TREATMENT OF HEPATITIS C IN THE LIVER TRANSPLANT SETTING

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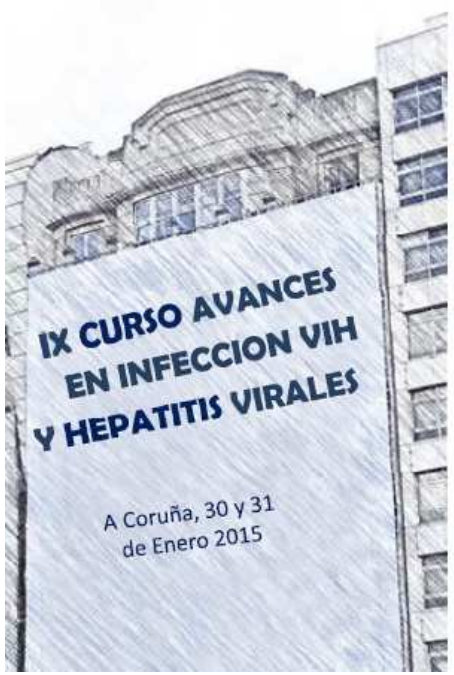
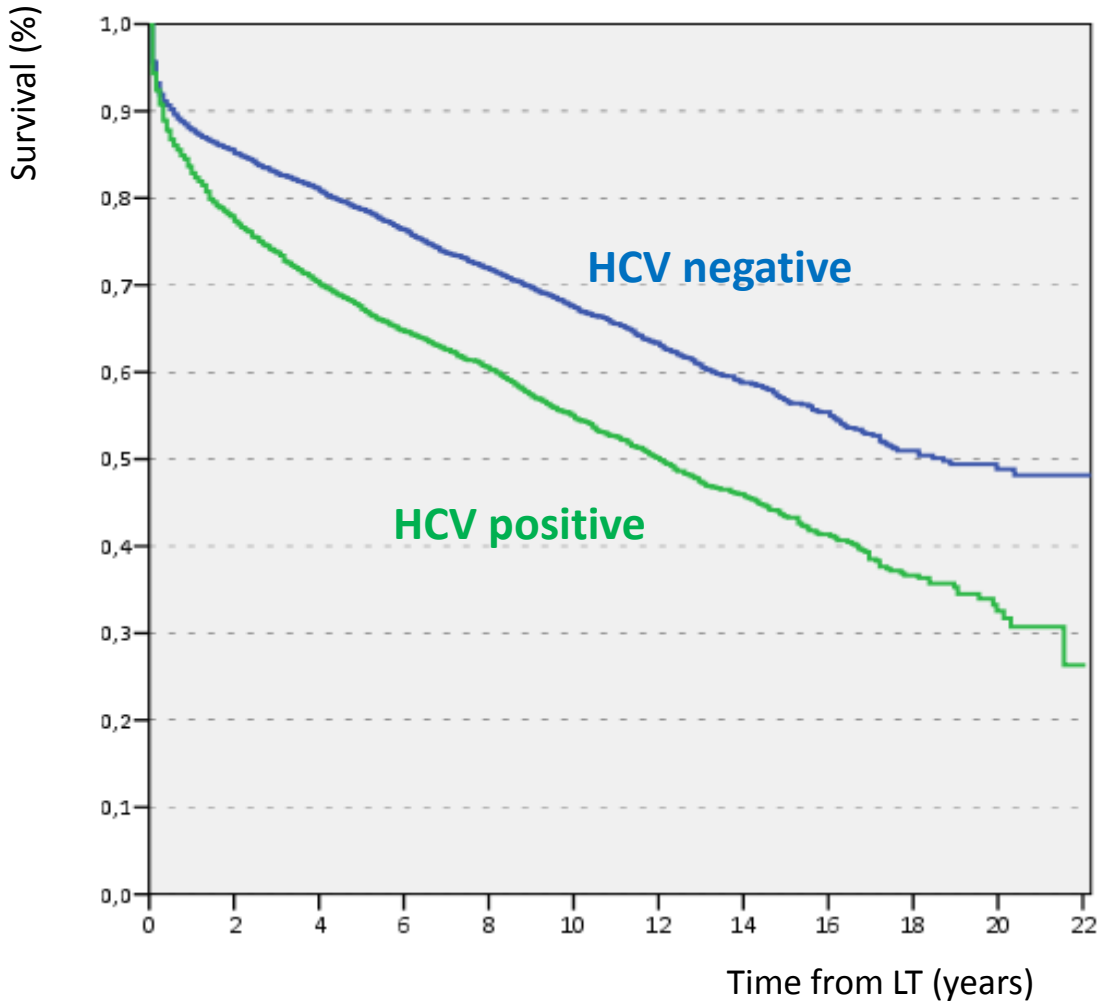


Hepatitis C after LT



SETH Sociedad Española de Trasplante Hepático

ONT ORGANIZACIÓN NACIONAL DE TRASPLANTES

HCV treatment strategies

1. Waiting List (“*preventive strategy*”):

Compensated and decompensated cirrhosis.

2. After LT:

When?

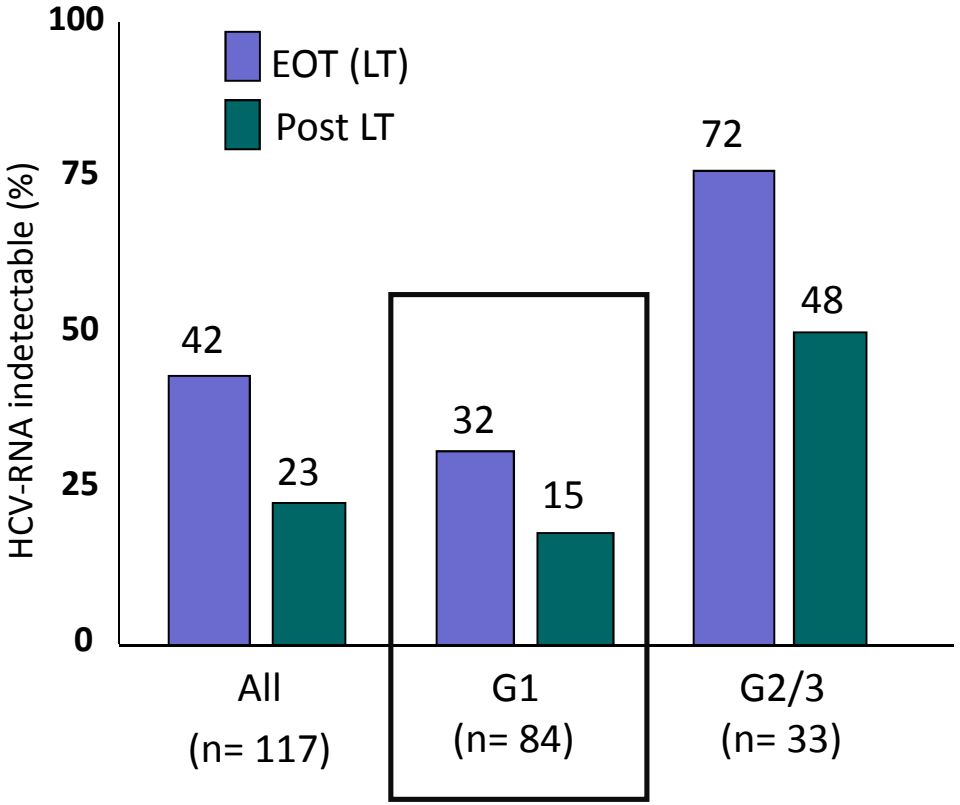
Why?

How?

IFN-based therapies in the waiting list

Peg-IFN+RBV

Duration (median) 12 w



Forns X, J Hepatol. 2003; Carrión J, J Hepatol. 2009; Everson GT, Hepatology 2005 y 2013

Peg-IFN+ RBV+ IPs (TLV/BOC)

ANECDOTAL EXPERIENCE (n=29)

SVR12 67% (8/12)

Better SVR rates in cirrhosis (~50%) but…….

