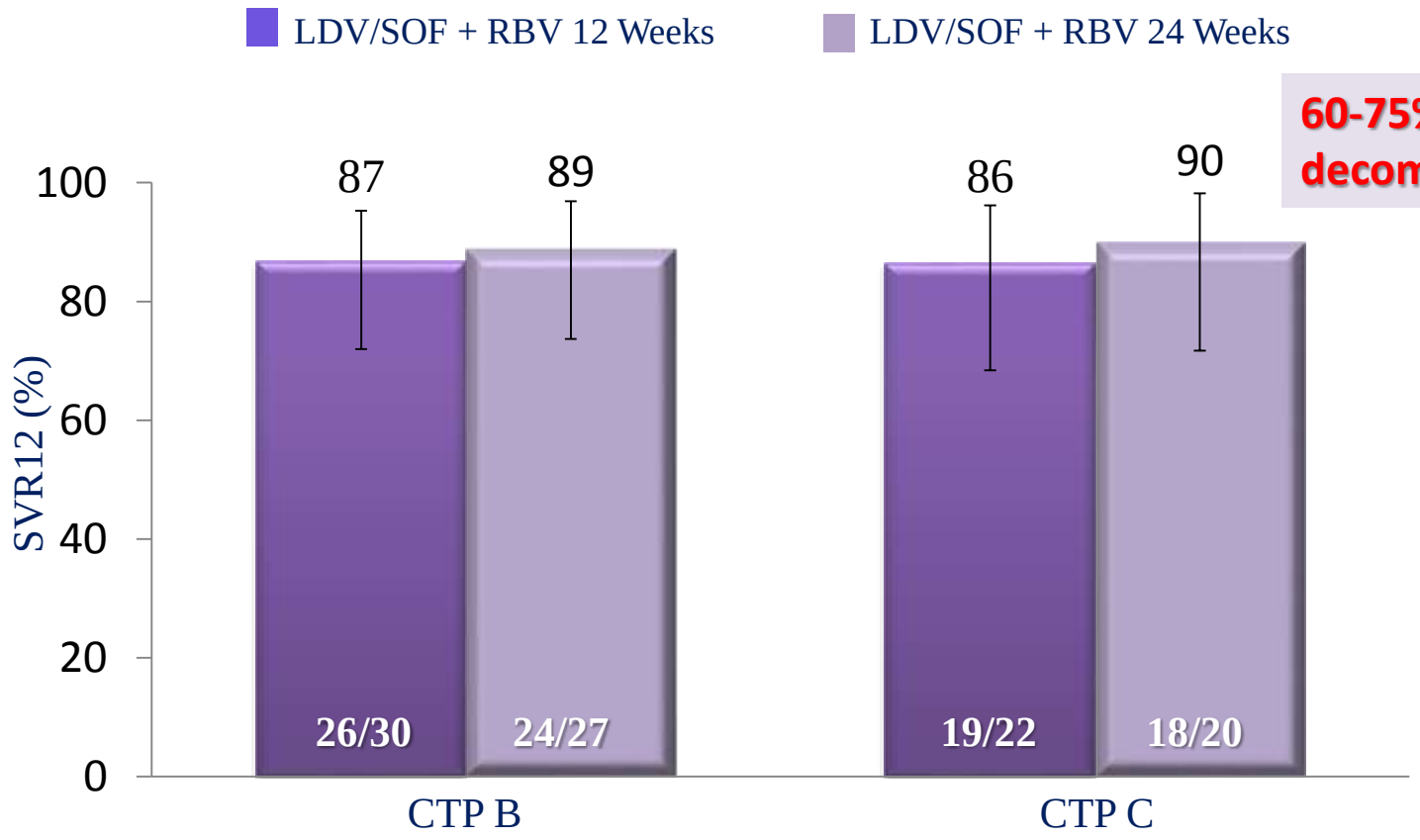
LDV/SOF + RBV IN DECOMPENSATED CIRRHOSIS: DEMOGRAPHICS (SOLAR-1)

	CTP B		CTP C	
	12 Weeks n=30	24 Weeks n=29	12 Weeks n=23	24 Weeks n=26
Median age, y (range)	60 (28-69)	58 (35-69)	58 (41-71)	59 (48-68)
Male, n (%)	22 (73)	18 (62)	14 (61)	18 (69)
White, n (%)	29 (97)	26 (90)	21 (91)	24 (92)
BMI ≥30 kg/m^2, n (%)	10 (33)	10 (34)	13 (57)	9 (35)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	5.9 (4.3-6.7)	5.8 (3.2-7.1)	5.6 (4.1-6.5)	5.8 (3.7-6.9)
GT 1a, n (%)	19 (63)	22 (76)	15 (65)	18 (69)
IL28B non-CC, n (%)	26 (87)	23/28 (82)	17 (74)	19 (73)
Prior HCV treatment, n (%)	22 (73)	19 (66)	11 (48)	18 (69)
MELD score, n (%)				
<10	6 (20)	8 (28)	0	0
10–15	21 (70)	16 (55)	16 (70)	13 (50)
16-20	3 (10)	5 (17)	7 (30)	12 (46)
21-25	0	0	0	1 (4)
Ascites, n (%)	17 (57)	17 (59)	22 (96)	25 (96)
Encephalopathy, n (%)	20 (67)	16 (55)	21 (91)	23 (88)

LDV/SOF + RBV IN DECOMPENSATED CIRRHOSIS: DEMOGRAPHICS (SOLAR-1)

	CTP B		CTP C	
	12 Weeks n=30	24 Weeks n=29	12 Weeks n=23	24 Weeks n=26
Median age, y (range)	60 (28-69)	58 (35-69)	58 (41-71)	59 (48-68)
Male, n (%)	22 (73)	18 (62)	14 (61)	18 (69)
White, n (%)	29 (97)	26 (90)	21 (91)	24 (92)
BMI ≥30 kg/m^2, n (%)	10 (33)	10 (34)	13 (57)	9 (35)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	5.9 (4.3-6.7)	5.8 (3.2-7.1)	5.6 (4.1-6.5)	5.8 (3.7-6.9)
GT 1a, n (%)	19 (63)	22 (76)	15 (65)	18 (69)
IL28B non-CC, n (%)	26 (87)	23/28 (82)	17 (74)	19 (73)
Prior HCV treatment, n (%)	22 (73)	19 (66)	11 (48)	18 (69)
MELD score, n (%)				
<10	6 (20)	8 (28)	0	0
10–15	21 (70)	16 (55)	16 (70)	13 (50)
16-20	3 (10)	5 (17)	7 (30)	12 (46)
21-25	0	0	0	1 (4)
Ascites, n (%)	17 (57)	17 (59)	22 (96)	25 (96)
Encephalopathy, n (%)	20 (67)	16 (55)	21 (91)	23 (88)

LDV/SOF + RBV IN DECOMPENSATED CIRRHOSIS
RESULTS: SVR12 (SOLAR-1)



60-75% in severe decompensation

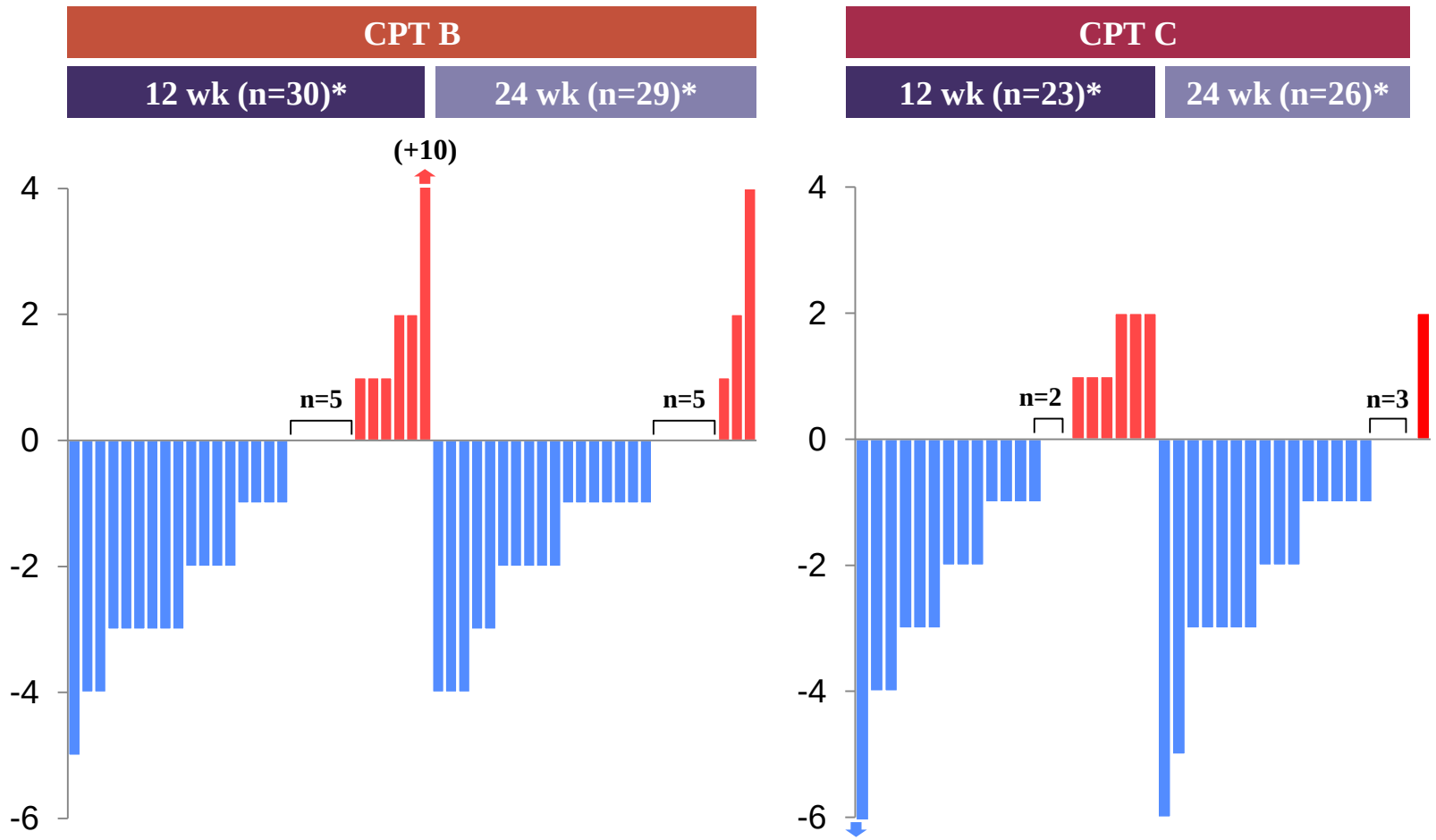
SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Error bars represent 90% confidence intervals.

LDV/SOF + RBV IN DECOMPENSATED CIRRHOSIS
RESULTS: SVR12 (SOLAR-1)

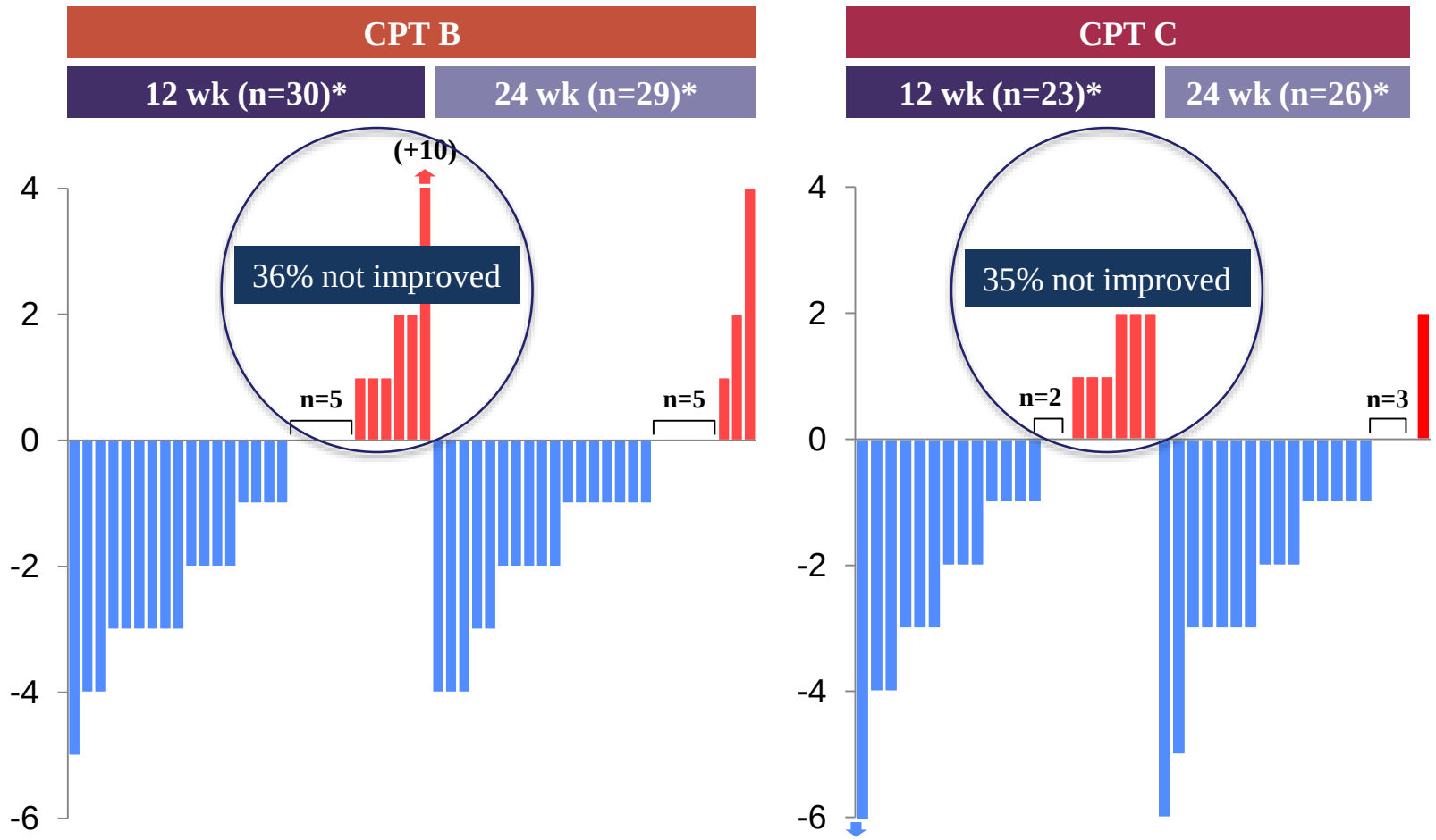
- Serious treatment-related adverse events were rare, **discontinuation** in 13/337 (**4%**) patients.
- **Death in 10** cases for hepatic **decompensation.**
- **Liver transplant in 6** cases: 1 patient died 2 weeks after transplant, 5 continued to have undetected HCV-RNA.

