Antiviral treatment in HCV cirrhotic patients on waiting list

Krzysztof Tomasiewicz

Department of Hepatology and Infectious Diseases

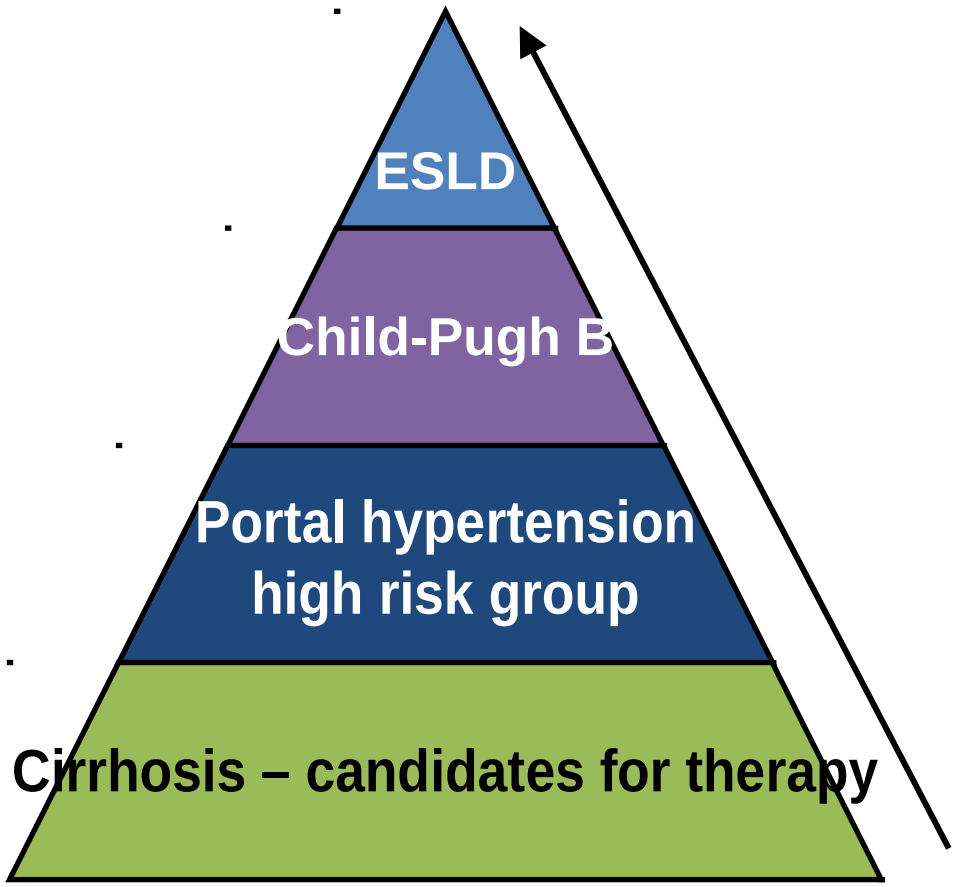
Medical University of Lublin, Poland

Disclosures

Consultancy/Advisory Board/Speaker: AbbVie, Alfa Wasserman, BMS, Gilead, Janssen, MSD, Roche

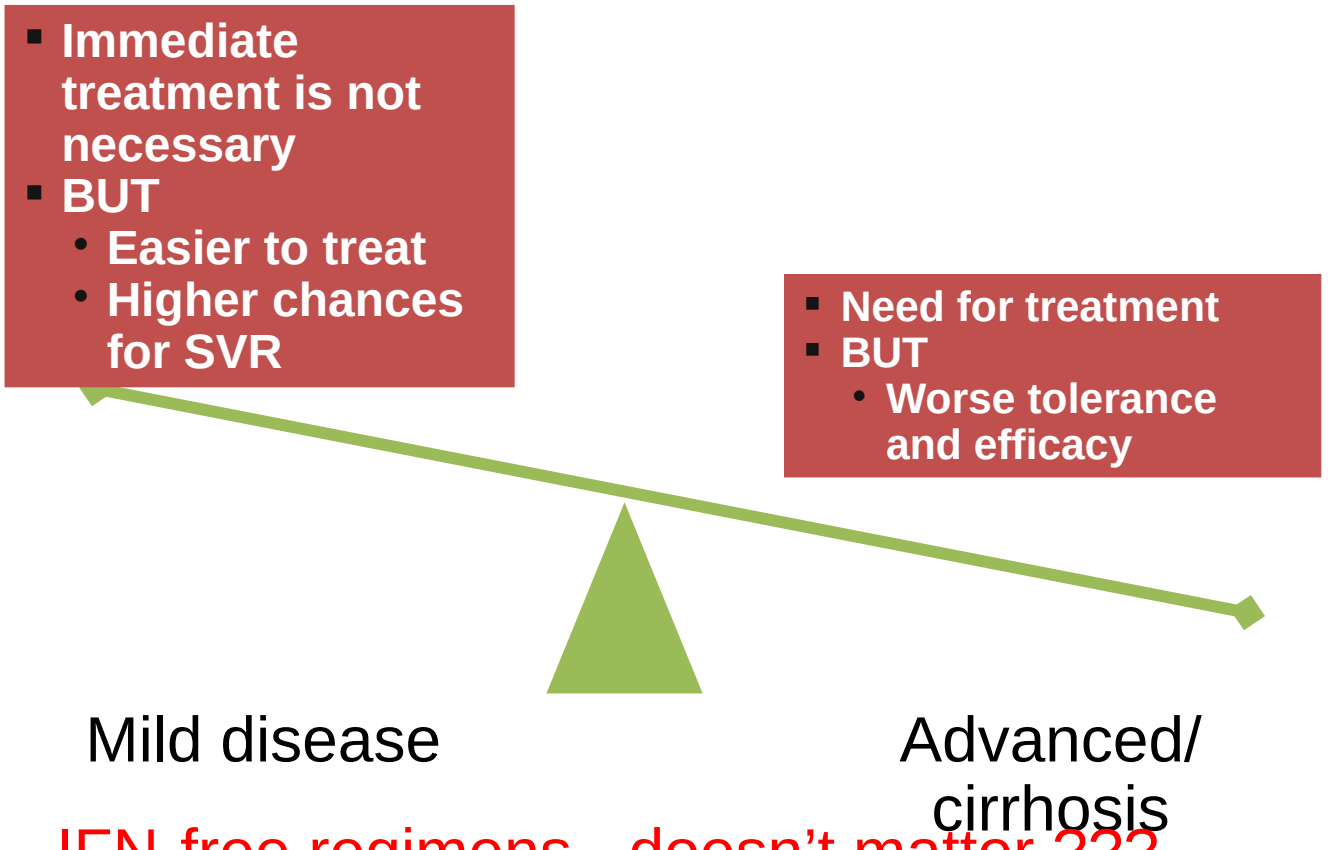
Grant/Research: AbbVie, BMS, Gilead, Janssen, MSD, Roche

Cirrhosis: Disease spectrum



Child-Pugh (A, B, or C) and MELD do not always reflect diseaes progresion

The milder the better and safer - true for IFN-based therapies.



IFN-free regimens - doesn’t matter ???

On the waiting list

Lab Test Frequency

MELD score greater than or equal to 25; Labs needed every 7 days

MELD score 24-19; Labs needed every 30 days

MELD score 18-11; Labs needed every 90 days

Within the MELD continuous disease severity scale, there are four levels. As the MELD score increases, and the patient moves up to a new level, a new waiting time clock starts. Waiting time is carried backwards but not forward. If a patient moves to a lower MELD score, the waiting time accumulated at the higher score remains. When a patient moves to a higher MELD score, the waiting time at the lower level is not carried to the new level. The clock at the new level starts at 0.