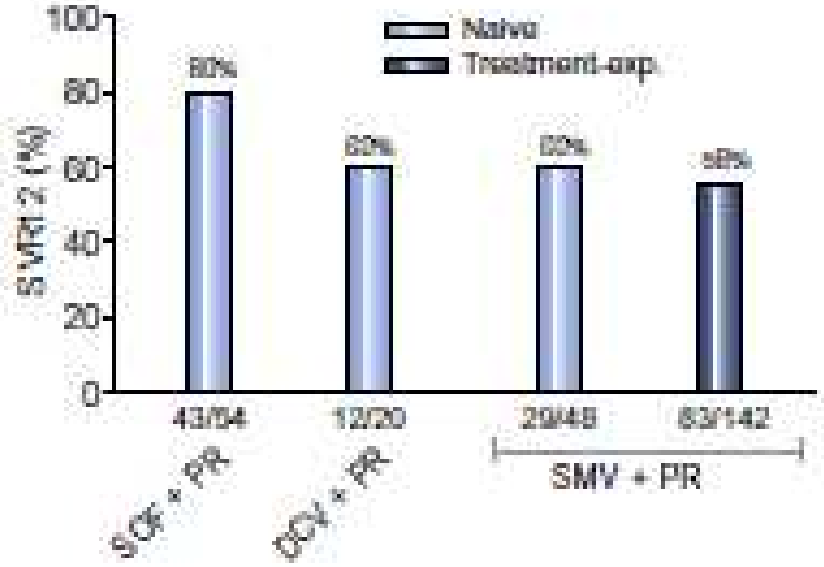
…….. **High rate of adverse events** (infections, liver decompensation… >40%).

Verna, Liver Int 2014; Rutter K et al, APT 2013; Hézode C et al, Gastroenterol 2014; Saxena et al, A&T 2014

IFN-based therapies in the waiting list

Peg-IFN+ RBV+ DAAs: SOF/ SIM/DCL

From general cirrhotic patients



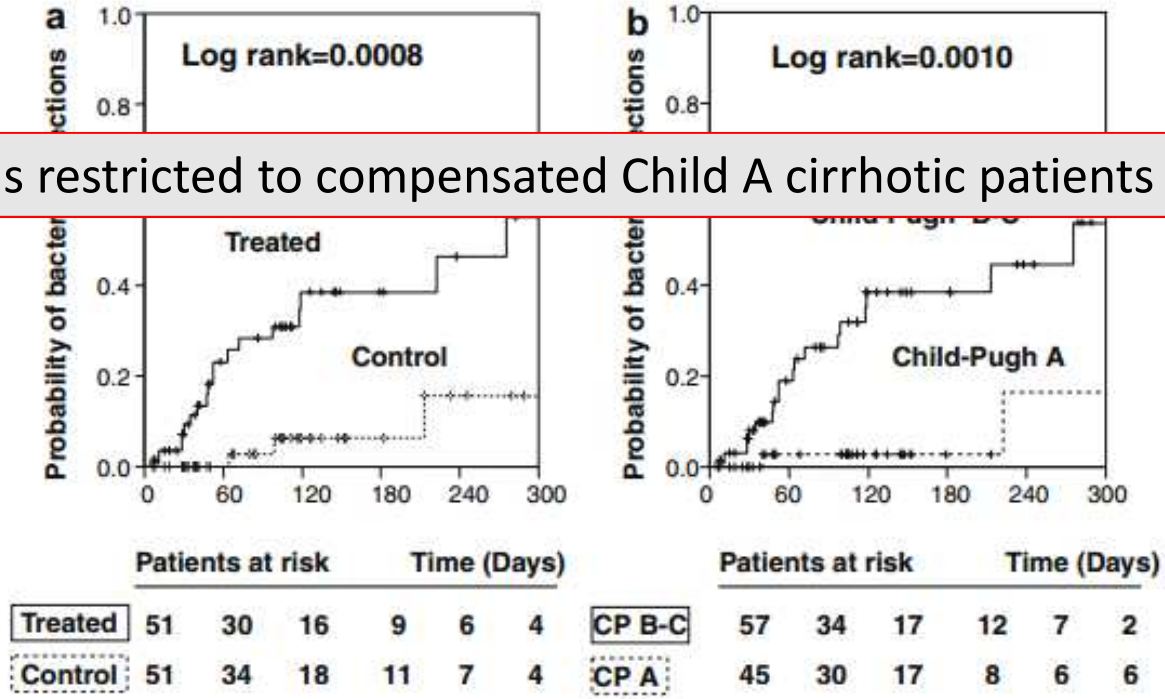
Gambato et al, J Hepatol 2014

Lawitz E, NEJM 2013;Hezode et al, Hepatol 2012; Jacbson et al, Lancet 2014; Manns et al, Lancet 2014; Zeuzem et al, Gastroenterol 2014; Forns et a, Gastroenterol 2014

IFN-based therapies in the waiting list

IFN should NOT be used in patients with decompensated liver disease (Child B>7 y/o MELD>18) as it is related with high rate of bacterial infections and liver impairement.

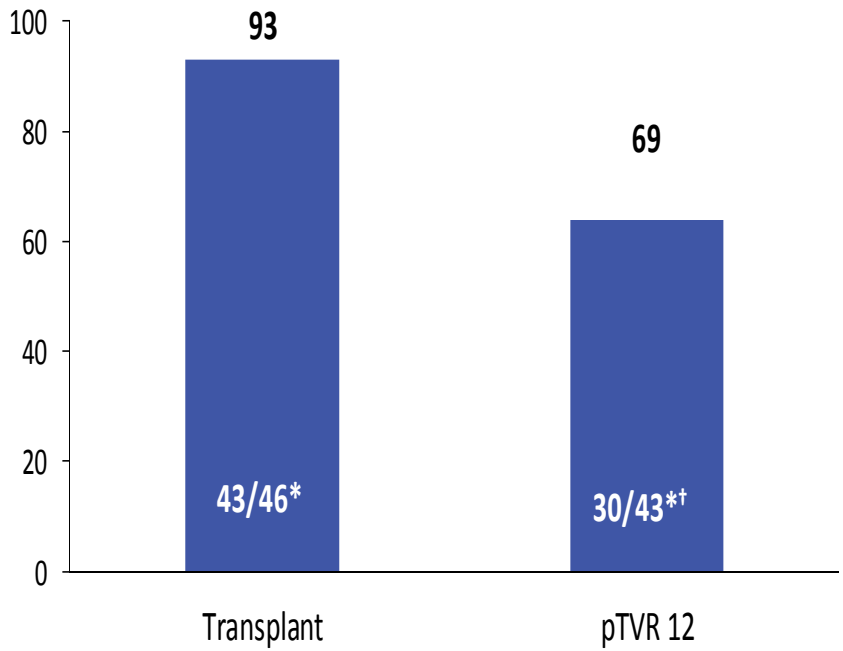
IFN use is restricted to compensated Child A cirrhotic patients with HCC

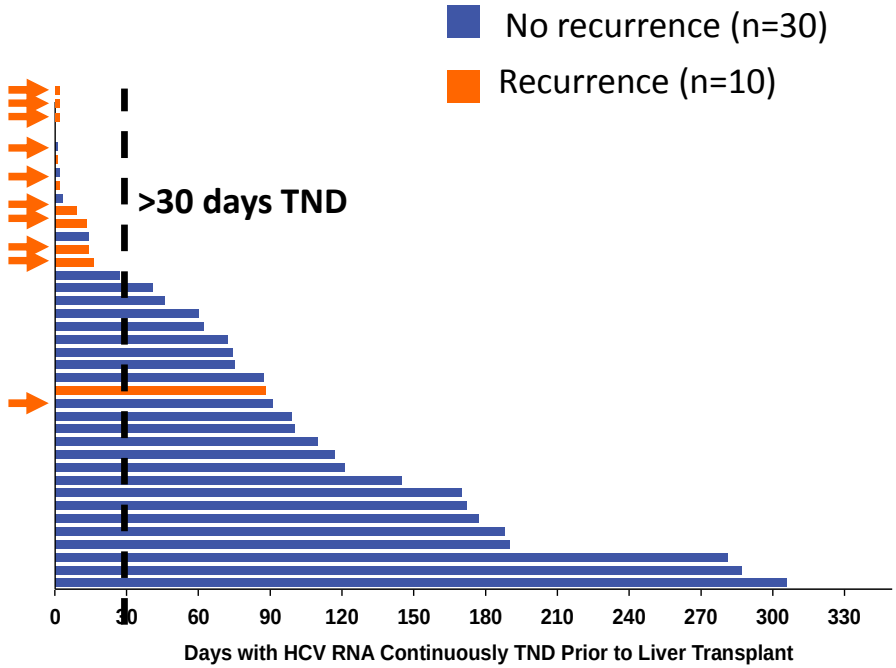


Carrión et al, J Hepatol 2009

IFN-free treatments in the waiting list (DAAs)

Containment trial (phase II):
Sofosbuvir + RBV WB until LT (or max 48w) in 61 HCV compensated cirrhotic patients enlisted for LT (Child A/ B7)





