Treatment of Hepatitis C in Liver Transplantation

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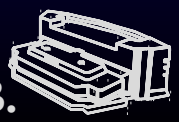


Current Situation of LT for Viral Hepatitis in Europe

Without HCC

INDICATIONS

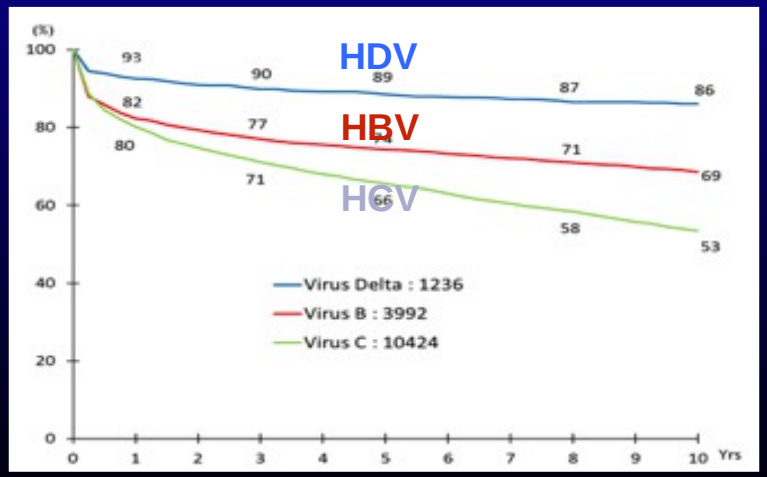
With HCC

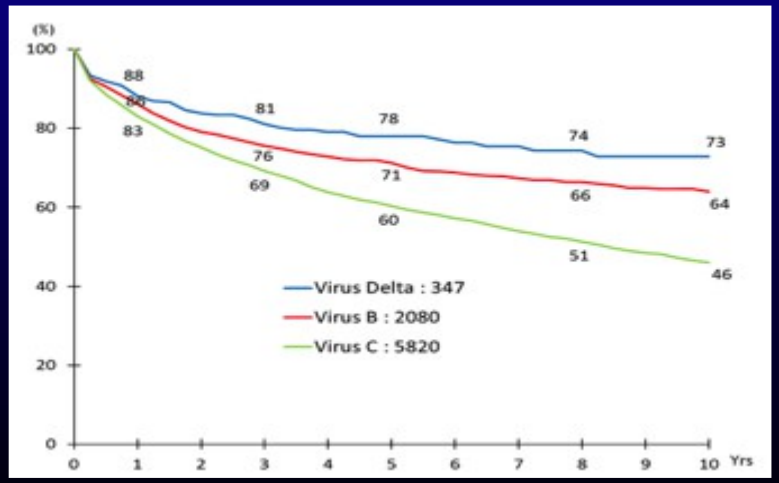
HCV

HBV

HDV

SURVIVAL





www.eltr.org

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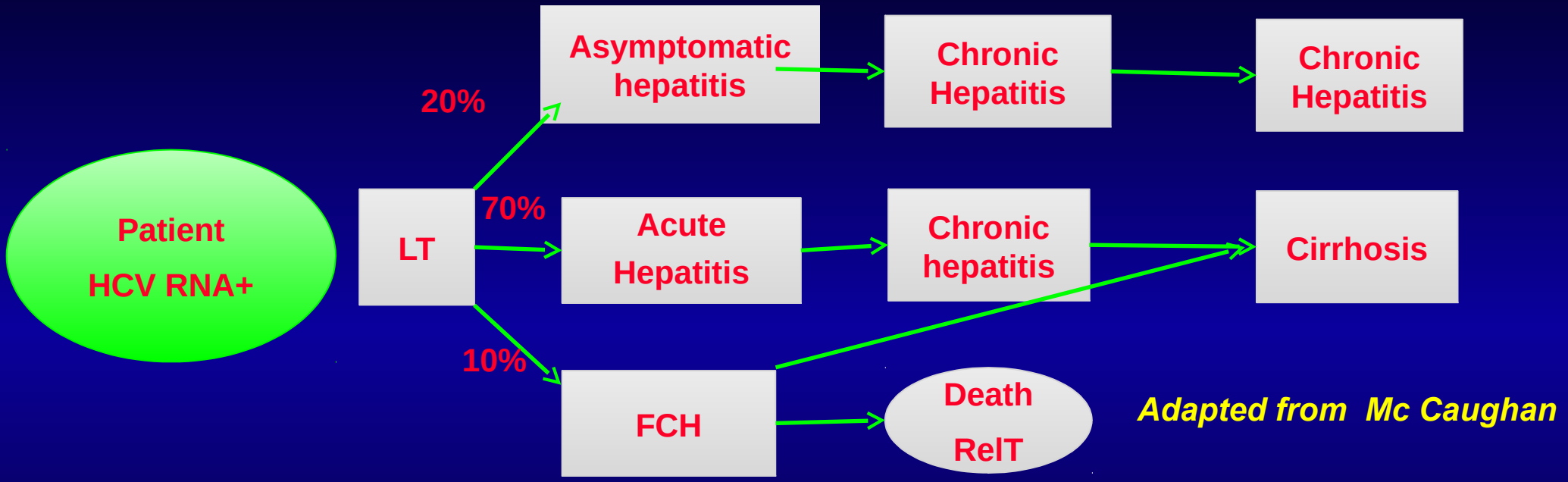
HCV Recurrence: a Main issue



- **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

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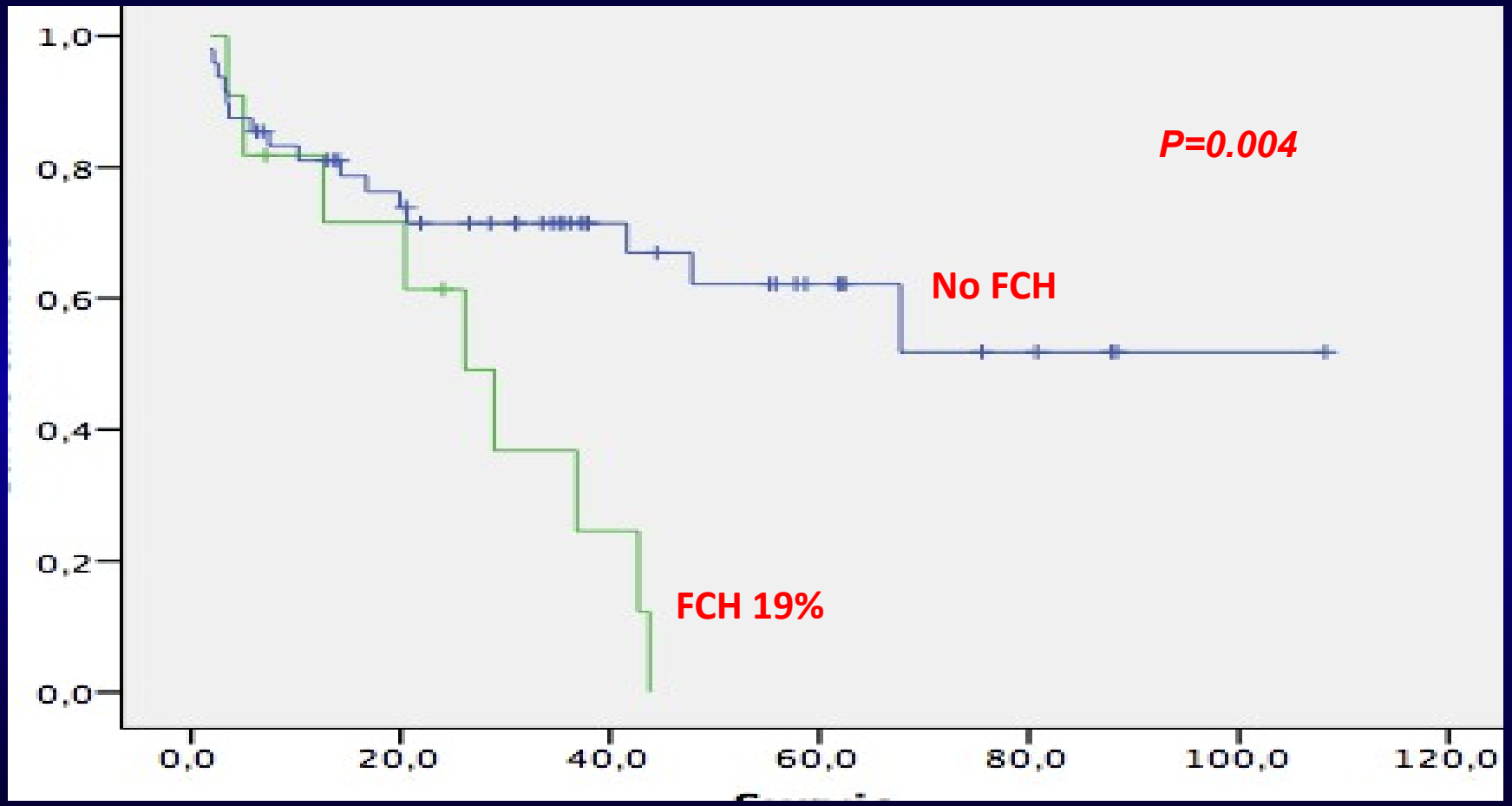
Impact of Fibrosing Cholestatic Hepatitis on Survival



