Optimal Therapy of HCV Transplant Patients With Direct Antiviral Agents

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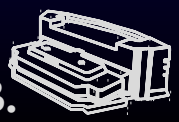
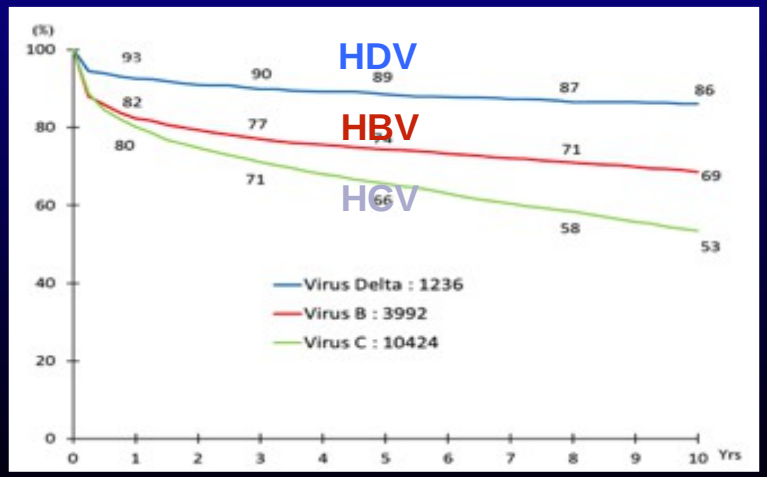
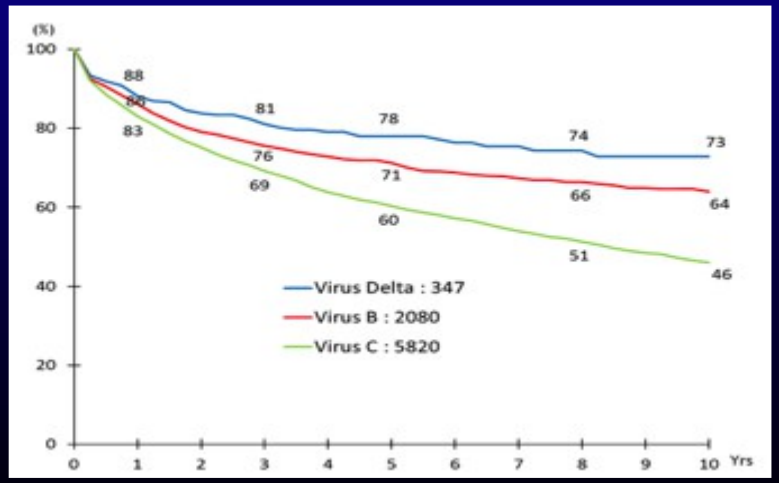


Current Situation of LT for Viral Hepatitis in Europe

Without HCC	INDICATIONS	With HCC
HCV		
HBV		
HDV		

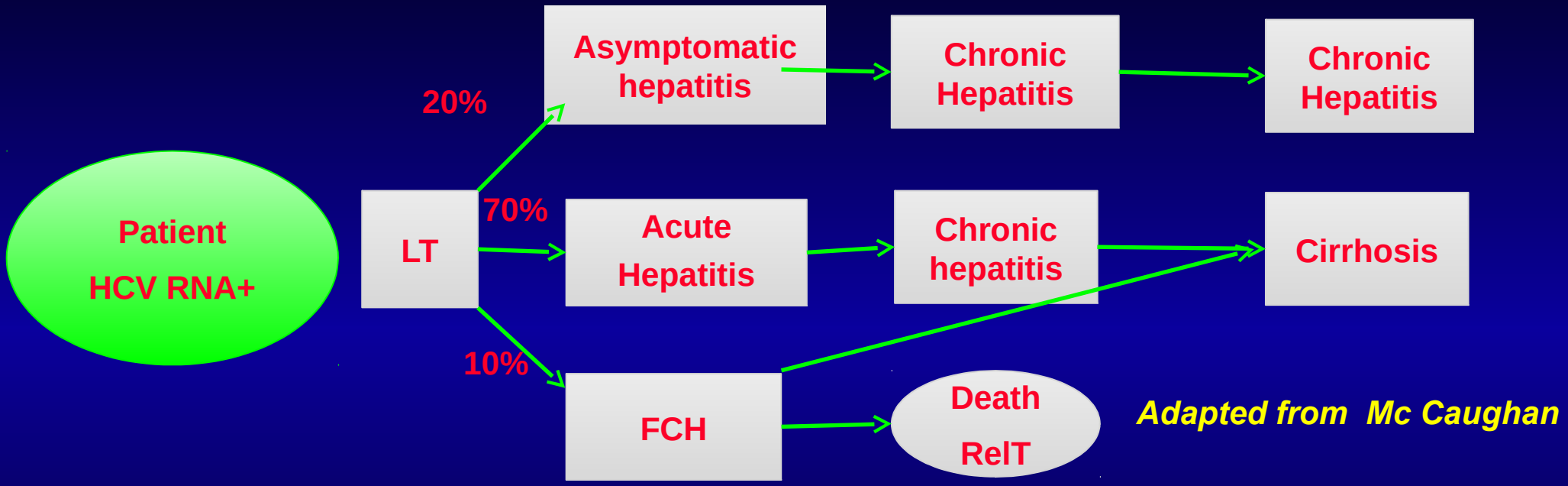
SURVIVAL



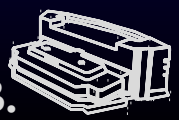


www.eltr.org C.H.B.

HCV Recurrence: a Main issue



- **HCV recurrence**
  - Poor outcome, accounting for 2/3 of graft lost
  - Five years post-LT, 30% of LT patients have a cirrhosis on the graft
  - First cause of mortality



Impact of SVR on Survival in Transplant HCV +ve Patients

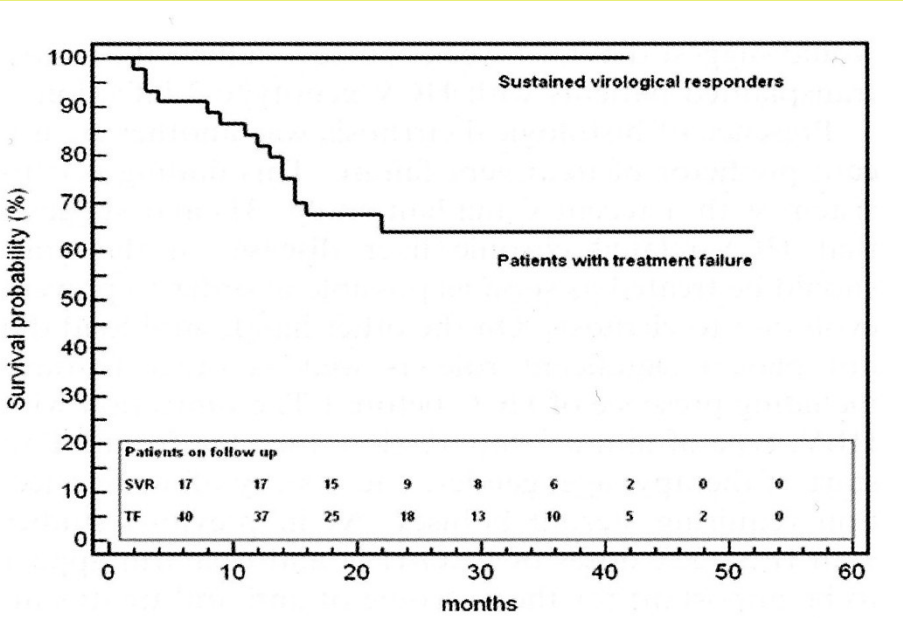
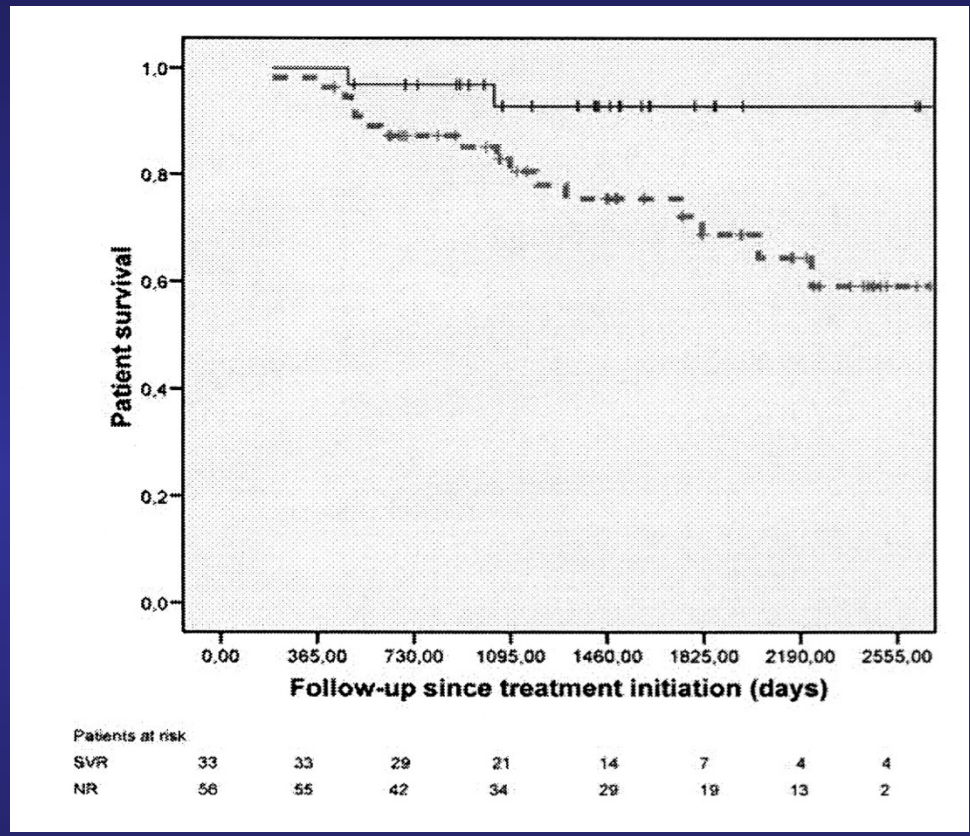


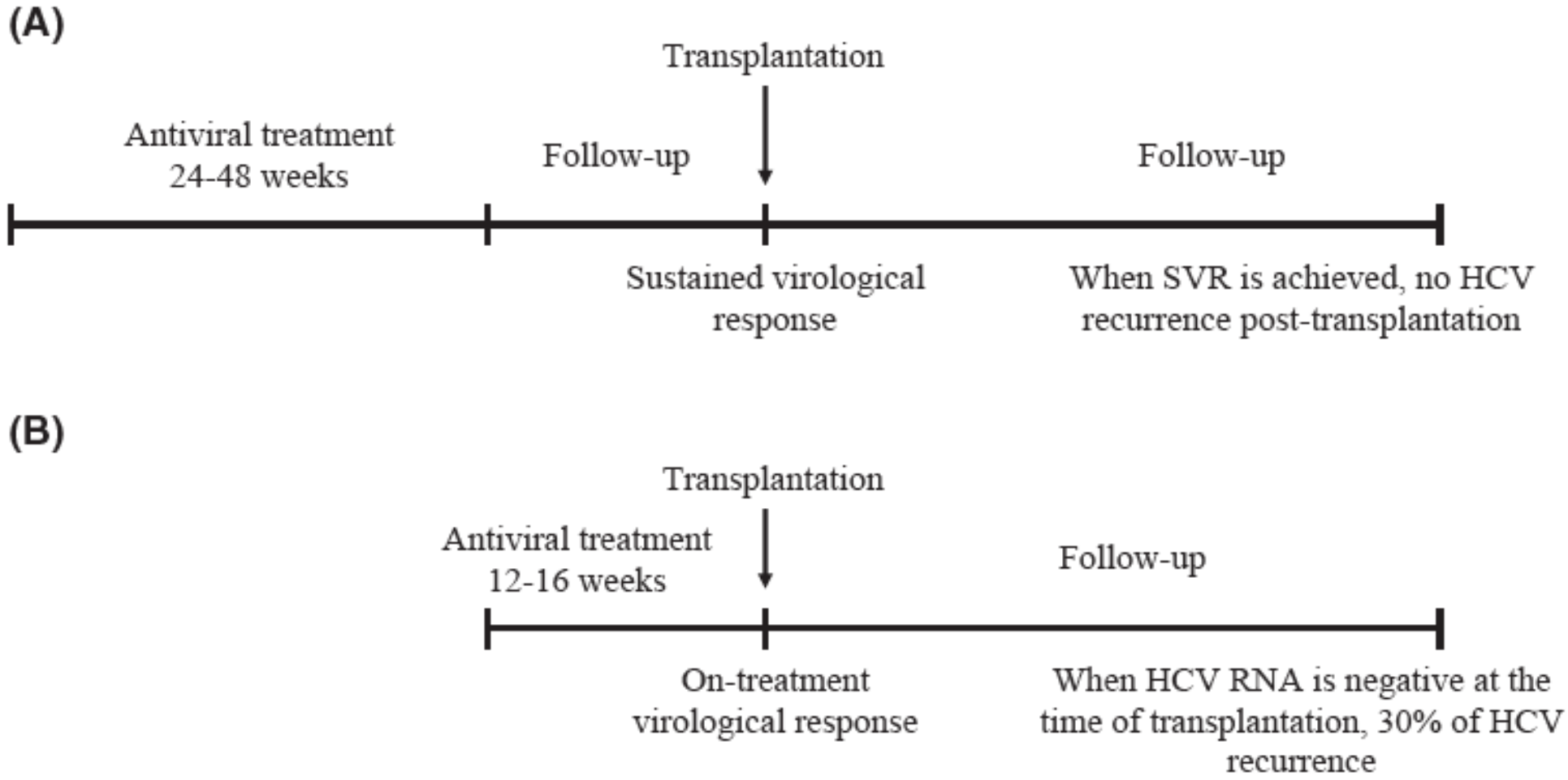
Fig. 1. Kaplan–Meier survival analysis starting at the end of treatment. Patients with SVR showed a significantly lower mortality compared to patients with treatment failure ($\chi^2 = 6.9$; $P < 0.01$; Log rank test). At the bottom: number of patients who have reached the different time points of follow up.