LABORATORY RESULTS: MELD SCORE
CHANGE FROM BASELINE TO FOLLOW-UP WEEK 4



*Missing FU-4: n=2 CPT B 12 wk; n=4 CPT B 24 wk; n=2 CPT C 12 wk; n=7 CPT C 24 wk.

LABORATORY RESULTS: MELD SCORE
CHANGE FROM BASELINE TO FOLLOW-UP WEEK 4

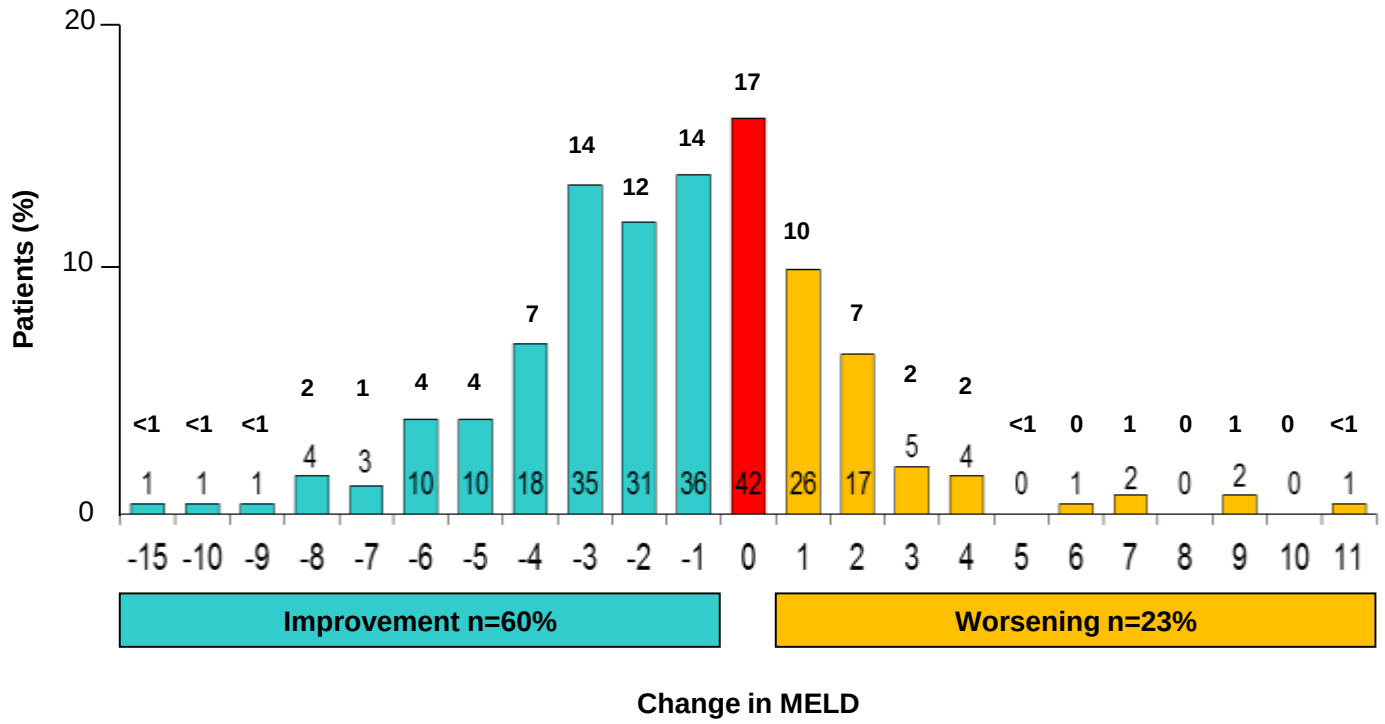


*Missing FU-4: n=2 CPT B 12 wk; n=4 CPT B 24 wk; n=2 CPT C 12 wk; n=7 CPT C 24 wk.

Combined Efficacy from the SOLAR-1 and SOLAR-2

LDV + SOF + RBV for 12/24 weeks

Total n=250 patients had no assessment at follow up week 12



Gane et al, AASLD 2015

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
2015
AASLD

Ledipasvir and Sofosbuvir in Patients With Genotype 1 Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Safety and Efficacy Analysis

K. Rajender Reddy,[1*] Marc Bourlière,[2*] Mark Sulkowski,[3] Masao Omata,[4] Stefan Zeuzem,[5] Jordan J. Feld,[6] Eric Lawitz,[7] Patrick Marcellin,[8] Tania M. Welzel,[5] Robert Hyland,[9] Xiao Ding,[9] Jenny Yang,[9] Steven Knox,[9] Phillip Pang,[9] Hadas Dvory-Sobol,[9] G. Mani Subramanian,[9] William Symonds,[9] John G. McHutchison,[9] Alessandra Mangia,[10] Edward Gane,[11] Masashi Mizokami,[12] Stanislas Pol,[13] and Nezam Afdhal[14]

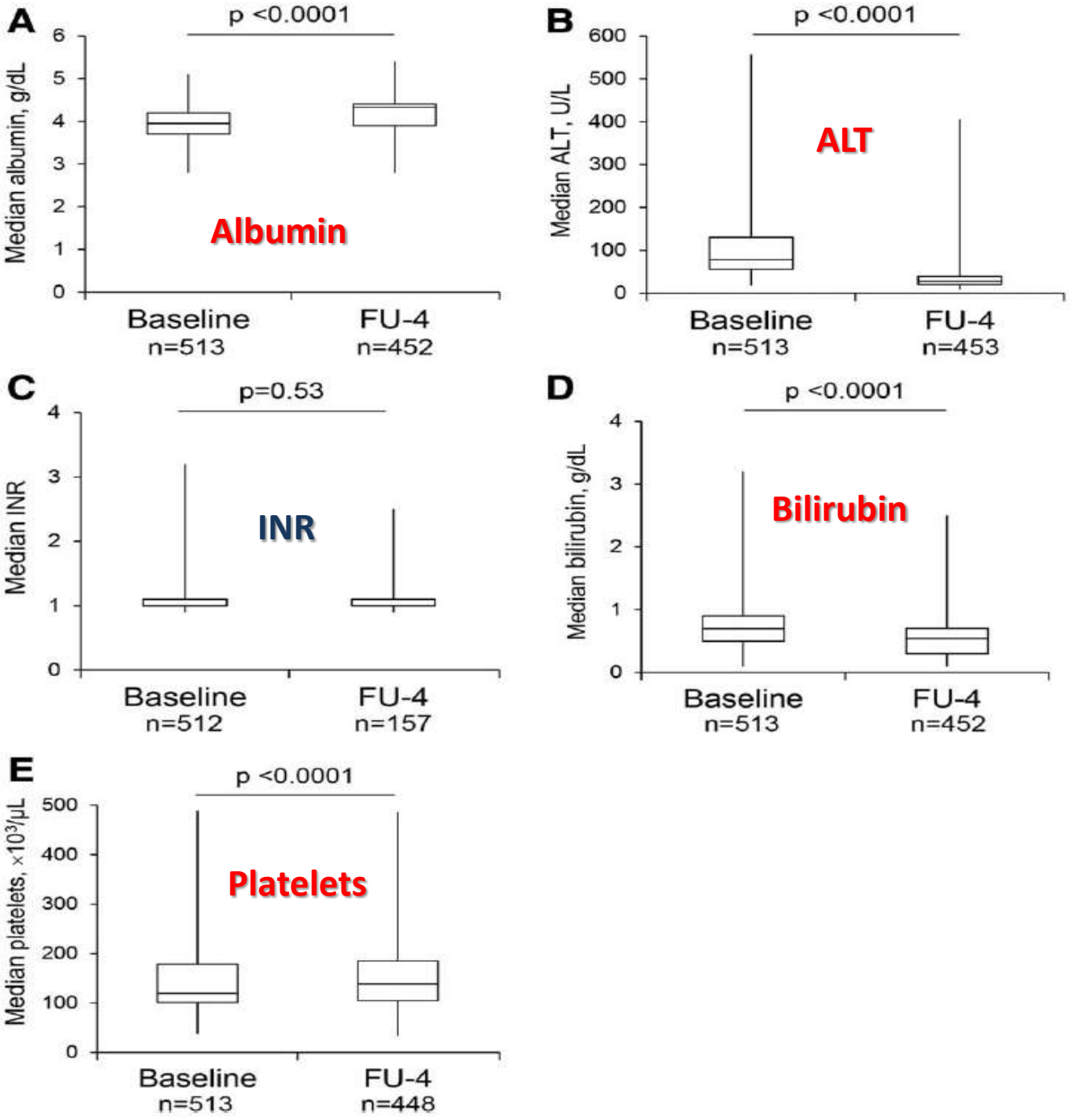


Fig. 1. Change from baseline in selected laboratory tests. (A) Albumin. (B) ALT. (C) International normalized ratio (INR). (D) Bilirubin. (E) Platelets. Panels show levels of laboratory tests at baseline and post-treatment week 4. Median level is indicated by the central line, the box outlines the IQR for the parameter, and the whiskers show the range of values.

Safety and efficacy of all oral HCV therapy in 277 patients with decompensated cirrhosis (MELD>10) - TARGET

Total cohort	SOF / RBV n = 120	SOF/SMV n = 123	SOF/SMV/RBV n = 34	All n = 277
Genotype, n (%)				
GT 1	45 (38%)	122 (99%)	32 (94%)	199 (71.8%)
GT 2	35 (29%)	0 (0%)	0 (0%)	35 (12.6%)
G3	37 (31%)	0 (0%)	0 (0%)	37 (13.4%)
G4	2 (2%)	0 (0%)	2 (6%)	4 (1.4%)
Other	1 (1%)	1 (1%)	0 (0%)	2 (1%)
MELD				
10–15	97 (81%)	104 (84%)	29 (85%)	230 (83%)
16–21	20 (17%)	12 (10%)	4 (12%)	36 (13%)
>21	3 (2%)	7 (6%)	1 (3%)	11 (4%)
Discontinued due to				
AE	3 (3%)	5 (4%)	3 (9%)	11 (4%)
Lack of efficacy	3 (3%)	0 (0%)	0 (0%)	3 (1.1%)
Died	0 (0%)	2 (2%) (liver failure, vascular shock)	1 (3%) (cause unknown)	3 (1.1%)
Virological response	(G2 only)	(G1 only)	(G1 only)	
SVR 4	18/24 (75%)	55/71 (77%)	13/16 (81%)	
Relapse	3/24 (12%)	15/71 (21%)	3/16 (19%)	
Breakthrough	1/24 (4%)	0/71 (0%)	0/16 (0%)	
Non-response	1/24 (4%)	1/71 (1%)	0/16 (0%)	
Loss to F-up	1/24 (4%)	0/71 (0%)	0/16 (0%)	

Reddy 2015

TARGET – Adverse events (AE)

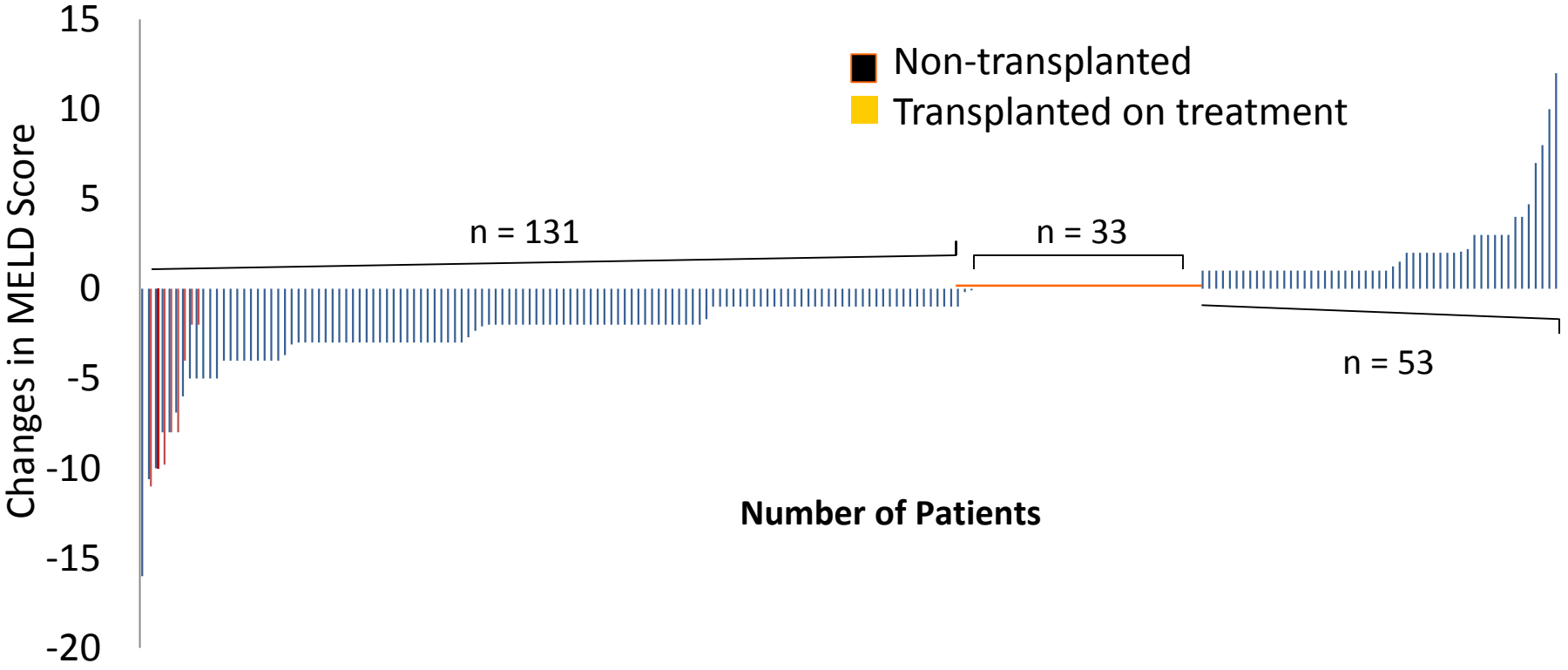
At least one AE was reported by 88% of all patients (most were mild)

