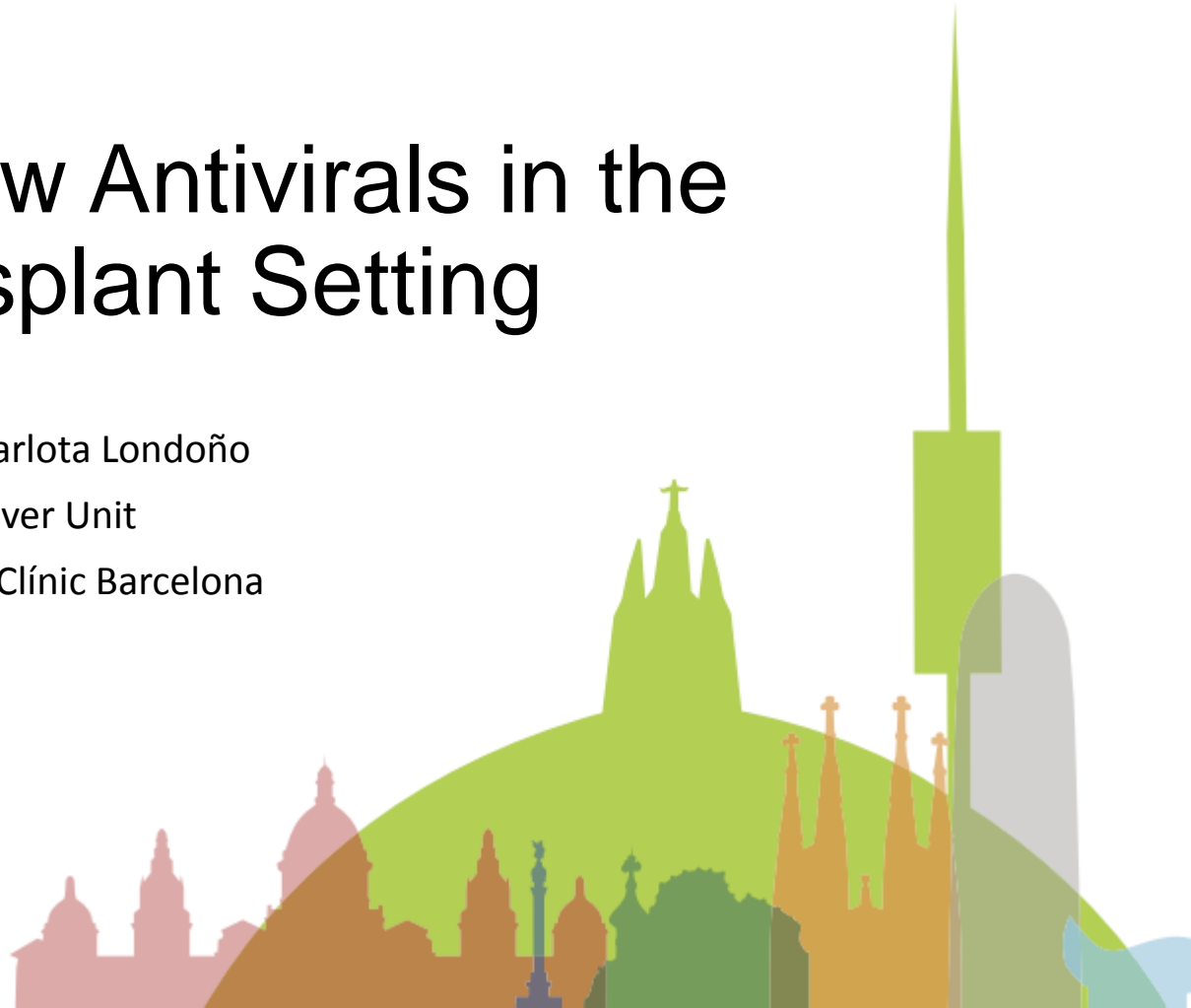


Hepatitis C: New Antivirals in the Liver Transplant Setting

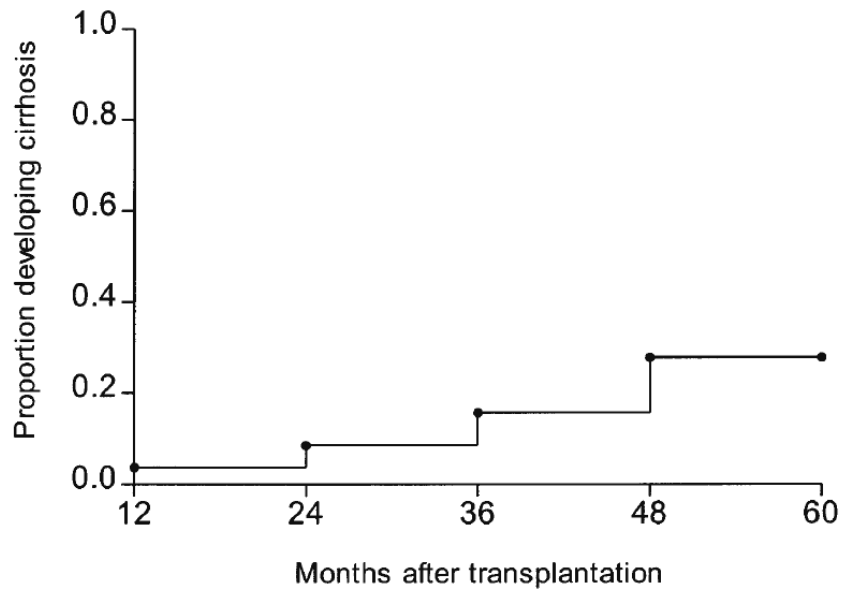
Maria Carlota Londoño

Liver Unit

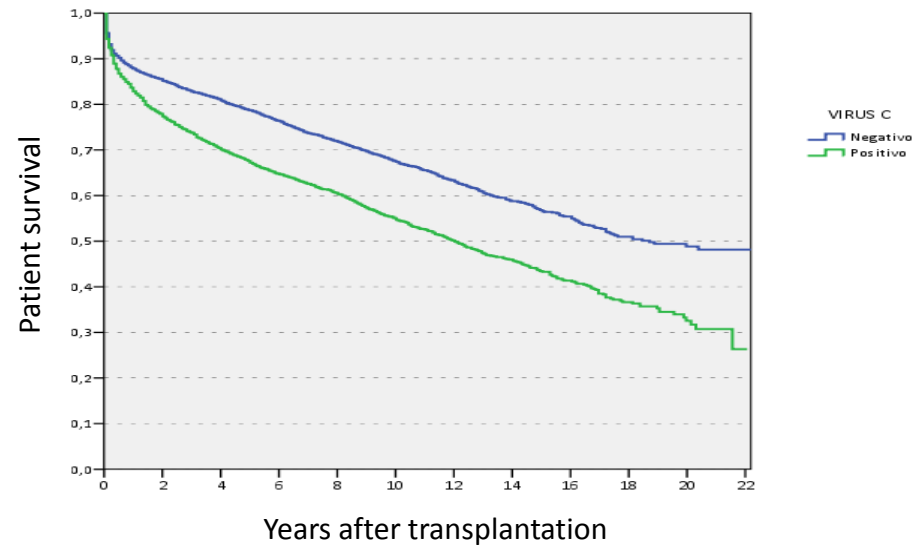
Hospital Clínic Barcelona