Piciotto J Hepatol 2007



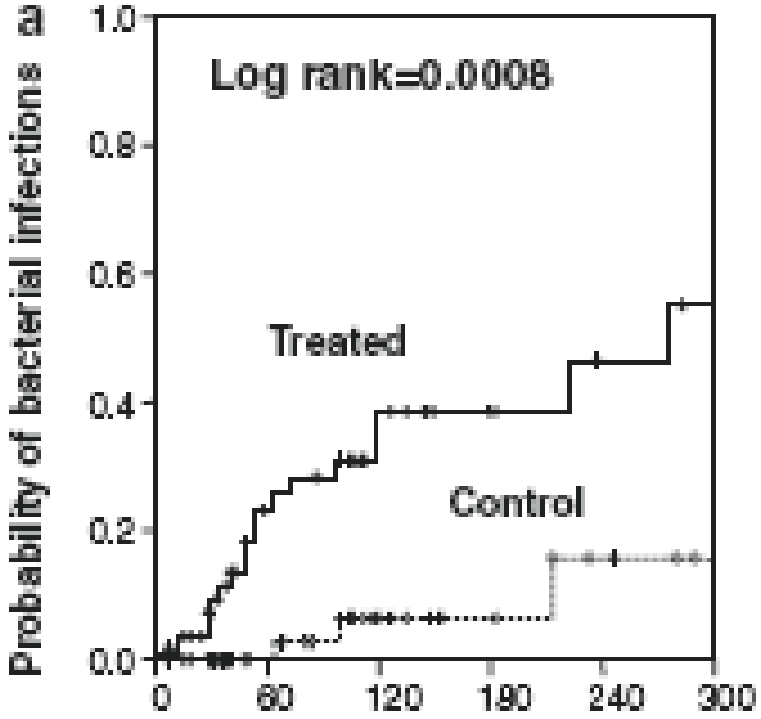
Berenguer M AJT 2008

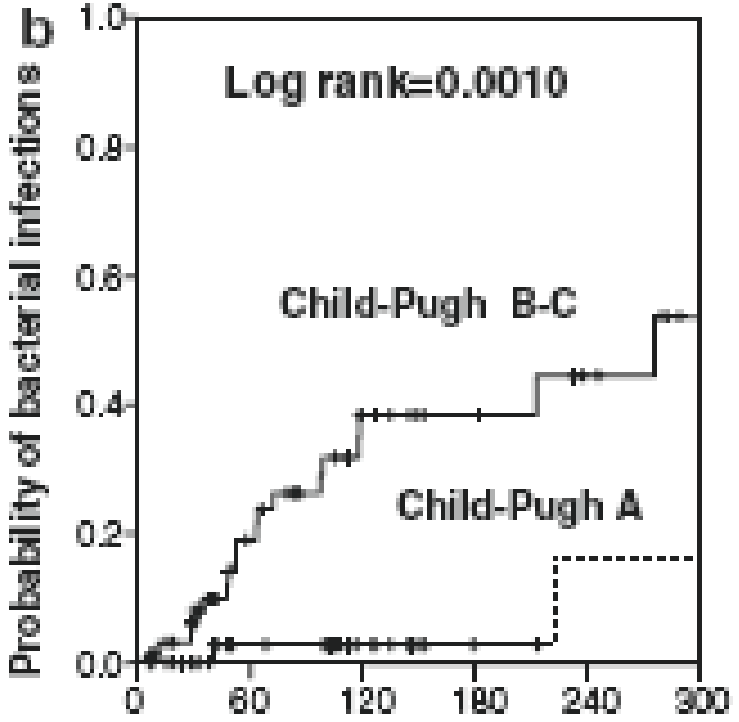
Antiviral Treatment Before Transplantation



Roche, Samuel Liver Int 2012

Antiviral Treatment with IFN in Cirrhotic Patients Waiting for Liver Transplantation, High Risk of Sepsis





	Patients at risk			Time (Days)		
Treated	51	30	16	9	6	4
Control	51	34	18	11	7	4

	Patients at risk			Time (Days)		
CP B-C	57	34	17	12	7	2
CP A	45	30	17	8	6	6

Carrión JA et al. J Hepatol. 2009;50:719-28.

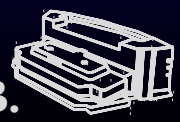
Risk Factors of Death and Severe infections in cirrhotics on Triple therapy with Boceprevir or Telaprevir

The Cupic Study

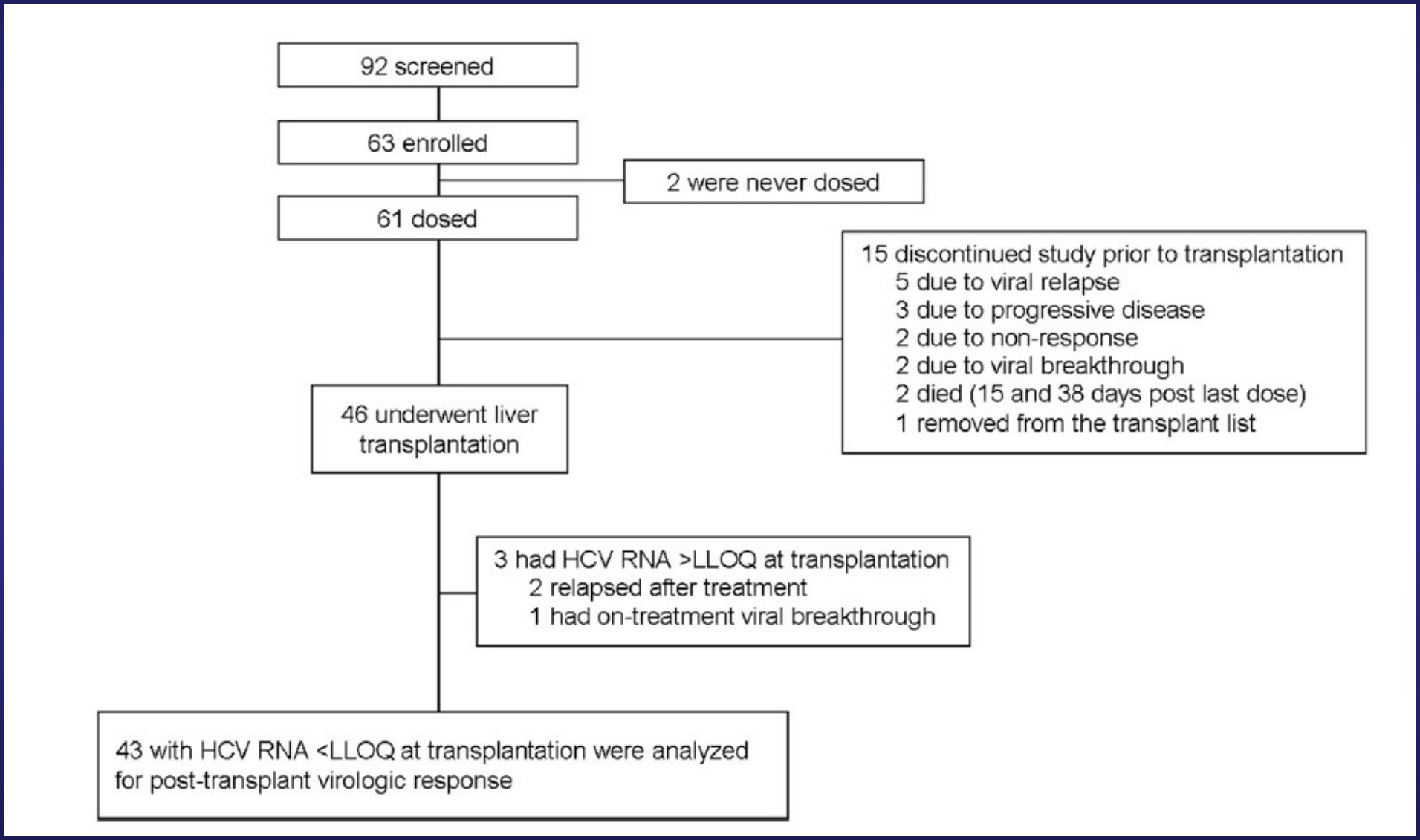
Table 4. Risk of occurrence of death or severe complications according to serum albumin level and platelet count during the first 16 weeks of therapy.*

Factors	Platelet count >100,000/mm^3	Platelet count ≤100,000/mm^3
Serum albumin		
≥35 g/L	3.4% (10/298)	4.3% (3/69)
<35 g/L	7.1% (2/28)	44.1% (15/34)

Hezode J Hepatol 2013



Sofosbuvir + Riba in Patients with HCC on the waiting List



Curry Gastro 2015

Sofosbuvir + Riba in Patients with HCC on the Waiting List
Post-Transplant SVR in those HCV RNA Negative at LT

Table 2. Post-Transplant Virologic Response by Visit for Patients With HCV-RNA Level Less Than the LLOQ at the Last Measurement Before Liver Transplantation

	Sofosbuvir-ribavirin for ≥12 weeks (N = 32)	Sofosbuvir-ribavirin for any duration (N = 43)
Post-transplant week 1		
<LLOQ, n/N (%)	28 (88%)	37 (86%)
90% CI	74%–96%	74%–94%
Post-transplant week 2		
<LLOQ, n/N (%)	26 (81%)	35 (81%)
90% CI	66%–92%	69%–90%
Post-transplant week 4		
<LLOQ, n/N (%)	24 (75%)	31 (72%)
90% CI	59%–87%	59%–83%
Post-transplant week 8		
<LLOQ, n/N (%)	24 (75%)	31 (72%)
90% CI	59%–87%	59%–83%
Post-transplant week 12		
<LLOQ, n/N (%)	24 (75%)	30 (70%)
90% CI	59%–87%	56%–81%

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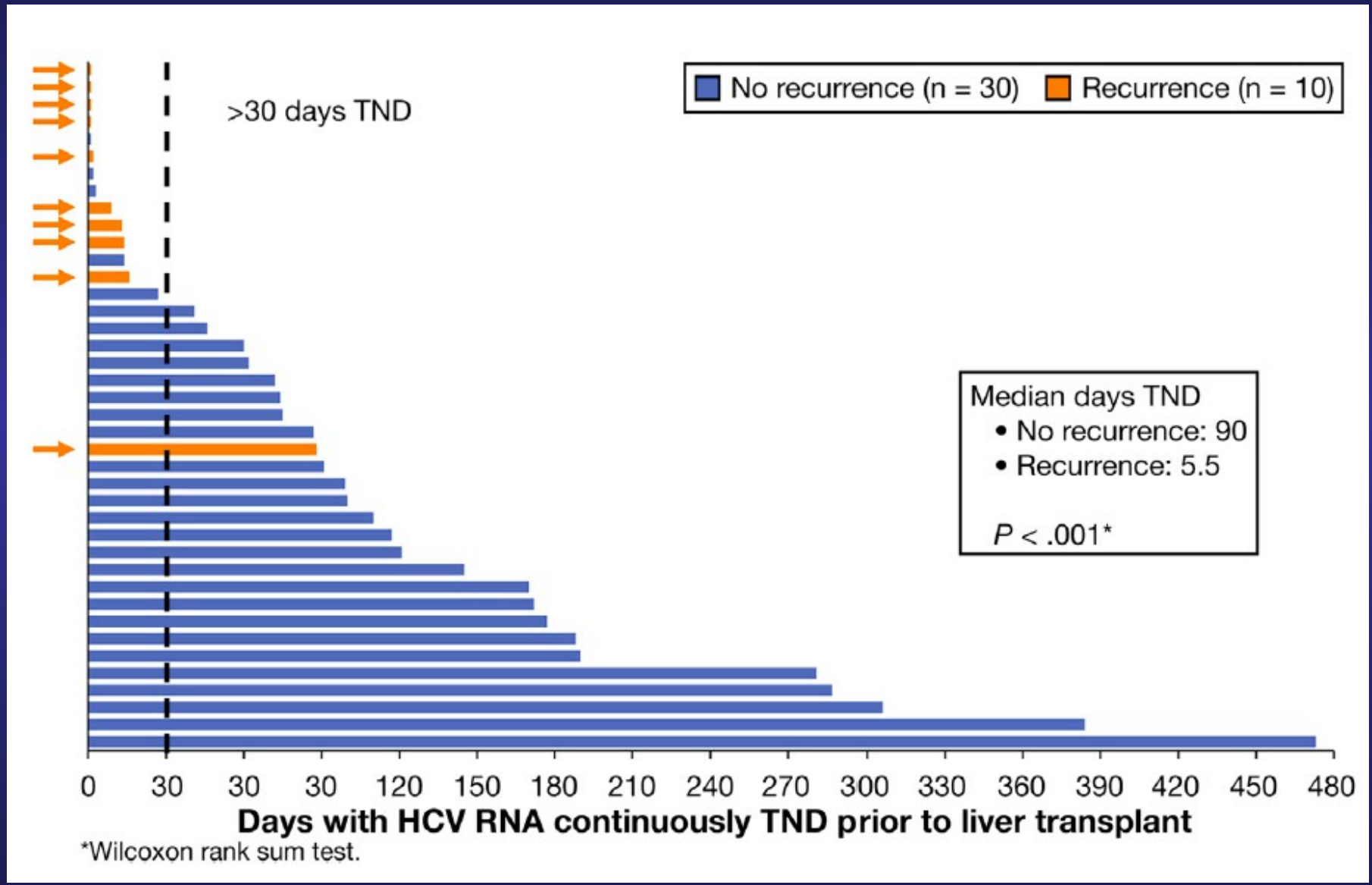
Sofosbuvir + Riba in Patients on the Waiting List
Recurrence Related to the Duration of HCV Indetectability Pre-LT



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DAA PK in Cirrhotics

Table 3. Pharmacokinetics (change in AUC) of DAAs in hepatic impairment (graded according to CTP score) and recommendation.

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

Gamballi J Hepatol 2014

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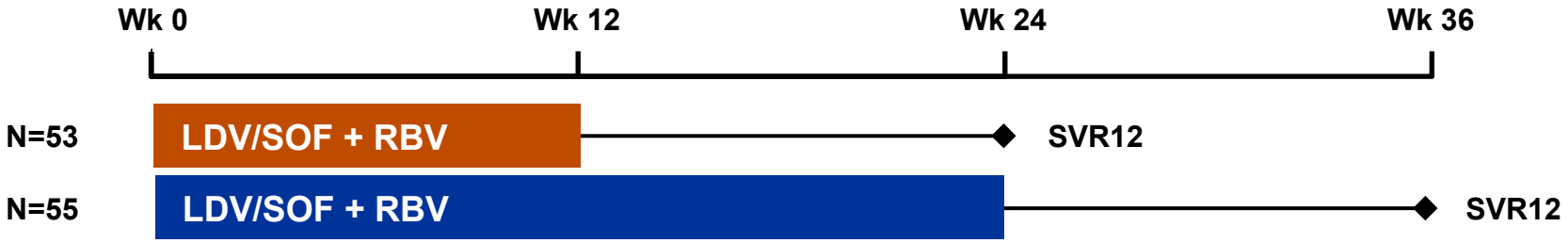
SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis



108 patients randomised 1:1 to 12 or 24 weeks of treatment

GT 1 or 4 treatment-naïve or -experienced patients with decompensated cirrhosis (CTP class B [7–9] or C [score 10–12]*)