- Pre/post-treatment **bilirubin** values:
  - *46/58 (80%) improved*
  - *2/58 (3%) unchanged*
  - ***10/58 (17%) worsened***
- Pre/post-treatment **albumin** values:
  - *33/54 (61%) increased*
  - *7/54 (13%) unchanged*
  - ***14/54 (26%) decreased***
- 26 patients had baseline **MELD** and post treatment W4 data available:
  - 18 improved
  - 5 unchanged
  - **3 worsened.**

Reddy EASL 2015

MELD Improvement in GT 1/3 Patients with History of Decompensated Cirrhosis

NHS England EAP: SOF+NS5A±RBV for 12 Weeks



Improvement of > 2 MELD scores was observed in 41% by FU Week 4

and

48% had no significant changes

Comparative MELD scores available for 217 patients

Foster, EASL, 2015, O002

Italian cohort of HCV cirrhotic patients on the waiting list treated with DAAs – Preliminary data – CNT 20.5.2015

DAAs	N	%
SOFOSBUVIR	15	7,2%
SOFOSBUVUR + RIBA	163	78,4%
SOFOSBUVIR + DACLATASVIR	9	4,3%
SOFOSBUVIR + RIBA + LEDIPASVIR	3	1,4%
SOFOSBUVIR + RIBA + PEG IFN a2a	1	0,5%
NA	17	8,2%
TOTAL	**208**	100,0%

Effect of DAAs on MELD in 208 cases treated while in the waiting list CNT 20.5.15

MELD	MELD variation	N cases	Media MELD points variation
From baseline to end of treatment	Improved	12 (23%)	-3,5
	Stable	14 (27%)	0
	Worsened	25 (50%)	2,7
	Total	51	0,49

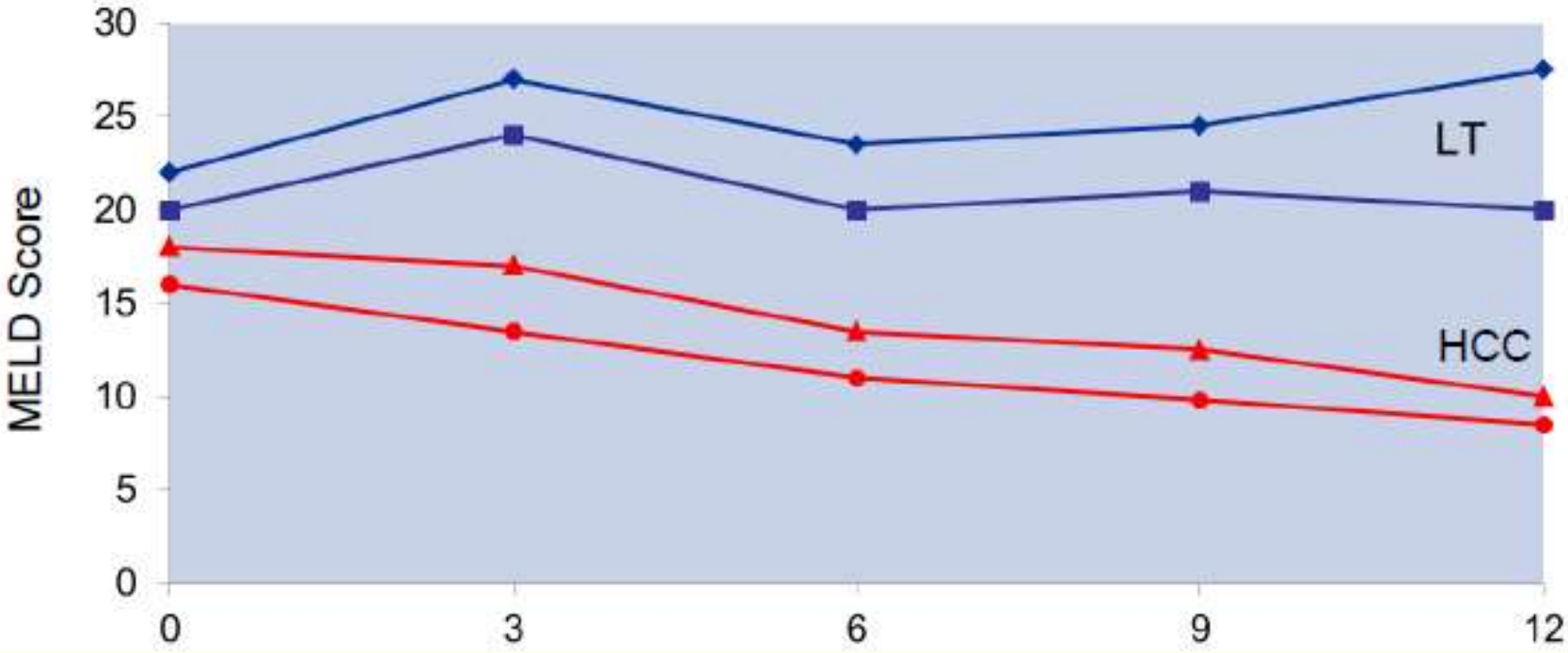
De-listing or priority (?)

- Lack of data in patients with decompensated cirrhosis who could benefit from such regimens and be removed from liver transplant waiting list.

Eradication of HCV: What about CURE ???

Point of NO RETURN ????

- 120 patients with advanced cirrhosis treated with SOF+SMV for 12 weeks
- Overall SVR=81%
- Patients with MELD >20 did not appear to improve
- HCC developed in some patients that appeared to improve

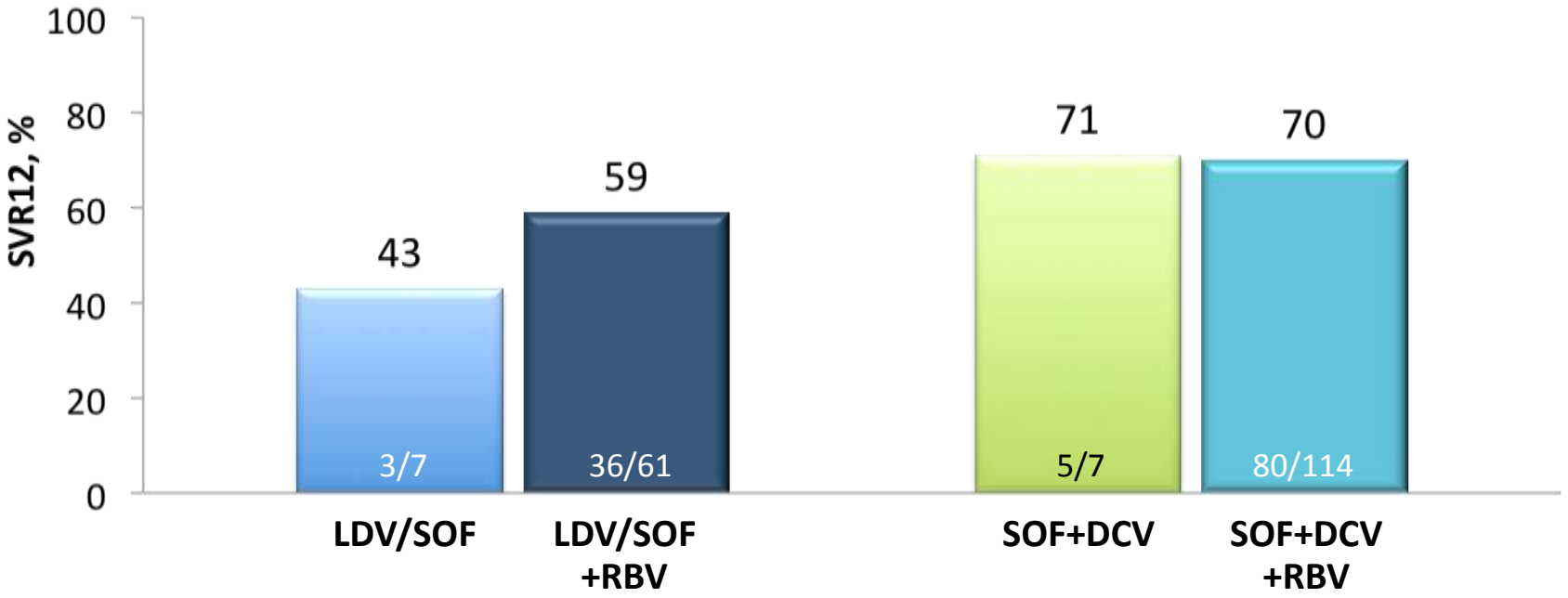


Shiffman et al, Hepatology 2015 submitted

Courtesy of Dr Shiffman

NHS England EAP: SOF+NS5A±RBV for 12 Weeks

SVR12 in GT 3 Patients with History of Decompensated Cirrhosis



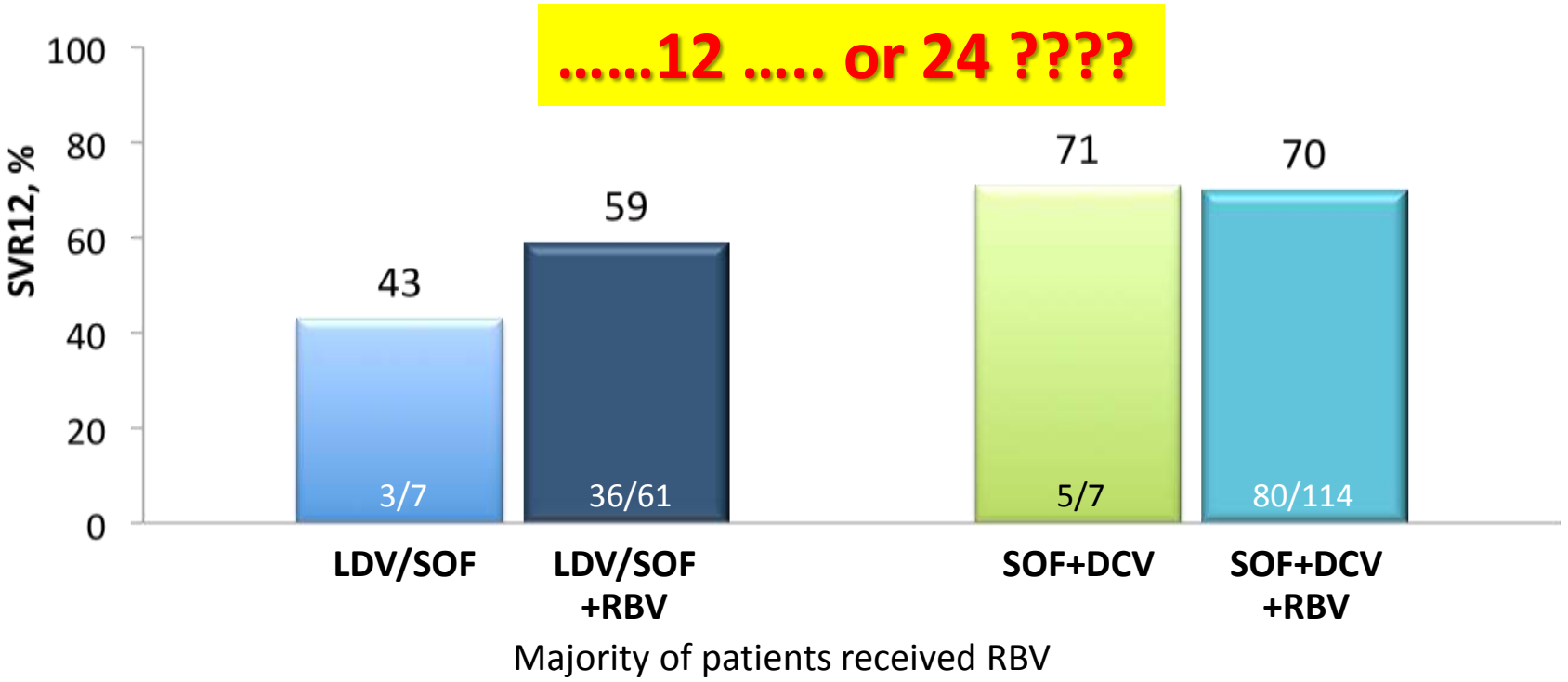
Majority of patients received RBV

SVR rates were comparable to those seen in other studies of SOF+NS5A±RBV for 12 weeks in decompensated cirrhotics