Antonini Am J Transplant 2011

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Impact of SVR on Survival in Transplant HCV +ve Patients

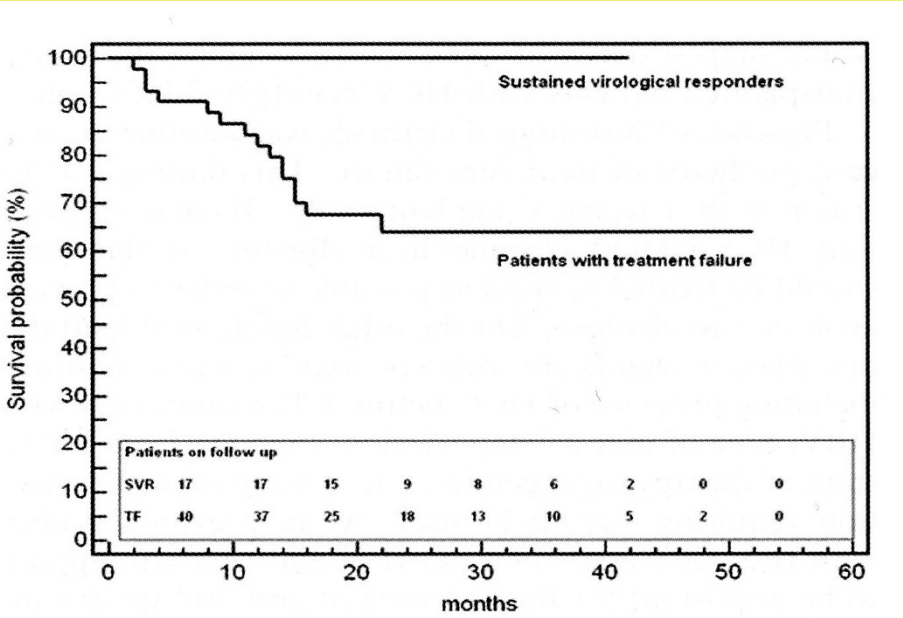
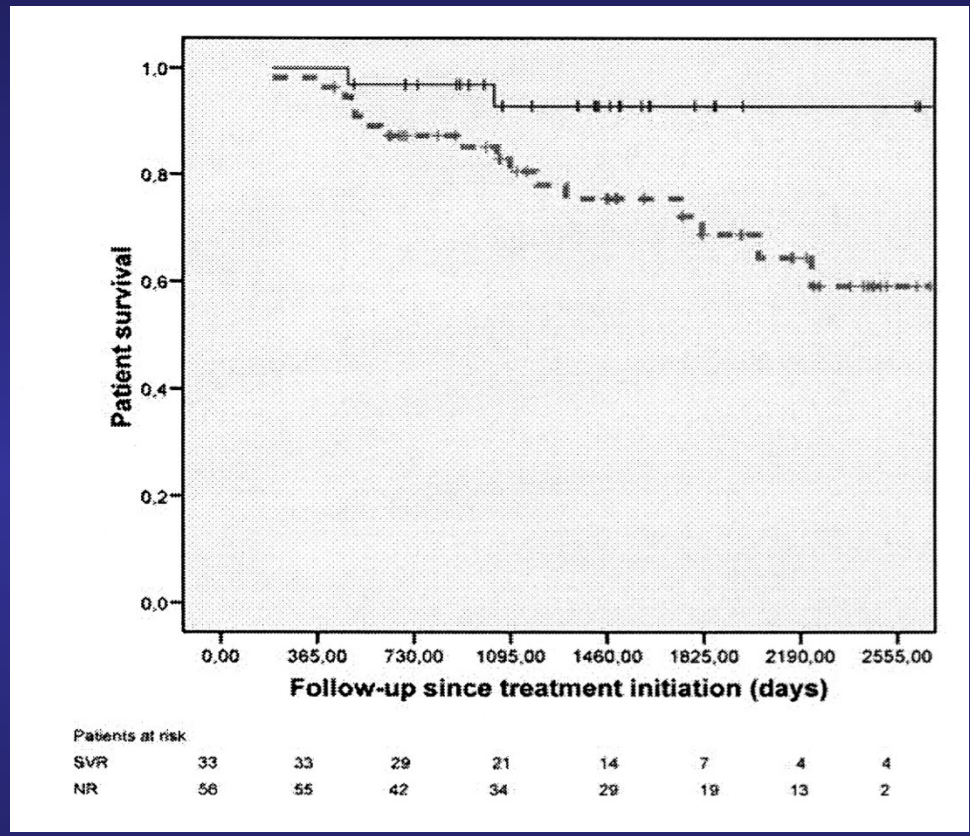


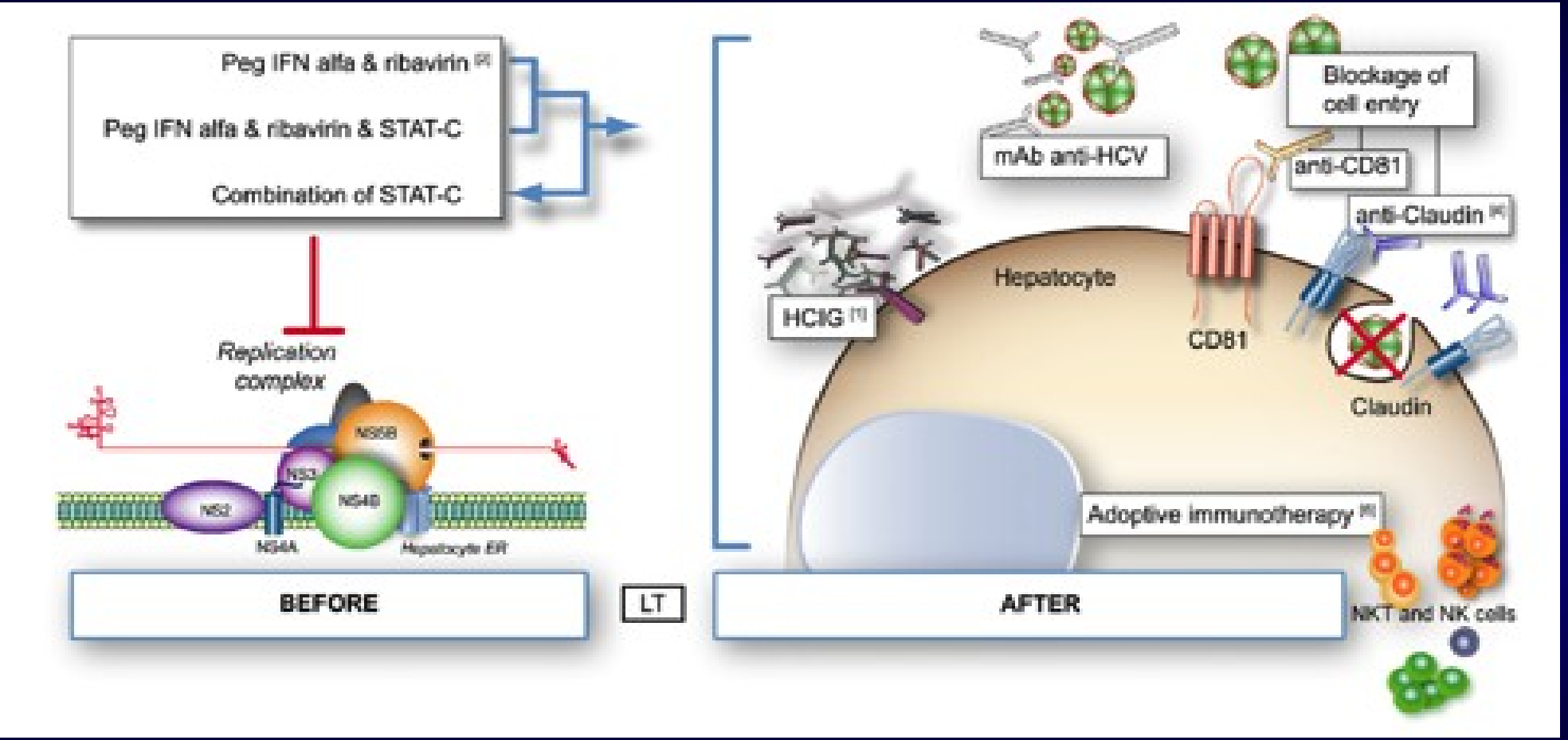
Fig. 1. Kaplan–Meier survival analysis starting at the end of treatment. Patients with SVR showed a significantly lower mortality compared to patients with treatment failure ($\chi^2 = 6.9$; $P < 0.01$; Log rank test). At the bottom: number of patients who have reached the different time points of follow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