*3 patients >LLOQ at LT
† 3 deaths, 10 recurred after LT

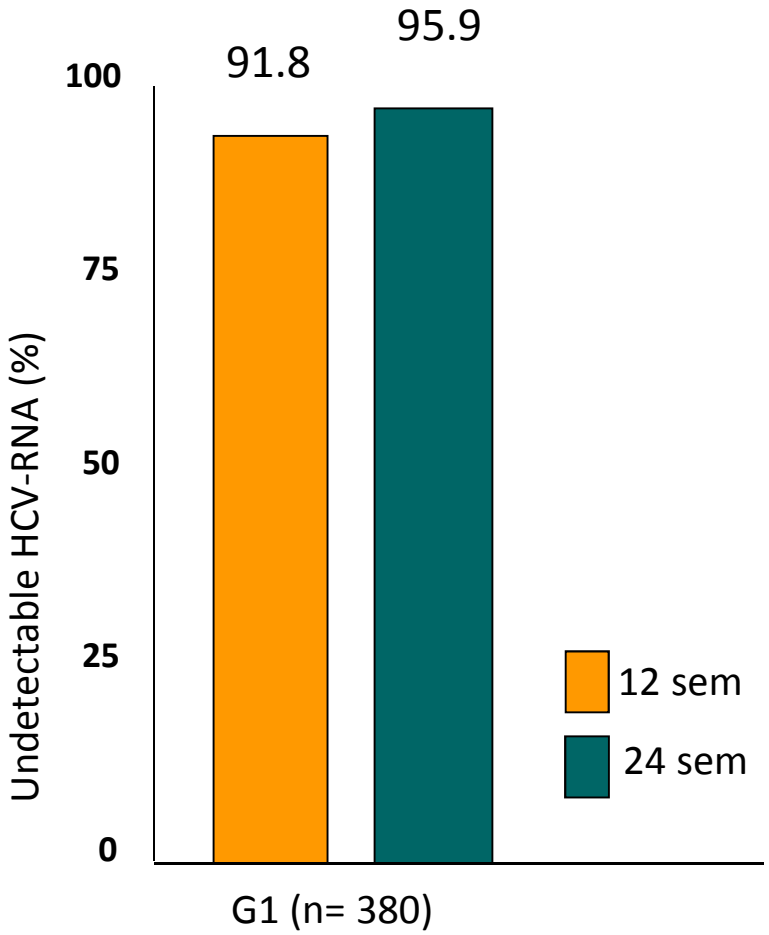
Curry et al, Gastroenterol 2014

IFN-free treatments in cirrhosis (DAAs)

TURQUOISE II trial:

Paritaprevir (ABT-450)/r/Ombitasvir (ABT-267)+ Dasabuvir (ABT-333) + RBV

380 compensated CH, 12-24 weeks, 70% G1a, naive/ TE



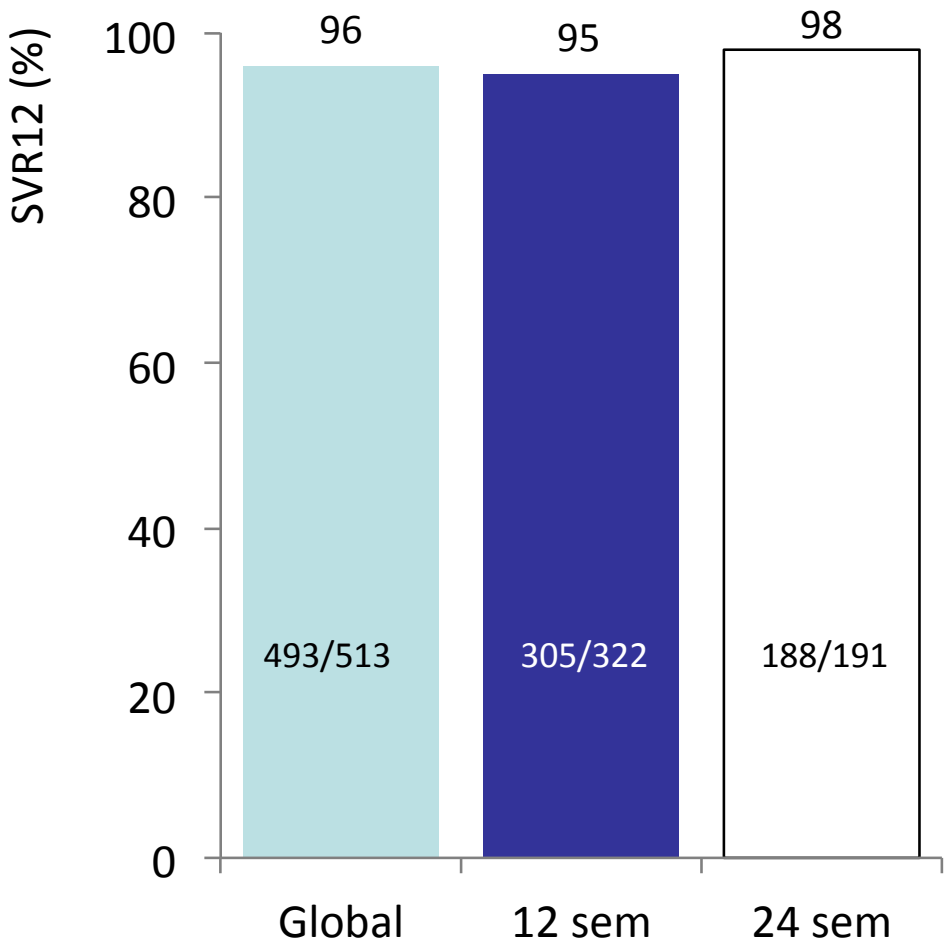
* Treatment failure was associated with G1a infection and null response → 90%

Poordad et al, NEJM 2014

IFN-free treatments in cirrhosis (DAAs)

Sofosbuvir/ Ledipasvir + RBV

Pooled report: G1 compensated cirrhosis (n=513)



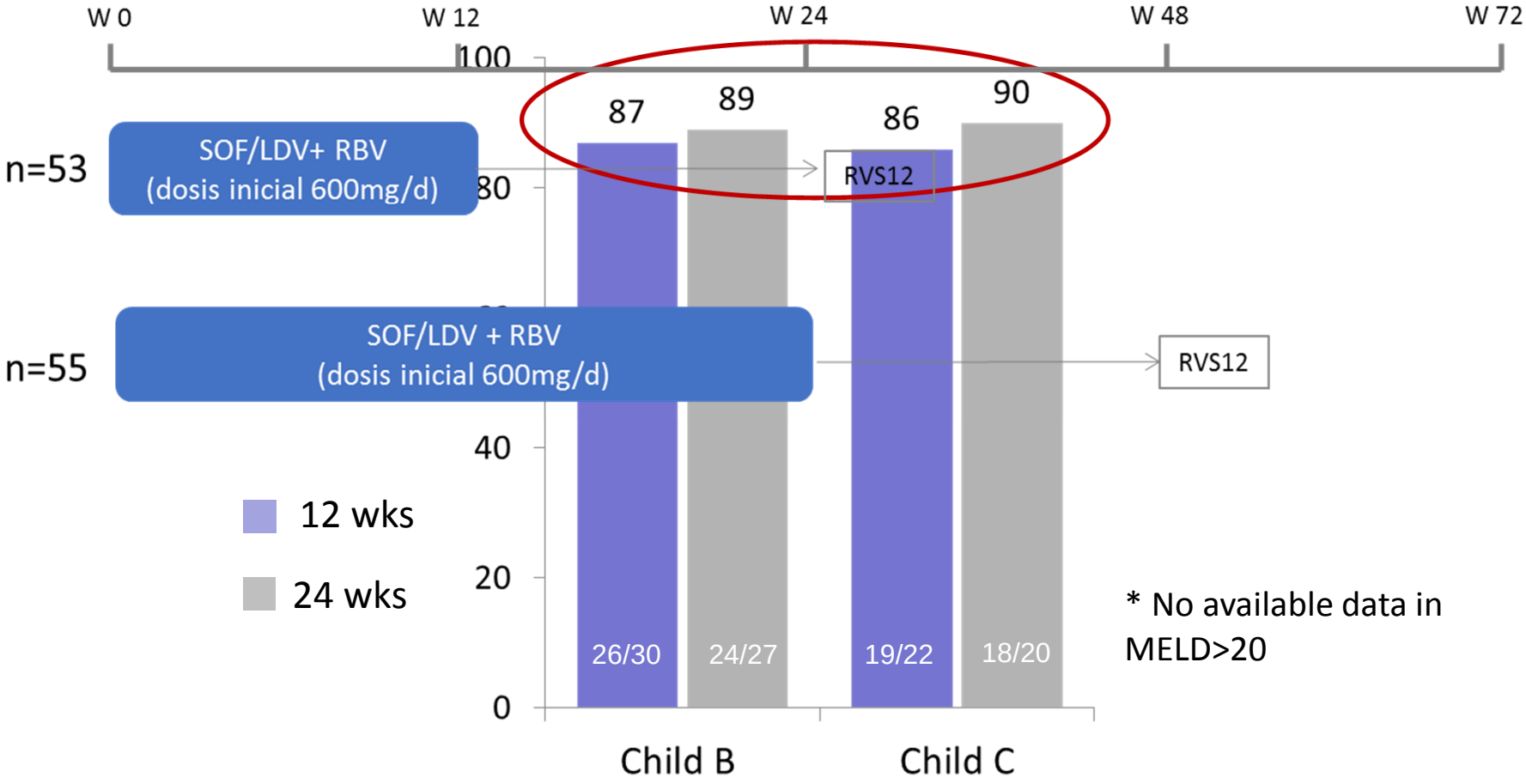
* SVR12>95% in all arms except:
CH /TE / wo RBV/ 12 weeks: 90%
In pats with <70 000 and TE: 82%