Hepatitis C and Liver Transplantation



Prieto et al, Hepatology 1999



Hepatitis C and Liver Transplantation

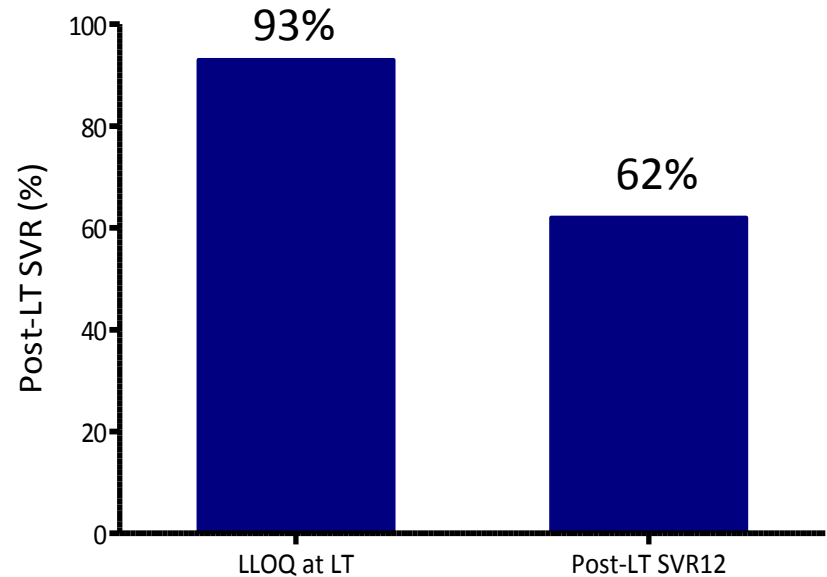
- Treatment on the waiting list
 - Prevents infection of the new liver
 - Might improve liver function