Piciotto J Hepatol 2007



Berenguer M AJT 2008

HCV Recurrence: a Main Issue



Feray J Hepatol 2011

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PegIFN + RBV Before LT

- Treatment PegIFN+RBV **until LT**
  - 47 G1/4/6 patients
    - 30 treated
    - 17 not treated
- 32 G2/3 patients treated
    - 29 treated
    - 3 not treated

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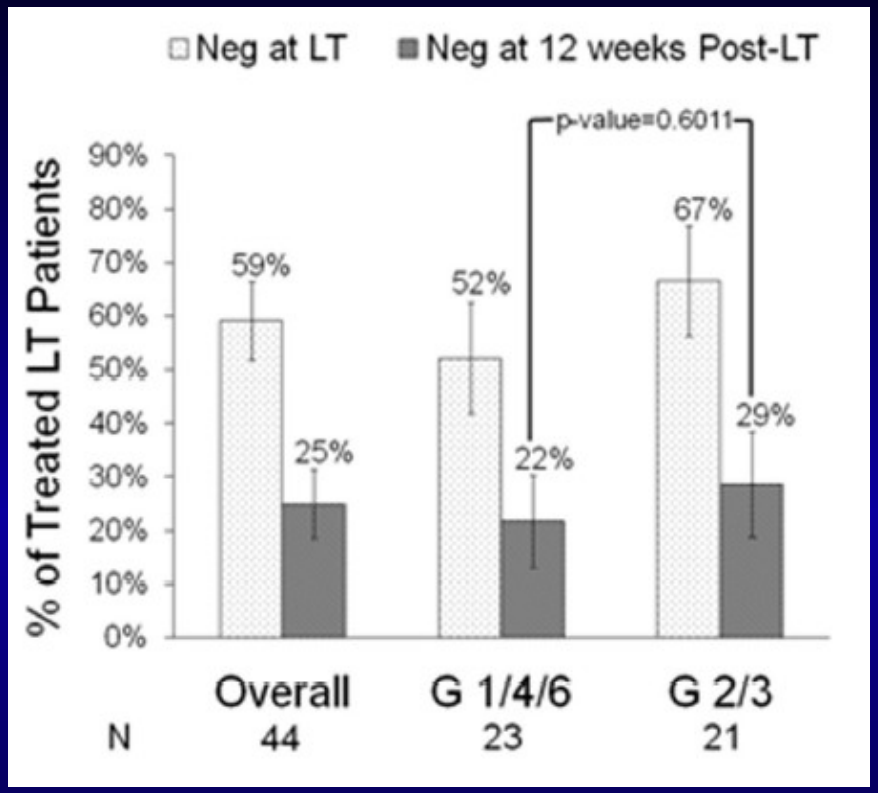
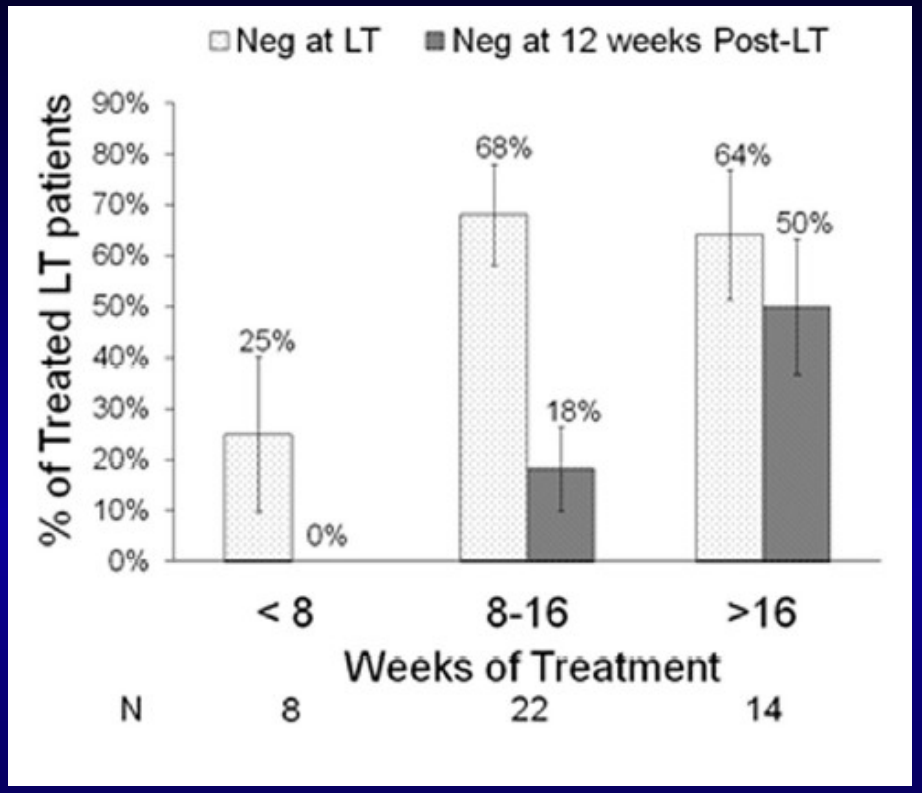
PegIFN + RBV Treatment Before LT





Meld score: 12, CTP score : 7

Serious Infection rate: 7/59 (12) pts vs 0% control

Death pre-LT: 5/59 vs 2/20 (NS)

Everson Hepatology 2012

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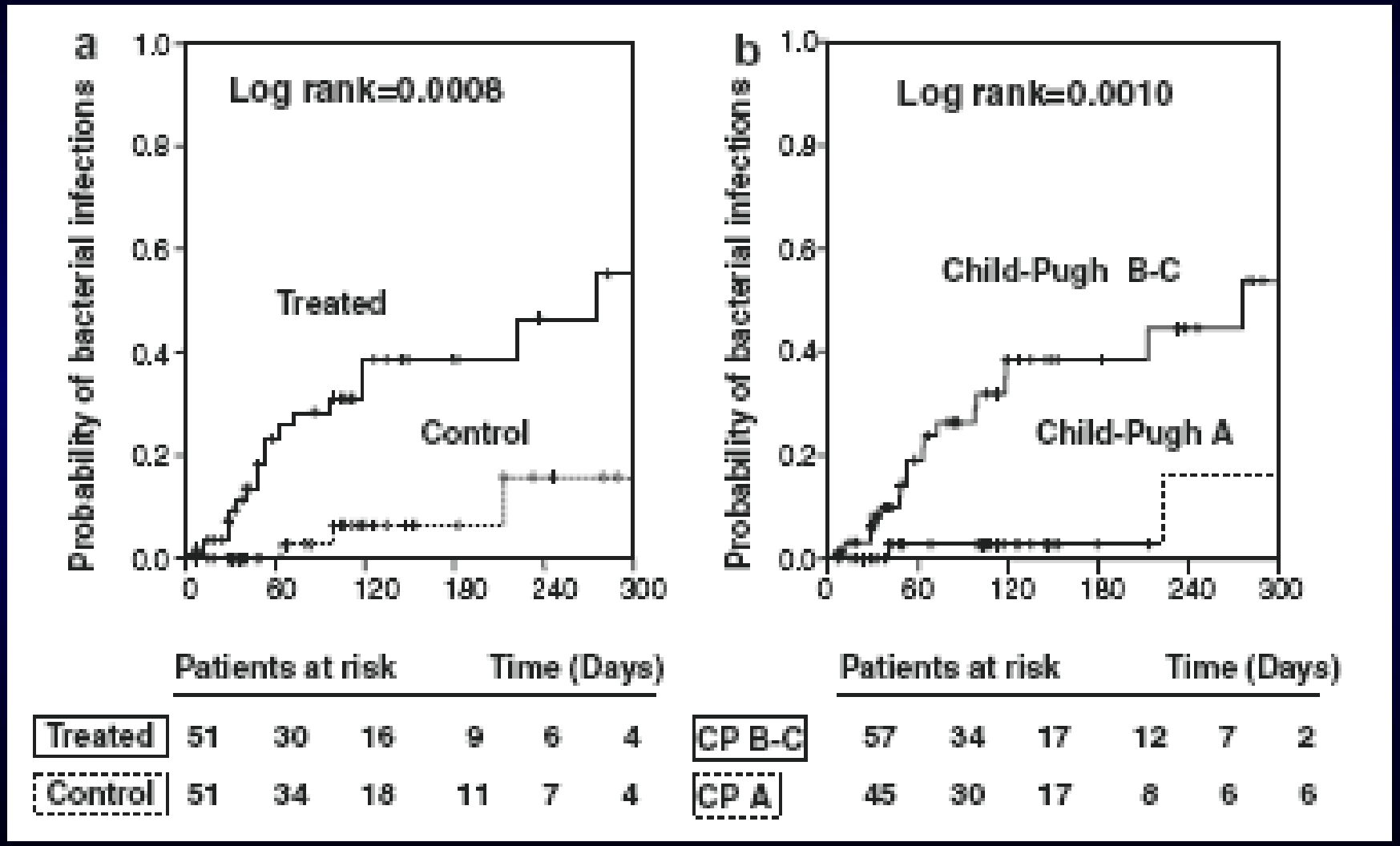
Antiviral Treatment in Patients Waiting for Liver Transplantation, Risk of Sepsis Related to CPT



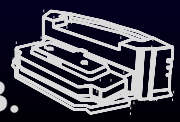
Carrión JA et al. J Hepatol. 2009;50:719-28.