Foster, EASL, 2015, O002

NHS England EAP: SOF+NS5A±RBV for 12 Weeks

SVR12 in GT 3 Patients with History of Decompensated Cirrhosis



Majority of patients received RBV

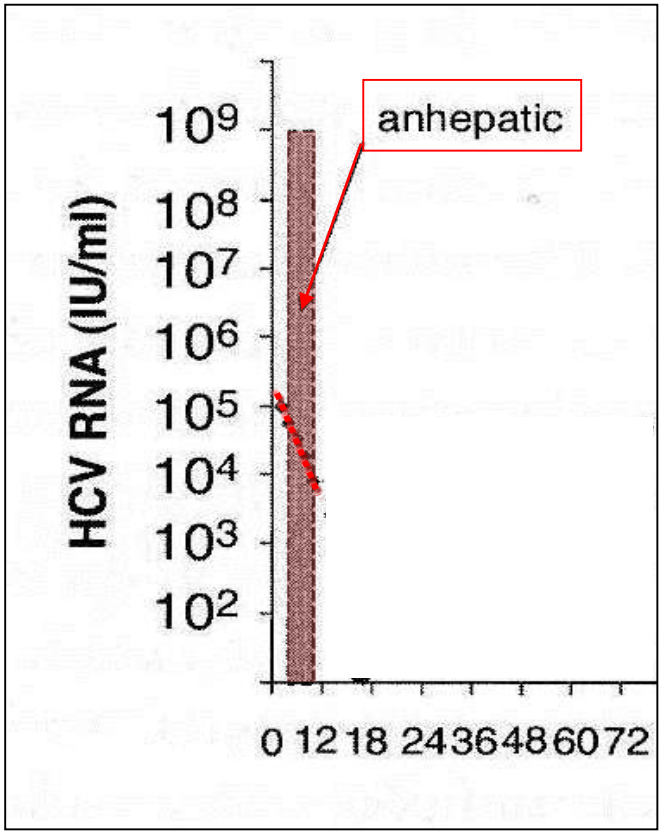
SVR rates were comparable to those seen in other studies of SOF+NS5A±RBV for 12 weeks in decompensated cirrhotics

Foster, EASL, 2015, O002

PREVENTION OF POST-TRANSPLANT HCV RECURRENCE

Kinetics of HCV-RNA after liver transplantation

1) HCV-RNA [ ] decreases in anhepatic phase ***(≅0,5 log_{10} IU/ml)***



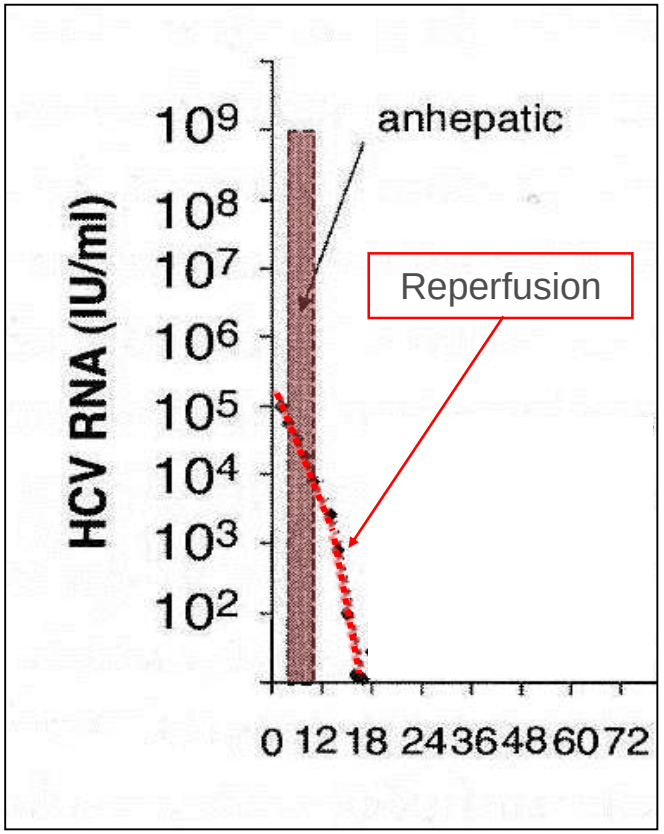
Removal of infected liver:

- *Reduction or lack of virion* ***production***
- *Blood loss and transfusion requirements*

Charlton, 2005

Kinetics of HCV-RNA after liver transplantation

2) [HCV-RNA] decreases after reperfusion at a rate exceeding that of anhepatic phase! ***(≅0,5 $\log_{10}$ IU/ml)***



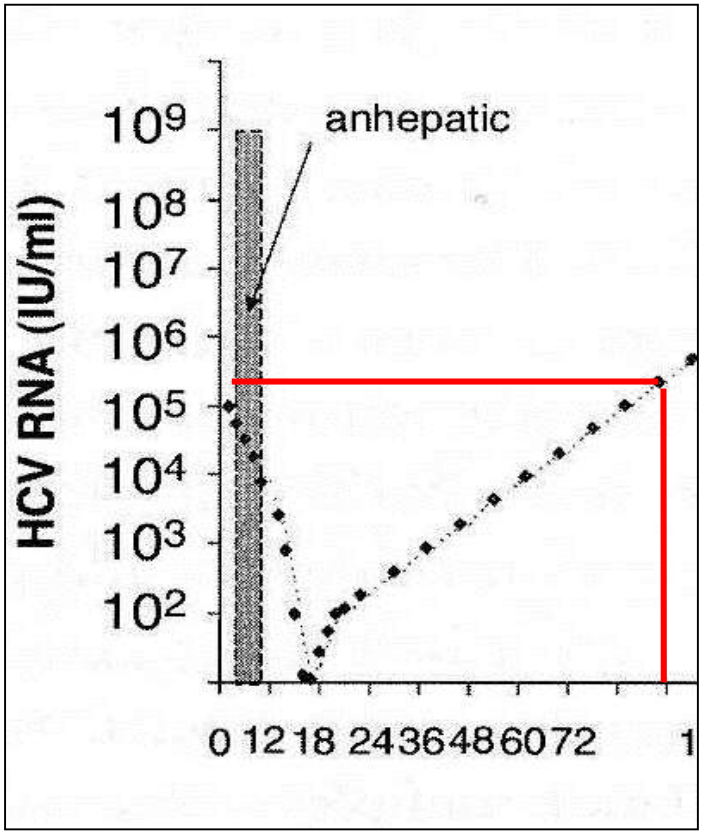
Reperfusion of "new liver":

- *HCV binding and/or uptake by hepatocytes*
- *HCV uptake by RE cells*

Rapid allograft infection: *narrow window for passive prophylaxis*

Kinetics of HCV-RNA after liver transplantation

3) HCV-RNA re-increases as soon as 12-24 hours after OLT and Pre-OLT HCV-RNA levels are usually reached at day 4

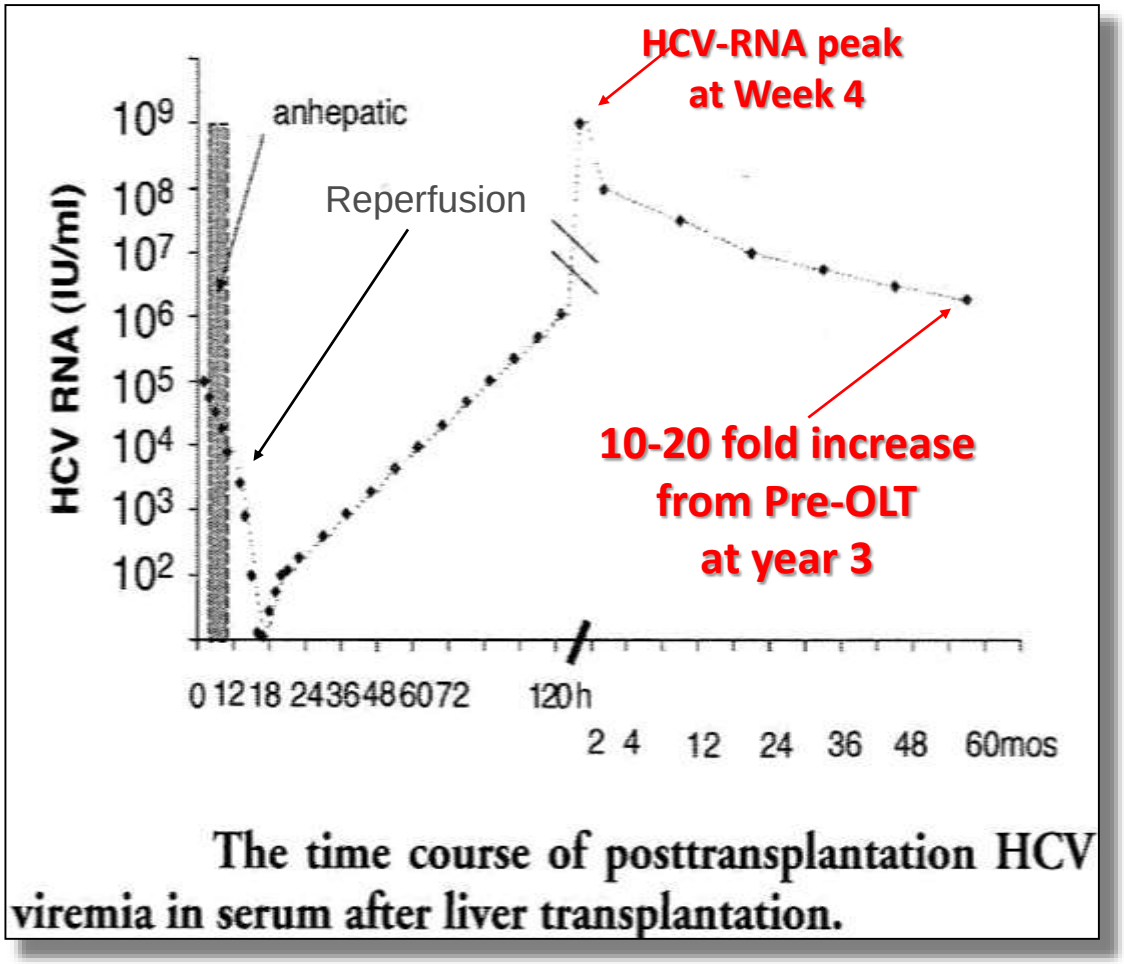


First post-OLT days:

- *Presence of ischemia – reperfusion injury*
- *Impact of Immunosoppression* *steroids = ↑ HCV-RNA*
- *Deranged inter-intracellular pathways ?*

Garcia-retortillo, 2002

Kinetics of HCV-RNA after liver transplantation



The time course of posttransplantation HCV viremia in serum after liver transplantation.

1989

HCV identification

The Fall of Berlin Wall

HCV Treatment
PRE-OLT

HCV Treatment
POST-OLT

1989

HCV identification

The Fall of Berlin Wall

Cirrhosis ± HCC

HCV Treatment
PRE-OLT

Transplant

HCV Treatment
POST-OLT

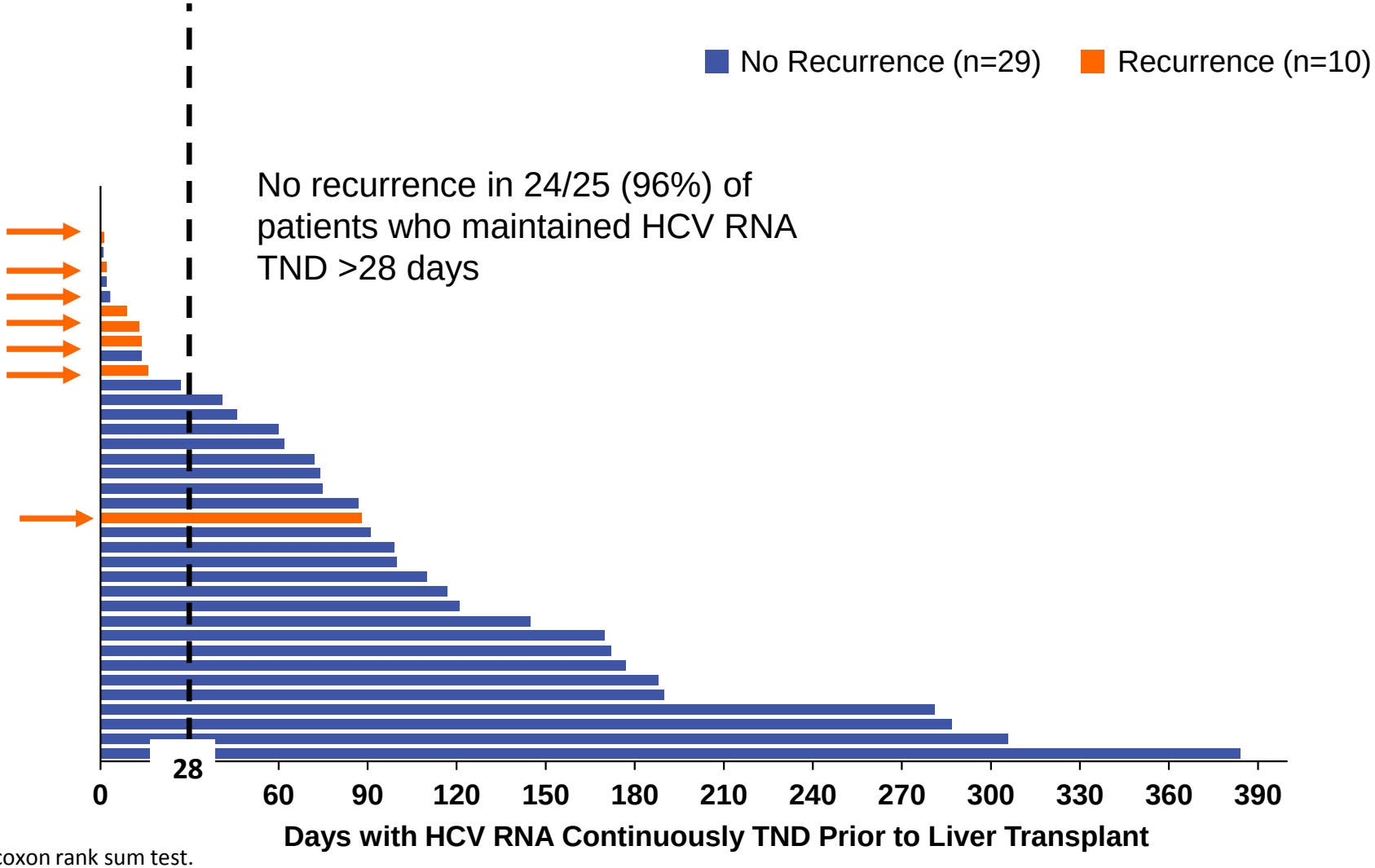
48 weeks of pre-transplant SOF/RBV to prevent recurrence of HCV infection after liver transplantation for HCC

Michael Curry, Boston, U.S. AASLD 2013 - Gastroenterology 2014

61 patients with compensated **cirrhosis** (CP<7) and **HCC** awaiting liver transplantation.