- Treatment of the recurrence
 - In patients with severe recurrence (F \geq 2, HVPG \geq 6mmHg, severe inflammation or FCH)

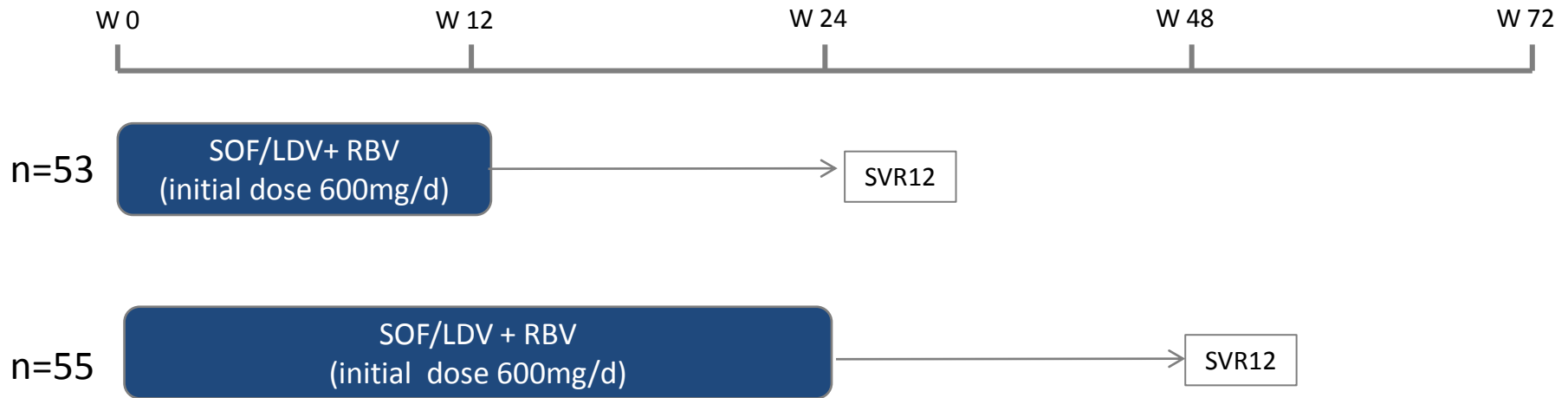
Treatment on the Waiting List

SOF+RBV

- Child A with HCC (Milan)
- 61 patients
- 44 transplanted
- Viral recurrence in 10 patients
- SAE in 18%
- More the 30 days being TND predicts post-LT SVR