Pre-Transplant Sofosbuvir + RBV Until LT

Patient Demographics

	SOF + RBV (n=61)
Male, n (%)	49 (80)
Median age, y (range)	59 (46–73)
White, n (%)	55 (90)
BMI < 30 kg/m2, n (%)	43 (70)
HCV RNA > 6 log10 IU/mL, n (%)	41 (67)
Genotype, n (%) 1a 1b 2 3a 4	 24 (39) 21 (34) 8 (13) 7 (12) 1 (2)
Non-CC allele, n (%)	47/60 (78)
CTP score, n (%) 5 6 7 8	 26 (43) 18 (30) 14 (23) 3 (5)
Median MELD score, (range)	8 (6–14)
Prior HCV treatment, n (%)	46 (75)

Curry AASLD 2013. Washington, DC. Oral #213



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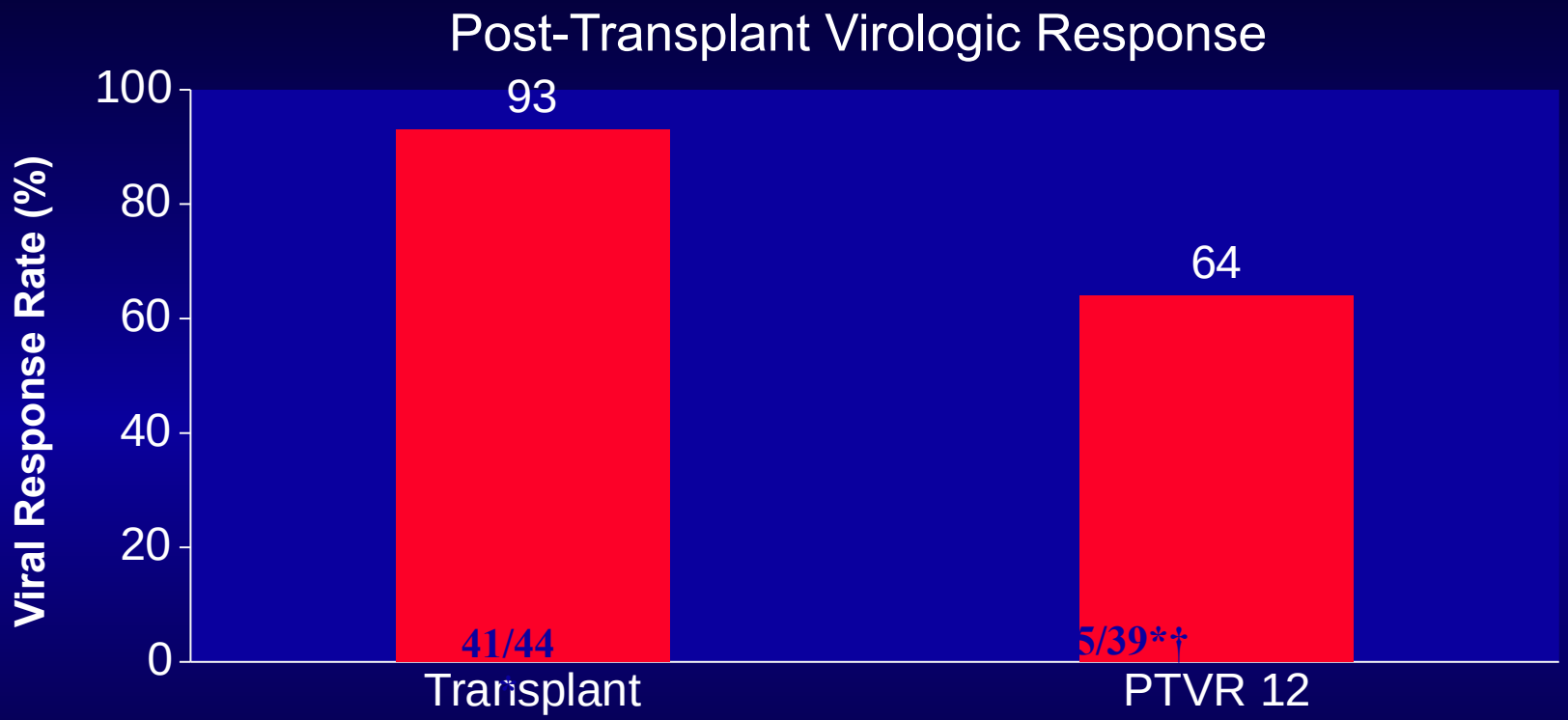
Pre-Transplant Sofosbuvir + RBV Until LT Pre-Transplant Virologic Response



SOF + RBV was safe and effective in patients with well compensated cirrhosis, and prevented post-transplant HCV recurrence in 64% of patients who had HCV RNA < 25 IU/mL prior to transplant

Curry AASLD 2013. Washington, DC. Oral #213

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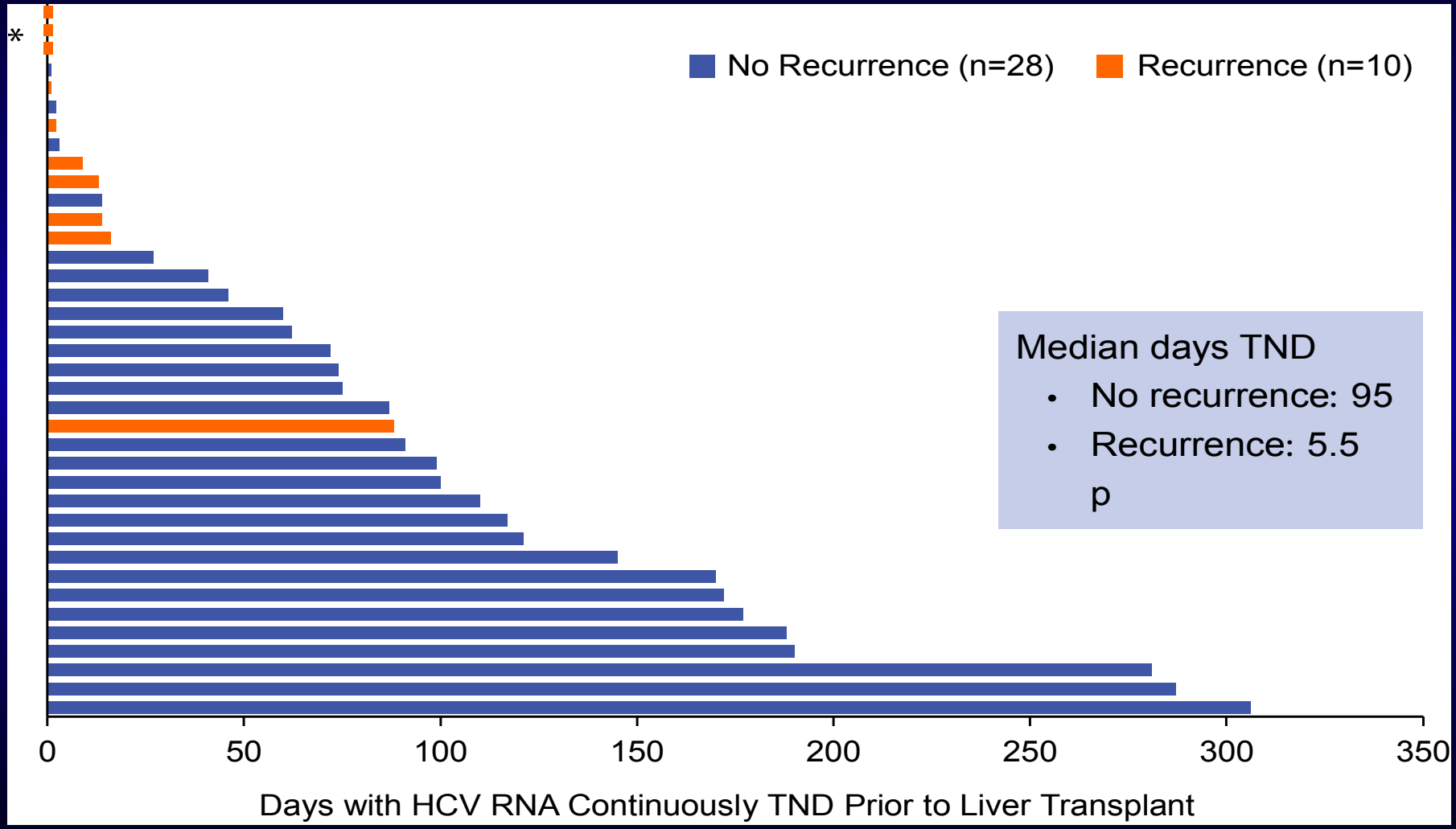
Pre-Transplant Sofosbuvir + RBV Until LT

Impact of Duration of Treatment on HCV Recurrence



*3 patients with recurrent HCV had 0 consecutive days TND before transplant.