40 transplanted, 37/40 HCV-RNA < 25 UI/L.

Analysis of Post-Transplant Recurrence in patients in whom HCV RNA was non detectable for 28 days prior to transplant



*Wilcoxon rank sum test.

Factors associated with no recurrence

	Exact Odds Ratio (95% c.l.)	P-value
IL28B CC allele *vs* not	3,000 (0.243- inf)	0.389
Not HCV GT 1b *vs* GT 1b	2.225 (0.258-inf)	0.483
Days of continuous HCV RNA undetectability prior to Tx	**1.042 (1.102-1.083**	**0.0007**

TREATMENT OF POST-TRANSPLANT HCV RECURRENCE

Compassionate use of SOFOSBUVIR in Europe

Table 2. Response (HCV RNA <25 IU/mL) During and After Treatment

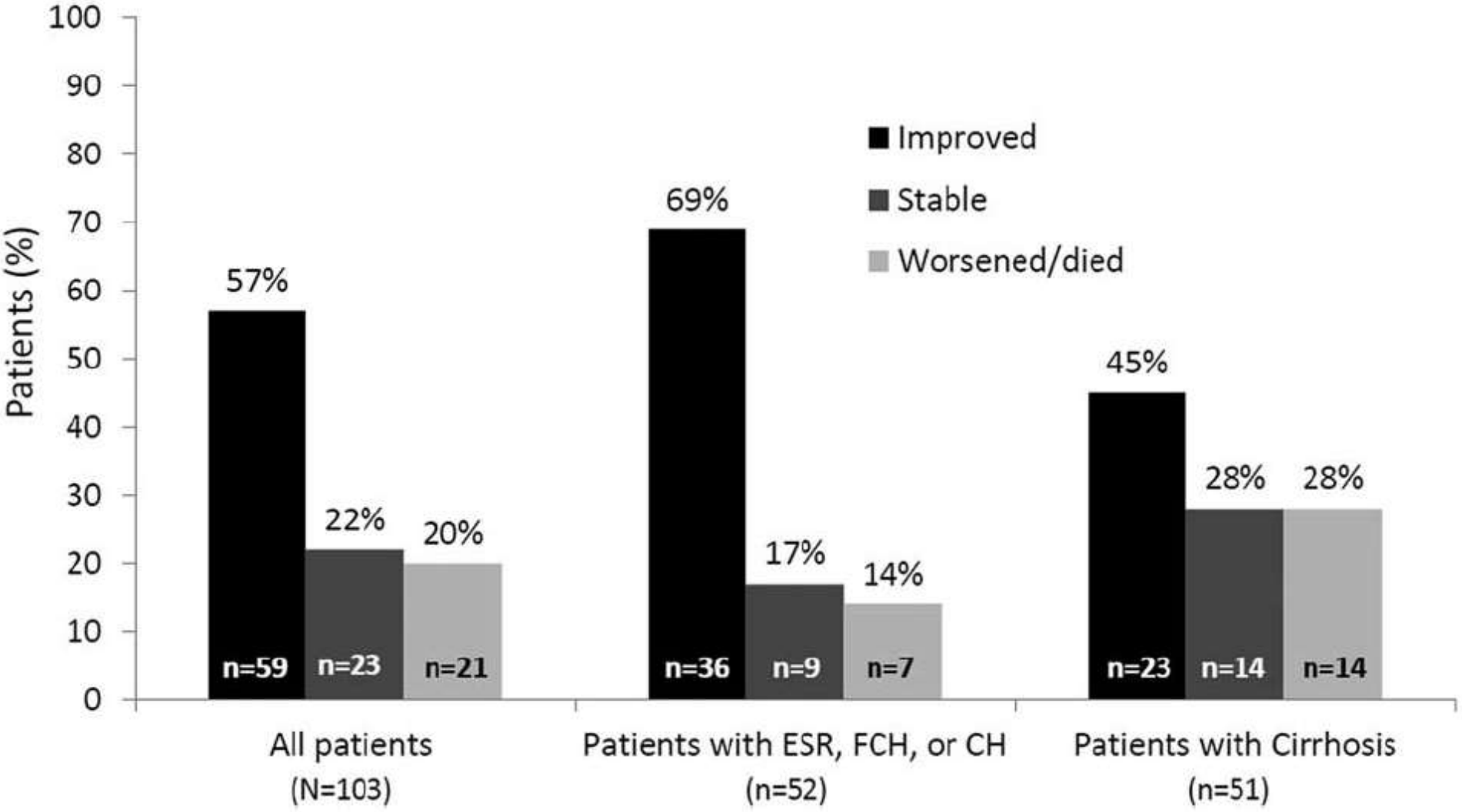
	Overall (N = 104)	Acute Hepatitis and Early Severe Recurrence (N = 52)	Compensated and Decompensated Cirrhosis (N = 52)
During treatment, % (n/n) %*			
At week 4	56/104 (54)	24/52 (46)	33/51 (65)
At week 12	82/104 (79)	42/50 (84)	40/49 (82)
At week 24	76/96 (73)	38/48 (79)	38/47 (81)
In post-treatment follow-up, n (%)			
At week 4 (SVR4)	62/93 (67)	38/48 (79)	24/46 (52)
At week 12 (SVR12)	54/92† (59)	35/48† (73)	19/44† (43)
Virological failure (%)			
On-treatment failure	0	0	0
Relapse	19/92 (21)	4/48 (8)	15/44 (34)
Lost to follow-up	2/92 (2)	2/48 (4)	0
Discontinuation because of SAE	3/92 (3)	1/48 (2)	2/44 (5)
Discontinuation because of nonadherence	1/92 (1)	0	1/44 (2)
Death	13/92 (14)	6/48 (13)	7/44 (16)

*HCV RNA <25 IU/mL response during treatment is in patients for whom HCV-RNA results are available.

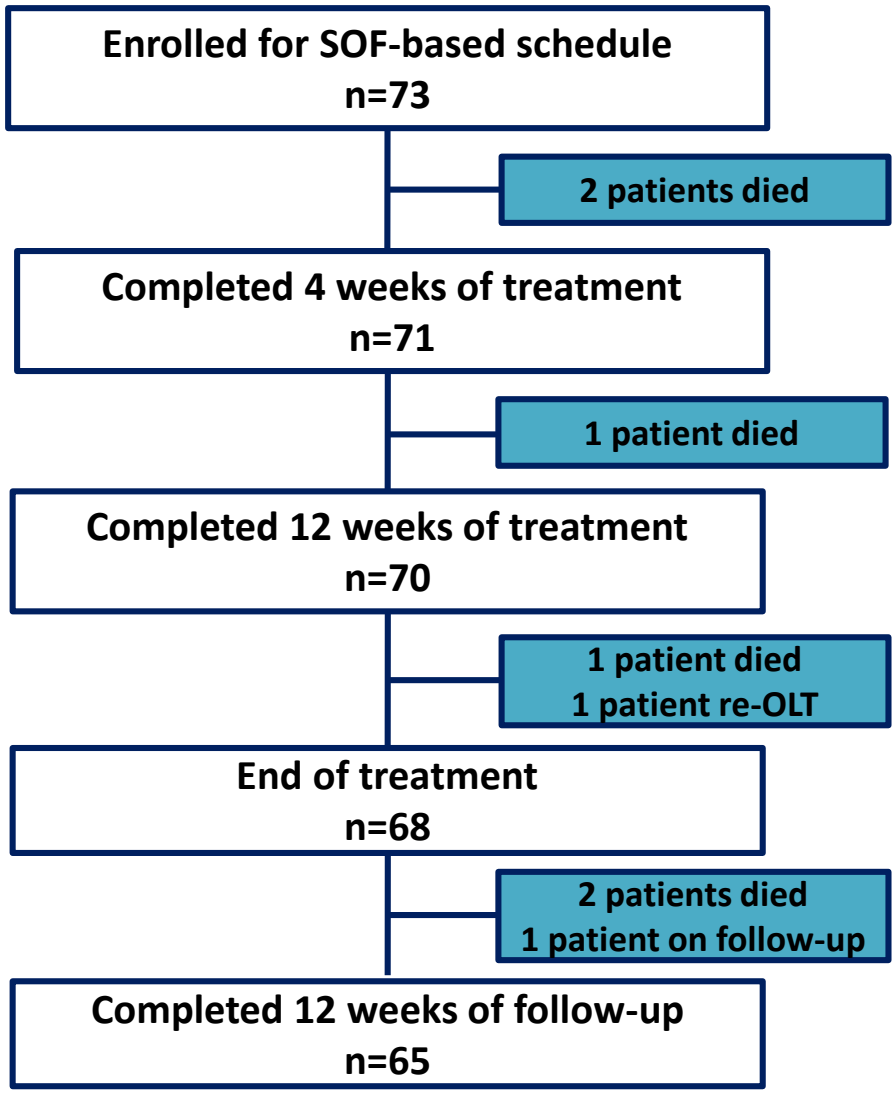
†Twelve patients underwent LT during the study and were not included in the efficacy analysis; 4 with acute hepatitis and early severe recurrence and 8 with compensated and decompensated cirrhosis.

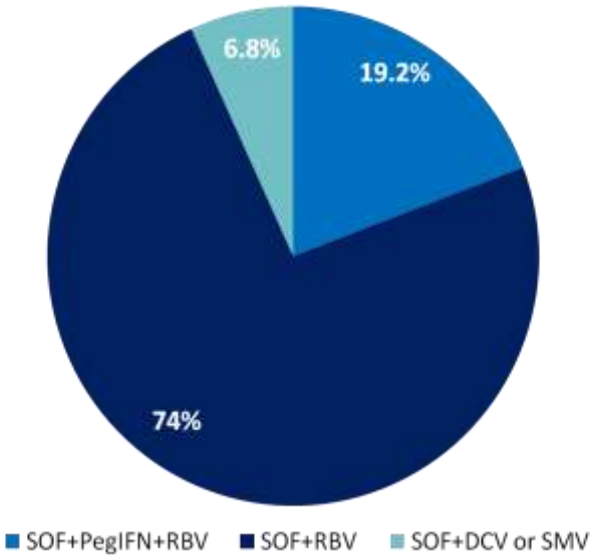
Forns Hepatology 2015

Clinical Outcome: significant decrease in hepatic encephalopathy, improvement or disappearance of ascites, or improvement in liver-related laboratory values



SOFOLT (AISF) Compassionate Use of DAAs
Andreone EASL 2015





Baseline characteristics

Variable	n=73
Male gender	54 (74%)
Age (years)	53 (25-73)
Time from liver transplantation (months)	26 (2-236)
FCH	**24 (32.9%)**
Previous antiviral treatment	46 (63%)
Genotype 1a/1b/2/3/4 (n)	20/37/1/6/9
HCV-RNA (Log_{10} IU/mL)	6 (2.7-9)
Total bilirubin (mg/dL)	2.6 (0.4-36.8)
Albumin (g/dL)	3.3 (2.1-4.7)
INR	1.2 (0.9-4.5)
Creatinine clearance (mL/min)	66.8 (25.5-141)
Platelets ($1x10^3/\mu L$)	82 (13-871)
MELD score*	**15 (7-36)**
Child Pugh score*	8 (5-15)

Values are expressed as median (range) or number (%)

*Data are calculated in 71 patients (2 were in anticoagulant oral therapy)