Bourlière et al, AASLD 2014

IFN-free treatments in cirrhosis (DAAs)

Cohort A, SOLAR-1: **Sofosbuvir/Ledipasvir + RBV** (12/ 24 weeks)

108 G1 or G4 decompensated cirrhotics: **Child B (7-9) or C (10-12)**

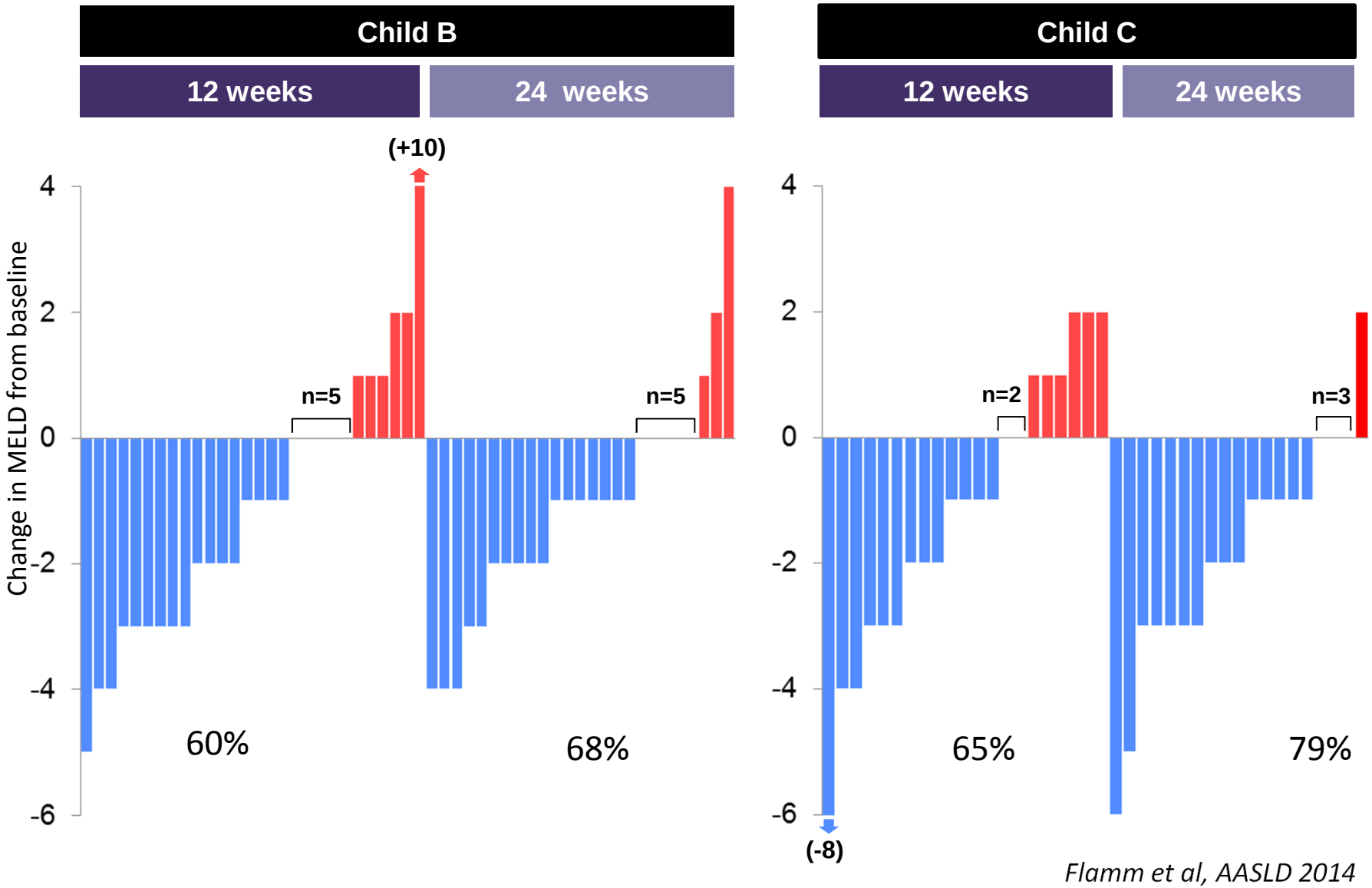


* No available data in MELD>20

Flamm et al, AASLD 2014

IFN-free treatments in cirrhosis (DAAs)

Impact of treatment on liver function and clinical status

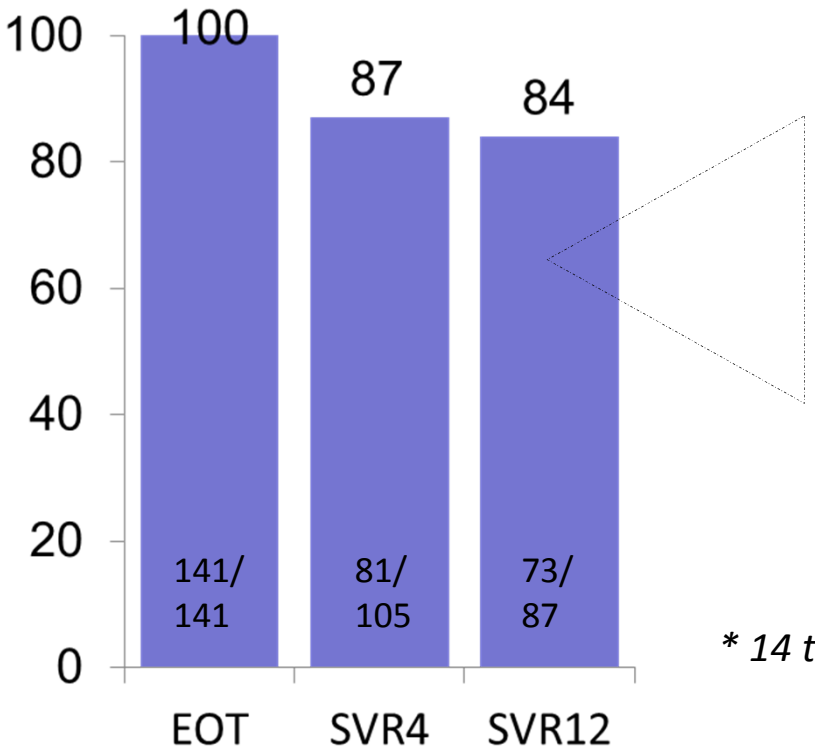


Flamm et al, AASLD 2014

IFN-free treatments in cirrhosis (DAAs)

Sofosbuvir + Simeprevir ± RBV 12 weeks(n=147)

Cirrhotic patients included (n=114), **93 were in WL**, (MELD 12), 65% TE (~18% PI-failures); 70% G1a



No cirrhosis 100% vs **cirrhosis 81%**
Child A 83% vs Child B 79%

Similar results reported from the HCV-TARGET, SVR4 in cirrhosis was 87% *(Jenssen, AASLD 2014)*

** 14 treatment failures (relapse), all cirrhosis*

Aqel et al, AASLD 2014

IFN-free treatments in cirrhosis (DAAs)

SAFETY PROFILE

IFN-free treatments are generally **SAFE** when used in cirrhotic patients (no significant difference from non cirrhotic patients)

There is still **lack of data** regarding safety and efficacy of DAAs in more advanced liver disease: Child >12 and /or MELD>20.

Afdhal et al, AASLD 2014; Aqel et al, AASLD 2014; Flamm et al, AASLD 2014; Bourliere et al, AASLD 2014; Gambato et al, J Hepatol 2014

HCV treatment strategies

1. Waiting List (“*preventive strategy*”):

Compensated and decompensated cirrhosis.

2. After LT:

When?

Why?

How?