Treatment on the Waiting List

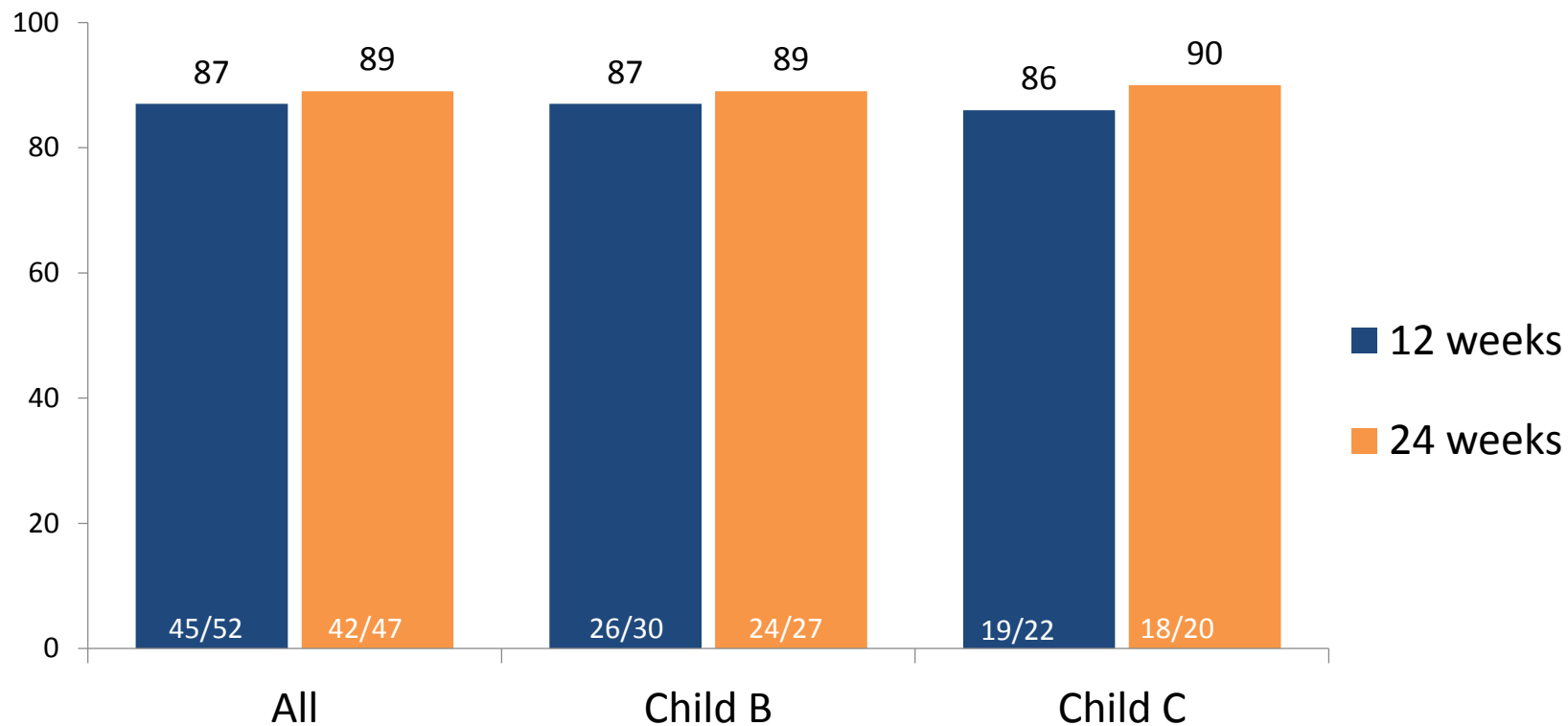


Randomized trial (1:1), Genotype 1 or 4, naïve or treatment experienced
Decompensated cirrhosis → Child B (7-9) or C (10-12)

Treatment on the Waiting List

Característica	Child-Pugh B		Child-Pugh C	
	12 semanas n=30	24 semanas n=29	12 semanas n=23	24 semanas n=26
Male gender (n,%)	22 (73)	18 (62)	14 (61)	18 (69)
Age (years)	60 (28-69)	58 (35-69)	58 (41-71)	59 (48-68)
Genotype 1a/4 (n,%)	19 (63) / 1 (3)	22 (76) / 0	15 (65) / 2 (9)	18 (69) / 0
Previous treatment (n,%)	22 (73)	19 (66)	11 (48)	18 (69)
MELD				
<10	6 (20)	8 (28)	0	0
10-15	21 (70)	16 (55)	13 (50)	13 (50)
16-20	3 (10)	5 (17)	12 (46)	12 (46)
21-25	0	0	1 (4)	1 (4)
Ascites / HE (n,%)	17 (57) / 20 (67)	17 (59) / 16 (55)	22 (96) / 21 (91)	25 (96) / 23 (88)
Bilrrubin (mg/dL)	2 (0,6-5,5)	1,4 (0,8-4,5)	2,9 (1,2-14,5)	3,8 (1,1-5,7)
INR	1,3 (1-1,59)	1,3 (1-2,6)	1,4 (1,2-1,9)	1,4 (1,1-2,2)
Albumin (g/dL)	2,9 (2,1-3,7)	3 (2,2-3,4)	2,6 (1,6-3,5)	2,6 (2-3,3)
Platelets	88 (36-212)	73 (30-154)	81 (39-177)	71 (32-179)