Comparison of baseline characteristics and outcome between ESLD or FCH

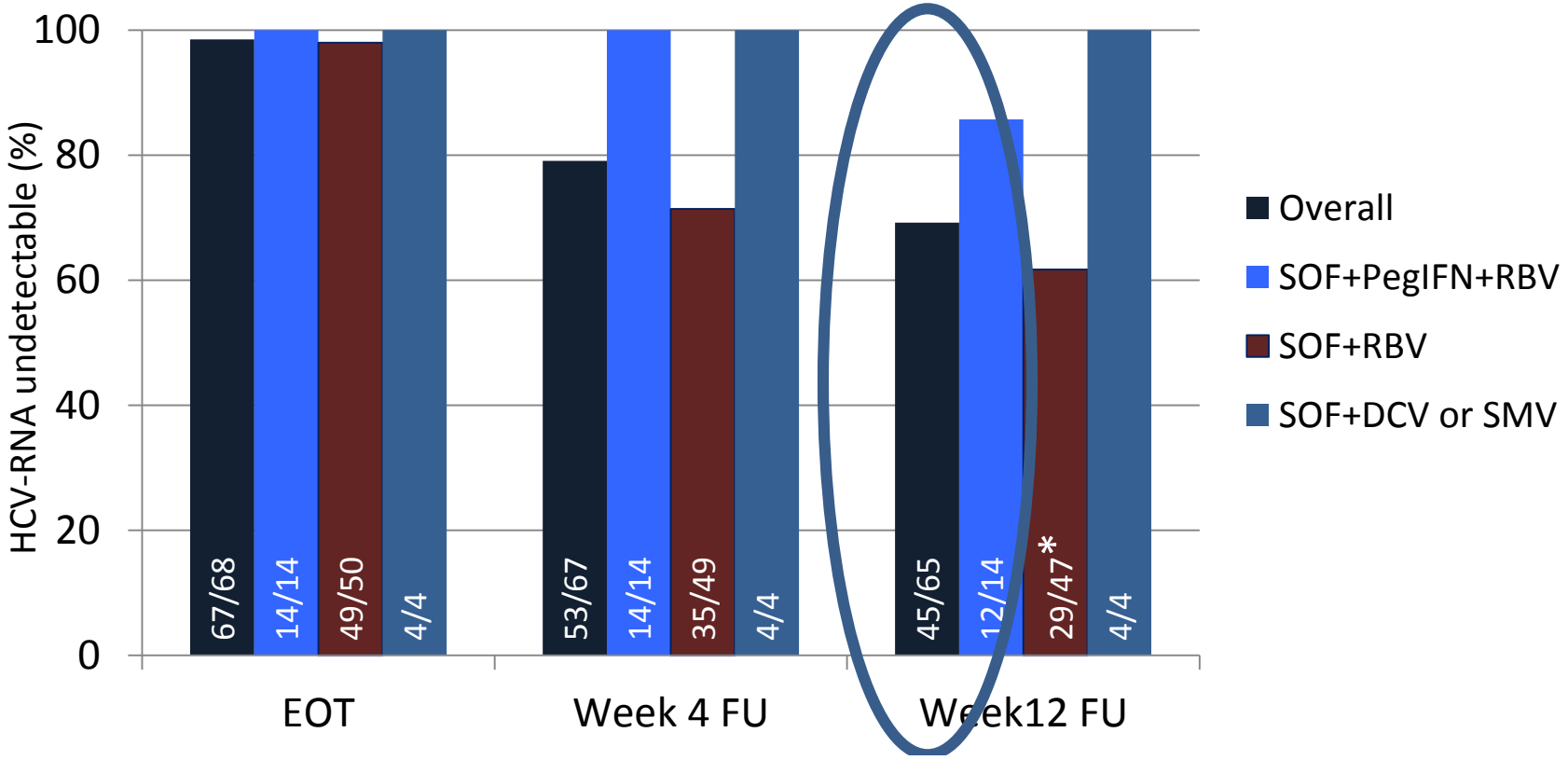
Variable	ESLD (n=49)	FCH (n=24)	P
Male gender	38 (77.6%)	16 (66.7%)	0.397
Age (years)	53 (25-73)	52 (44-70)	0.716
Previous antiviral treatment	31(63.3%)	15 (62.5%)	1
Genotype 1-4	43 (87.8%)	23 (95.8%)	0.414
HCV-RNA (Log_{10} IU/mL)	5.9 (3.6-9)	6.2 (2.7-7.7)	0.110
Total bilirubin (mg/dL)	2.1 (0.4-36.2)	5.8 (1.5-36.8)	<0.001
Albumin (g/dL)	3.2 (2.1-4.7)	3.5 (2.6-4.3)	0.015
INR	1.3 (1-2.8)	1.1 (0.9-4.5)	0.017
Creatinine clearance (mL/min)	66.5 (25.5-141)	67 (27.2-118.1)	0.851
Platelets ($1x10^3/\mu L$)	72 (13-871)	83 (41-693)	0.050
MELD score*	13 (7-36)	17 (8-32)	0.139
Child Pugh score*	9 (5-15)	8 (5-14)	0.388
SVR12	**30 (61.2%)**	**15 (65.2%)#**	**0.799**
Death	3 (6%)	3 (12.5%)	0.388

Values are expressed as median (range) or number (%); categorical variables were compared using the X^2 and quantitative variables were compared by the Mann-Whitney test

*Data are calculated in 71 patients (2 were in anticoagulant oral therapy)

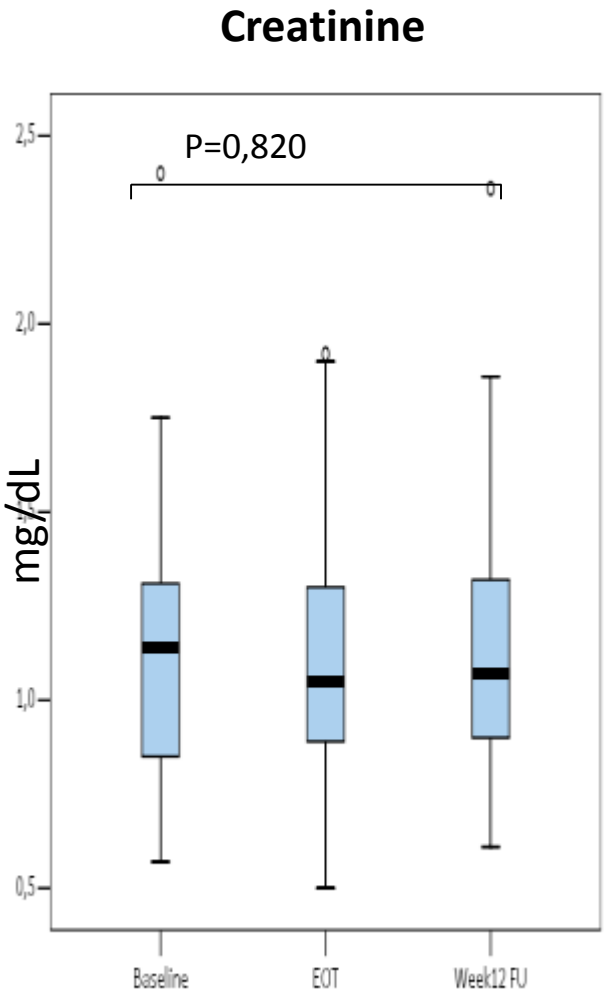
#Data are available in 23 patients

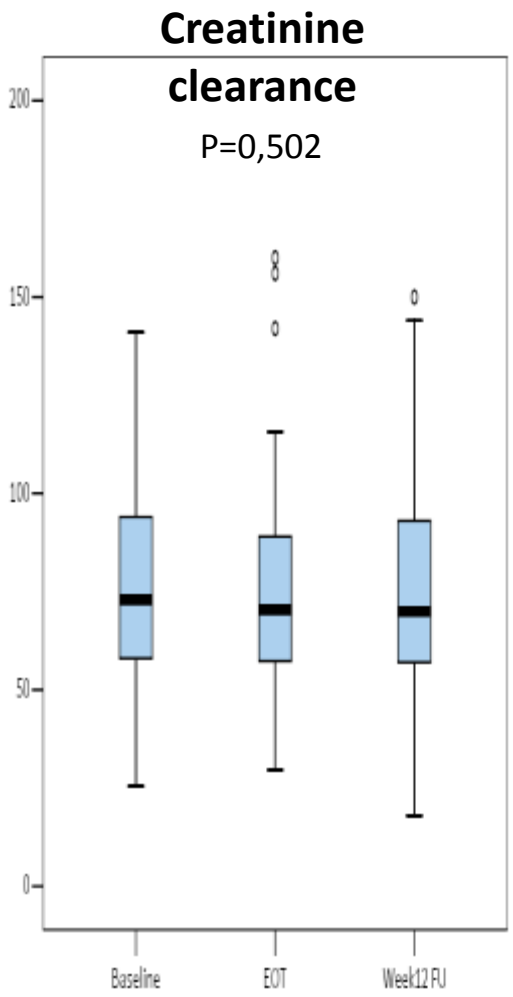
Virological response according to antiviral treatment



***SVR according genotype (G):** G1=21/36 (58.3%); G3=5/6 (83.3%); G4=3/5 (60%)

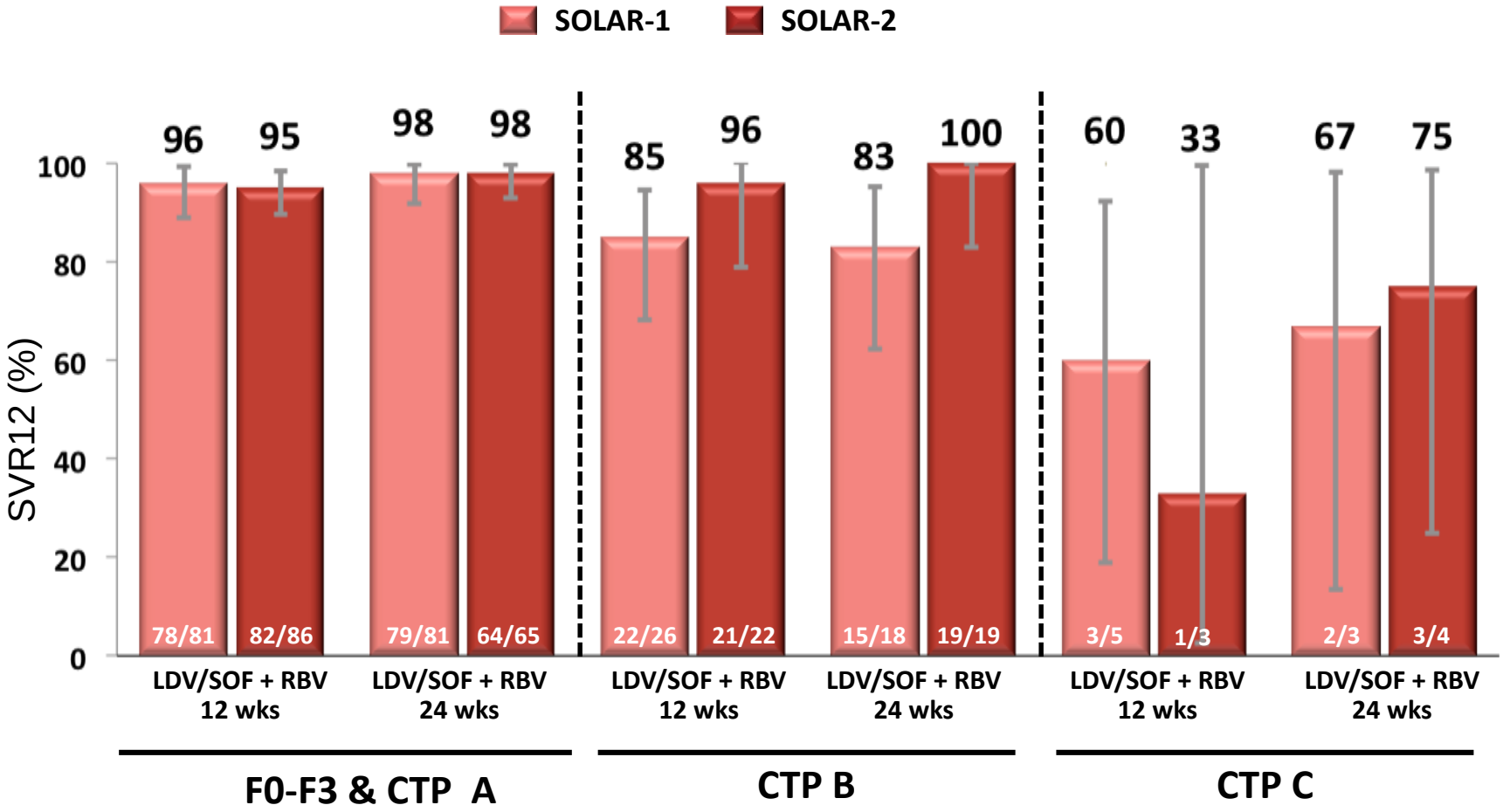
Preserved renal function in patients with SVR12





Overall Efficacy Post-Transplant in GT 1 and GT 4

Reddy, AASLD, 2014, Oral #8;
Manns, EASL, 2015, GO2;

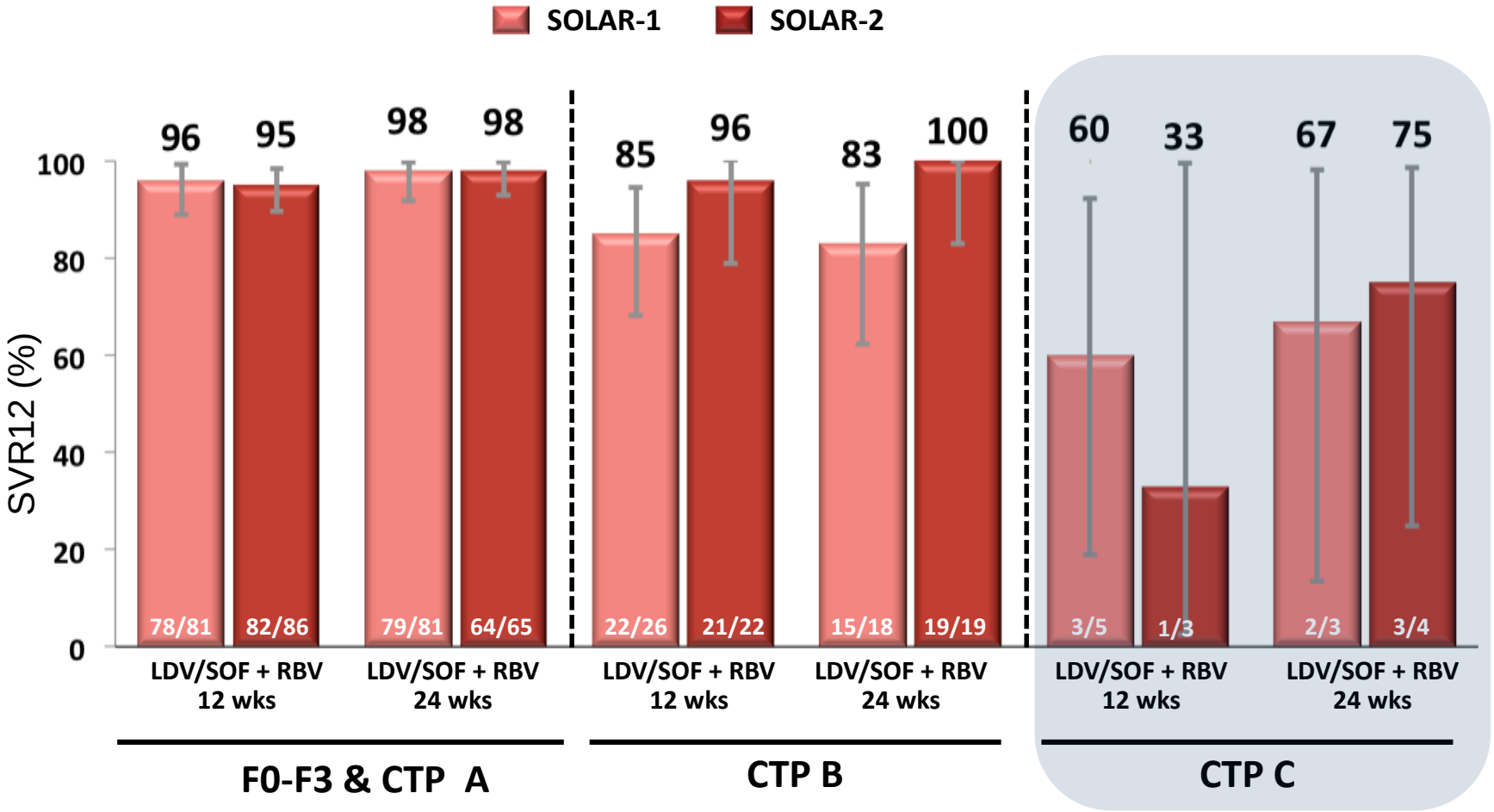


The SVR12 analysis included all subjects except those who had undergone transplantation prior to SVR12 at last visit prior to transplantation.