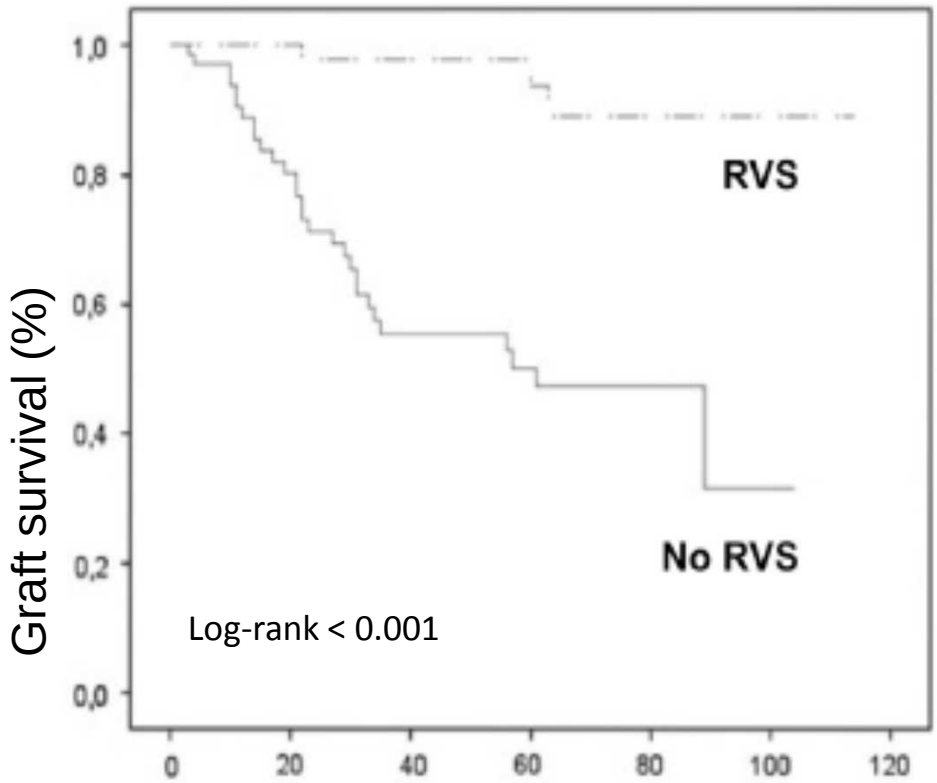
HCV treatment after LT: WHEN?

Type of therapy	Advantages	Disadvantages
Pre-emptive	1. It may prevent the infection of the graft 2. It may prevent the development of liver fibrosis	1. Difficult administration (renal function, potential for DDI, ability to take oral medications) **2. No data on safety and efficacy with DAAs.**

Mariño et al, Curr Op Organ Transplant 2015 (submitted); Gambato et al, J Hepatol 2014

HCV treatment after LT: WHY?

Beneficial effects of SVR on graft and patient survival after LT

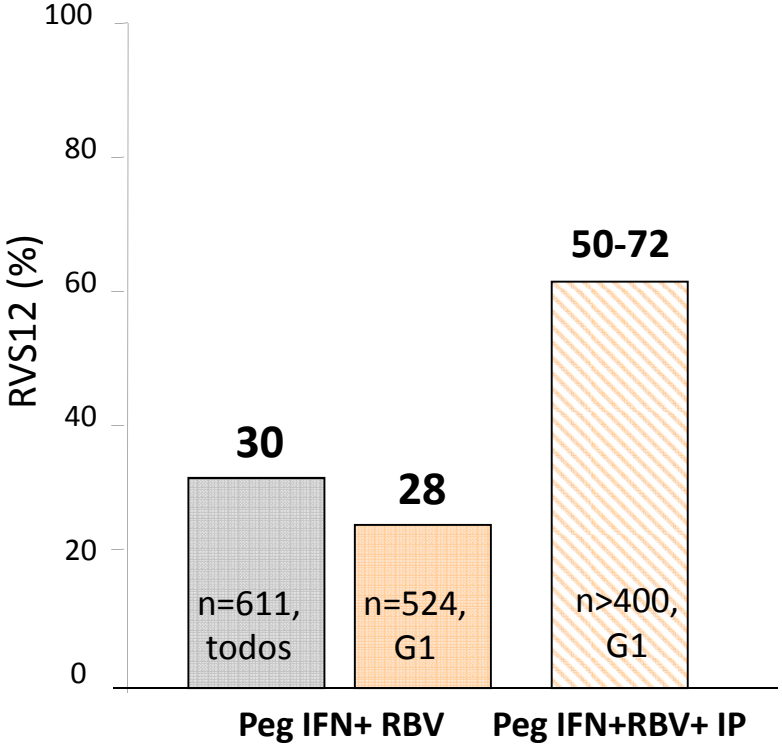


Carrión, Gastroenterol 2007; Berenguer, Am J Transpl 2008; Crespo, J Gastroenterol 2012; Crespo, Am J Transplant 2014

HCV treatment after LT: HOW?- IFN based

Peg IFN+RBV and **triple Peg IFN+RBV+ IPs**
(telaprevir/ boceprevir) after LT

EFFICACY



SAFETY

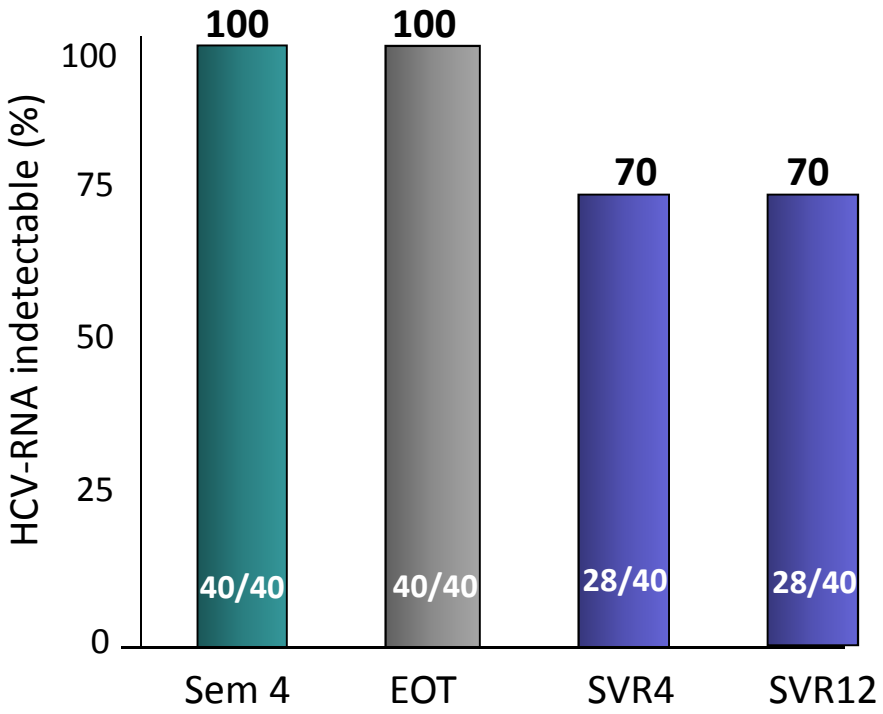
Anemia (HB≤10g/L)	**85-95%**
RBV DR/EPO/Transfusion	**95%/~50%**
ACR (biopsy-proven)	4-6%
Renal failure	13-40%
Infections	~20%
Early D/C (NR/EAs)	**25-56%**
SAEs	**25%**
Mortality rate	1-5%

Berenguer M, J Hepatol 2008
Faisal, J Hepatol 2013; Coilly, Liver Int 2013; Stravitz, Hepatol 2013; Pungpapong, Hepatol 2013; Forns, J Hepatol 2014

HCV treatment after LT: HOW?- IFN free

Sofosbuvir + RBV (initial 400mg) (24 weeks) in 40 liver recipients: 63% F3-4, 83% G1, 88% previous TE after LT

EFFICACY



*No on-treatment virological failures; all relapse after EOT.