Curry MP, et al. AASLD 2013.

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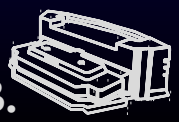
HCV Treatment after LT
Standrad of Care Until 2012

- Antiviral treatment with Peg-IFN+RBV
  - Treatment can be 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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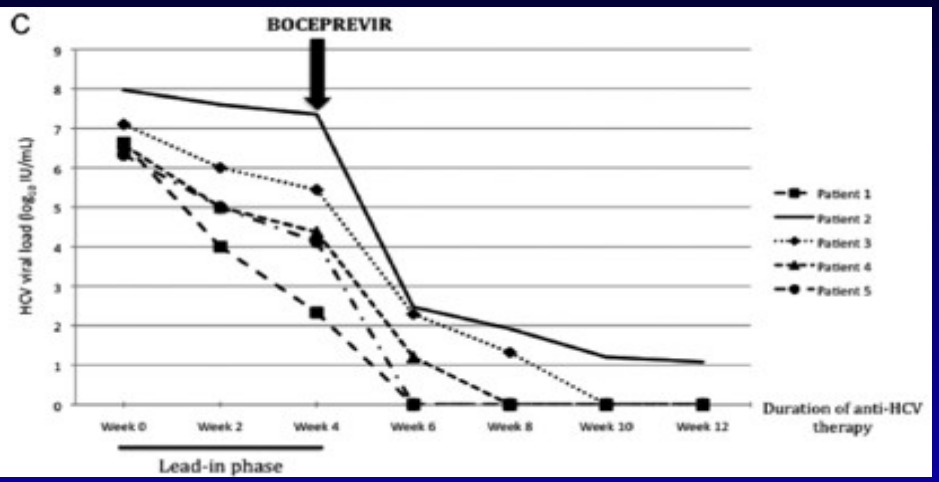
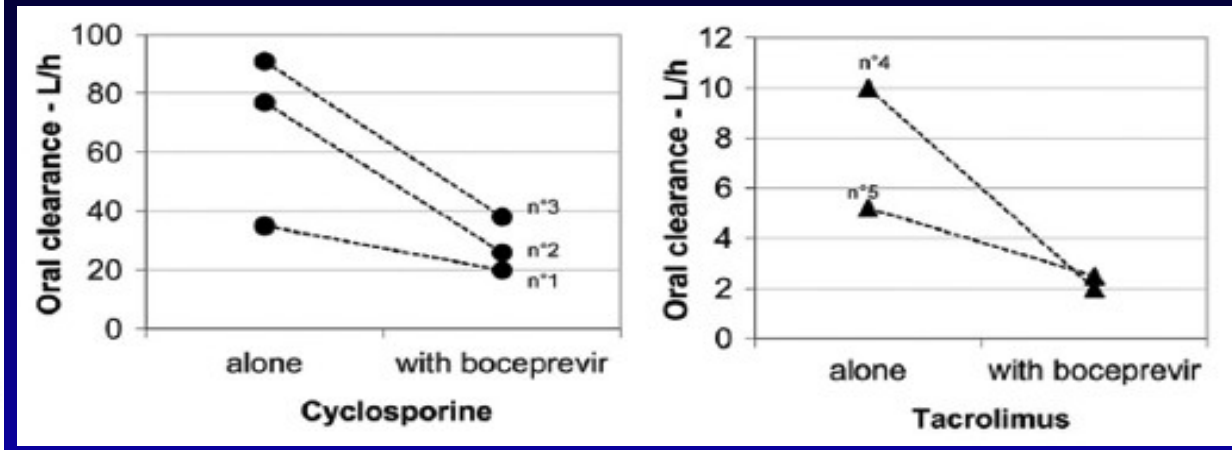
New Direct Acting Agent in HCV Recurrence
Boceprevir and Telaprevir





Coilly AAC 2012

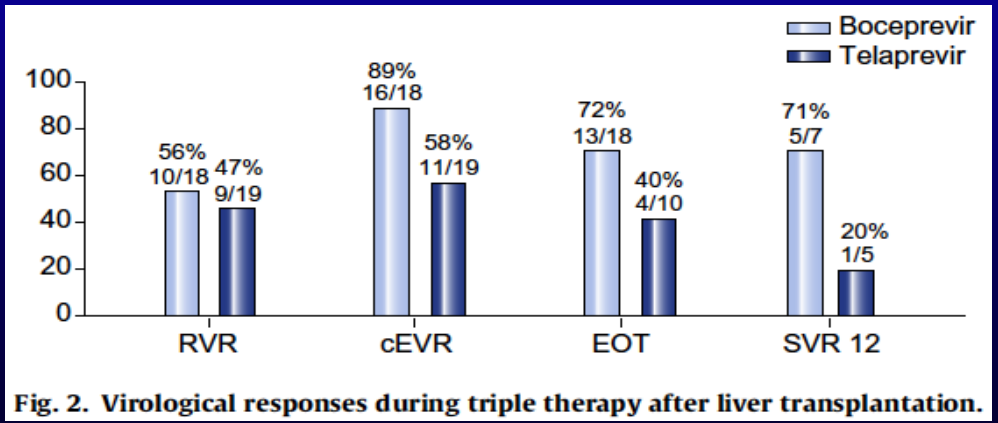
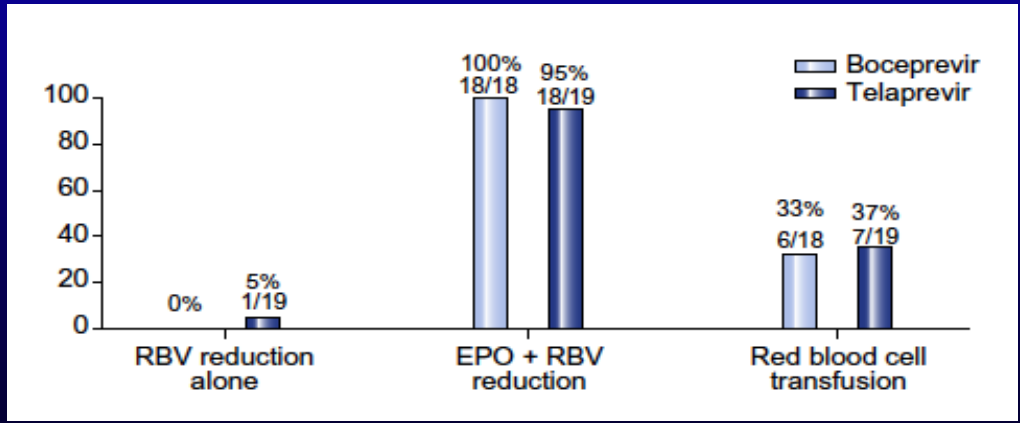


Fig. 2. Virological responses during triple therapy after liver transplantation.



Coilly J Hepatol 2014

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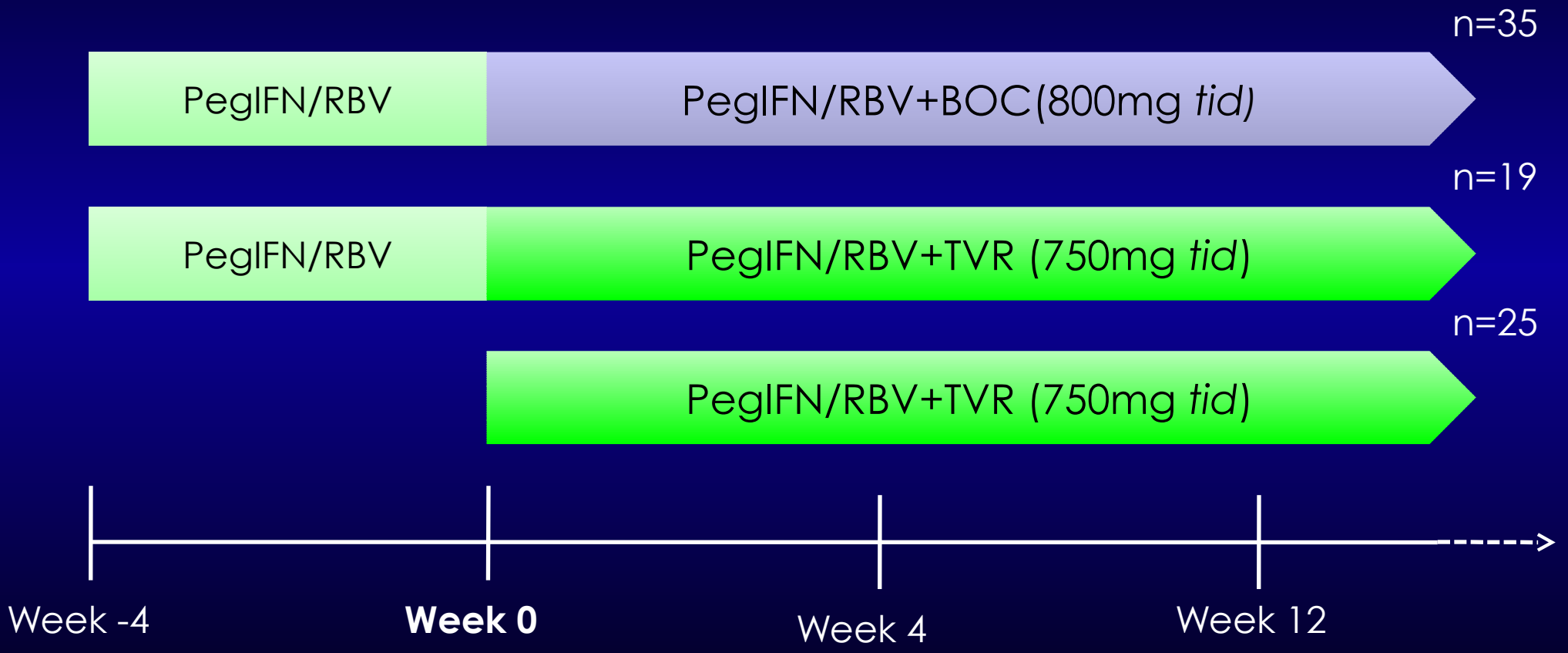
First Generation Protease inhibitors
Telaprevir, Boceprevir