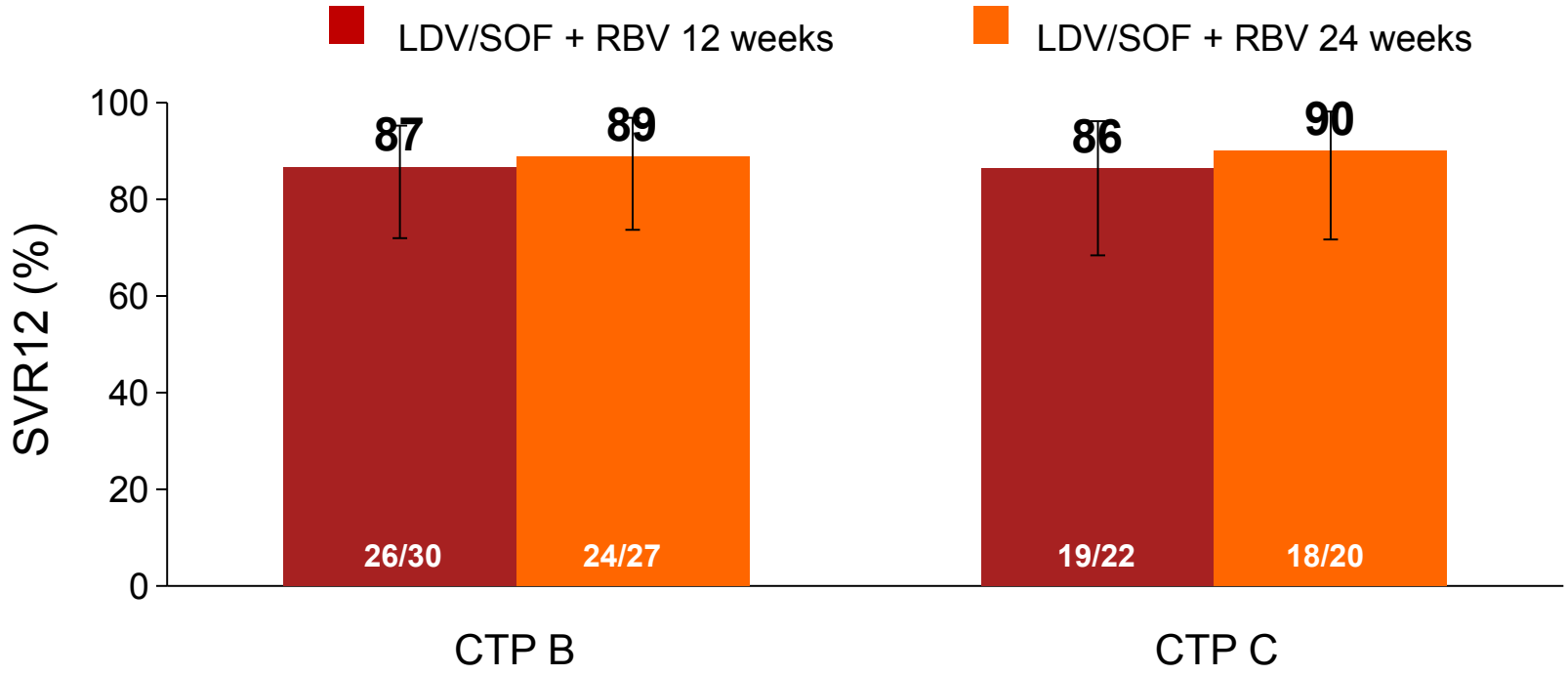
Broad inclusion criteria

- No history of major organ transplant, including liver
- No hepatocellular carcinoma (HCC)
- Total bilirubin ≤10 mg/dL, Hb ≥10 g/dL
- CrCl ≥40 mL/min, platelets >30,000/mm3

LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen;
*Patients with CTP scores 13–15 excluded; CrCl: creatinine clearance;
EMA: European Medicines Agency

SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis

Prospective, multicentre 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



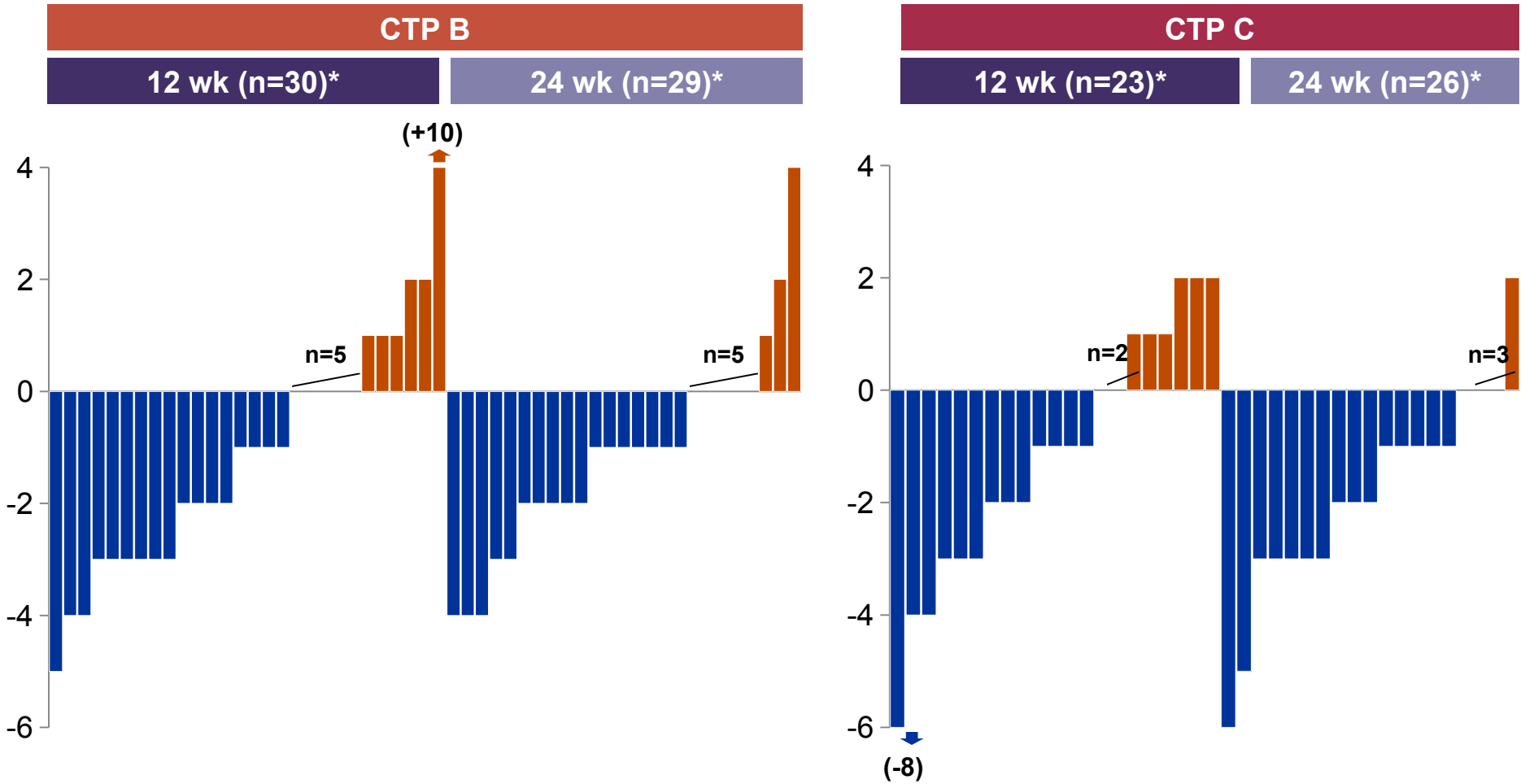
SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Virological response was associated with improvements in bilirubin, albumin, MELD and CTP scores in both CTP class B and C patients

LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen;
Error bars represent 90% confidence intervals;
TE: treatment-experienced; TN: treatment-naïve

Kanwal F, et al. AASLD 2014. Oral #239.

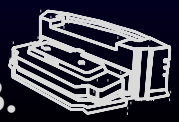
SOLAR-1: LDV/SOF + RBV in decompensated cirrhosis: Change in MELD from BL to Week 4



LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen
*Missing FU-4: n=2 CTP B 12 wk; n=4 CTP B 24 wk; n=2 CTP C 12 wk; n=7 CTP C 24 wk; Bl = baseline; FU = follow-up
Oral #239.

HCV Treatment after LT
Standard of Care Until 2012

- Antiviral treatment with Peg-IFN+RBV
  - Treatment done at the stage of chronic hepatitis
  - Peg-IFN +RBV = standard of care:
    - Overall SVR: 30%;
    - SVR G1: 25- 30%, SVR G3: 50% (Berenguer *J Hepatol 2008, Calmus J Hepatol 2012)*
    - EPO in 40% of patients
    - Poor tolerance of treatment when F3-F4 *(Carrion Gastro 2007, Roche LT 2008):* 30% of premature discontinuation



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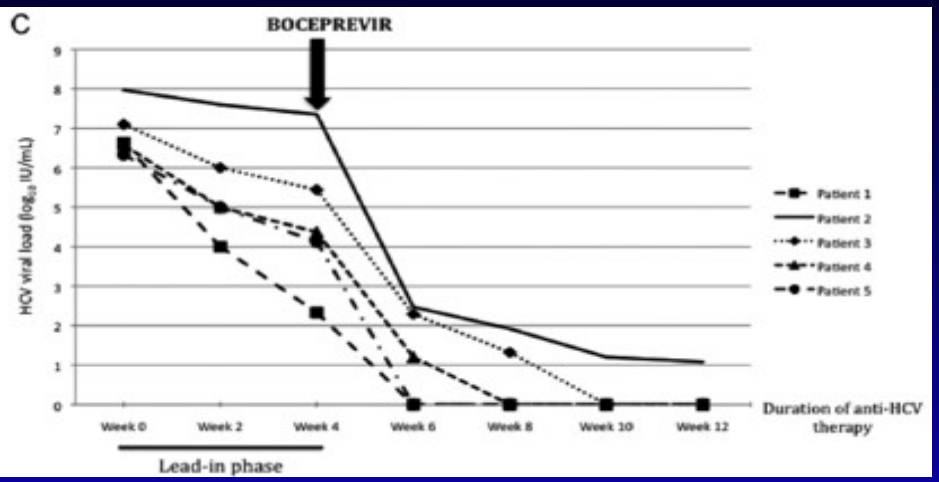
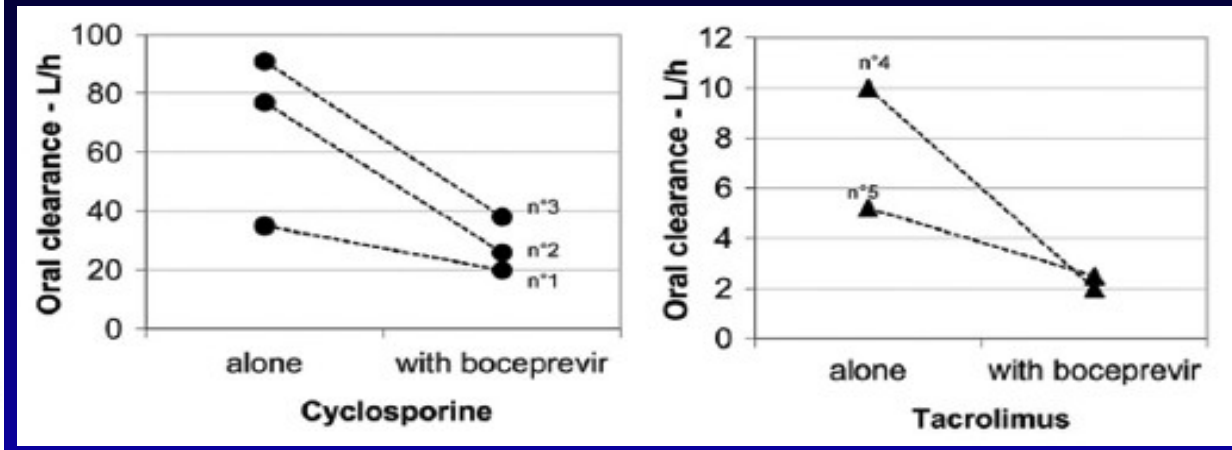
First Generation Protease inhibitors in HCV Recurrence
Boceprevir and Telaprevir





Coilly AAC 2012

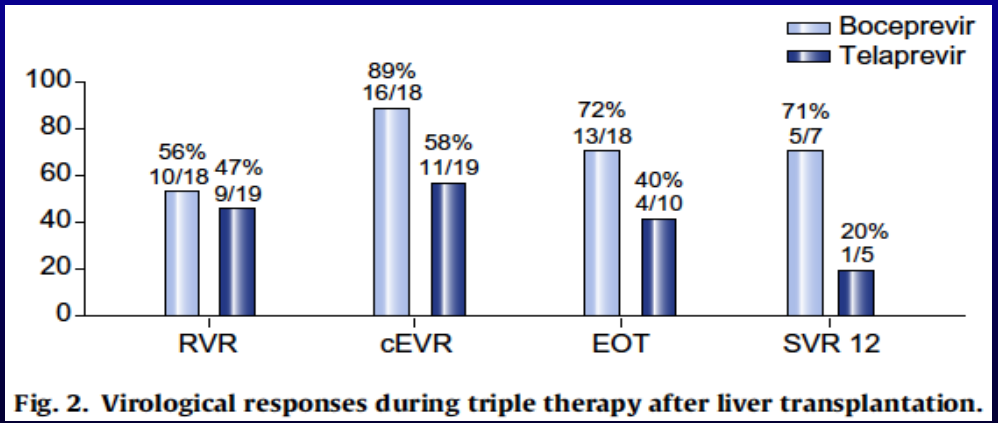
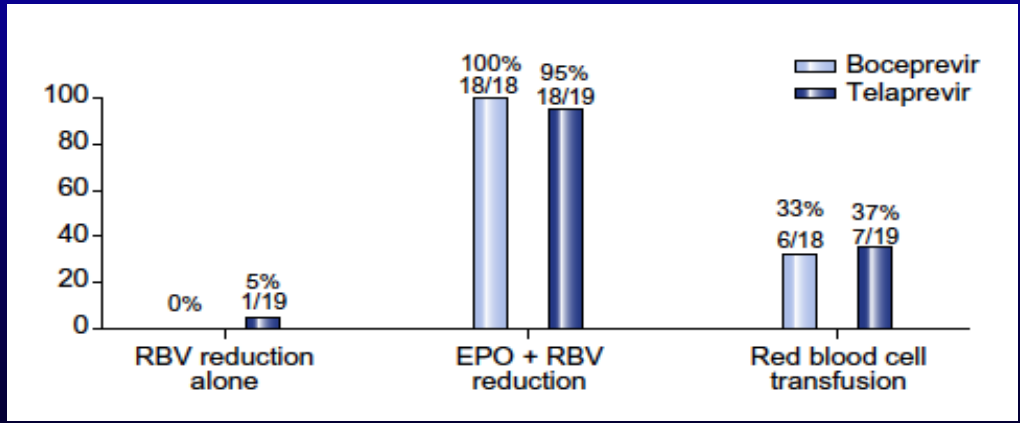


Fig. 2. Virological responses during triple therapy after liver transplantation.