SAFETY

Anemia	20%
ACR	0
Renal failure	0
Early D/C	5%
SAEs	15%
Mortality	0

NO expected DDIs with IMS

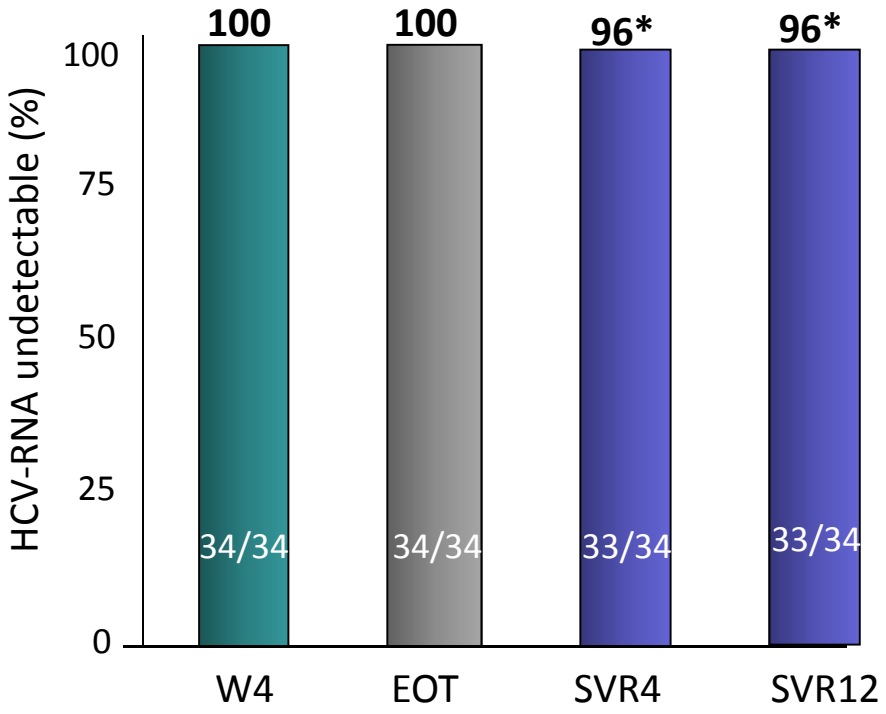
Samuel D et al, J Hepatol 2014

HCV treatment after LT: HOW?- IFN free

Paritaprevir/R/Ombitasvir+ Dasabuvir+ RBV in 34 HCV stable liver recipients.

F0-2, naive, 85% G1a → *extension to F3-4 soon*

EFFICACY



SAFETY

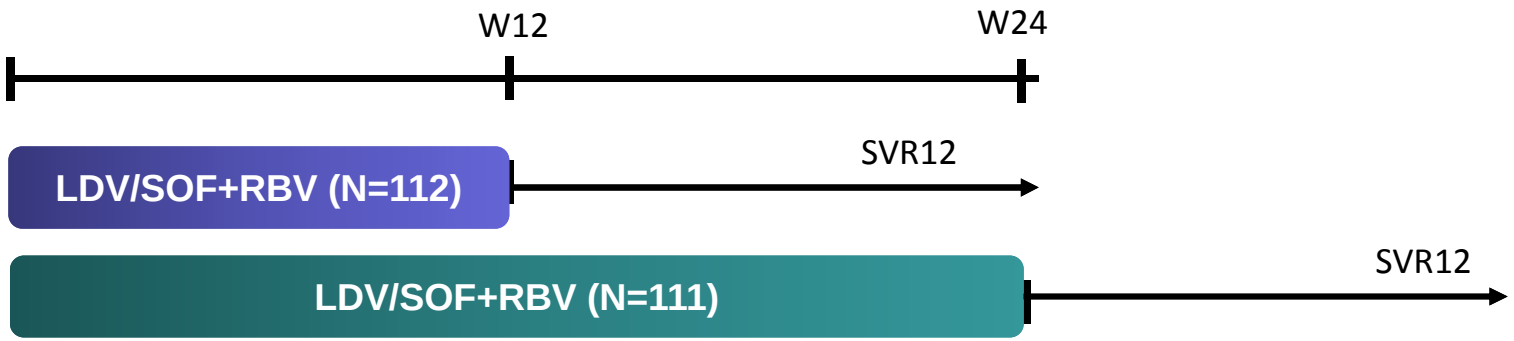
Anemia	**17%**
ACR	0
Renal failure	0
Early D/C	**3%**
SAEs	**6%**
Mortality	0

Expected DDIs: reduce TAC 0.2-0.5/weekly and CyA to 1/5 of baseline dose.

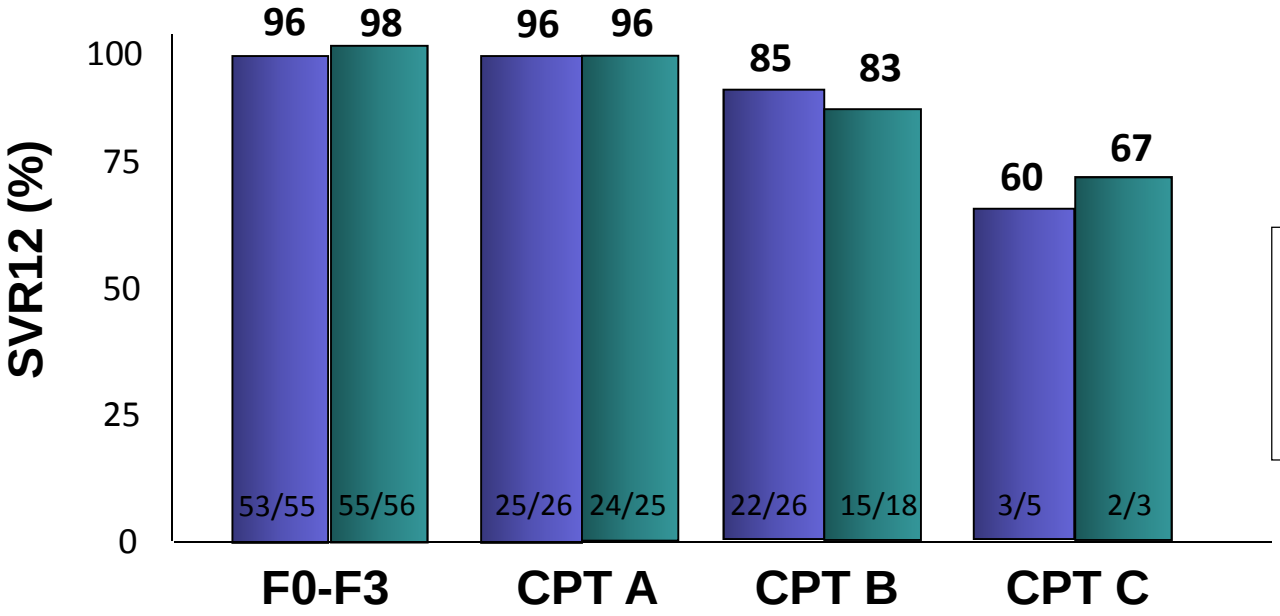
- 1 relapse*; the patient showed RAVs not seen at baseline.

Kwo et al, J Hepatol 2014

HCV treatment after LT: HOW?- IFN free



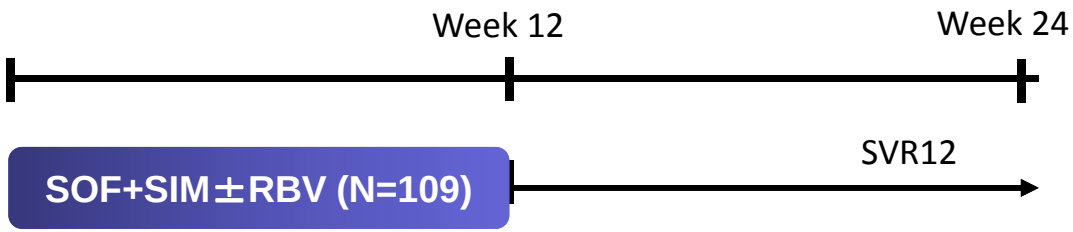
Cohort B SOLAR-1 trial: 223 G1 o G4 patients, naïve or TE after LT.
F0-F3, CPT A, B C



Treatment was SAFE
7 reported deaths (2 CPT A, 5 CPT B), diverse causes and no related with medication

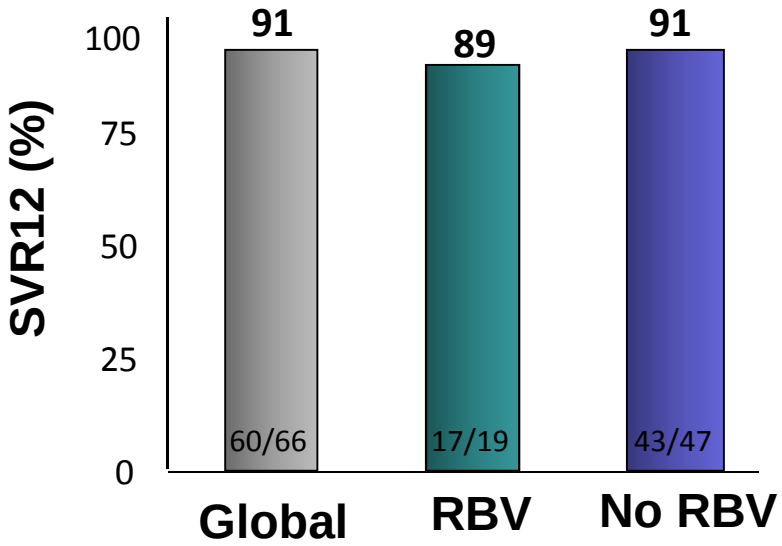
Reddy et al, AASLD 2014

HCV treatment after LT: HOW?- IFN free



Multicentric not randomized study (Mayo Clinic)