Comparable efficacy between SOLAR-1 and SOLAR-2 studies

Overall Efficacy Post-Transplant in GT 1 and GT 4

Reddy, AASLD, 2014, Oral #8;
Manns, EASL, 2015, GO2;



The SVR12 analysis included all subjects except those who had undergone transplantation prior to SVR12 at last visit prior to transplantation.

Comparable efficacy between SOLAR-1 and SOLAR-2 studies

Simeprevir Compassionate Use Programme with DCV or SOF

Inclusion criteria
(at least one of the following)

- Fibrosing cholestatic hepatitis
- Severe hepatitis C recurrence with a high risk of death within 12 months
- Genotype 1 or 4 hepatitis C

Received SMV as part of compassionate use program in Europe (Spain, Italy, Belgium, Germany, Denmark)

Treatment options were :

SMV + SOF ± RBV 24 weeks (n=16)

SMV + DCV ± RBV 24 weeks (n=12)

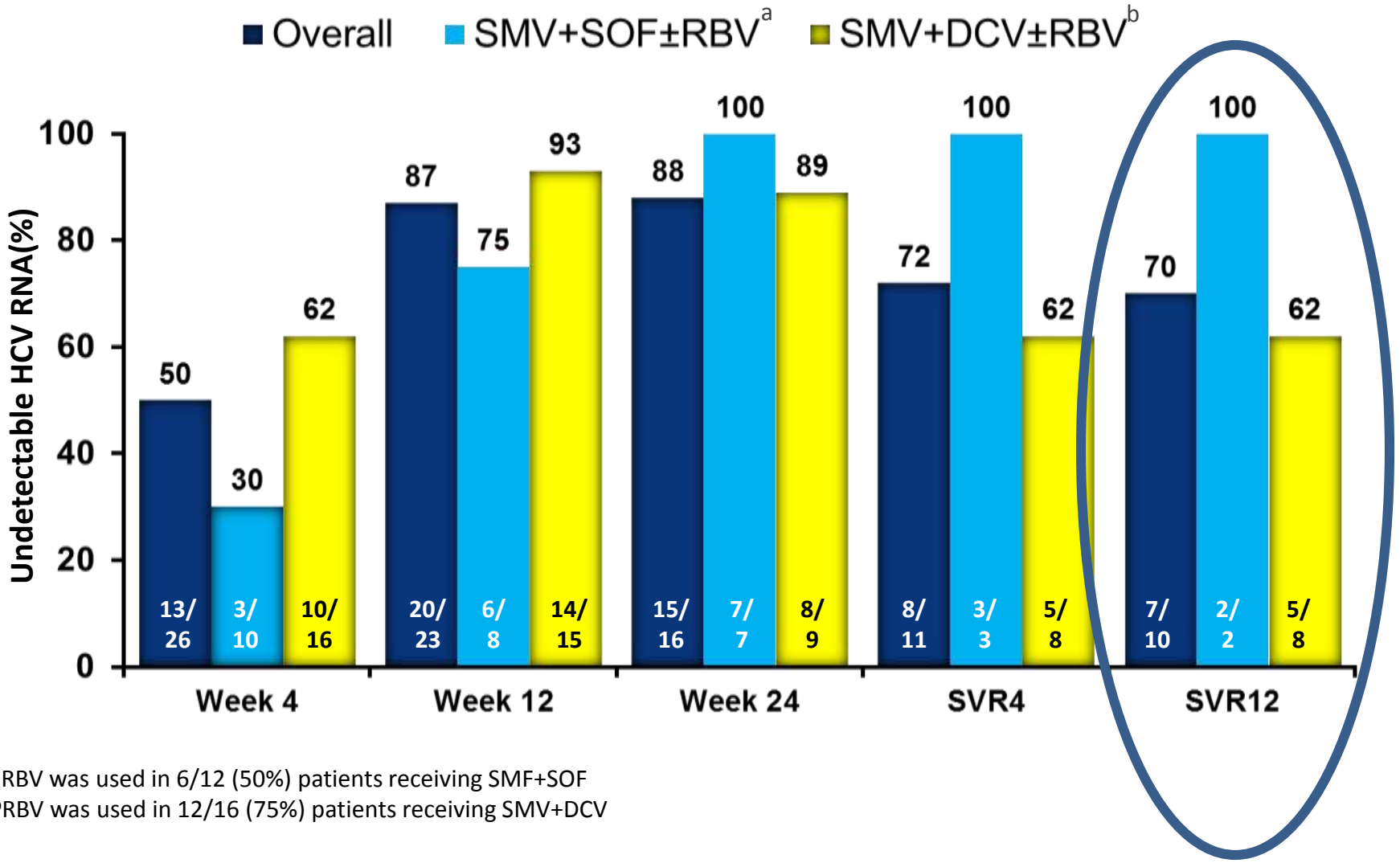
Londoño AASLD 2014

Simeprevir Compassionate Use Programme, with DCV or SOF-Baseline characteristics

Characteristics	All patients N=28
Age, years, median (range)	59 (52-65)
Male, n (%)	19 (68)
Time since transplant, months, median (range)	30 (13-116)
HCV genotype, n (%)	
1b	26 (**93**)
4	2 (7)
Fibrosing cholestatic hepatitis, n (%)	3 (11)
Cirrhosis, n (%)	18 (64)
Decompensated cirrhosis	14 (50)
Immunosuppressant regimen, n (%)	
Tacrolimus	15 (**54**)
Cyclosporine	6 (21)
Other	7 (25)
HCV RNA, IU/mL, median (range)	$2.5x10^6$ ($8.0x10^5$-$6.0x10^6$)
Bilirubin, mg/dL, median (range)	1 (0.7-2.7)
INR, median (range)	1.2 (1-1.3)
AST/ALT, IU/mL, median (range)	79 (51-129) / 53 (33-111)
AP/GGT, IU/mL, median (range)	167 (126-252) / 145 (66-250)
MELD score, median (range)	11 (8-16)
CPT score, median (range)	6 (5-8)

Londoño AASLD 2014

Simeprevir Compassionate Use Programme, with DCV or SOF-Virologic response over time



[a]RBV was used in 6/12 (50%) patients receiving SMF+SOF
[b]RBV was used in 12/16 (75%) patients receiving SMV+DCV

An Interferon-free Antiviral Regimen for HCV after Liver Transplantation

- **Ombitasvir-ABT**-450/r (25mg/150mg/100mg) plus **ABT333 (Dasabuvir)** (250mgx2)
- Ribavirin 1000-1200mg
- 24 weeks
- Liver biopsy **Metavir F=<2**
- 34 patients enrolled, Genotype 1 (1a 85%), 71% previously treated (Peg-IFN+RBV)

Kwo PY, NEJM 2014

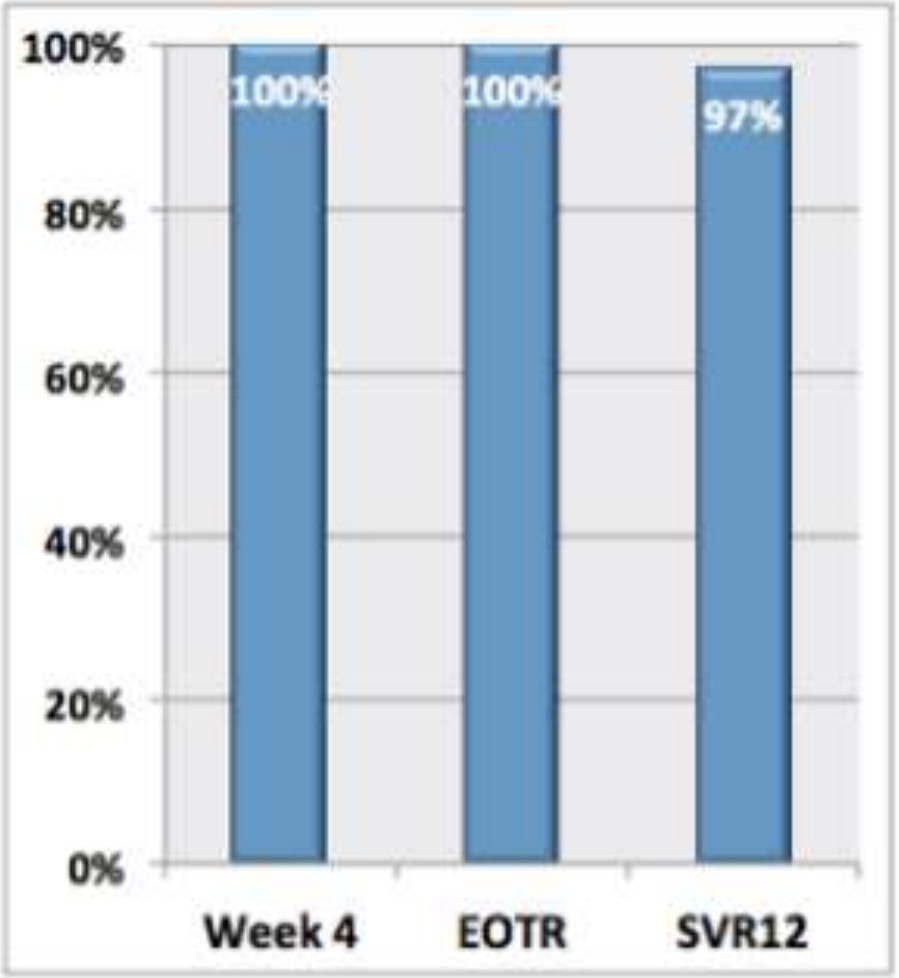
SVR in Liver Transplant Recipients With Recurrent HCV Geno 1 Infection Receiving ABT-450/r + Ombitasvir + Dasabuvir Plus Ribavirin

- 34 pts post-OLT (~4 yrs) treated for 24 weeks
- Non-cirrhotics, most G1a (85%)
- RBV dosing varied (400-1200mg)
- Drug-drug interactions:
  - 7-fold incr in TAC half-life
  - 3-fold incr in CSA half-life
  - Tacrolimus dosing 0.5mg qweek or 0.2mg q3days
  - CycA dosing 1/5 of daily pre-study dose
- Adverse events
  - Fatigue and headache
- 5 patients treated with EPO
- Only 1 early discontinuation

Mantry, Abst# 198

SVR in Liver Transplant Recipients With Recurrent HCV Geno 1 Infection Receiving ABT-450/r + Ombitasvir + Dasabuvir Plus Ribavirin

- 34 pts post-OLT (~4 yrs) treated for 24 weeks
- Non-cirrhotics, most G1a (85%)
- RBV dosing varied (400-1200mg)
- Drug-drug interactions:
  - 7-fold incr in TAC half-life
  - 3-fold incr in CSA half-life
  - Tacrolimus dosing 0.5mg qweek or 0.2mg q3days
  - CycA dosing 1/5 of daily pre-study dose
- Adverse events
  - Fatigue and headache
- 5 patients treated with EPO
- Only 1 early discontinuation



Mantry, Abst# 198

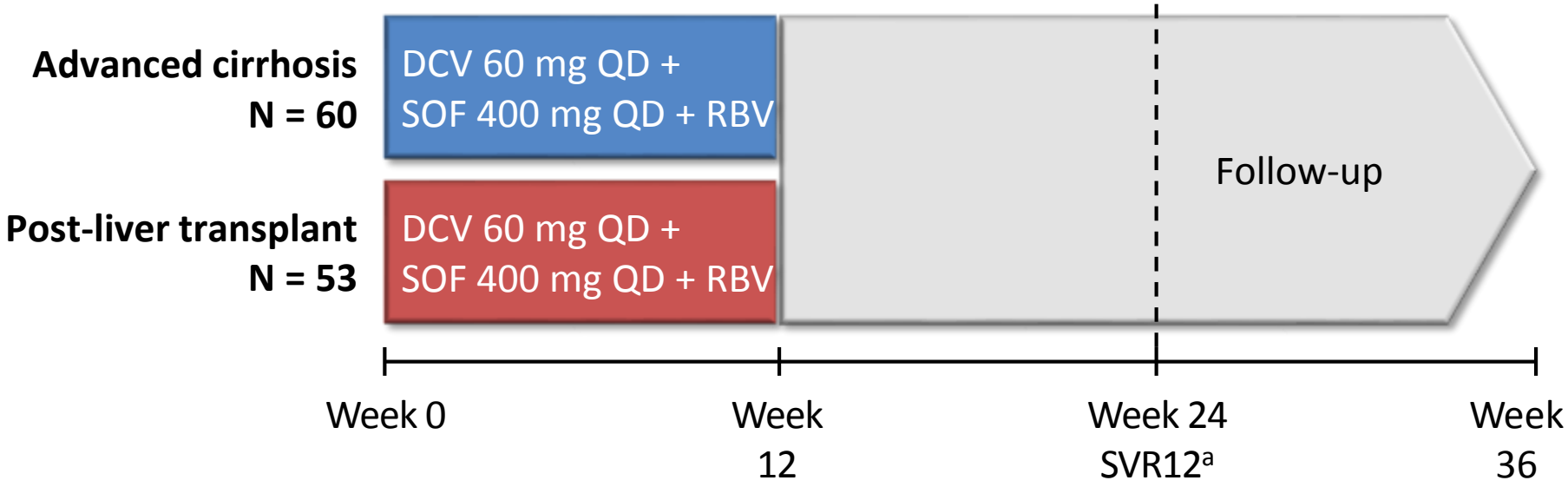
Daclatasvir, Sofosbuvir, and Ribavirin Combination for HCV Patients with Advanced Cirrhosis or Post-transplant Recurrence: ALLY-1 Phase 3 Study