Coilly J Hepatol 2014

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Triple Therapy with Telaprevir or Boceprevir
The Crush Study

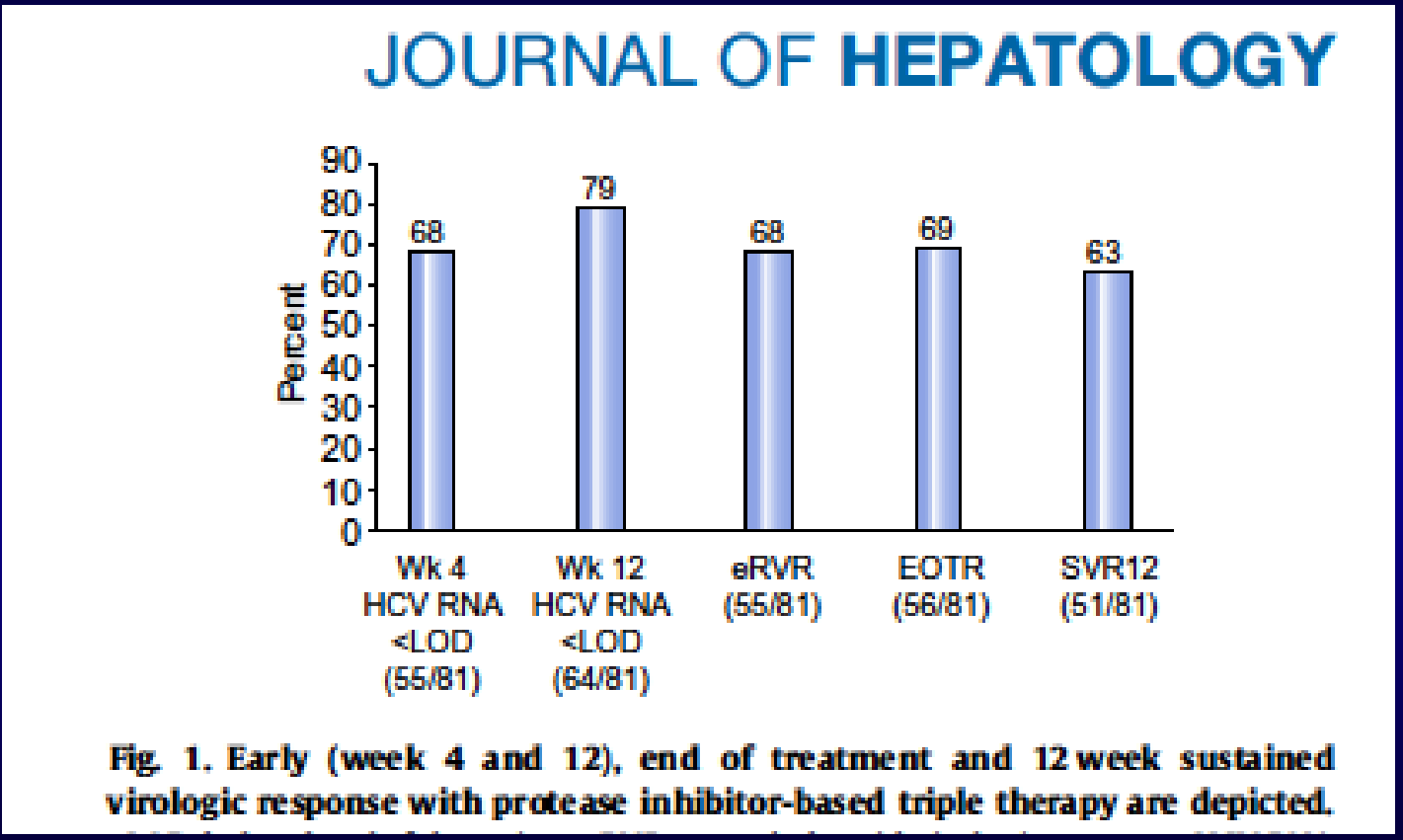

Fig. 1. Early (week 4 and 12), end of treatment and 12 week sustained virologic response with protease inhibitor-based triple therapy are depicted.

Tolerance

Anemia < 10 : 78%

Blood Transfusion: 57%

EPO: 81%

GCSF: 41%

Creat ↗ 0.5 mg/l : 38%

Rash: 11%

Hospitalizations for infection: 11%

Discontinuation: 15%

Deaths : 9%

Burton J Hepatol 2014

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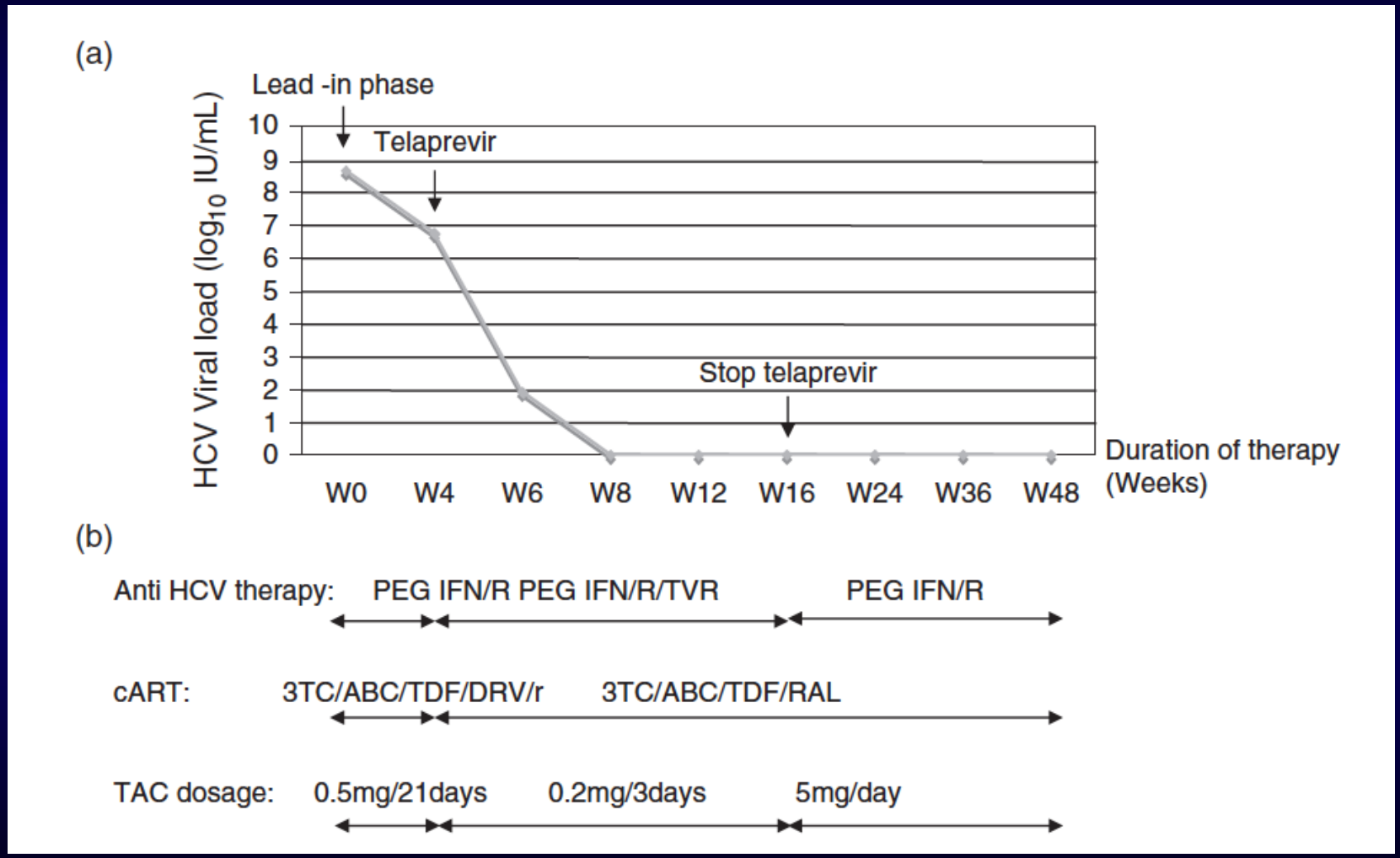
Triple Antiviral Therapy with Telaprevir in HIV-HCV Liver Transplant Recipients



Antonini et al. AIDS 2013

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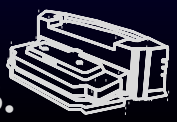
The Advent of Second Generation DAAs After Liver Transplantation



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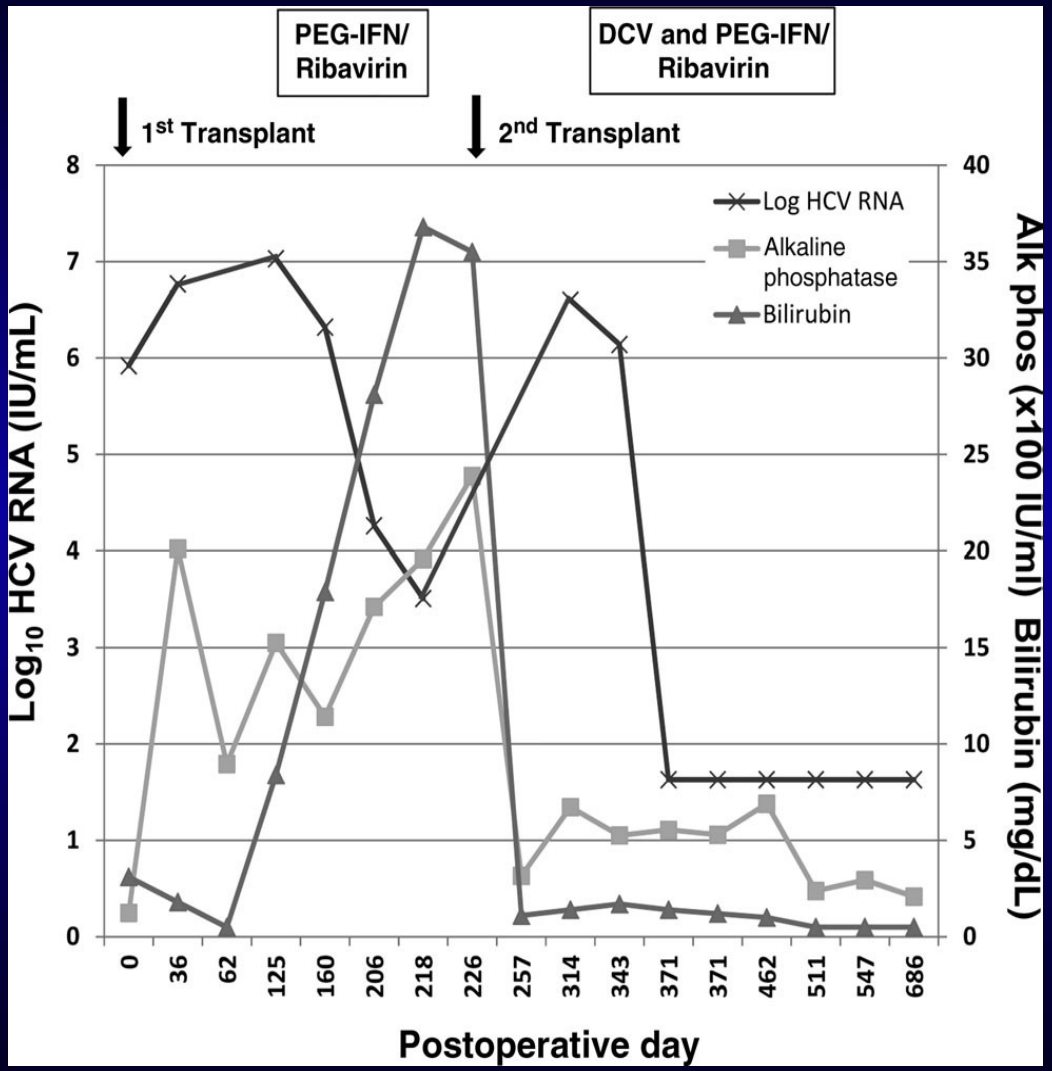
PegIFN +RBV+Daclatasvir for FCH after LT



Fontana Liver Transpant 2012

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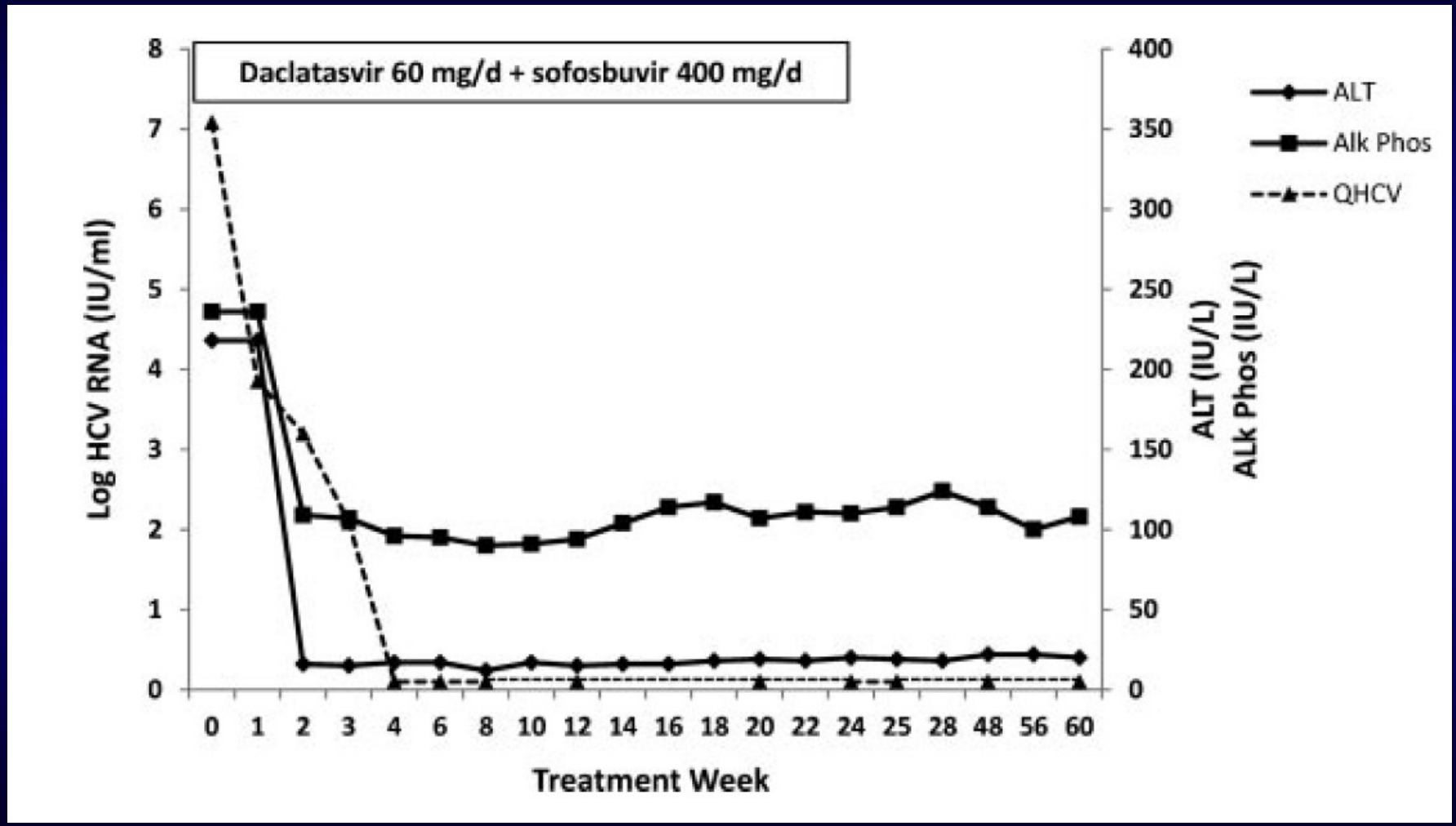
Sofosbuvir+Daclatasvir for FCH after LT



Fontana Am J Transplant 2013

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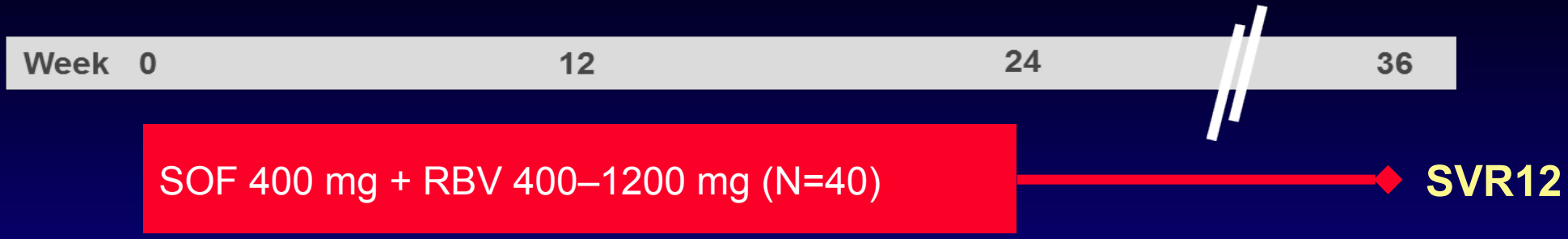
Sofosbuvir + Ribavirin After Transplantation



- Patients with recurrent HCV post-liver transplant
  - Liver transplant ≥6 and ≤150 months prior to enrollment
  - Any HCV genotype
  - Naïve or treatment-experienced
  - CTP ≤7 and MELD ≤17
- Low, ascending-dose RBV regimen starting at 400 mg/day, escalated based on hemoglobin levels