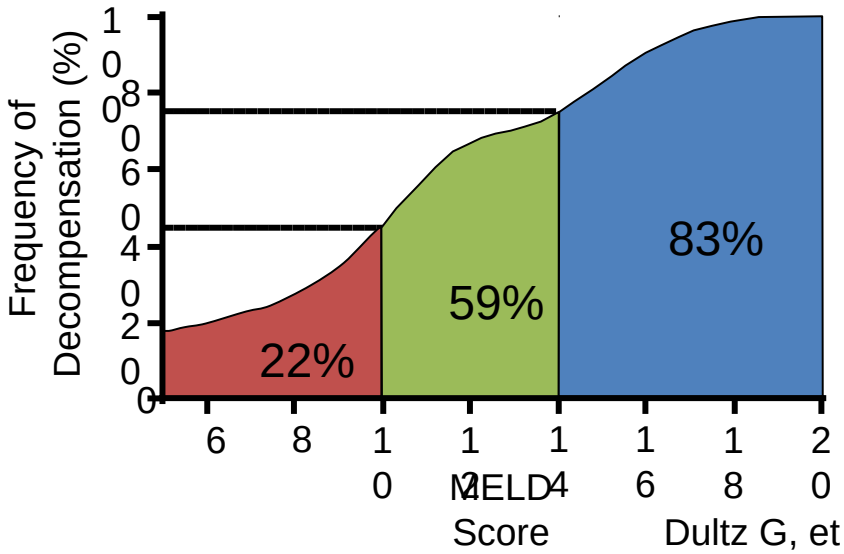
The average MELD score for a patient undergoing a liver transplant is 20. (US data)

The average MELD score for liver transplant patients in some regions varies from 26-33

Verna et al. Curr Opin Org Transpl 2015

Liver decompensation in cirrhotic patients treated with PEG-IFN-based therapies

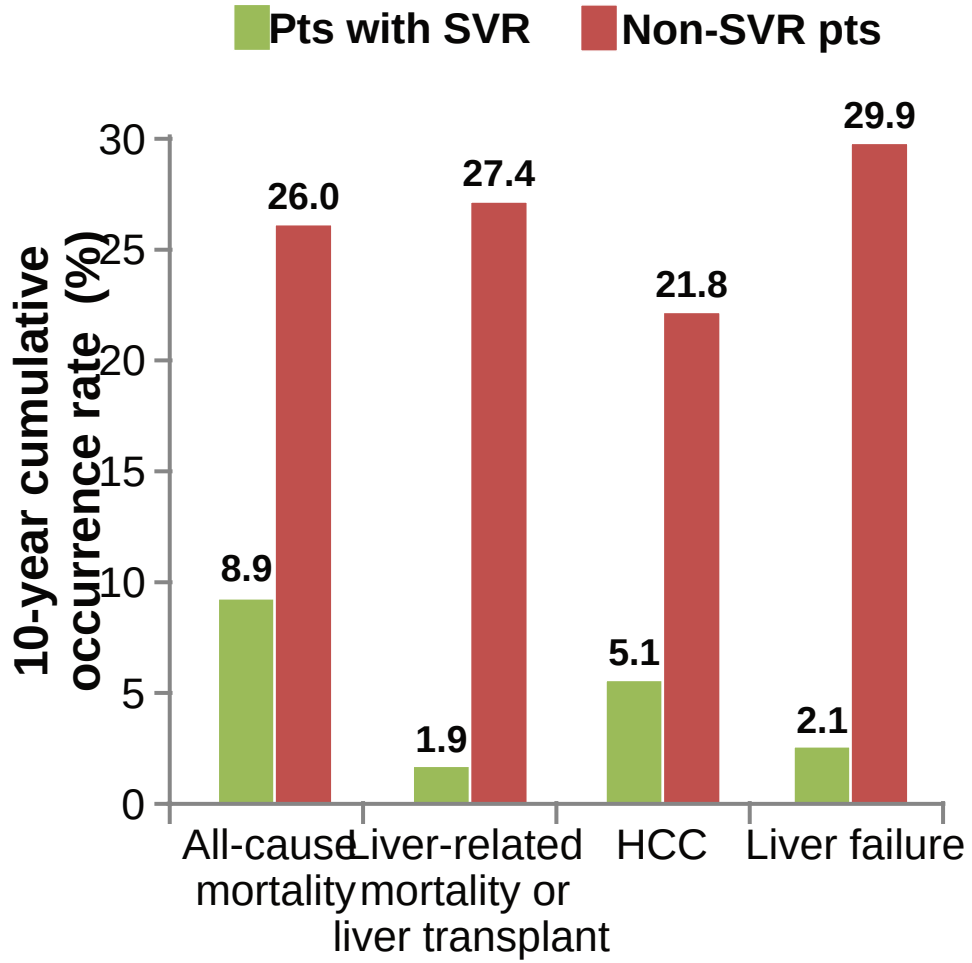
- Retrospective study: 68 cirrhotic pts HCV-positive
  - Median age : 51 years; baseline MELD: 9.2 (5-20)
- Liver decompensation in 36.8% of patients
- Baseline MELD correlation with liver decompensation OR: 1.56 (1.18-2.07; *P* = .002)



Dultz G, et al. PLoS One. 2013

Influence of SVR on *all-cause mortality* in patients with advanced fibrosis

530 pts observed med. 8.4 years



Basline factors increasing mortality

- Older age
- Genotyp 3 (↑↑ mortality and HCC)
- Higher fibrosis in Ishak
- Diabetes
- Alcohol consumptio n

van der Meer A, *et al. JAMA* 2012; **308:**2584–2593.

Why should we treat patients on the waiting list?

To avoid HCV recurrence.

HCV recurrence is universal after LT and may progress rapidly to graft cirrhosis.

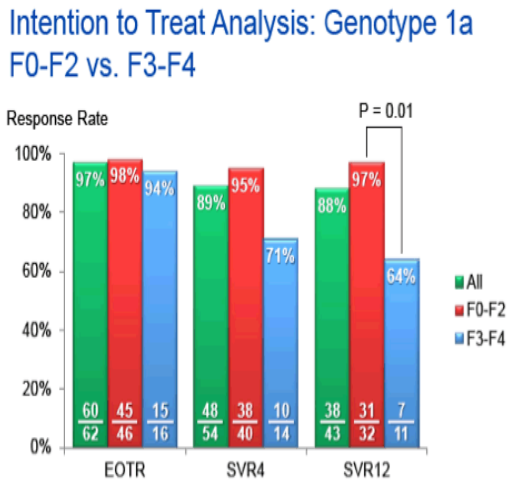
Successful antiviral treatment after LT can improve patient and graft outcomes.

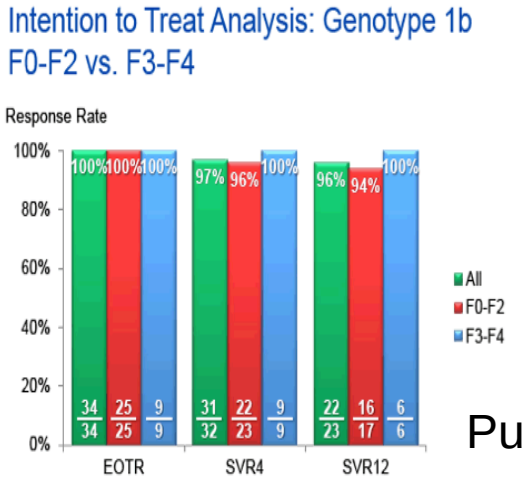
Treatment after liver transplantation versus pretransplant treatment???