Treatment on the Waiting List



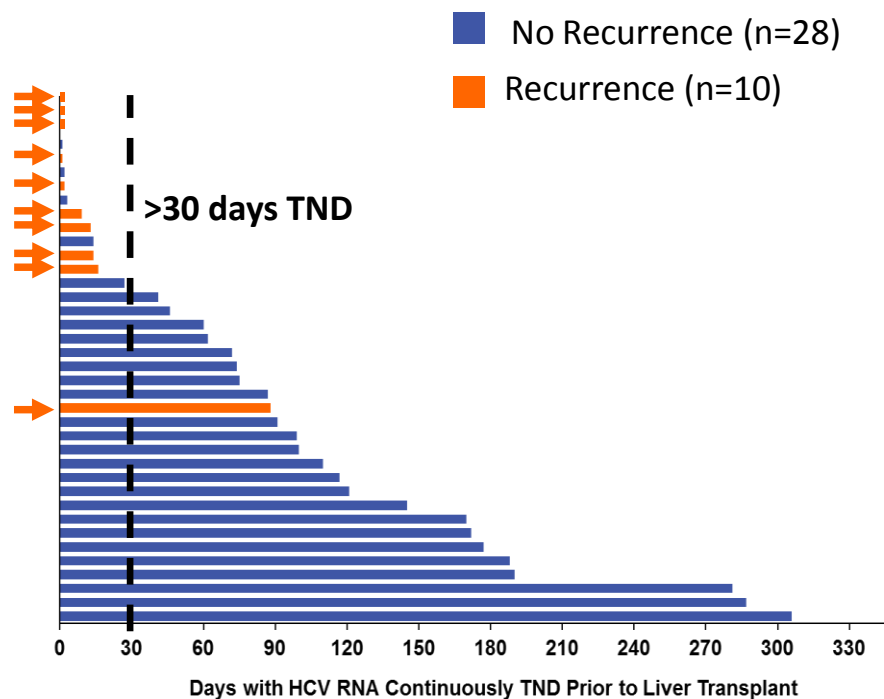
* 6 patients received a liver trasplant during the study and were expluded from the analysis of efficacy

Treatment on the Waiting List: Unsolved Issues

- Which is the right time to start antiviral therapy?
- Do we have to treat all patients? Is there a limit to decide not to treat the patients before liver transplantation?
- Is it safe to treat all patients before liver transplantation?
- Viral eradication and improvement in liver function will affect the access to transplantation?

Treatment on the Waiting List: Unsolved Issues

- Which is the right time to start antiviral therapy?



Treatment on the Waiting List: Unsolved Issues

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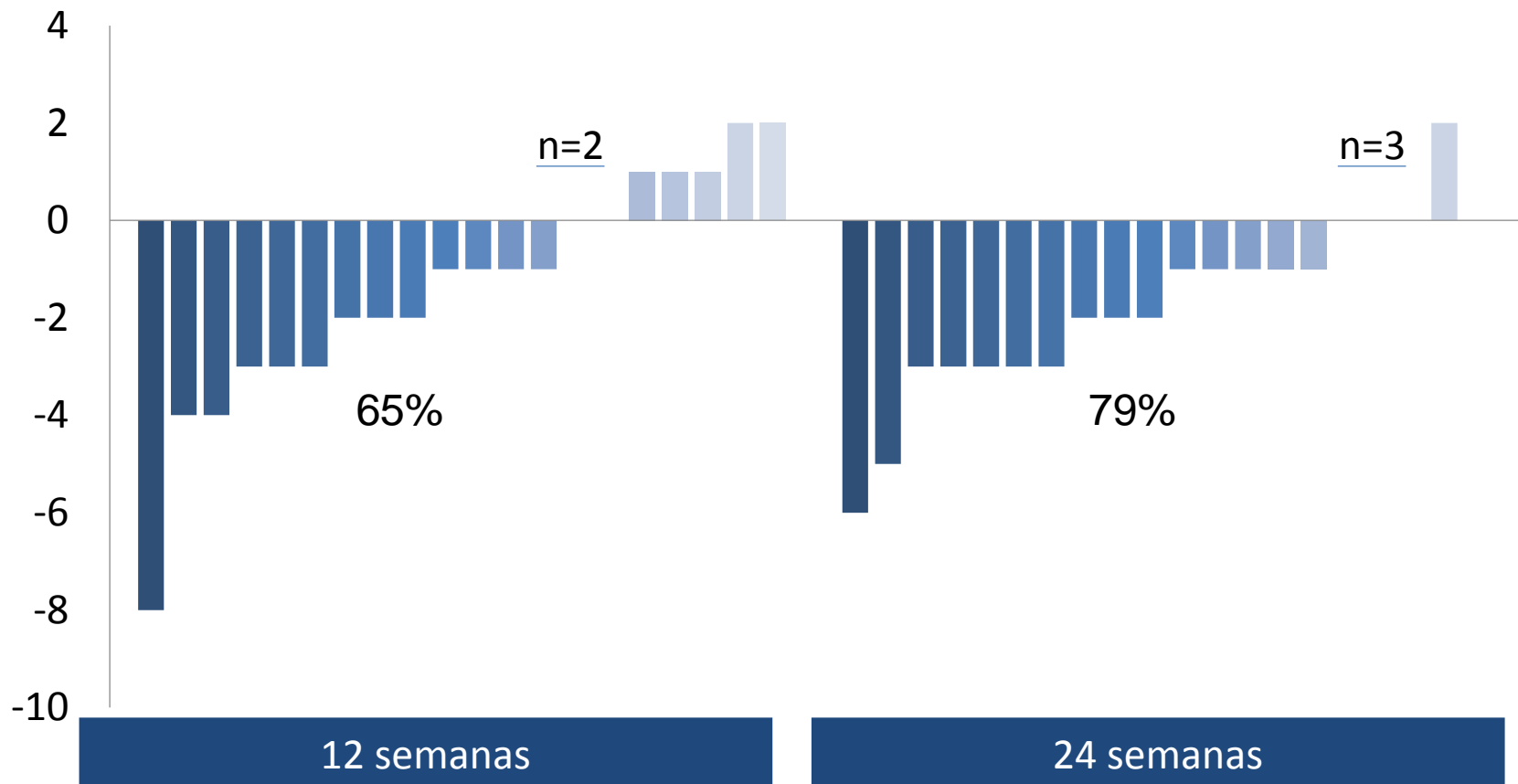
Treatment on the Waiting List: Unsolved Issues