Coilly AASLD 2013

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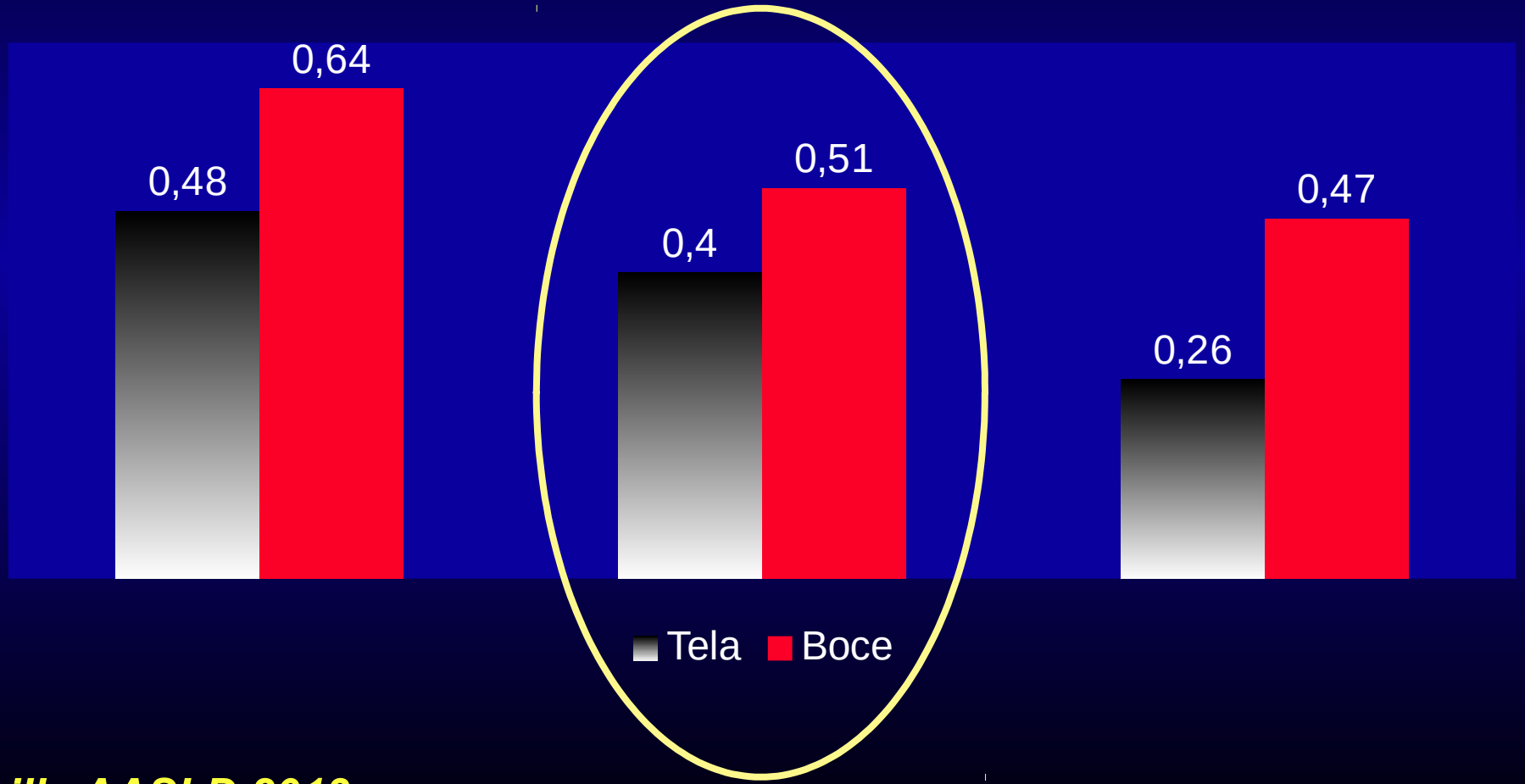
First Generation Protease inhibitors
Telaprevir, Boceprevir



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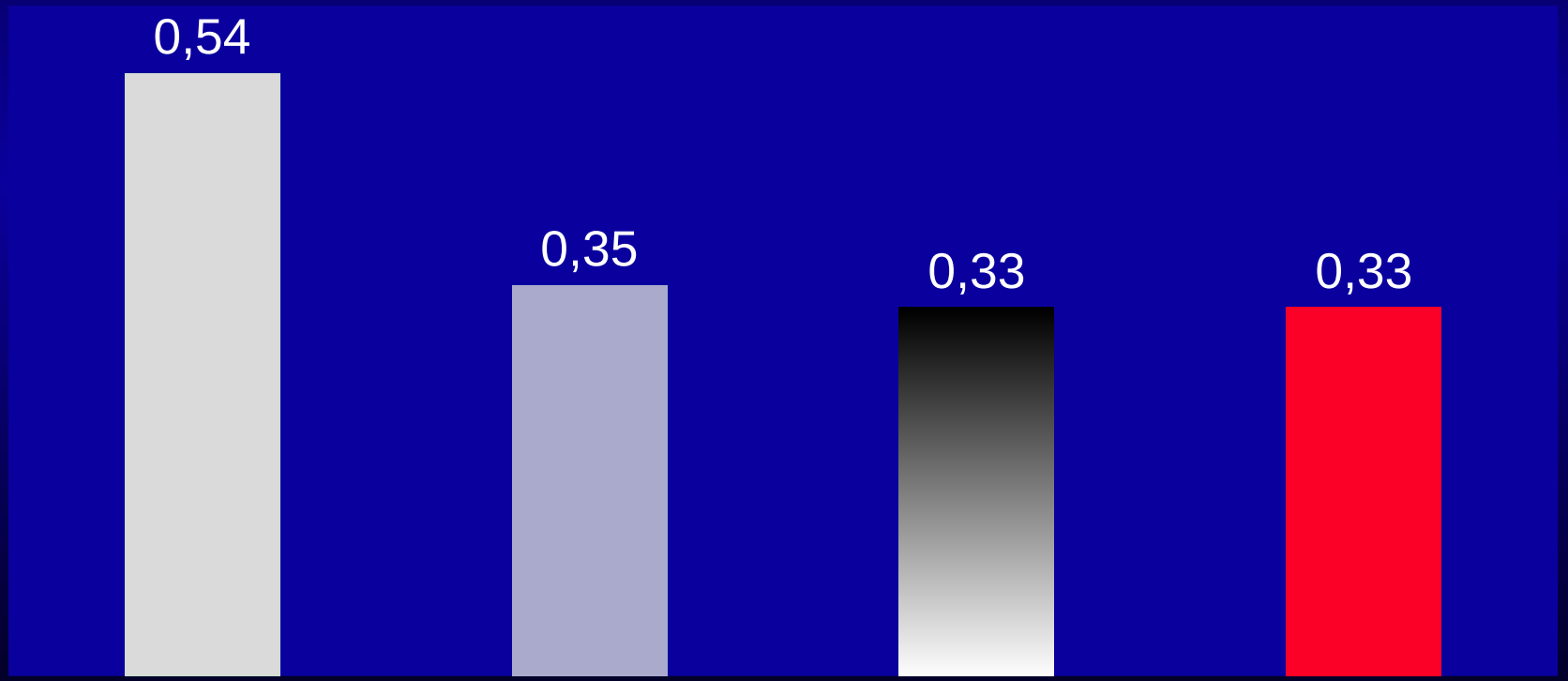
First Generation Protease inhibitors
Telaprevir, Boceprevir