Levin J, et al. AASLD 2014

Therapeutic success after LT is not guaranteed, but…

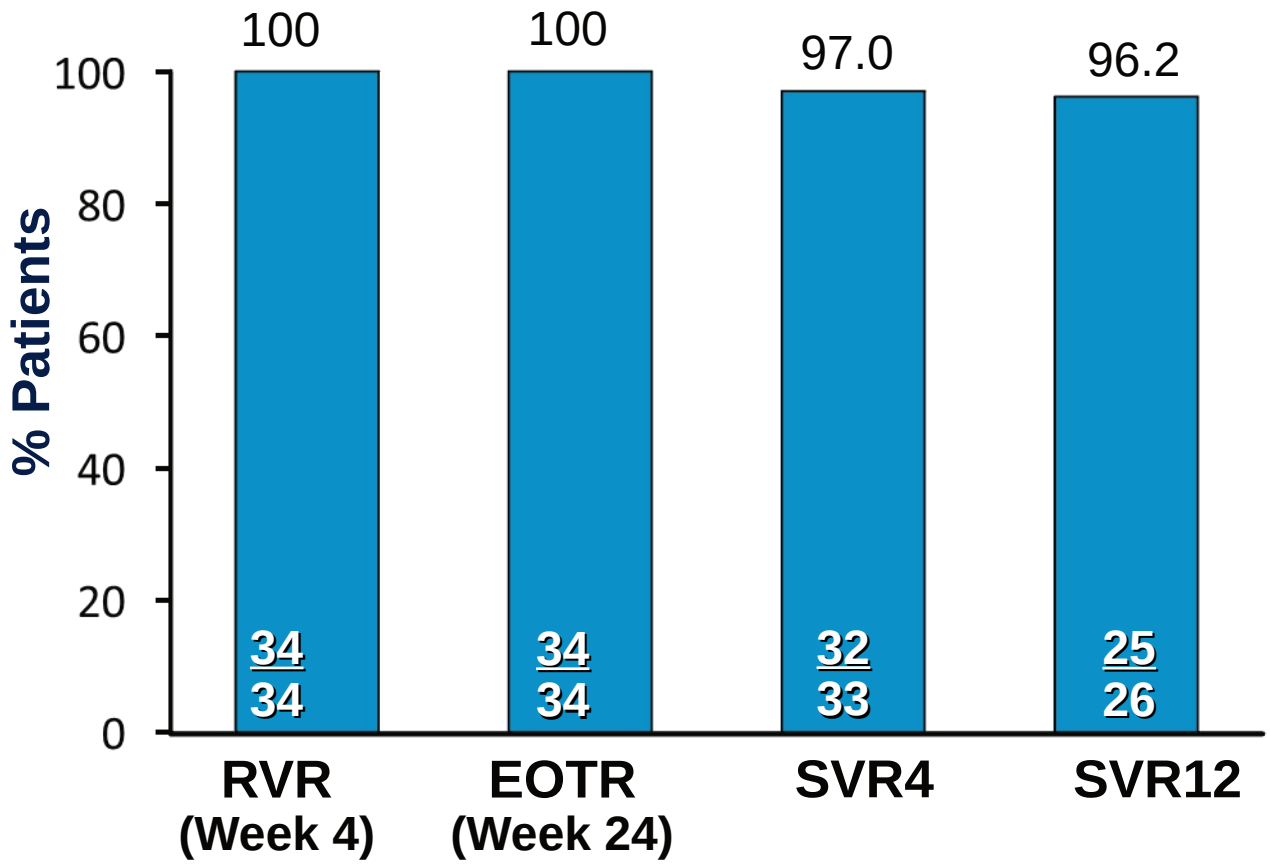
V





Pungpapong S, et al. AASLD 2014

results are excellent…
Study M12-999: liver transplant recipients with recurrent HCV GT1



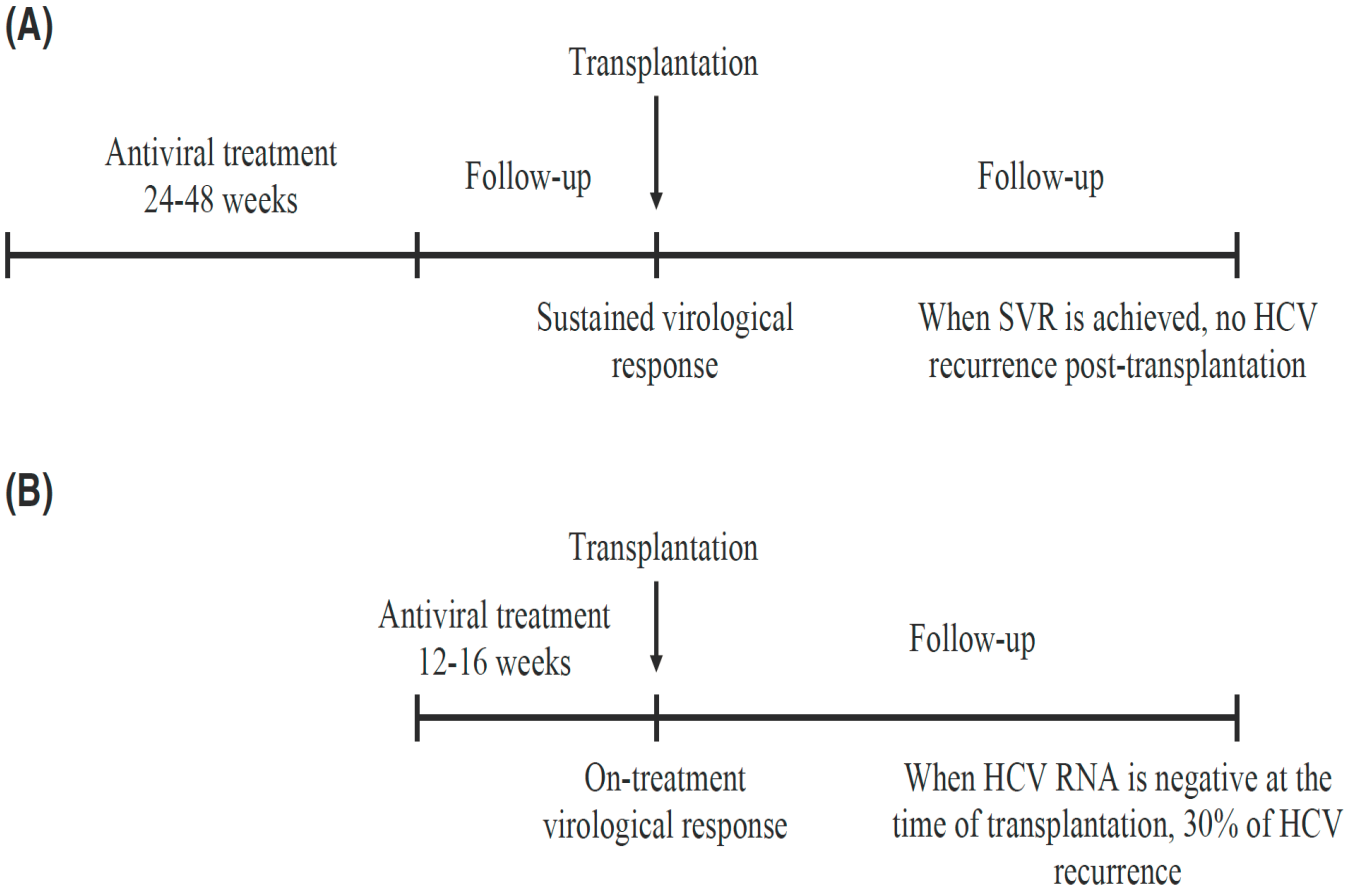
No patient had breakthrough

One patient had a relapse (post-treatment day 3)

- At the time of relapse, this patient had R155K in NS3 protease, M28T + Q30R in NS5A, and G554S + G557R in NS5B, none of which were present at baseline