G1 (G1a 62%), F3-F4 29%, cholestatic recurrence 11%, TE to PR 69%/ PI-failures in12%



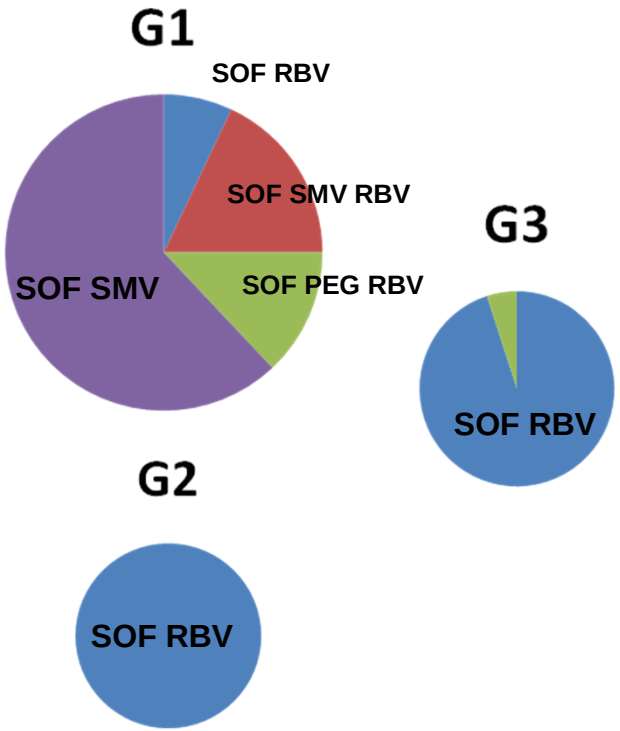
Good SAFETY profile
Anemia was 42% in RBV vs 2% in non-RBV
1 reported death (pharmacological lung toxicity?)

Pungpapong et al, AASLD 2014

HCV treatment after LT: HOW?- IFN free

G1, G2, G3 patients after Lt, DAA-based therapies, including cirrhotic and treatment experienced after LT (**HCV-TARGET** Consortium)

TREATMENT OPTIONS



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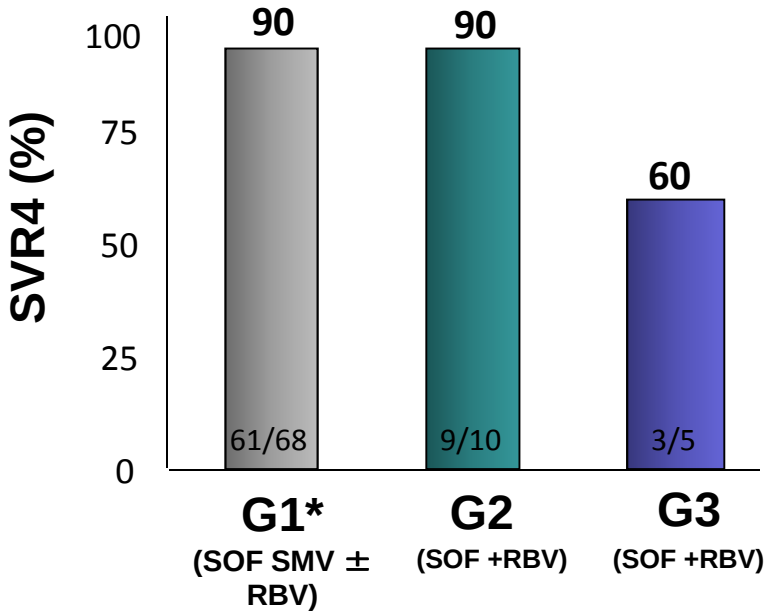
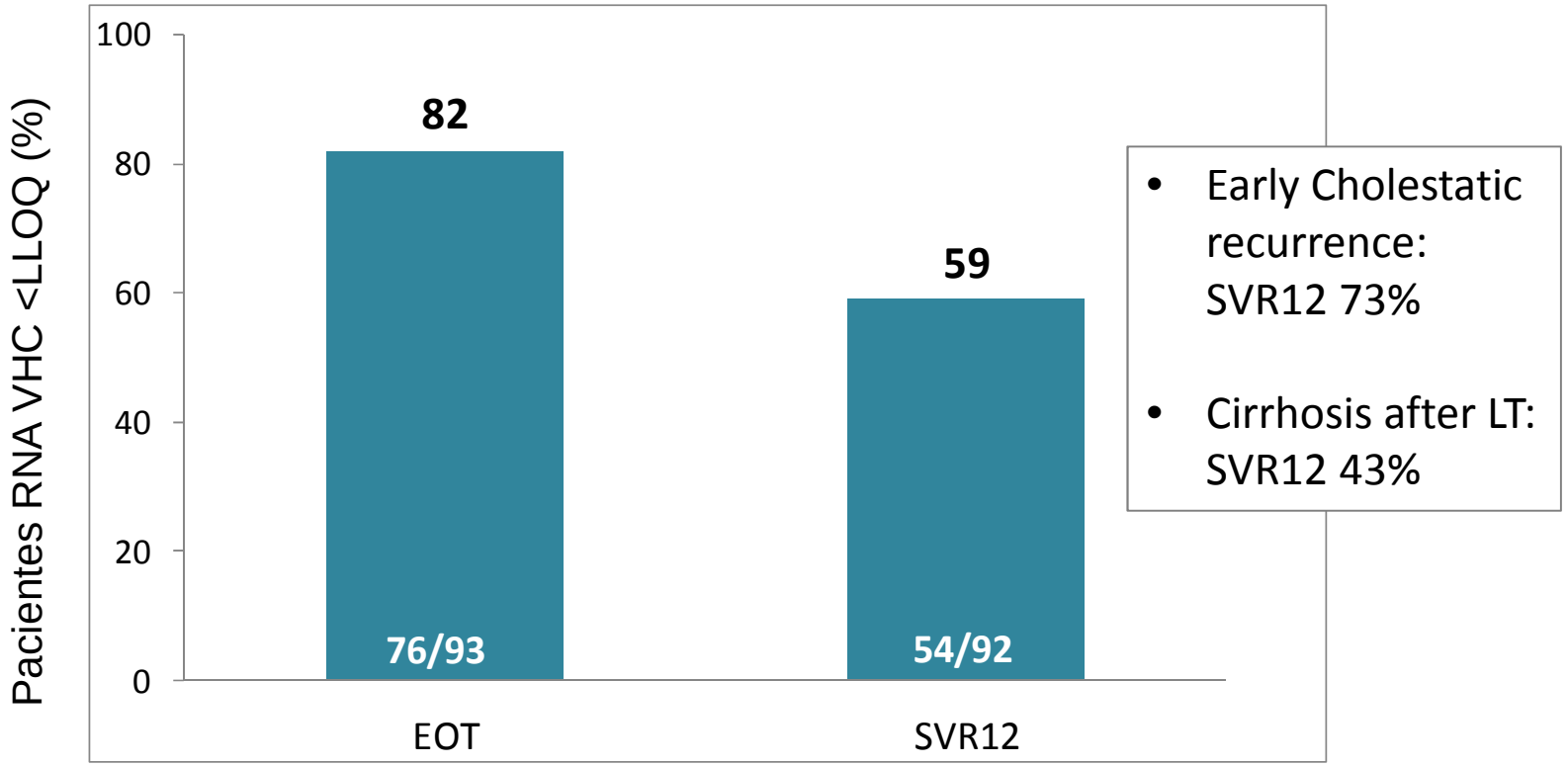


*SVR4 86% in cirrhosis (77% if MELD>10)

Brown et al, AASLD 2014

Antiviral therapies in HCV severe recurrences

Compassive use program: **Sofosbuvir + RBV (± PEG-IFN),**
Fibrosing cholestatic hepatitis (FCH) or graft cirrhosis after LT (n=104)