SVR 12 According to Fibrosis

P= NS



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First Generation Protease inhibitors
Telaprevir, Boceprevir
Hematological Safety

	BOCEPREVIR (n=35)	TELAPREVIR (n=44)	*p*
Anemia (Hb<10g/dL)	95%	96%	ns
Anemia (Hb<8g/dL)	63%	45%	ns
RBV dose reduction + EPO use	**94%**		**ns**
Red blood cell transfusion	**49%**		**ns**
Neutropenia (NC<1G/L)	73%	45%	0.011
Thrombopenia (Plat<50G/L)	48%	28%	ns

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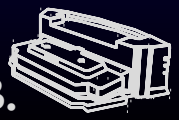
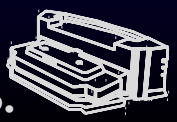


The Advent of Second Generation DAAs After Liver Transplantation



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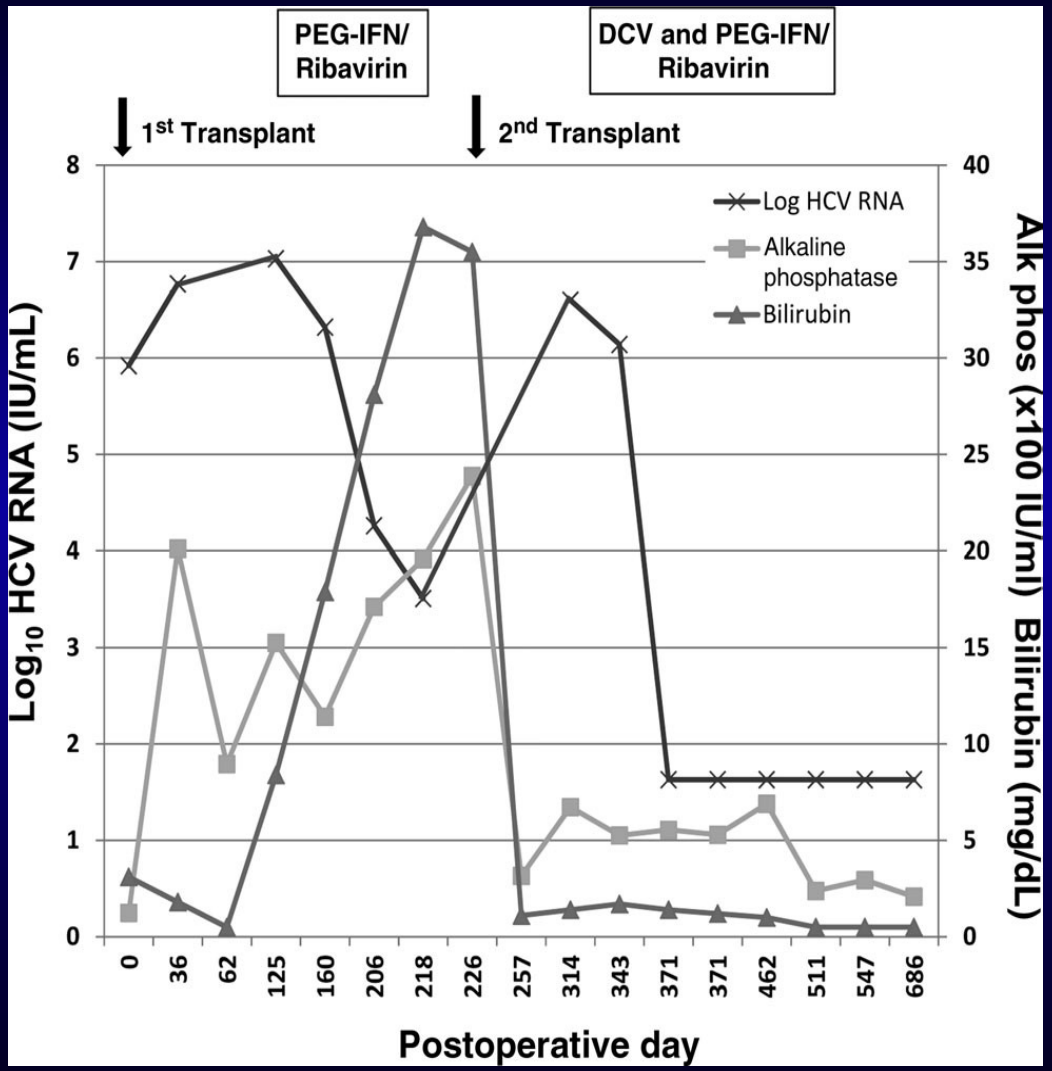
PegIFN +RBV+Daclatasvir for FCH after LT



Fontana Liver Transpant 2012

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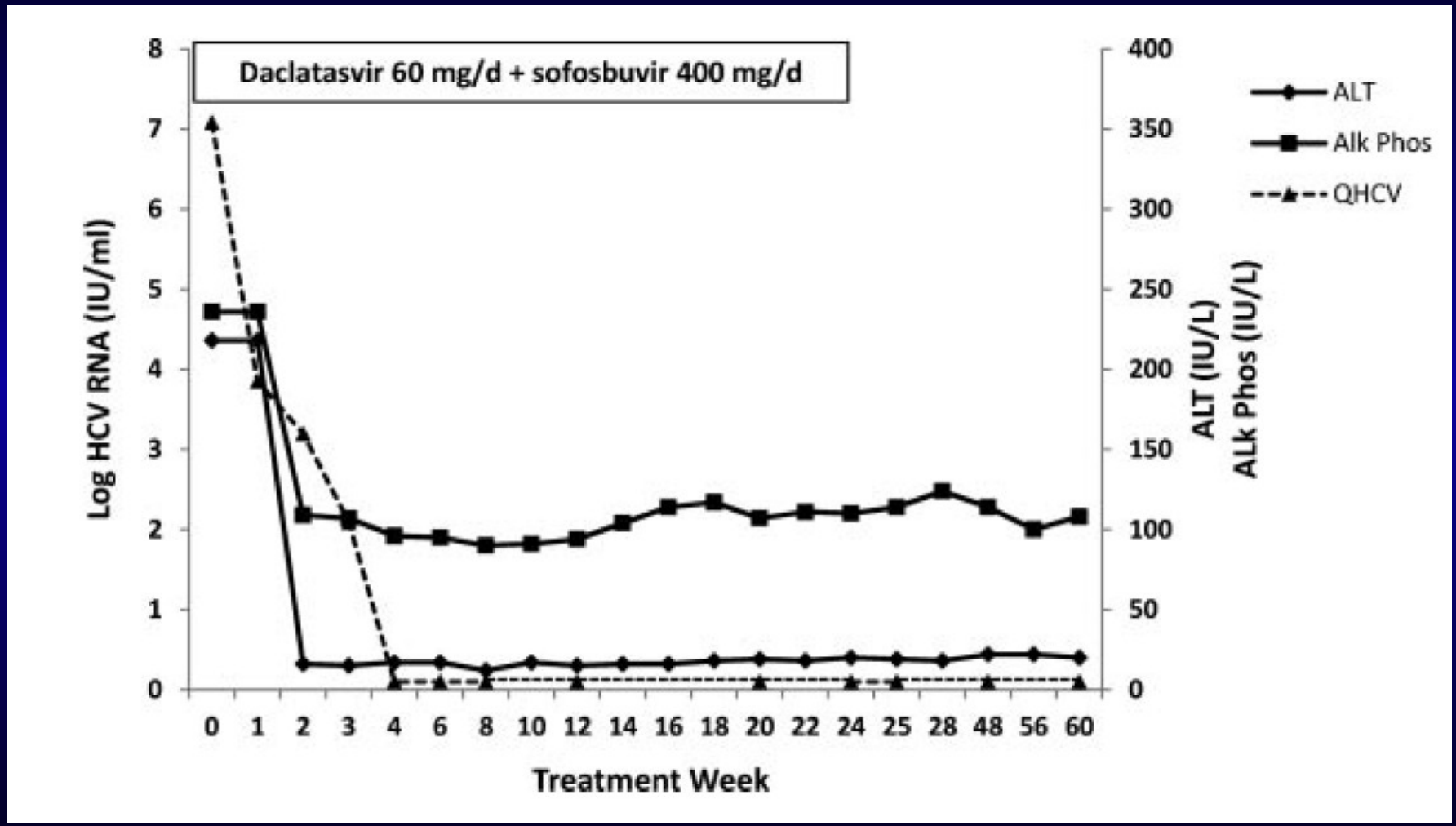
Sofosbuvir+Daclatasvir for FCH after LT