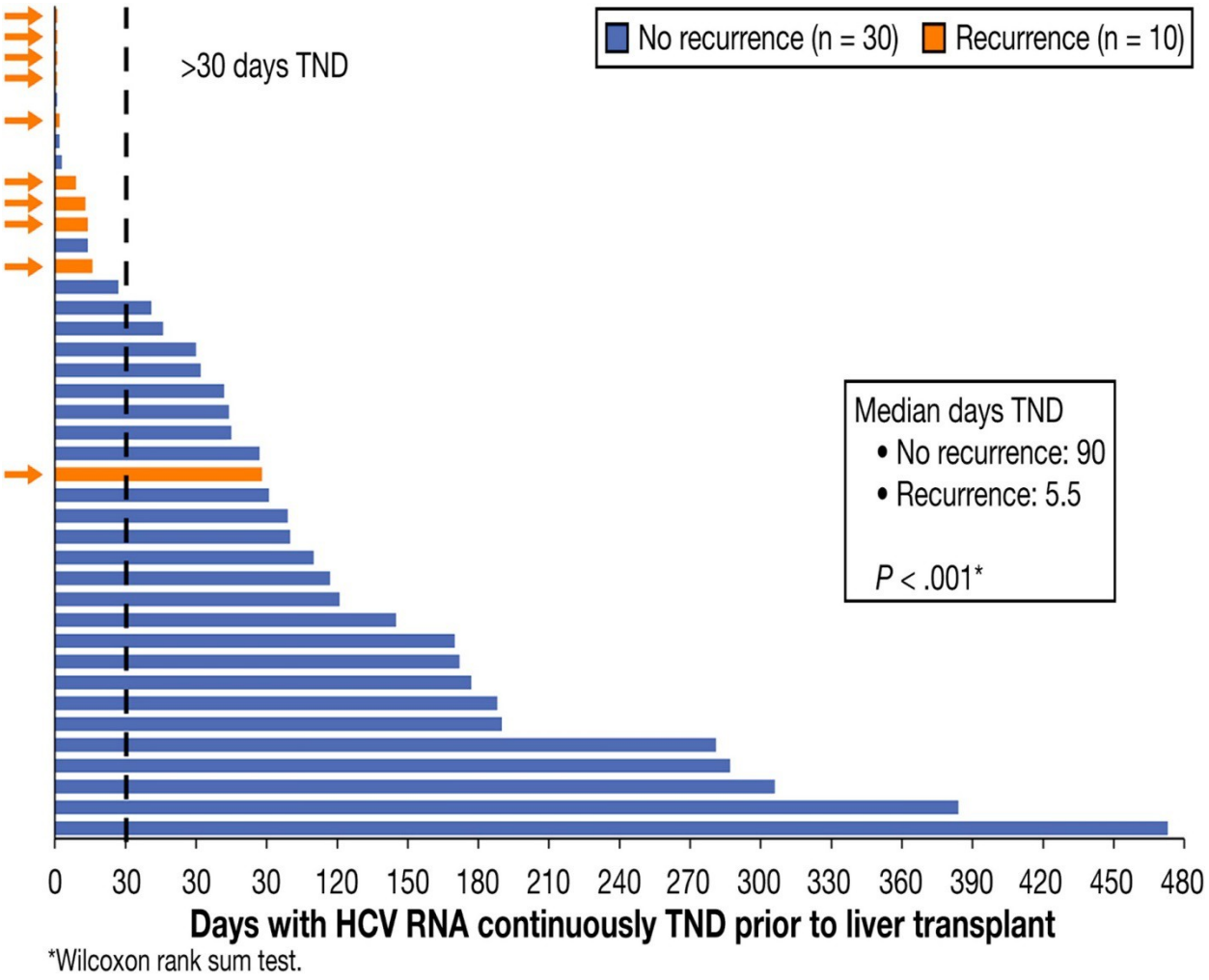
Kwo P, *et al.* EASL 2014 Abstract 114.

What is required to prevent HCV recurrence?
SVR or negativity at the time of LT ?



Roche B and Samuel D. Liver Int 2012; 32 (Suppl 1):120

Sofosbuvir and Ribavirin Prevent Recurrence of HCV Infection After Liver Transplantation



Curry MP, et al. Gastroenterology 2015 148, 100-107

Why should we treat patients on the waiting list?

To avoid HCV reccurence.

To avoid liver transplantation?

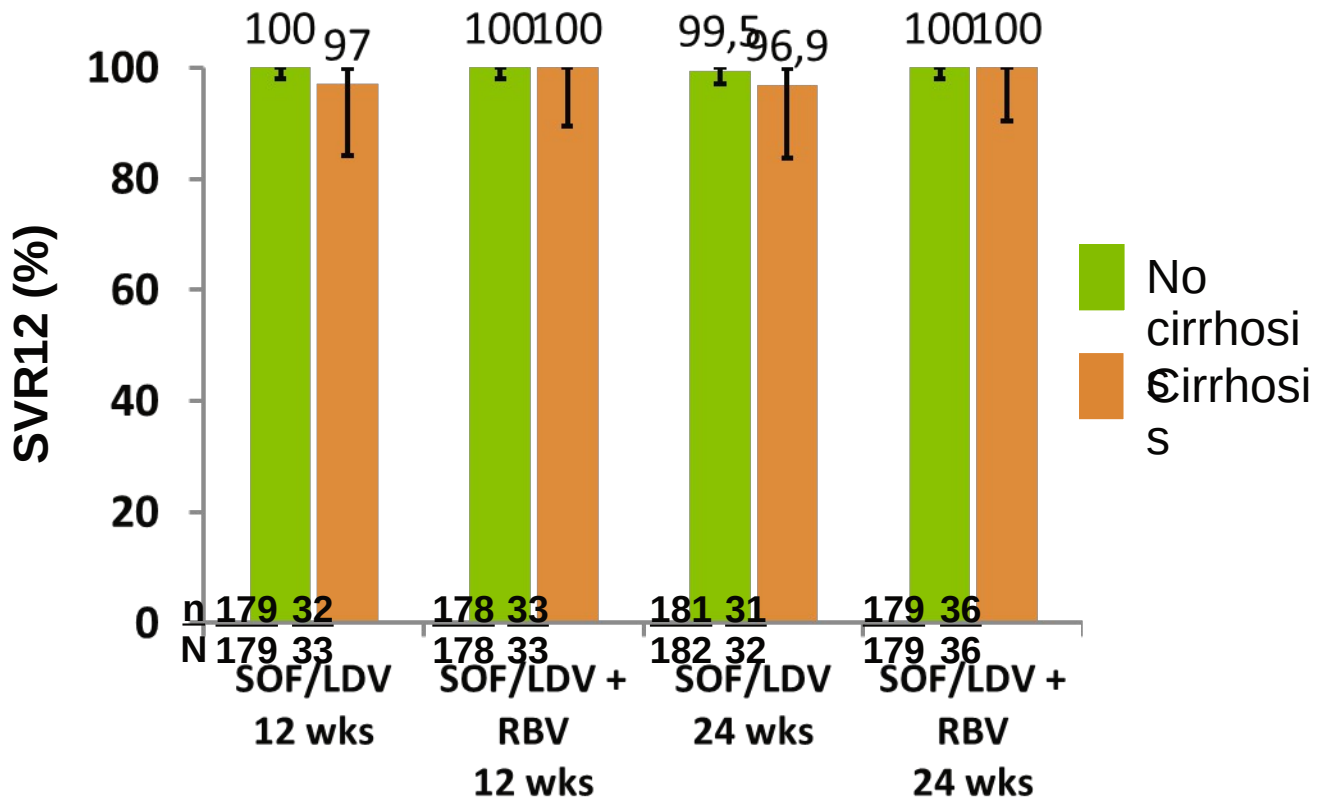
Cirrhotic populations treated in Phase 3 clinical trials

Therapeutic regimen in trial arm including cirrhotic population (Trial name)	Response to previous IFN based therapy	Lower limit of platelets (mm^3)	Treatment duration in the specific arm (wk)	Cirrhotic patients enrolled in the study N (%)	Genotype spectrum	SVR in cirrhotic patients
SOF + RBV [104]	Naïve and treatment-experienced	n.s.	12 24	14 (23)	4	SVR12 79% and 100% in naïve 59% and 87% in treatment-experienced (12 and 24 wk respectively)
DCV + ASV + BMS-791325 [105]	Naïve	n.s.	12	2 (10)	4	SVR12 100%
SOF + RBV (FISSION) [21]	Naïve	75,000	12	50 (20)	2, 3	SVR12 47%
SOF + RBV (POSITRON) [106]	IFN intolerant	No lower limit	12	31 (15)	2, 3	SVR12 61% (G2 94% and G3 21%)
SOF + RBV (FUSION) [106]	Non-responder	50,000	12 16	36 (35) 32 (33)	2, 3	SVR12 G2 60% and 78% G3 19% and 61% (12 and 16 wk respectively)
SOF + RBV (VALENCE) [36]	Naïve and treatment-experienced	50,000	12 G2 24 G3	10 (14) G2 59 (22) G3	2, 3 (G3 78%)	SVR12 G2 100% and 88% G3 92% and 60% (naïve and treatment-experienced respectively)
LDV/SOF ± RBV (ION-1) [32]	Naïve	50,000	12 24	136 (16)	1	SVR12 97 and 100% ± RBV (both 12 and 24 wk)
LDV/SOF ± RBV (ION-2) [33]	Treatment-experienced	50,000	12 24	88 (20)	1	SVR12 82-86% 12 wk arm (± RBV) and 100% 24 wk arm
DCV + ASV [107]	IFN ineligible naïve/ intolerant and non-responder	n.s.	24	22 (10)	1b	SVR24 90.9%
DCV + ASV (HALLMARK-DUAL) [35]	Naïve, IFN ineligible/ intolerant and non-responder	n.s.	24	223 (30)	1b	SVR12 91%, 87% and 81% in naïve, non-responders and ineligible/intolerant respectively
ABT-450/r + ombitasvir + dasabuvir + RBV (TURQUOISE II) [34]	Naïve and treatment-experienced	60,000	12 24	380 (100)	1	SVR12 91.8% and 95.9% in 12 and 24 wk