Charlton Gastro 2015

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Sofosbuvir + Ribavirin After Transplantation

	SOF + RBV (N=40)
Male, n (%)	31 (78)
Median age, y (range)	59 (49-75)
White, n (%)	34 (85)
BMI <30 kg/m2, n (%)	30 (75)
Mean HCV RNA log10 IU/mL (range)	6.55 (4.49-7.59)
Genotype, n (%) 1a 1b 2 3 4	 22 (55) 11(28) 0 6 (15) 1 (3)
IL28B, n (%) CC CT TT	 13 (33) 16 (40) 11 (28)
Metavir-equivalent fibrosis stage, n (%) None or minimal (F0) Portal Fibrosis (F1-F2) Bridging Fibrosis (F3) Cirrhosis (F4)	 1 (3) 14 (35) 9 (23) 16 (40)
Prior HCV Treatment, n (%)	Yes 35 (88)
Median years since liver transplantation (range)	4.3 (1.02-10.6)

Charlton AASLD 2013

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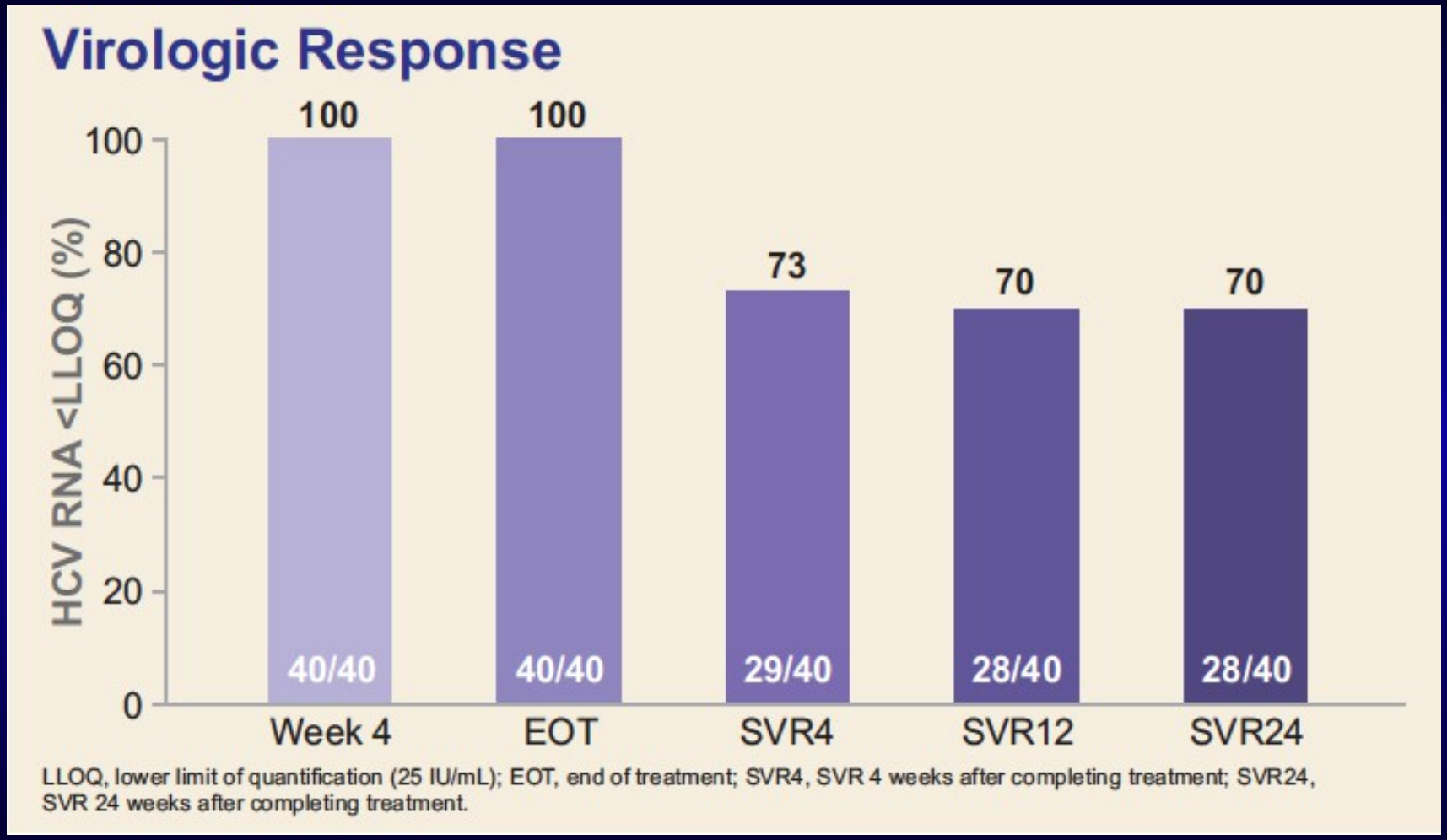
Sofosbuvir + Ribavirin After Transplantation



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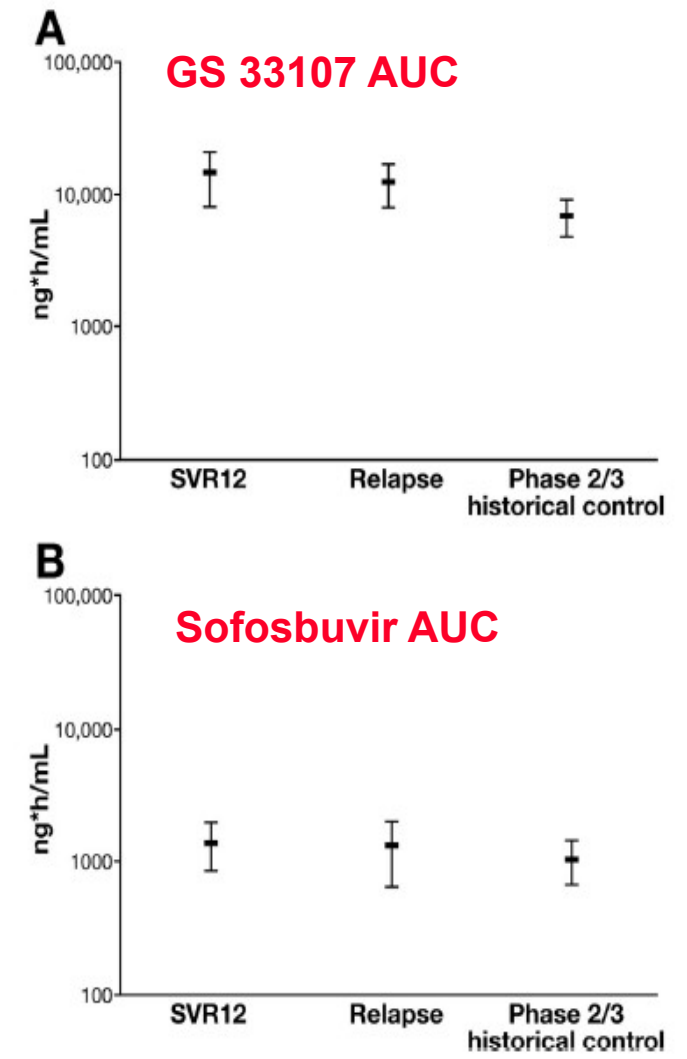
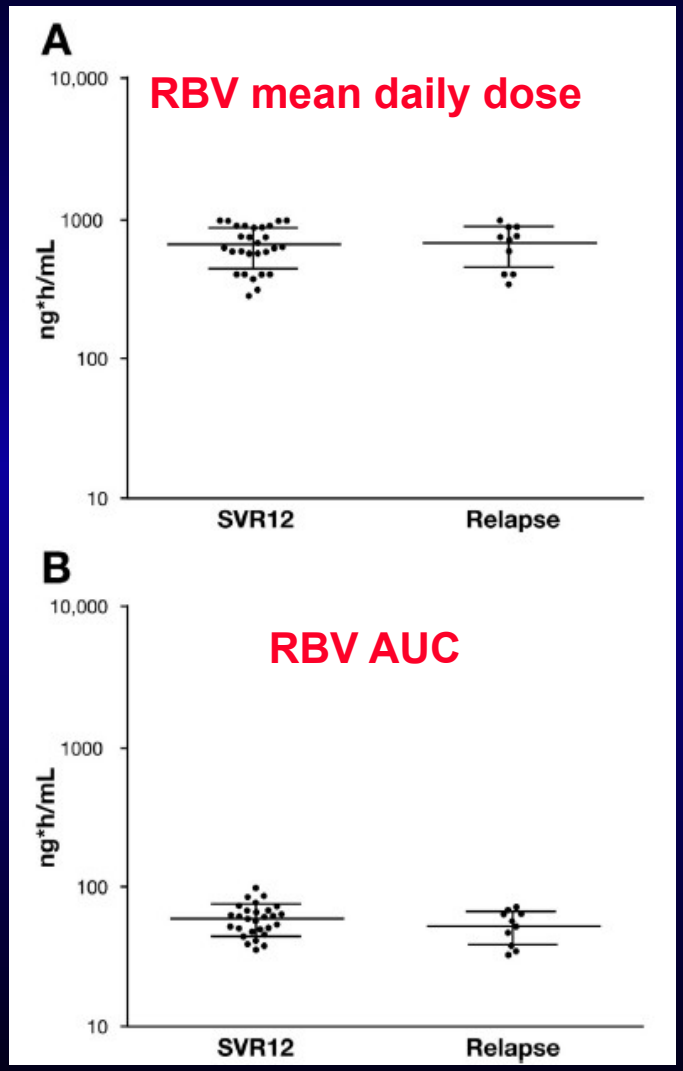
Sofosbuvir + Ribavirin in Liver Transplant Patients
Diff culty to identify Relapsers





M Charlton Gastro 2015

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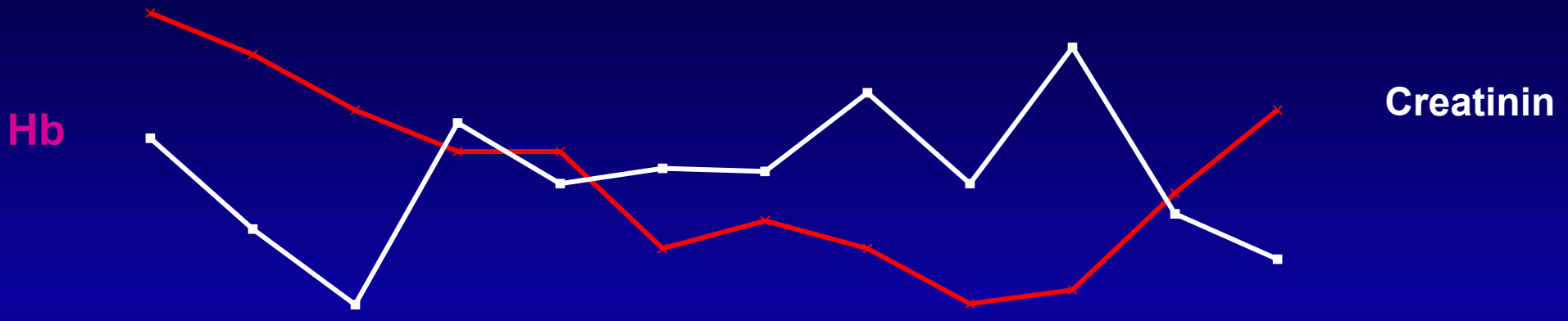
Sofosbuvir + Ribavirin After Transplantation Tolerance



SAE: 15%, SAE leading to discontinuation: 5%, fatique 30%,

Hb< 10g:/dl: 33%; Hb< 8g: 3%, 20% Received EPO

Charlton AASLD 2013 and Gastro 2015

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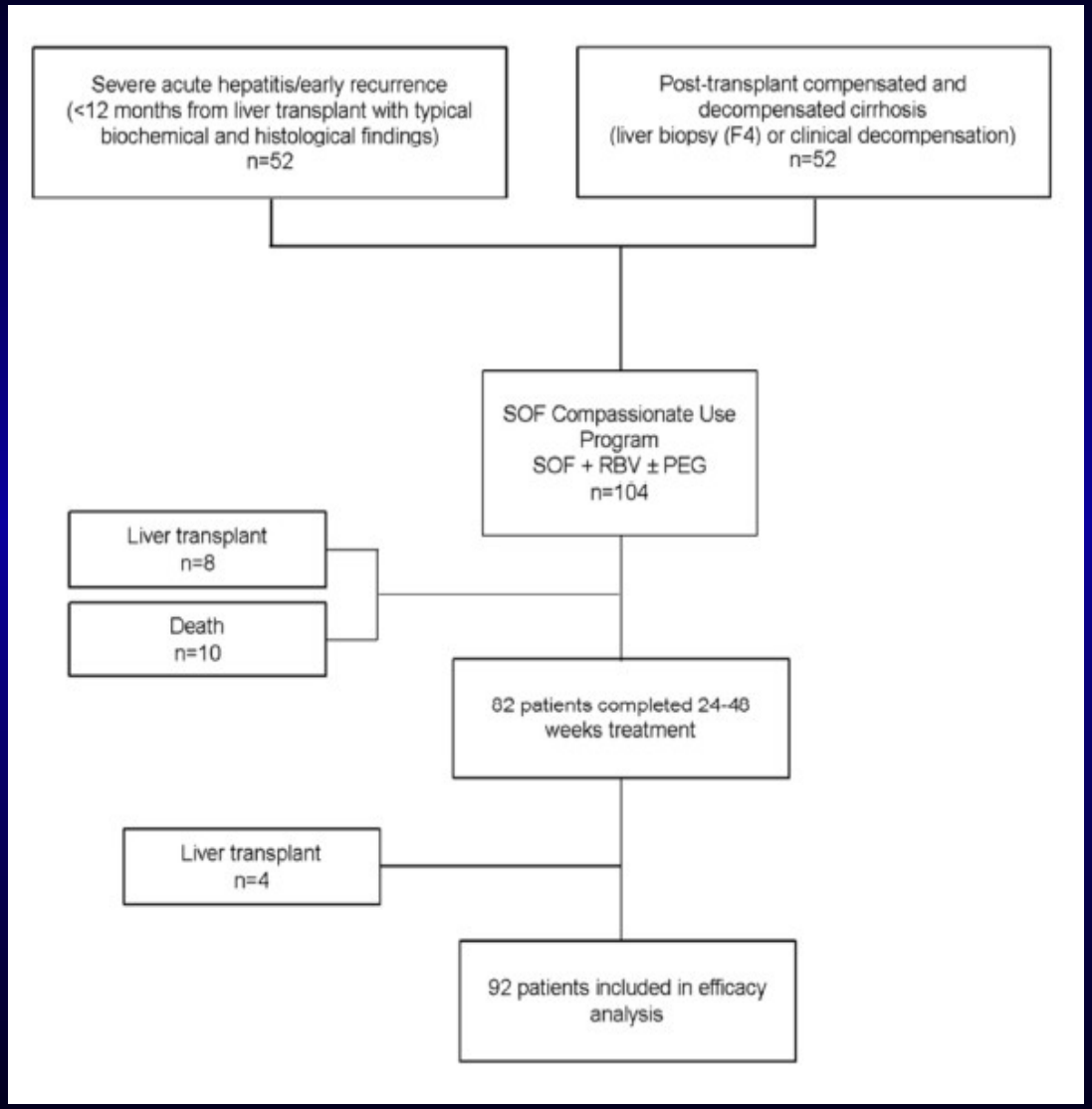
Compassionate Use Sofosbuvir + Ribavirin ± PegIFN in Liver Transplant Patients