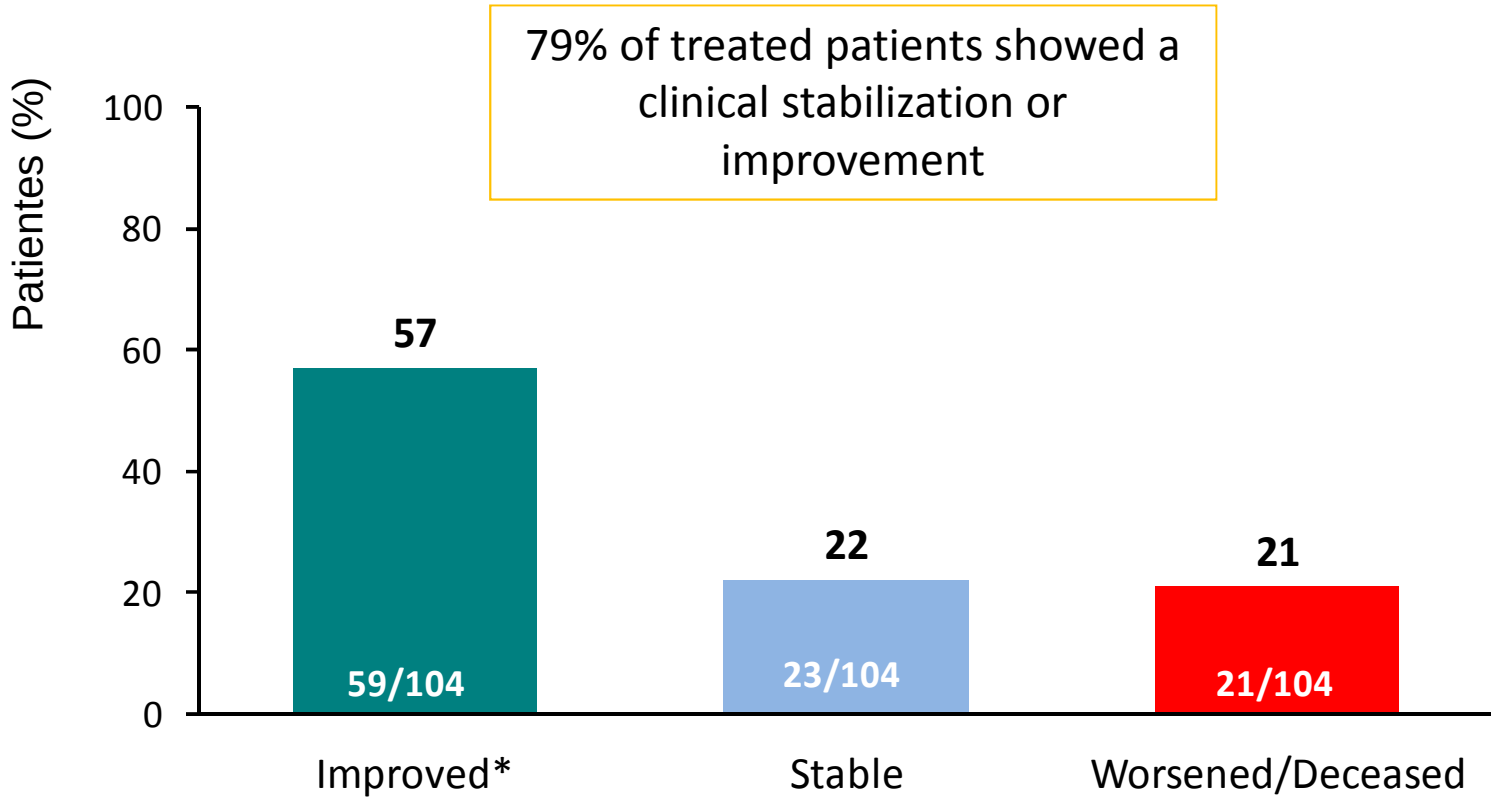


Patients receiving a liver graft while on treatment (n=12) were excluded from the efficacy analysis.

Forns et al, Hepatology 2015

Antiviral therapies in HCV severe recurrences

Clinical outcomes: impact of treatment (SOF + RBV ± PEG-IFN, n=104)



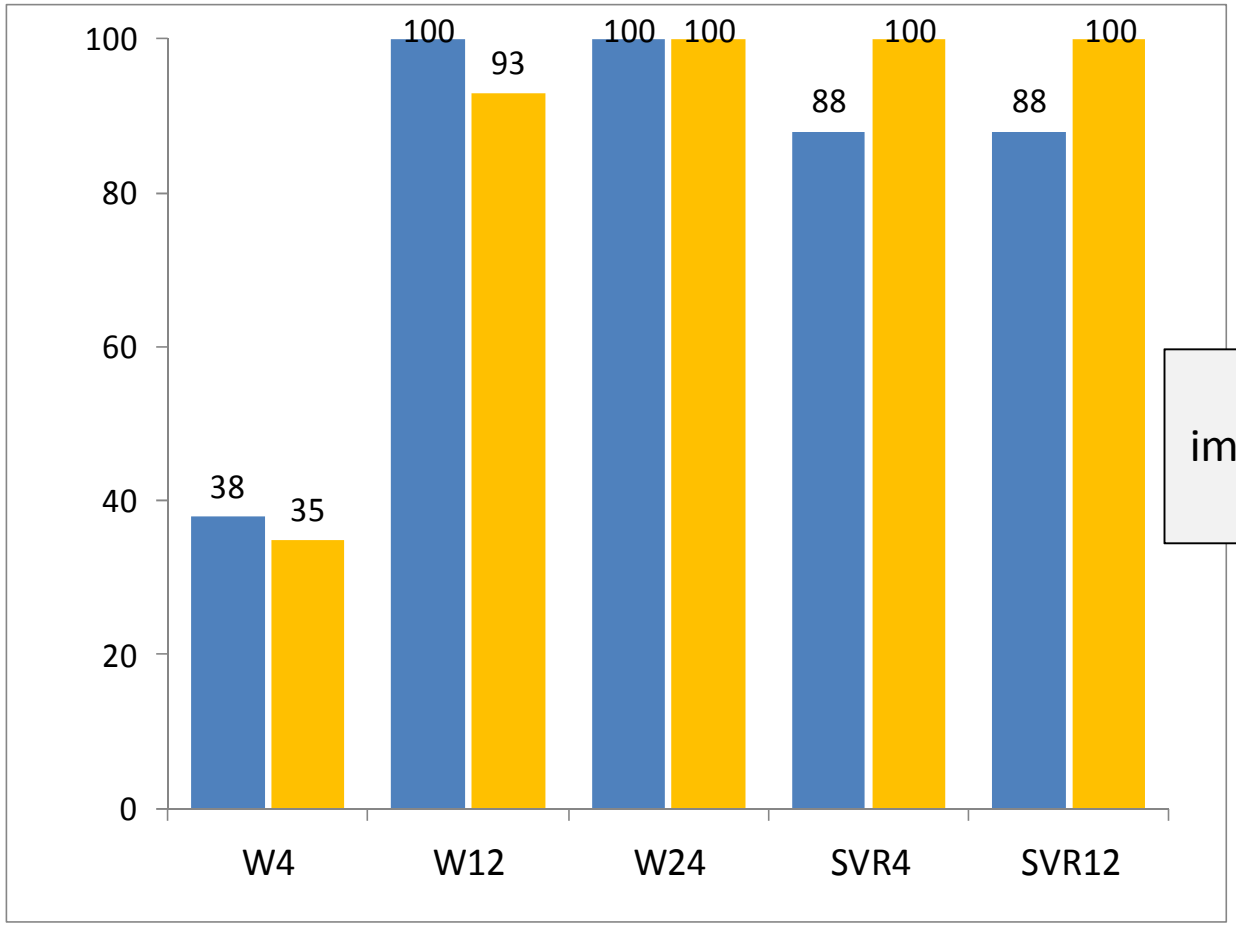
*Significant decrease in hepatic encephalopathy, improvement or disappearance of ascites, or improvement in liver-related laboratory values.
** 8 worsened and 13 died.

Forns et al, Hepatology 2015

Antiviral therapies in HCV severe recurrences

SOF+ RBV±PegIFN (n=8) 24 weeks

SOF+ DCL±RBV (n=15) 24 weeks



French cohort of FCH: CUPILT (N=23)

All TE after LT, ascitis/ EH 27-50%

Clinical and analytical improvement in the majority of patients.

* Relapse, n=1, coinfected HIV-HCV, F4, G1b

Dumortier et al, AASLD 2014

Summary

✓ **IFN-free regimens** in cirrhotic patients before LT are generally safe, although data is lacking concerning patients with Child>12 and/or MELD>20.

✓ In the next few years, the **current scenario of hepatitis C in the transplant setting will radically change**, as we will be able to cure almost all patients on the waiting list, or easily after LT.

✓Trials and real-clinical practice with **IFN-free regimens after LT** are encouraging. Their safety profile and virological results are very good. Efficacy is reduced in advanced cirrhosis after LT, and therefore treatment should be done before advanced disease is reached.

✓Data in patients with **severe hepatitis C recurrence**, including FCH, are good and importantly, clinical outcomes improve in those achieving viral clearance.

Mariño et al, Curr Op Organ Transplant 2015 (submitted); Gambato et al, J Hepatol 2014

Viral Hepatitis Group

Liver Transplantation Group

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