Gambato M, et al. J Hepatol 2014

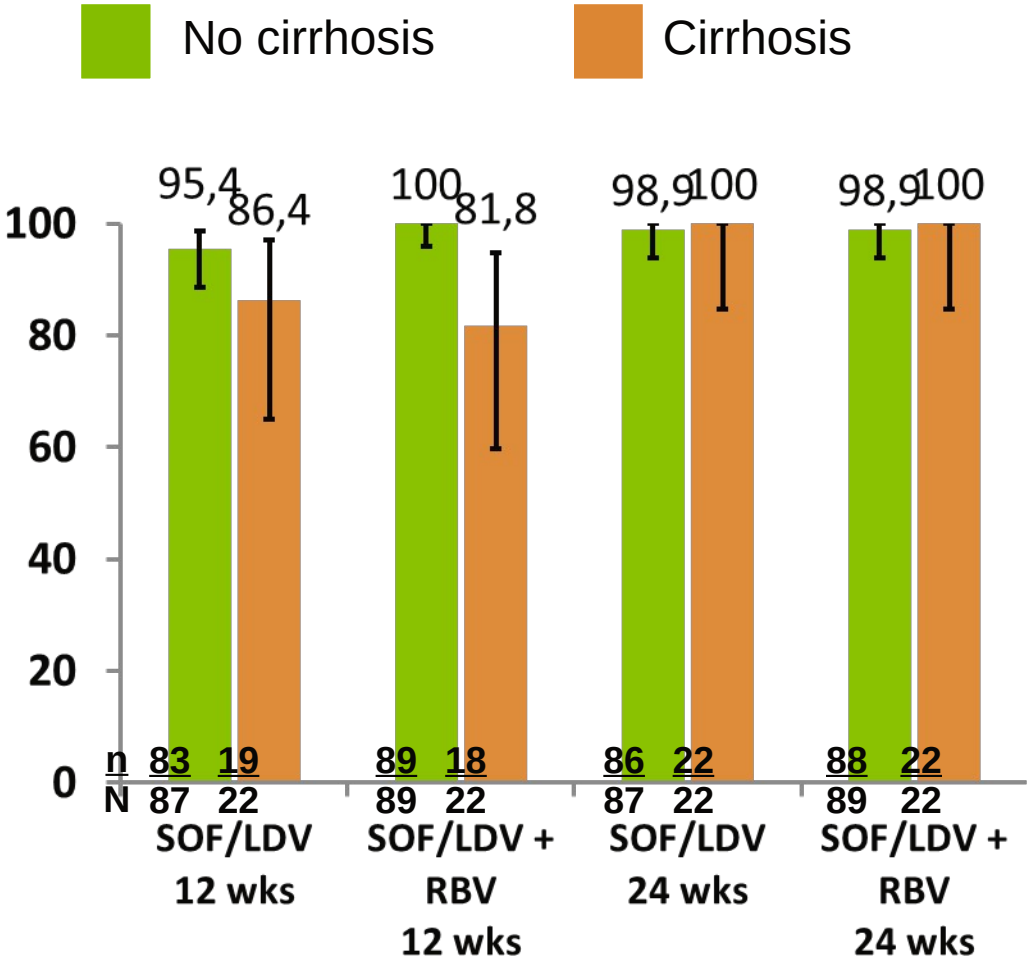
ION-1: SVR rates* in GT1 treatment-naive cirrhotic patients (subgroup analysis)

- SVR12 rates in the mITT population (N=852): subgroup results do not include patients who withdrew consent or who were lost to follow-up



Afdhal N, *et al. New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1402454.

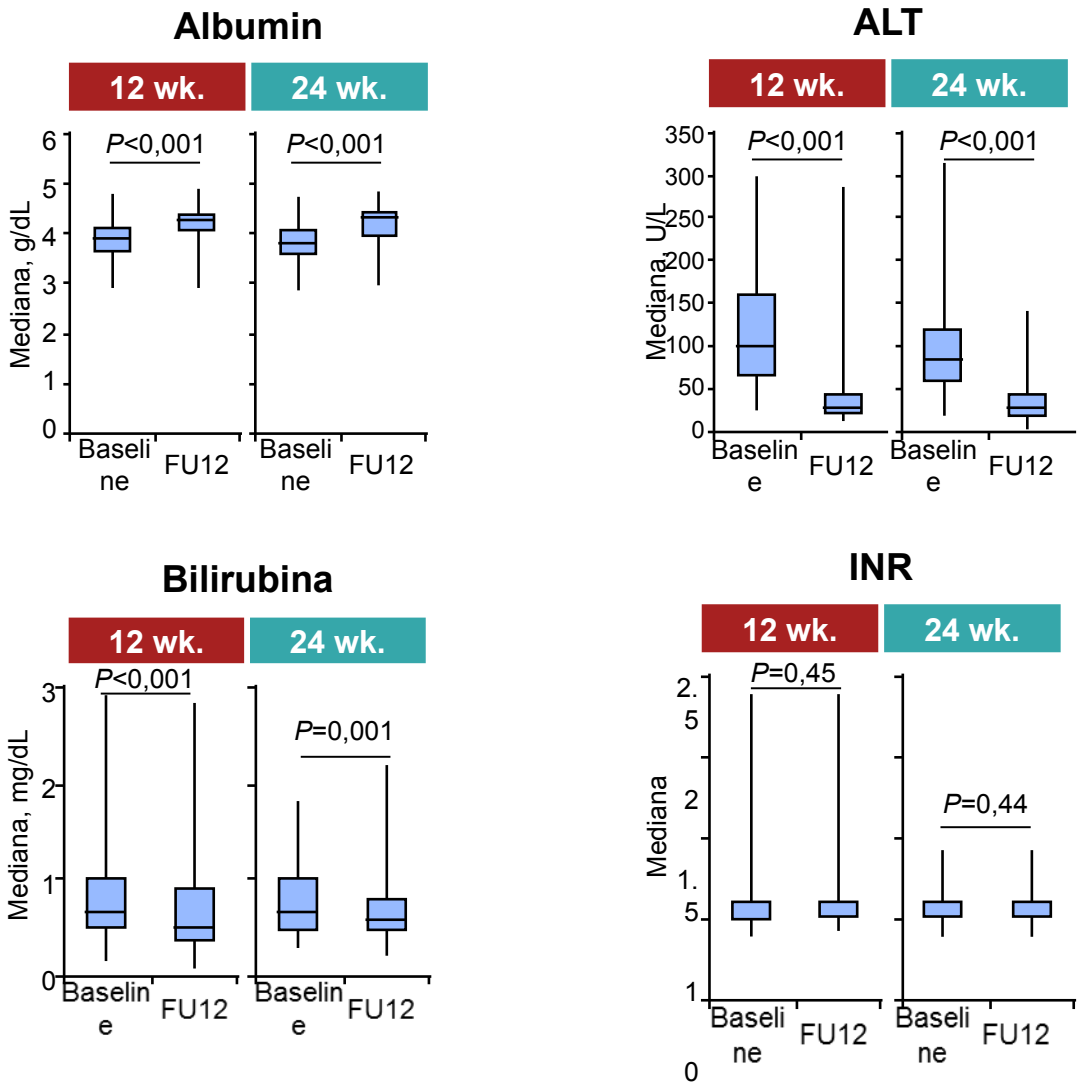
ION-2: SVR rates in GT1 treatment-experienced cirrhotic patients (subgroup analysis)



Afdhal N, *et al. New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1316366.