Poordad F,[1] Schiff ER,[2] Vierling JM,[3] Landis C,[4] Fontana RJ,[5] Yang R,[6] McPhee F,[7] Hughes EA,[6] Noviello S,[6] Swenson ES[7]

[1]Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA; [2]Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, FL, USA; [3]Baylor College of Medicine, Houston, TX, USA; [4]University of Washington School of Medicine, Seattle, WA, USA; [5]University of Michigan Medical Center, Ann Arbor, MI, USA; [6]Bristol-Myers Squibb, Princeton, NJ, USA; [7]Bristol-Myers Squibb, Wallingford, CT, USA

EASL The Home of Hepatology | 50th THE INTERNATIONAL LIVER CONGRESS™ 2015
APRIL 22-26, VIENNA, AUSTRIA

ALLY-1: Multicenter, Open-Label Phase 3 Study



- Primary endpoint: SVR12 in GT1 in each cohort
- 12 weeks of treatment: DCV 60 mg + SOF 400 mg + RBV
  - RBV initially 600 mg/day, adjusted to 1000 mg/day based on Hgb levels and CrCl
- Advanced cirrhosis patients with treatment interrupted by liver transplantation could receive an additional 12 weeks of treatment immediately post-transplant

[a] HCV RNA < lower limit of assay quantitation (LLOQ) at posttreatment Week 12 by Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL).

Key Inclusion/Exclusion Criteria

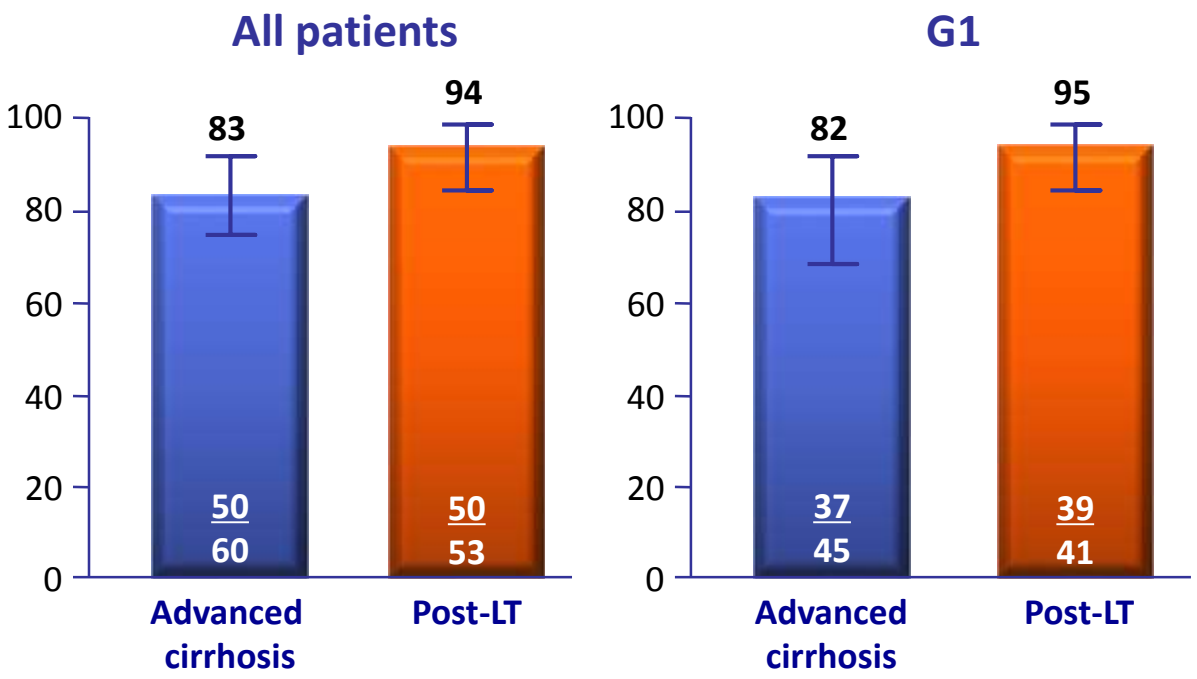
- Treatment-naive or experienced adults with any HCV genotype
- DAA failures allowed except NS5A

Two cohorts

Advanced cirrhosis	Post-liver transplant recurrence
■ Child-Pugh score A, B, C ■ MELD scores 8-40 ■ HCC allowed	■ ≥ 3 months post-transplant ■ No evidence of rejection at time of enrollment ■ Any immunosuppressive regimen

ALLY-1: SOF + DCV + RBV in cirrhotic and after liver transplantation

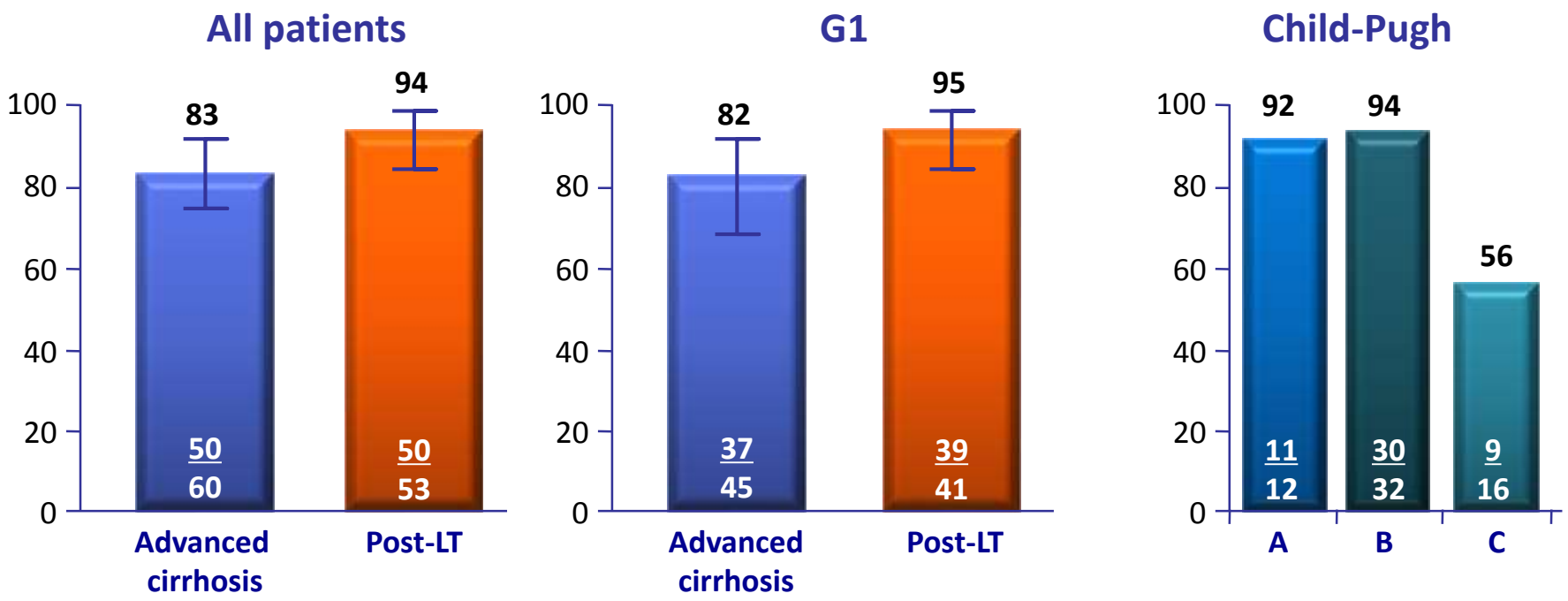
SVR12



Poordad F, Etats-Unis, EASL 2015, Abs. LO8 actualisé

ALLY-1: SOF + DCV + RBV in cirrhotic and after liver transplantation

SVR12



Poordad F, Etats-Unis, EASL 2015, Abs. LO8 actualisé

HCV DAAs AND IMMUNOSUPPRESSIVE DRUG–DRUG INTERACTIONS

Table 4. Drug-drug interactions between DAAs and calcineurin inhibitors.

DAA	Cyclosporine		Tacrolimus	
	Healthy volunteers	Dose adjustment	Healthy volunteers	Dose adjustment
Boceprevir [115, 116]¥	AUC ↑ 2.7 fold	↓ 2 fold	AUC ↑ 17 fold	↓ 5 fold
Telaprevir [77, 117]¥	AUC ↑ 4.6 fold	↓ 4 fold	AUC ↑ 70 fold	↓ 35 fold
ABT450/r [86]	AUC ↑ 5.8 fold	↓ 5 fold	AUC ↑ 58 fold	↓ 100 fold
Simeprevir [118]§	AUC ↑ 19%	Under investigation	AUC ↓ 17%	Not necessary
Sofosbuvir [119]¥	No change	Not necessary	No change	Not necessary
Daclatasvir [120]	No change	Not necessary	No change	Not necessary

¥AUC_{inf} is given.
§AUC_{Last} is given.

Gambato J Hep 2014

Take home message

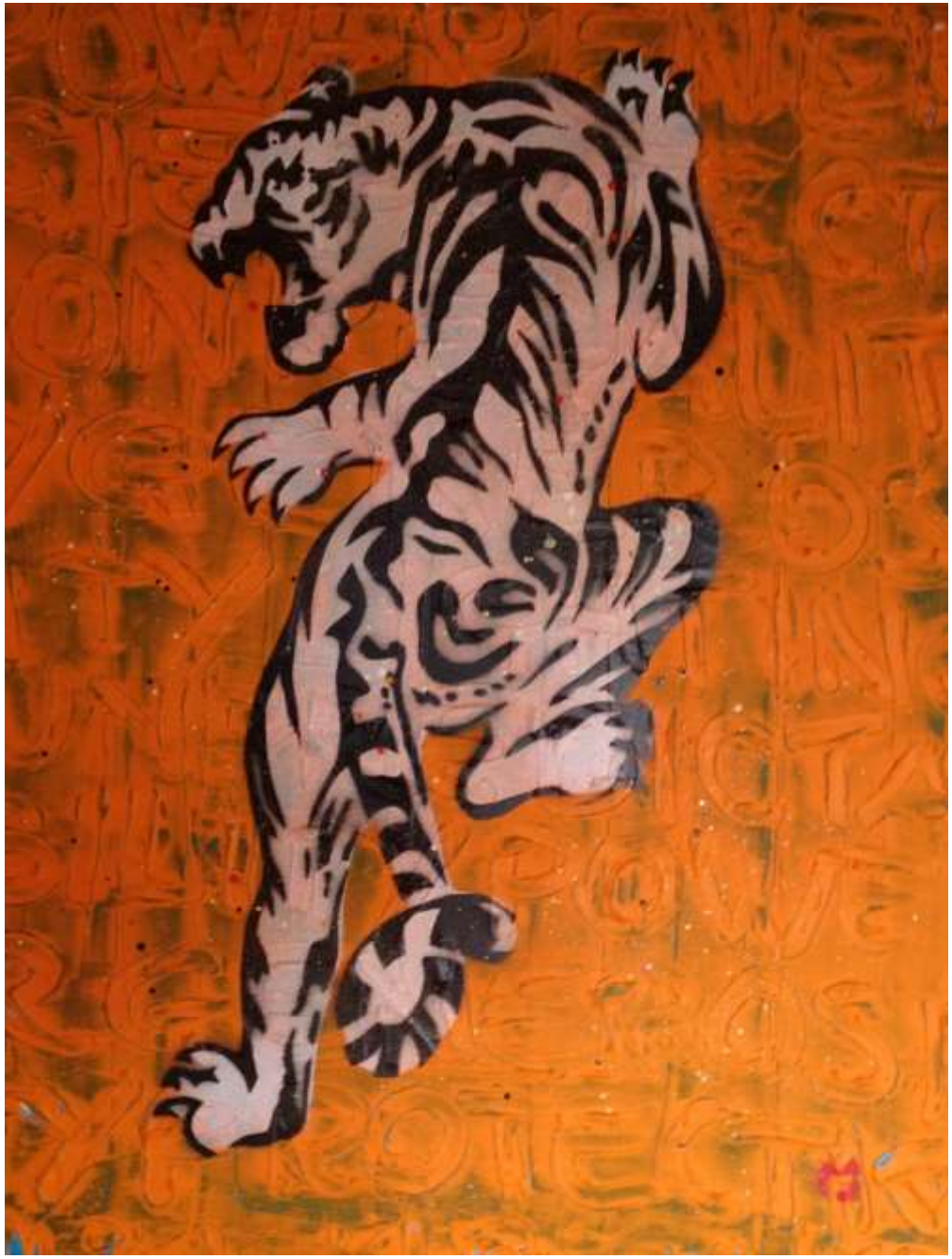
Antiviral therapy before and after liver transplantation

1. **Effective** in decompensated cirrhosis and liver transplant recipients.

2. Clinical improvement in patients on the waiting list is reported in nearly 40% of cases, but still not conclusive data are available for **de-listing**.

3. **Deterioration** of liver function may occur in 4-5% of patients despite virological response.

4. **Side effects** are common, but mild. No impairment of renal function. Mild/no interference with immunosuppression.



The Artist
A Transplant Recipient