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Compassionate Use Sofosbuvir + Ribavirin ± PegIFN in Liver Transplant Patients

	Overall (N=104)	Acute hepatitis and early severe recurrence (N=52)	Compensated and decompensated cirrhosis (N=52)
Age, years (IQR)	55 (51-60)	54 (50-60)	56 (51-64)
Male, n (%)	76 (73)	39 (75)	37 (71)
Genotype, n (%)			
1a	36 (35)	22 (42)	14 (27)
1b	49 (47)	23 (44)	26 (50)
2	1 (1)	1 (2)	0
3	7 (7)	1 (2)	6 (12)
4	7 (7)	5 (10)	2 (4)
>1	4 (4)	0	4 (8)
HCV RNA, log_{10} IU/mL (IQR)	6.2 (5.3-7.0)	6.7 (5.5-7.5)	5.8 (5.1-6.4)
Months from OLT (IQR)[1]	16.8 (18-54)	8.4 (4.8-12.7)	53.1 (33.1-92.1)
Bilirubin, mg/dL median (IQR)	3.1 (1.3-9.7)	4.7 (1.5-19.2)	1.9 (1.2-4.8)
Albumin, g/dL median (IQR)	3.1 (2.7-3.5)	3.1 (2.6-3.6)	3.1 (2.7-3.5)
INR median (IQR)	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.4 (1.2-1.6)
Platelet count $\times 10^3$/mL median (IQR)	75 (52-119)	91 (59.3-134.5)	69 (50.3-99.3)
ALT, U/L median (IQR)	71.0 (39.3-167.0)	102.0 (38.5-200.8)	60.0 (39.5-101.3)
AST, U/L median (IQR)	124.5 (70.8-210.5)	145.5 (93.5-339)	101.0 (62.3-180.0)
ALP, U/L median (IQR)	164.0 (117.5-263.3)	190.0 (124.5)	148.0 (362.5)
GGT, U/L median (IQR)	144.0 (64.0-426.5)	383.0 (121.0-915.5)	112.7 (45-148.0)
Hemoglobin, g/dL median (IQR)	10.9 (9.6-12.5)	10.9 (9.4-12.2)	11.0 (9.8-12.9)
Creatinine, mg/dL median (IQR)	1.1 (0.9-1.4)	1.1 (0.9-1.4)	1.2 (0.9-1.4)
CPT (IQR)	8 (7-10)	N/A	8.0 (7-10)
MELD (IQR)	15 (11-21)	16 (10-22)	14 (11-19)
Antiviral regimens used			
SOF + RBV alone, n/N (%)	80/104 (77)	36/52 (69)	44/52 (85)
SOF + RBV + PEG, n/N (%)	24/104 (23)	16/52 (31)	8/52 (15)

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Compassionate Use Sofosbuvir + Ribavirin ± PegIFN in Transplant Patients: Virologic Response

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%)
Virologic 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 due to SAE	3/92 (3%)	1/48 (2%)	2/44 (5%)
Discontinuation due to non-adherence	1/92 (1%)	0	1/44 (2%)
Death	13/92 (14%)	6/48 (13%)	7/44 (16%)

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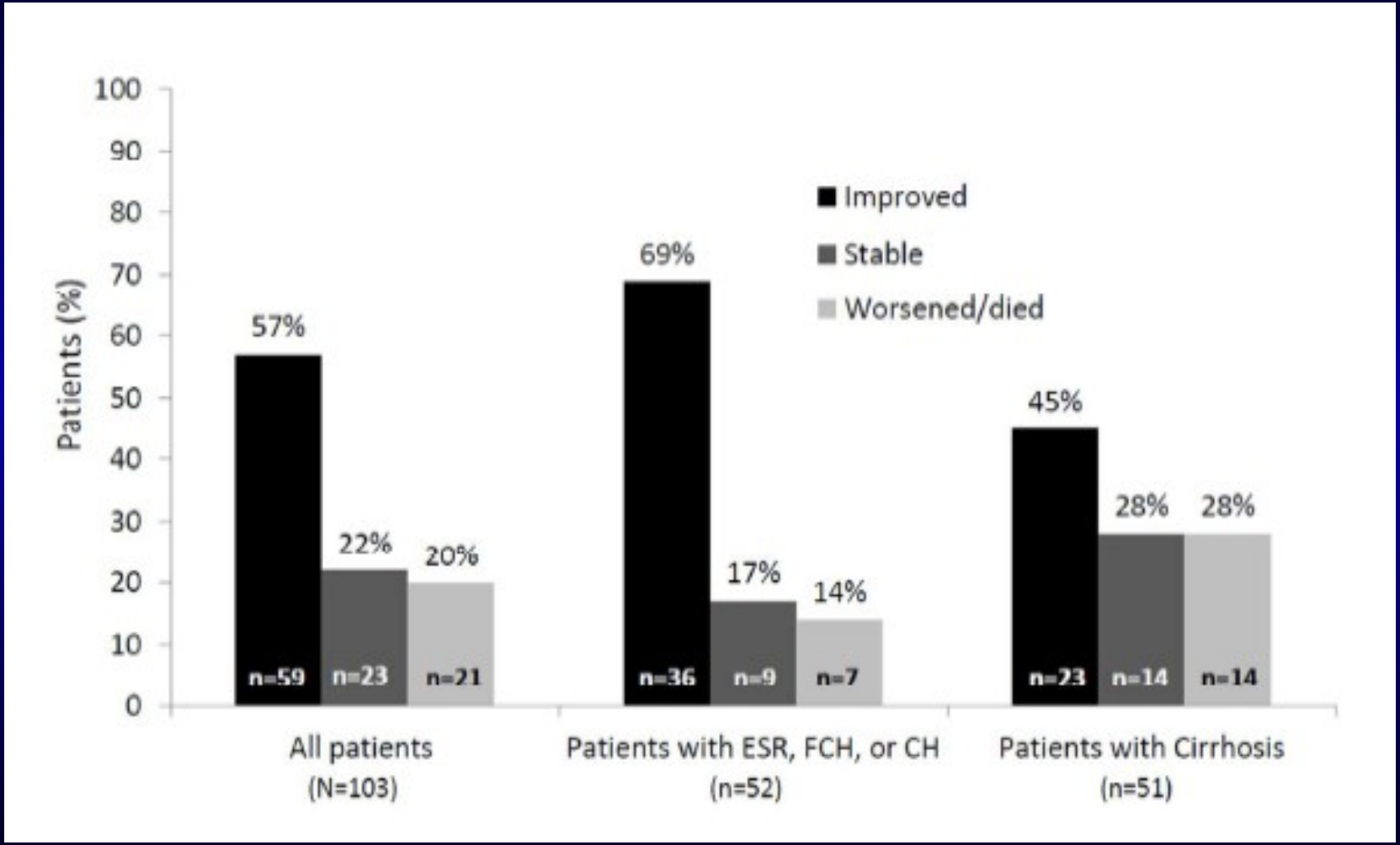
C.H.B.

Compassionate Use Sofosbuvir + Ribavirin ± PegIFN in Transplant Patients: Virologic Response: Clinical Outcome



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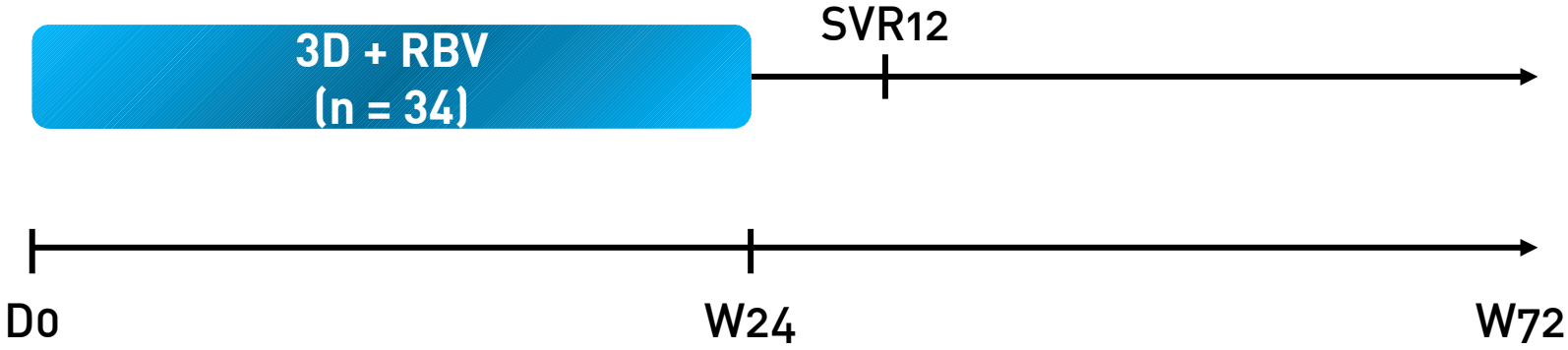
ABT450/Ritonavir/Ombitasvir + Dasabuvir + RBV in LT Recipients with Recurrent HCV GT 1

- Phase II Study on efficacy and tolerance of ABT-450/r/ombitasvir 150 mg/100m g/25 mg/d + dasabuvir 250 mg x 2/d in patients with HCV reinfection post-LT
- Patients G1, fibrosis ↙ F2 at Liver biopsy, no prior PEG/RBV after LT
- Dosing RBV free for the investigator
- CNI adaptation
  - Tacrolimus 0.5 mg/week or 0.2 mg/3 days
  - Ciclosporine 1/5 of initial daily dosing once a day



Kwo P, Etats-Unis, EASL 2014, Abs. 0114 actualise

ABT450/Ritonavir/Ombitasvir + Dasabuvir + RBV in LT Recipients with Recurrent HCV GT 1

Table 2. Response during and after Treatment.

Outcome	Patients with Outcome	
	no.	*% (95% CI)*
HCV RNA <25 IU/ml		
During treatment period		
At wk 4	34	100 (90–100)
At wk 24	34	100 (90–100)
After end of treatment		
At wk 4	33	97 (85–100)
At wk 12	33	97 (85–100)
At wk 24	33	97 (85–100)
Virologic failure during treatment	0	0 (0–10)
Relapse*	1	3 (0–15)

P Kwo NEJM 2015

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ABT450/Ritonavir/Ombitasvir + Dasabuvir + RBV in LT Recipients with Recurrent HCV GT 1

Anemia

n (%)	3D + RBV (n = 34)
8-10 g/dl	8 (23,5)
6,5-8 g/dl	1 (2,9)
EPO	5 (14,7)

Dosing of RBV

n (%)	J0 (n = 34)	Fin TTT (n = 34)
400 mg/d	3 (9)	4 (12)
600-800 mg/d	19 (56)	25 (73)
1 000-1 200 mg/d	12 (35)	5 (15)

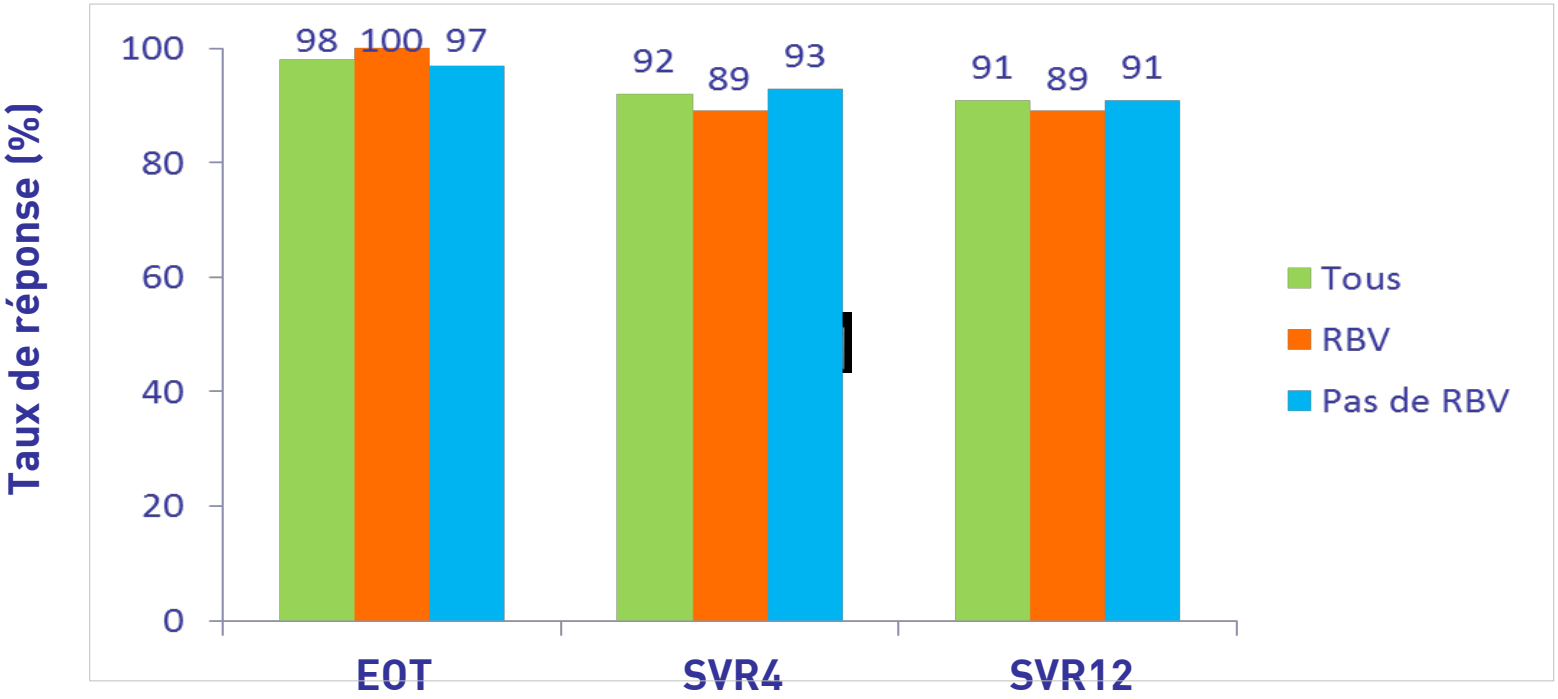
- 1 premature discontinuation for Rash (rash, anxiety)
- No rejection
- 4 patients Tac though level ↑ 15 mg/ml (15,7-34)→ ↑ réversible of créatinin in 2 patients

Kwo P, Etats-Unis, EASL 2014, Abs. 0114 actualise

Sofosbuvir/Simeprévir ± RBV 12 weeks for HCV Recurrence Post-Transplantation

- Multicenter study, 109 transplant patients with histologically proven recurrent HCV.
- Delay post-LT : 29 months (median). Median FU : 23 weeks
- Cholestatic recurrence: 11 % ; METAVIR F3-F4 : 29 %