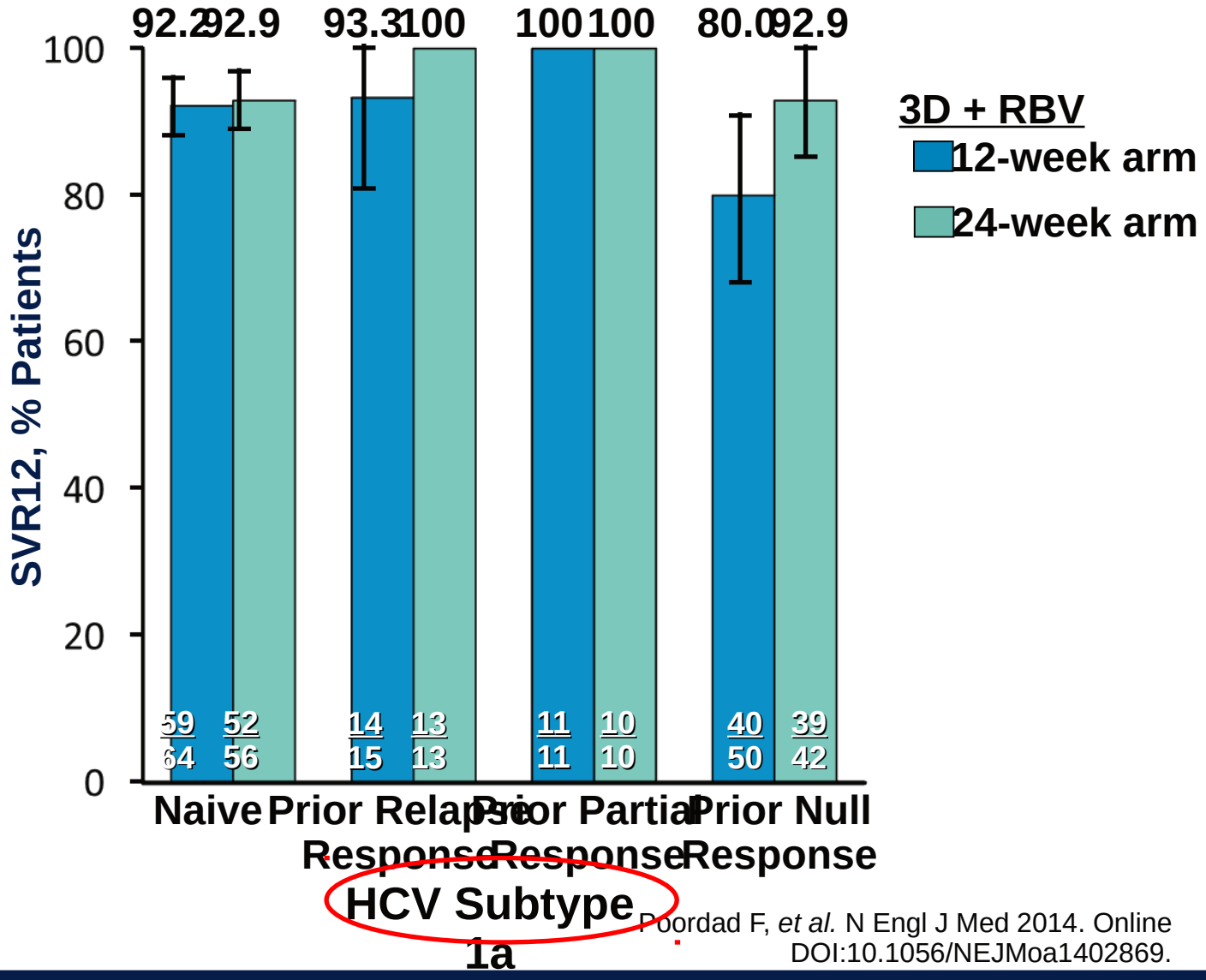
SIRIUS: Treatment of cirrhotic patients after IFN-based therapy failure

Lab improvement



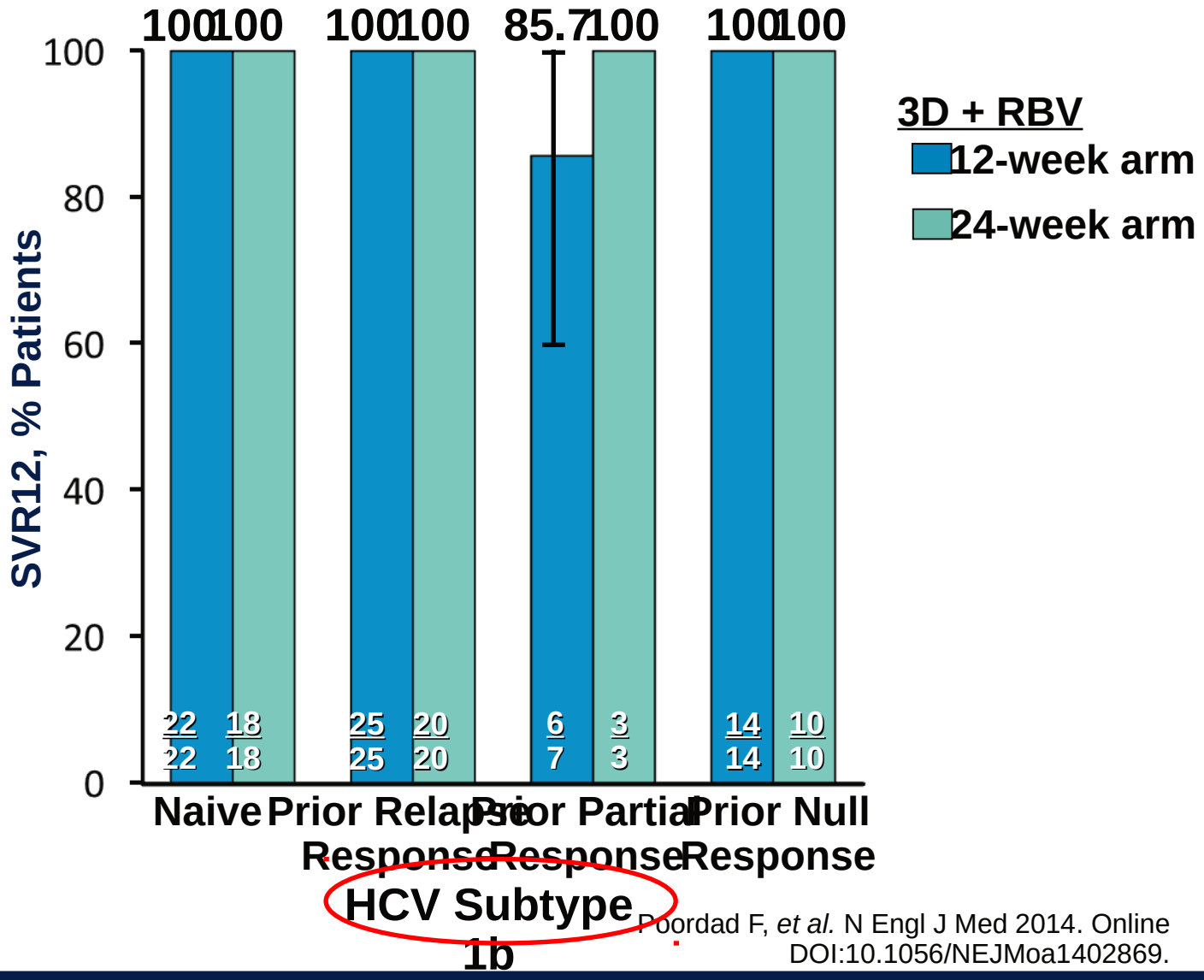
Bourliere, AASLD, 2014, Oral #LB-6

TURQUOISE-II: SVR12 rates in GT1a treatment-naive and experienced cirrhotic patients by prior treatment response



Poordad F, *et al.* N Engl J Med 2014. Online DOI:10.1056/NEJMoa1402869.