Fontana Am J Transplant 2013

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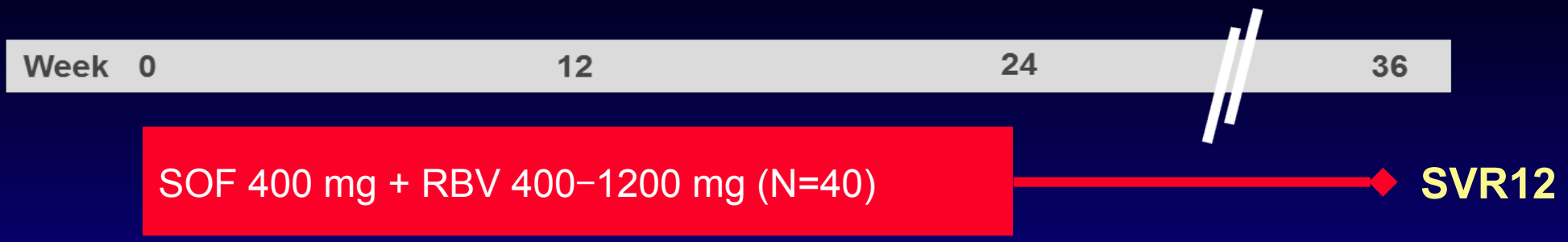
Sofosbuvir + Ribavirin After Transplantation



- 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

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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)

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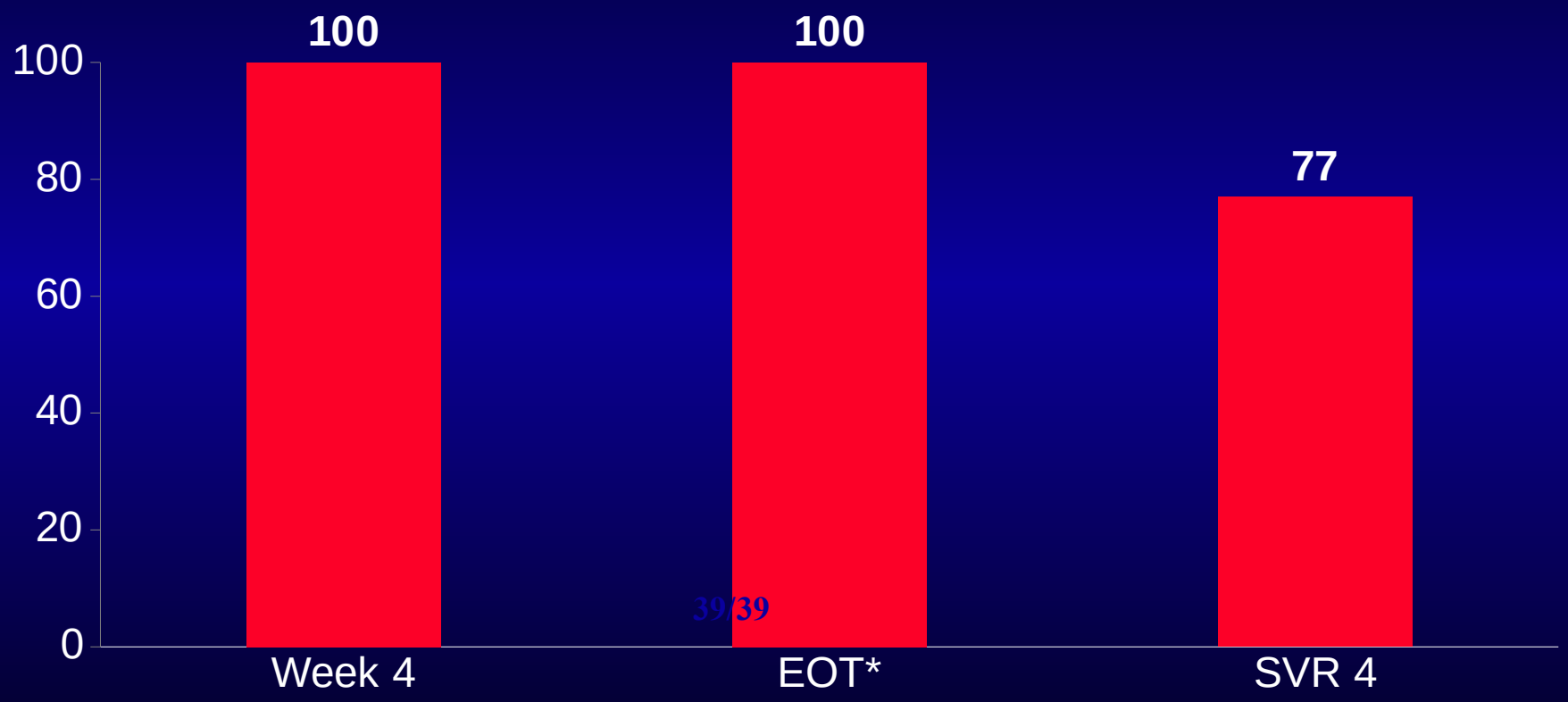
Sofosbuvir + Ribavirin After Transplantation



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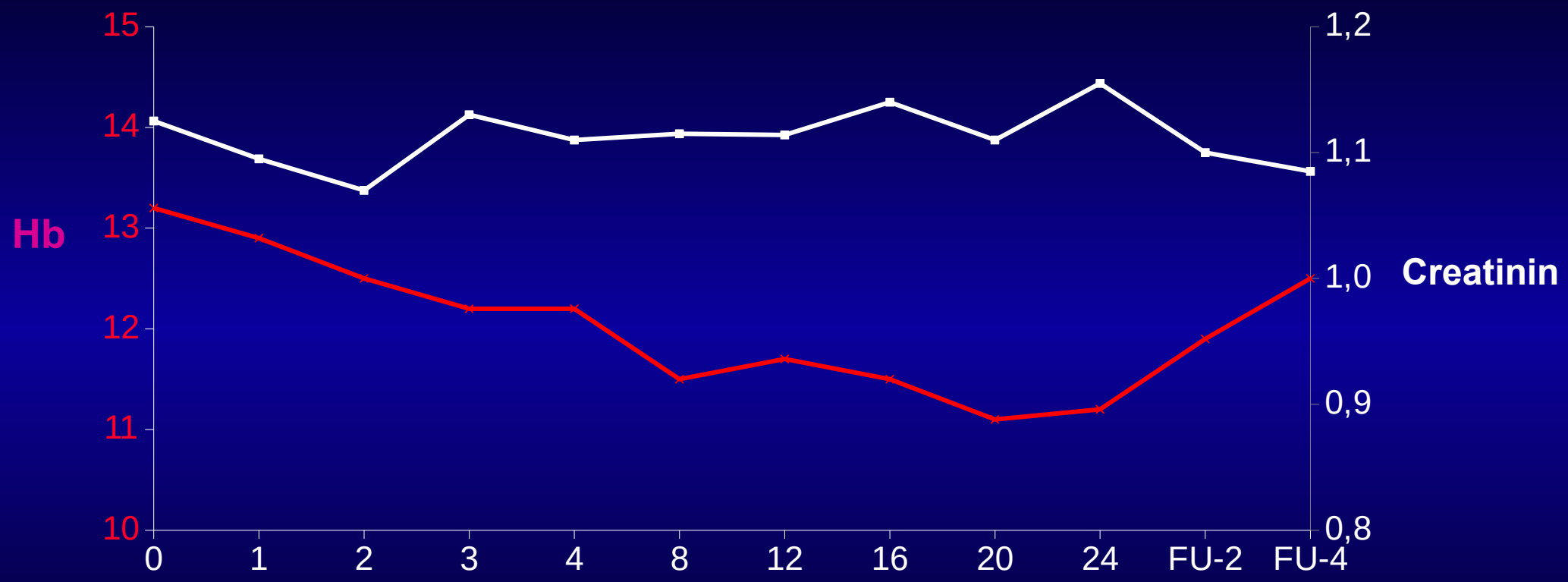
Sofosbuvir + Ribavirin After Transplantation Tolerance



20% Received EPO

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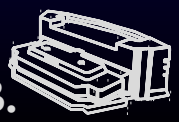
CONCLUSION

- **Before Liver Transplantation**
  - **Triple antiviral therapies with IFN in cirrhotics is diff cult**
  - **Treatment without IFN will be necessary**
  - **Strategies of on treatment virological response to be priorized**
  - **Questions:**
    - **Duration of treatment, Timing in relation to LT?**
    - **Virological resistance?**
    - **Improvement of liver function on DAAs?**
    - **Relapse and risk of liver failure?**



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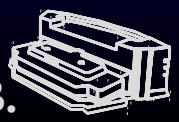
CONCLUSION

- **First results of triple therapies after LT are encouraging**
  - Increased virologic response
  - Drug-drug interactions manageable
  - However tolerance is a limiting factor
- **Treatment without IFN awaited but IFN might remain necessary in some patients:**
  - Transplant HCV infected patients diff cult to treat
- **Keep in mind the objective:**
  - Not to treat without IFN
  - **The eradication of HCV after Transplantation**



C.H.B.

Focus

Scott L. Friedman*

"There are decades where nothing happens; and there are weeks where decades happen" – Vladimir Ilyich Lenin.

SL Friedman Journal of Hepatology 2014 In press

Aknowledgements

AFEF prospective group
of liver transplantation

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- V Leroy
- SN Si-Ahmed

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