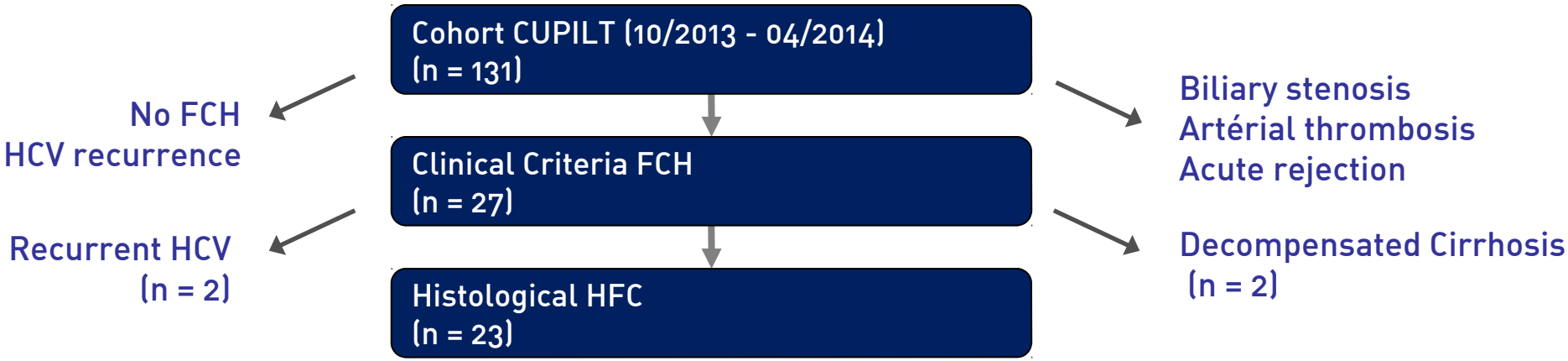
Virologic Response ITT

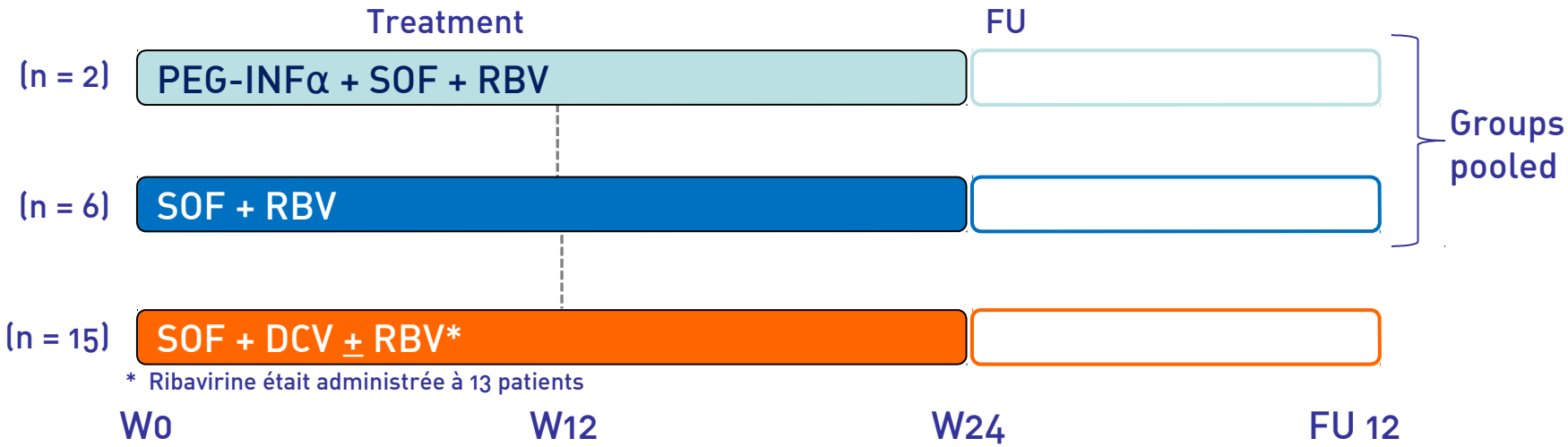


Pungpapong S, Etats-Unis, AASLD 2014, Abs. 9 actualis

Sofosbuvir/Daclatasvir for Fibrosing Cholestasis after LT(CUPILT Study)

- Prospective multicenter French cohort Study





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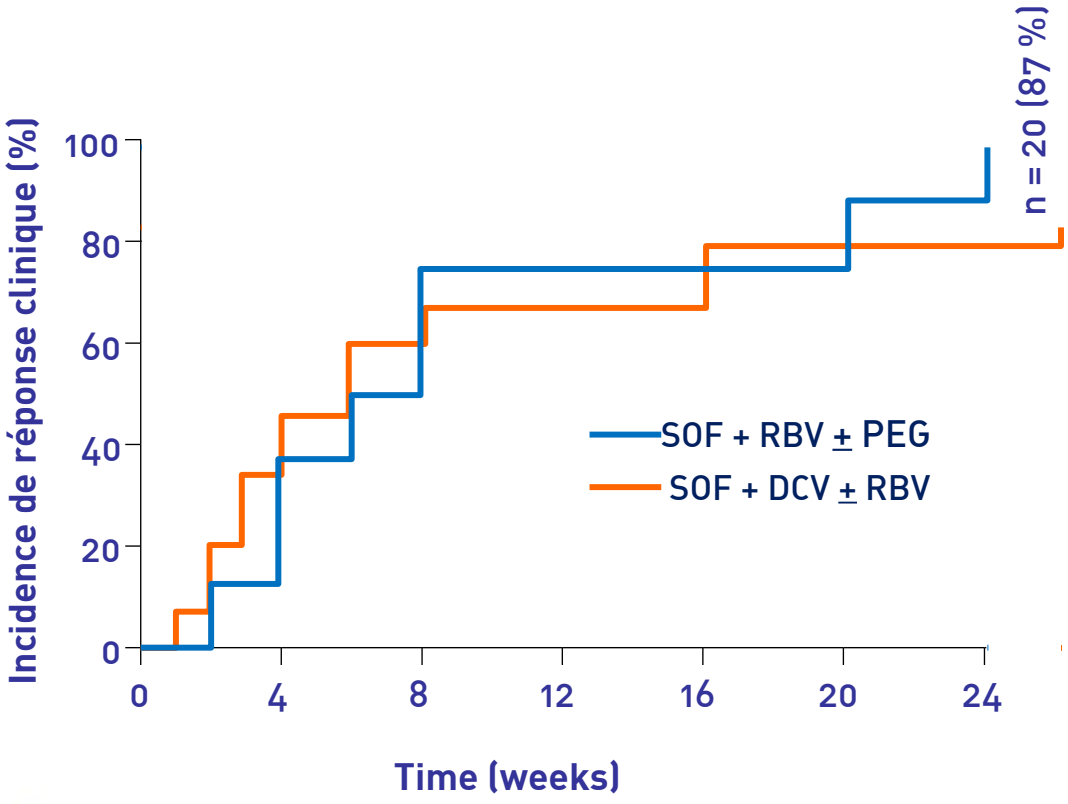
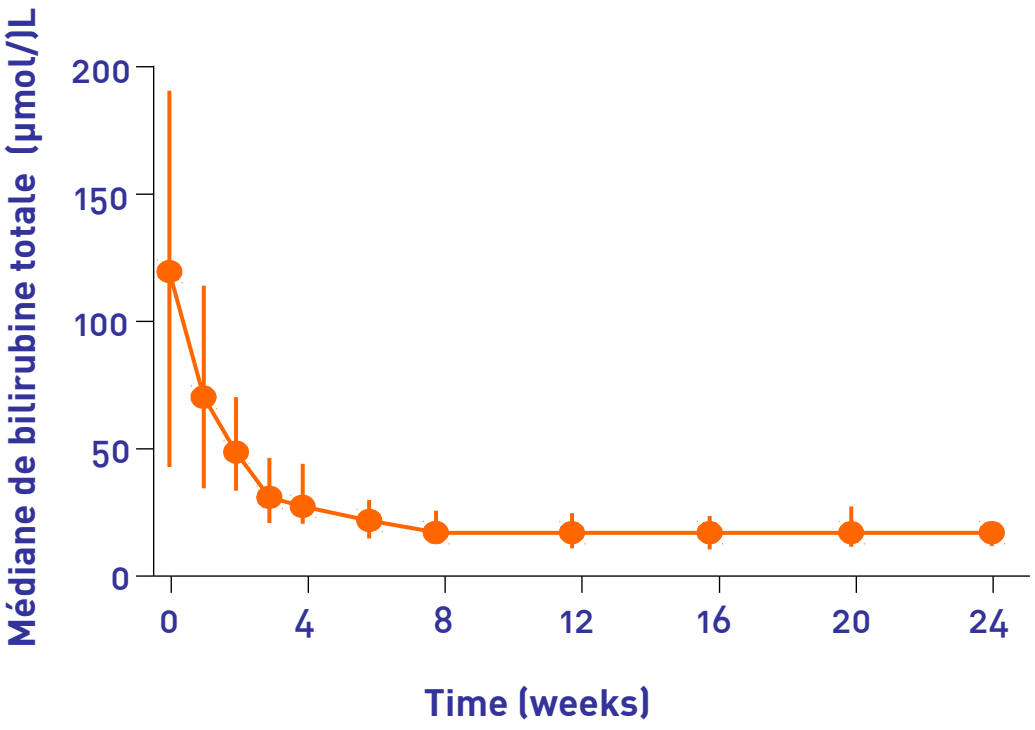
Sofosbuvir/Daclatasvir for Fibrosing Cholestasis after LT(CUPILT Study)

Clinical response 24*



Evolution of Bilirubin at 24 weeks

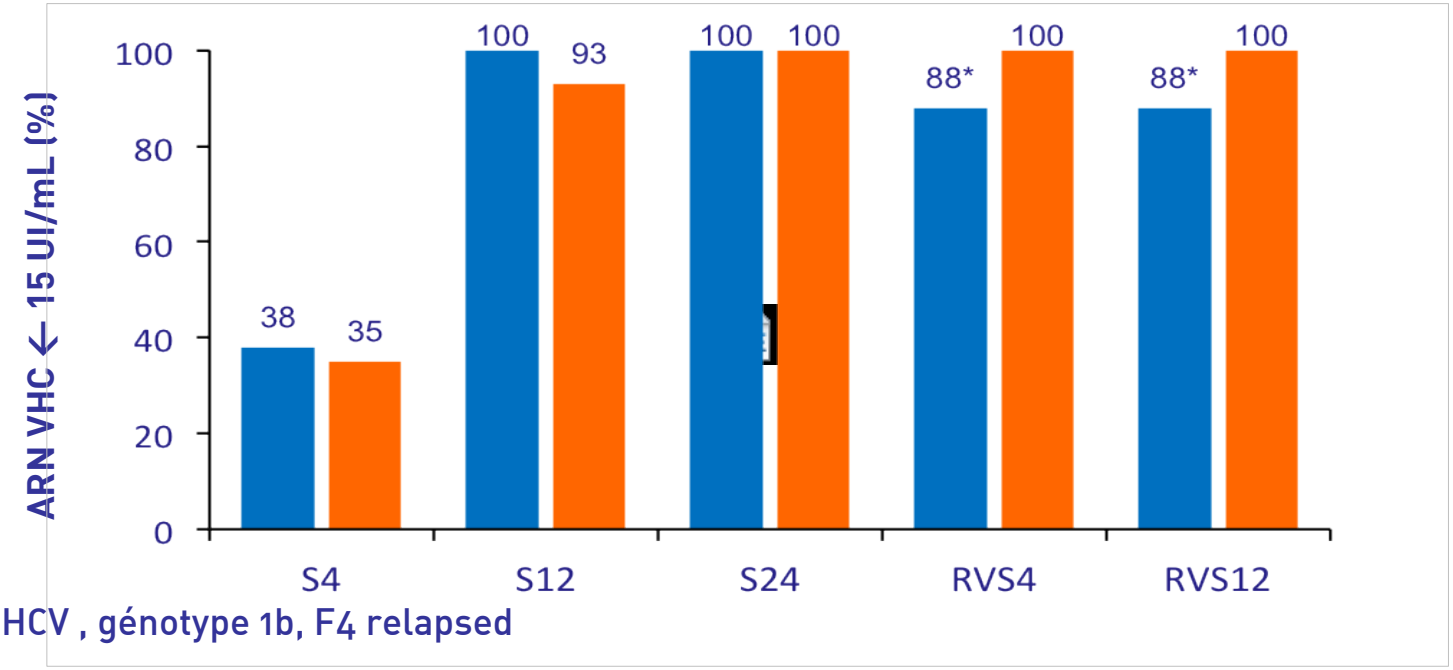


urvival without retransplantation, total bilirubine ↓ 34 mmol/l, absence of ascites and no encephalopathy

Leroy V, France, AASLD 2014, Abs. 21 actualise

Sofosbuvir/Daclatasvir for Fibrosing Cholestasis after LT(CUPILT Study)

Virologic Response According to Treatment



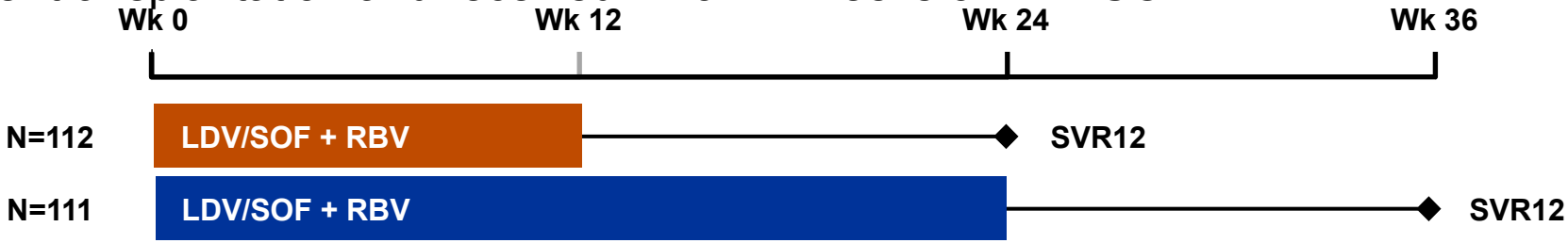
*1 patient HIV-HCV , génotype 1b, F4 relapsed

- Tolerance
  - SAE : 12 (52 %)
  - Anaemia grade 3-4 : 6/26 %)
  - Infection : 7 (30 %)
  - Neutropenia grade 3-4 : 3 (13 %)
  - Renal failure : 1

Leroy V, France, AASLD 2014, Abs. 21 actualise

LDV/SOF + RBV for treatment of HCV in patients with post-transplant recurrence

Prospective, multicentre study in TN and TE GT 1 and 4 patients, who were post-liver transplantation and received 12 or 24 weeks of LDV/SOF + RBV



223 patients randomised 1:1 to 12 or 24 weeks of treatment

- ≥3 months from liver transplant
- No hepatocellular carcinoma

Stratified at screening: F0–F3, CTP A, B, C

Broad inclusion criteria:

- Total bilirubin ≤10 mg/dL, Hb ≥10 g/dL
- CrCl ≥40 mL/min, platelets > 30,000

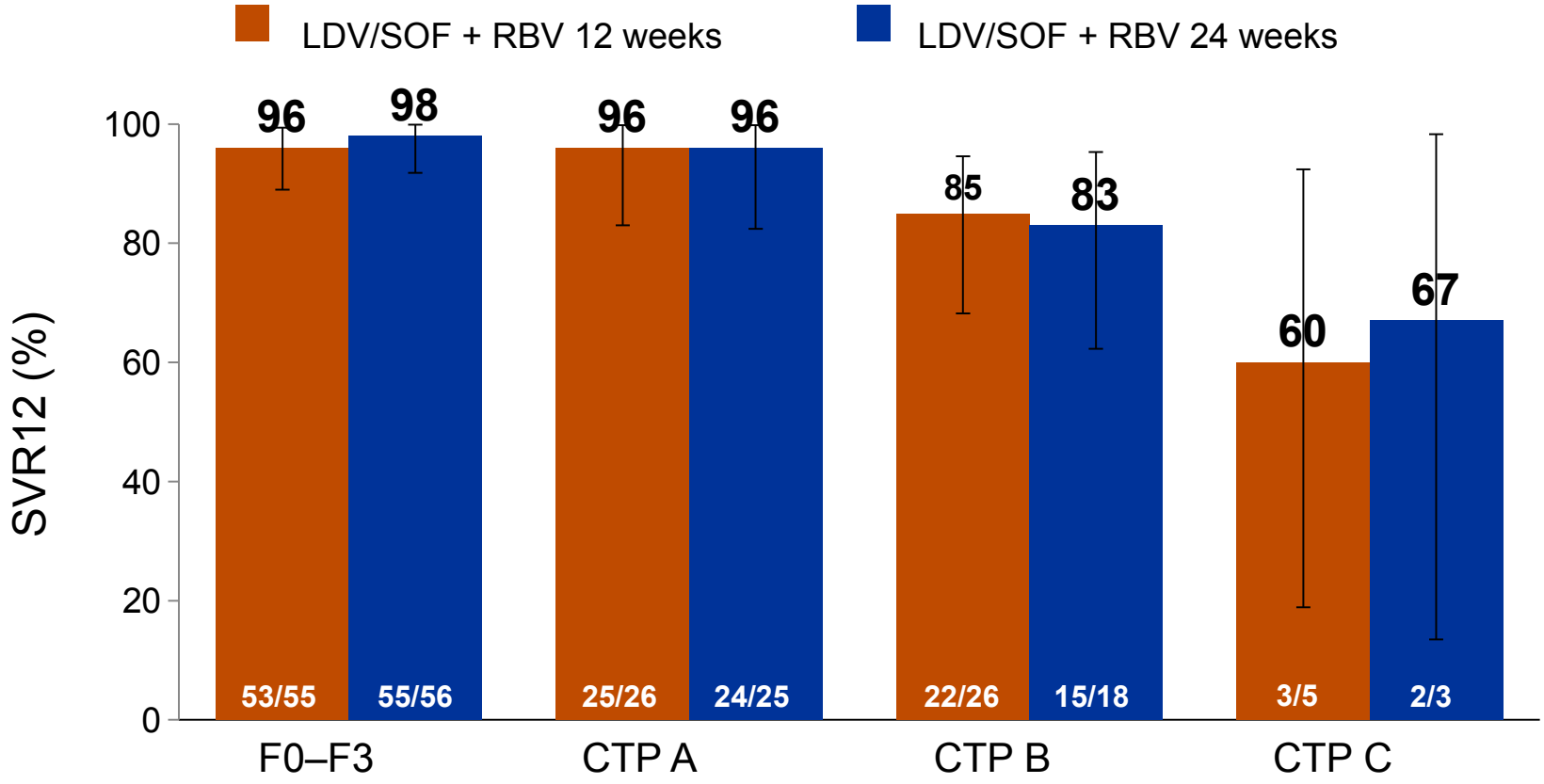
RBV dosing

- 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

Reddy KR, et al. AASLD 2014, Oral #3

LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen

LDV/SOF + RBV in Post-Transplant Recurrence



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

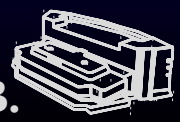
LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen;
Reddy KR, et al. AASLD 2014, Oral #9. Error bars represent 2-sided 90% exact confidence intervals

DAA Interactions with CNI (Tacrolimus and Cyclosporine)

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

Gamballi J Hepatol 2014



SVR with DAA in LT Patients

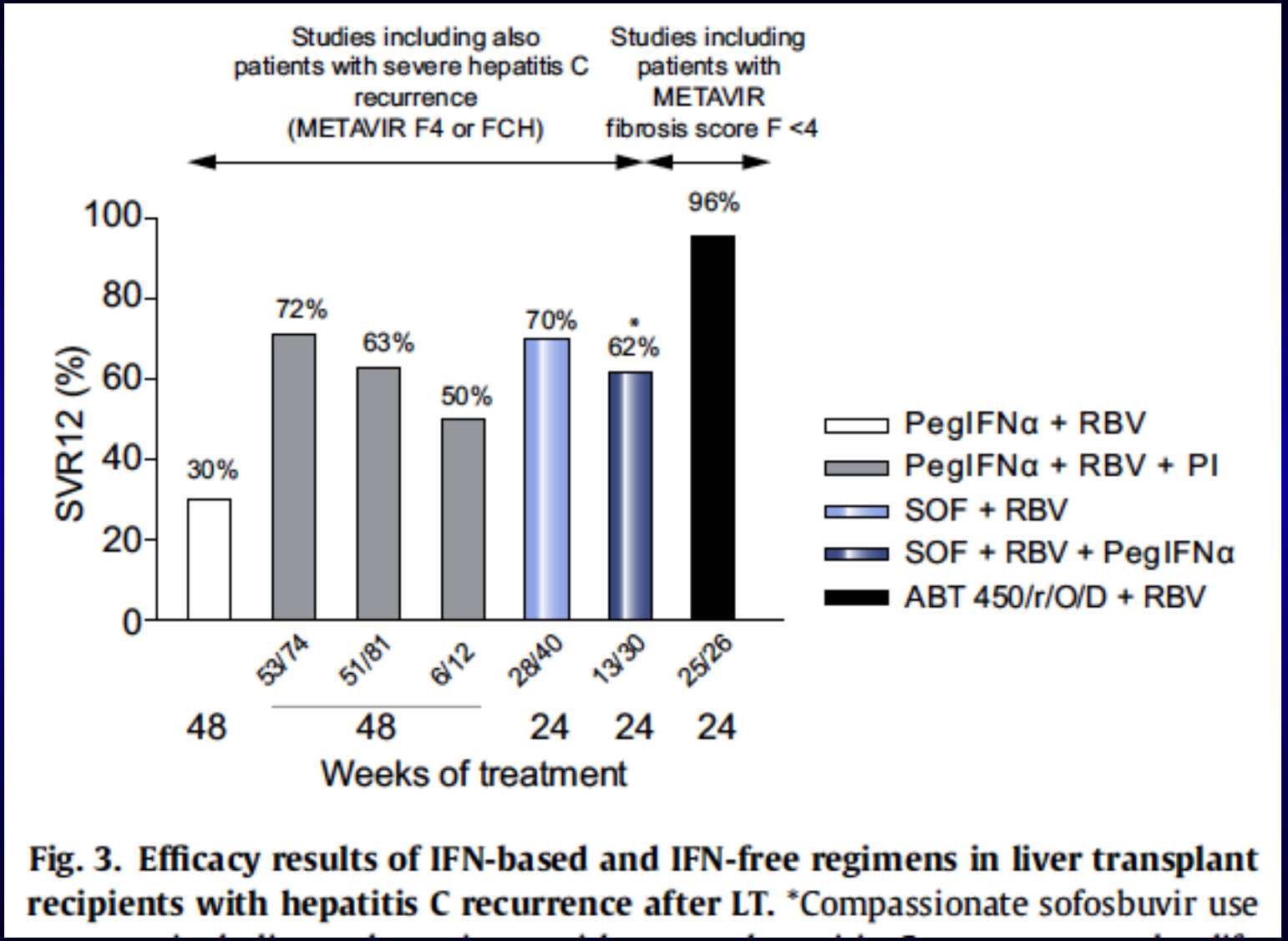


Fig. 3. Efficacy results of IFN-based and IFN-free regimens in liver transplant recipients with hepatitis C recurrence after LT. *Compassionate sofosbuvir use

Gamballi J Hepatol 2014

C.H.B.

Figure 1: Alternative strategies to treat HCV infection in patients on a waiting list in 2014-2015

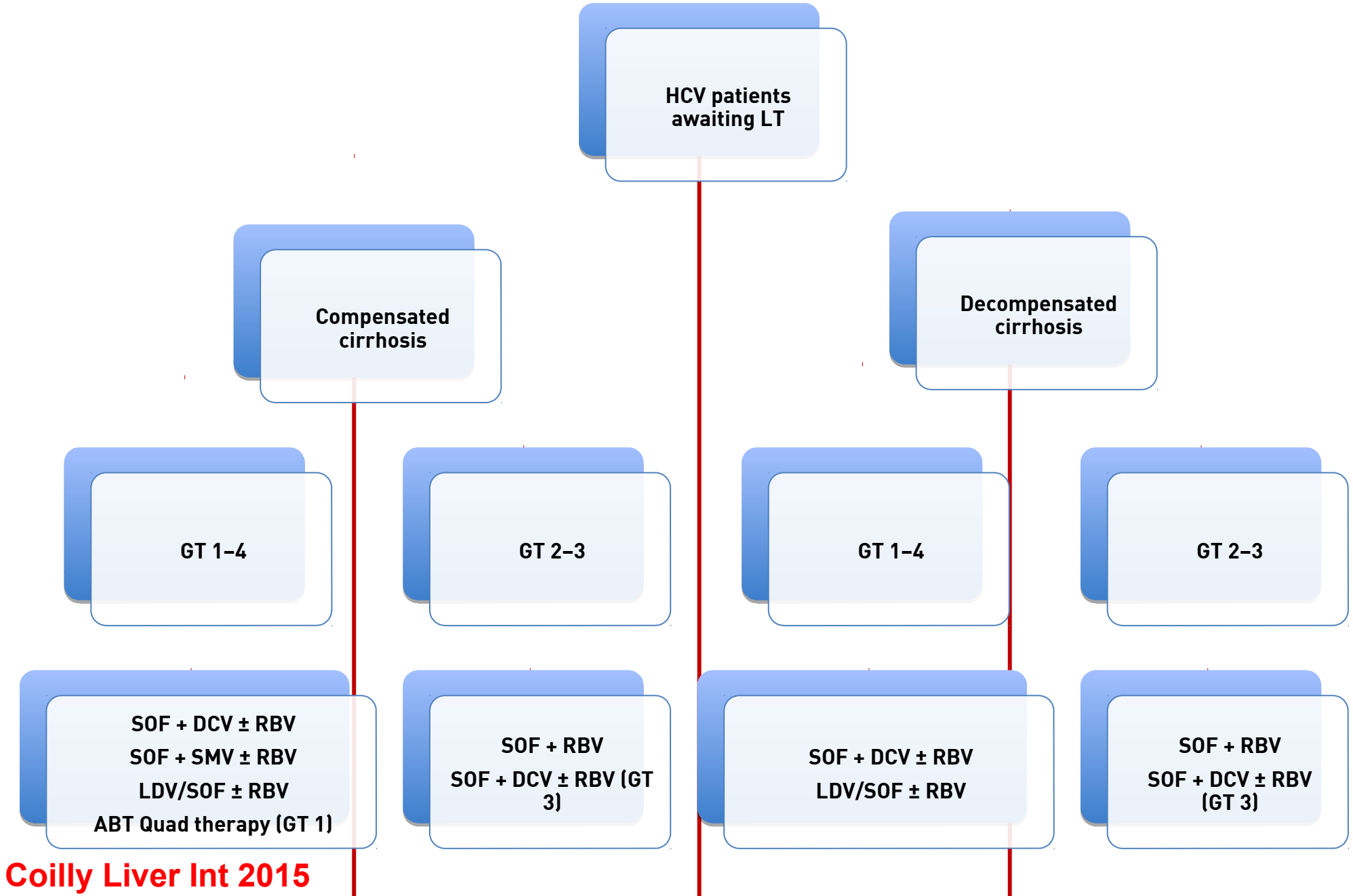


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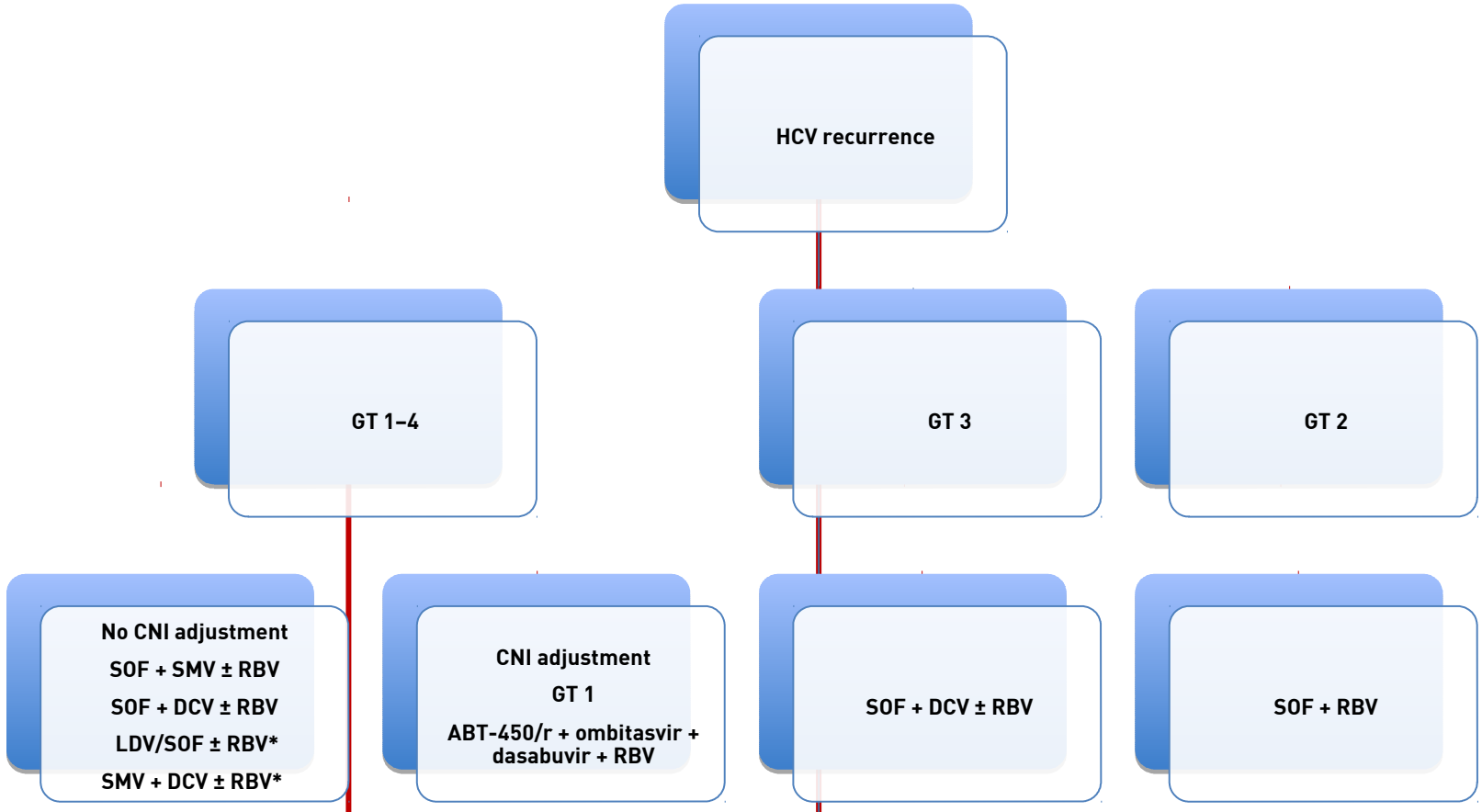
Figure 2: Alternative strategies to treat HCV recurrence after liver transplantation in 2014-2015



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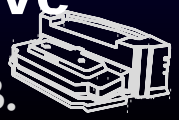
CONCLUSION

- The Field of Liver Transplantation In HCV Patients is moving dramatically with IFN-free regimen
- Some questions are open:
  - Treat before or after Transplantation?
  - Remove patients from the waiting list?
  - Which combination?
  - Duration of treatment ? Use of RBV?
  - How to avoid relapse? Risk of liver failure in case of relapse?
- The survival after transplantation for HCV infection will improve



C.H.B.

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