TURQUOISE-II: SVR12 rates in GT1b treatment-naive and experienced cirrhotic patients by prior treatment response



Poordad F, *et al.* N Engl J Med 2014. Online DOI:10.1056/NEJMoa1402869.

Treatment of patients with decompensated cirrhosis

Limited data.

Clinical trials ongoing.

Case reports and personal experience.

Bonacci M, et al. **Antiviral treatment with sofosbuvir and simeprevir in a kidney transplant recipient with HCV-decompensated cirrhosis: viral eradication and removal from the liver transplant waiting list.** Transpl Intern 2015

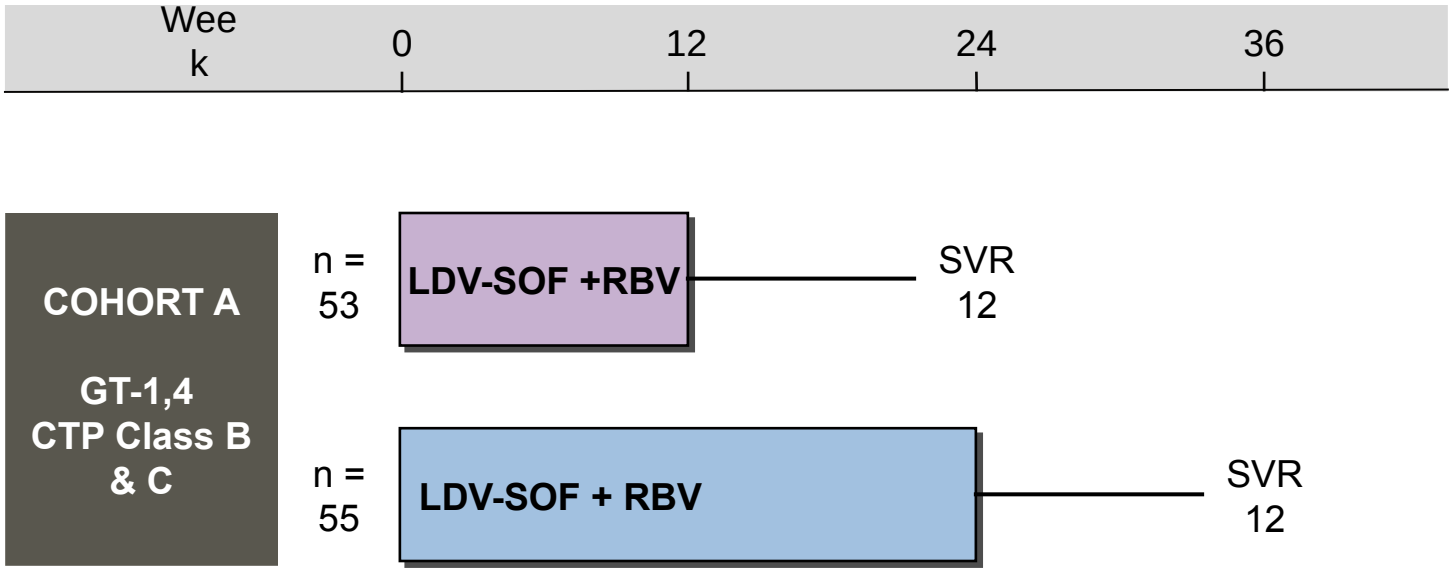
Disease
SOLAR-1 (Cohorts A and B)
Treatment Naïve and Treatment Experienced

SOLAR-1 (Cohorts A and B): Design

- **Design**: Phase 2, open label, randomized prospective, trial, using fixed-dose combination of ledipasvir-sofosbuvir plus ribavirin for 12 or 24 weeks in treatment-naïve and treatment-experienced patients with HCV GT 1 or 4.
- **Cohorts**
  Cohort A = cirrhosis and moderate to severe hepatic impairment who had not undergone liver transplantation
  Cohort B = post liver transplantation
- **Setting**: multicenter study in United States
- **Entry Criteria**
  - Adults with Chronic HCV Genotype 1 or 4
  - Treatment-naïve or treatment experienced
  - Total bilirubin ≤ 10 mg/dL; Creatinine clearance ≥ 40 mL/min
  - Hemoglobin ≥ 10 g/dL; Platelet count > 30,000/mm^3
  - Exclusion: hepatitis B or HIV coinfection or prior receipt of NS5a inhibitor
- **Primary End-Point**: SVR12

Charlton M, al. Gastroenterology. 2015

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4 SOLAR-1 (Cohort A = Pre-transplantation): Study Design



Abbreviations: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

Drug Dosing
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily
Ribavirin: started at 600 mg/day and then escalated as tolerated up to maximum of 1200 mg/day

Charlton M, al. Gastroenterology. 2015; [Epub ahead of print]

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4 SOLAR-1 (Cohort A = Pre-transplantation): Baseline Characteristics

Cohort A Characteristic	CTP B		CTP C	
	12-Weeks n=30	24-Weeks n=29	12-Weeks n=23	24-Weeks n=26
Median age, years	60	58	58	59
Male, n (%)	22 (73)	18 (62)	14 (61)	18 (69)
White, n (%)	29 (97)	26 (90)	21 (91)	24 (92)
HCV RNA, $\log_{10}$ IU/mL	5.9	5.8	5.6	5.8
IL28B genotype CC, n (%)	4 (13)	5 (17)	6 (26)	7 (27)
HCV Genotype				
1a, n (%)	19 (63)	22 (76)	15 (65)	18 (69)
1b, n (%)	10 (33)	7 (24)	6 (26)	8 (31)
4, n (%)	1 (3)	0	2 (9)	0
Prior Treatment	22 (73)	19 (66)	11 (48)	18 (69)

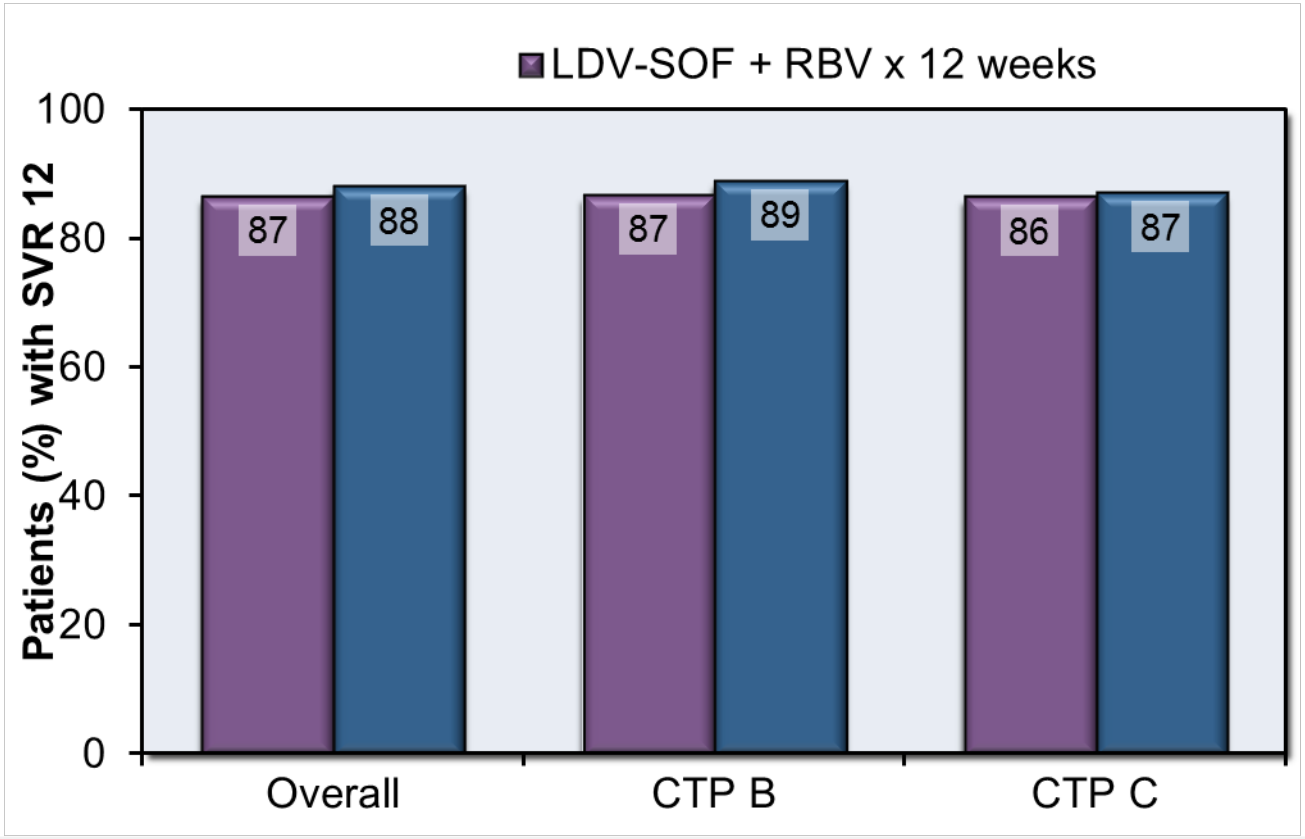
Charlton M, al. Gastroenterology. 2015; [Epub ahead of print]

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4 SOLAR-1 (Cohort A = Pre-transplantation): Baseline Liver Status

Cohort A Characteristic	CTP B		CTP C	
	12-Weeks n=30	24-Weeks n=29	12-Weeks n=23	24-Weeks n=26
Child-Turcotte-Pugh				
Class A (5-6)	0	1 (3)	0	0
Class B (7-9)	27 (90)	27 (93)	7 (30)	4 (15)
Class C (10-12)	3 (10)	1 (3)	16 (70)	22 (85)
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)
Median eGFR, mL/min	98	81	77	78
Median platelets, x 10^3 µL	88	73	81	71

Charlton M, al. Gastroenterology. 2015; [Epub ahead of print]

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4 SOLAR-1 (Cohort A= Pre-transplantation): SVR 12 Results



6 subjects excluded because received transplant while on study: (2 CTP B/24 week; 1 CTP 2/12 week; 3 CTP C/24 week

Charlton M, al. Gastroenterology. 2015; [Epub ahead of print]

Safety of Ledipasvir-Sofosbuvir + RBV treatment in decompensated cirrhosis

	CPT B		CPT C	
Patients (%)	12 Weeks (n=30)	24 Weeks (n=29)	12 Weeks (n=23)	24 Weeks (n=26)
Advers Events (AE)	97%	93%	100%	100%
Grade 3-4 AE	7%	28%	26%	42%
Serious and Related AEs	7%	0	0	8%
Treatment discontinuation due to AE	0	3%	0	8%
Death	3%	7%	9%	4%

Related SAEs: Anemia, hepatic encephalopathy, peritoneal hemorrhage

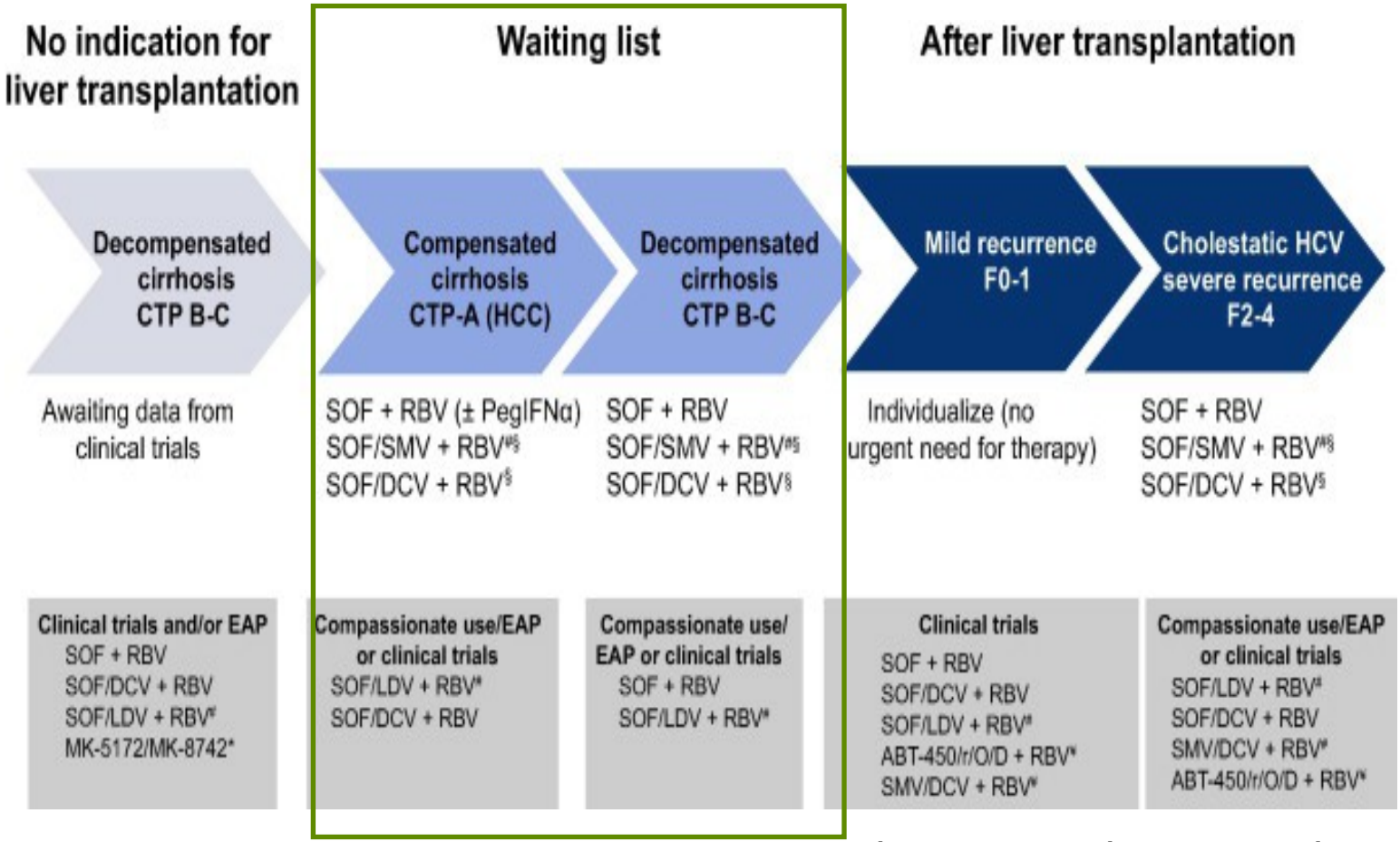
Flamm S, et al. Abstract #239, AASLD 2014

Dose adjustment (mostly) not required

Drug	CTP A (5-6 points)	CTP B (7-9 points)	CTP C (≥10 points)
Sofosbuvir [38,108]	NR	NPD	NPD
Simeprevir [109]†	NR	NR	AUC x 3
Daclatasvir [110, 111]¥	NR	NR	NR
Asunaprevir [112]	NR	AUC x 9.8	AUC x 32
Ledipasvir [113]	NR	NR	NR
ABT-450/r [114]§	NR	NR	AUC x 11
Dasabuvir [114]	NR	NR	NR
Ombitasvir [114]	NR	NR	NR
MK-8742 [103]	NR	NR	NPD
MK-5172 [103]	NR	NR	NPD

NR, dose adjustment not required; NPD, no pharmacokinetic data or studies ongoing

Gambato M, et al. J Hepatol 2014



Gambato M, et al. J Hepatol 2014

- Based on past and current data, SMV should not be used in CPT C patients ?

Conclusions

- The precondition for protecting transplanted liver from HCV infection is the suppression of viremia to undetectable levels at least a month prior to the transplantation procedure, which justifies the initiation of therapy as early as possible after approval for liver transplantation.
- HCV eradication may cause the removal of cirrhotic patient from liver transplant list, but „the point of no return” has not been defined.
- HCV eradication may be associated with clinical improvement and finally with increased survival in patients who are not on the waiting list, increasing their survival (e.g. elderly or with comorbidities contraindicating a LT).
- Excellent safety profile and no need for dose adjustment (LDV-SOF).
- When (if ever) is too late for treatment initiation?
- Still more data expected.