- Is it safe to treat all patients before liver transplantation?

	METABOLISM	CIRRHOSIS			RENAL FAILURE
		CTP-A	CTP-B	CTP-C	
Sofosbuvir	Kidney	Yes	Yes	Yes	No if CrCl < 30 mL/min
Simeprevir	Liver	Yes	Yes	No	Yes
Paritaprevir/r	Liver	Yes	Yes	No	Yes
Ledipasvir	Liver	Yes	Yes	Yes	Yes
Daclatasvir	Liver	Yes	Yes	Yes	Yes

Treatment on the Waiting List: Unsolved Issues

- Viral eradication and improvement in liver function will affect the access to transplantation?



Hepatitis C and Liver Transplantation

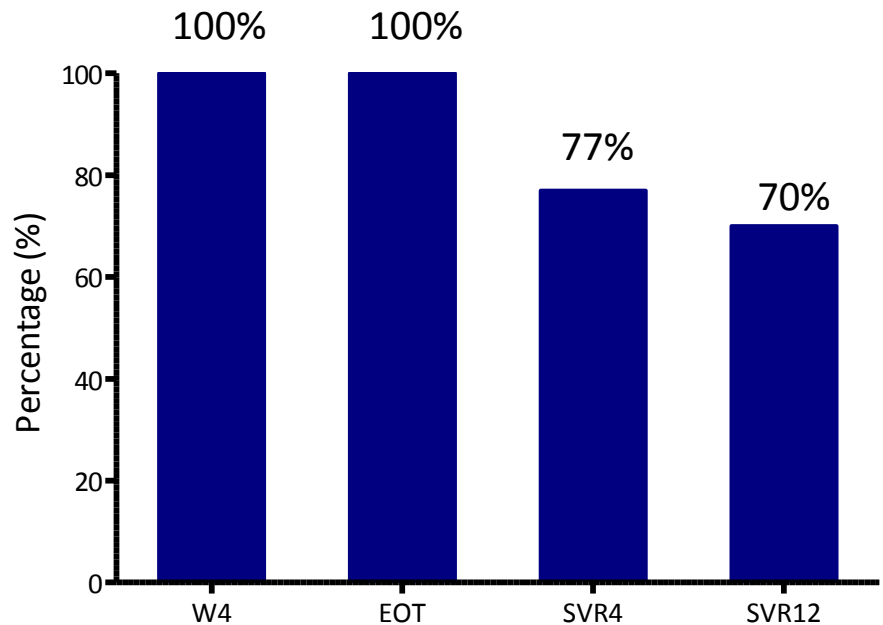
- Treatment on the waiting list
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After Liver Transplantation

SOF+RBV

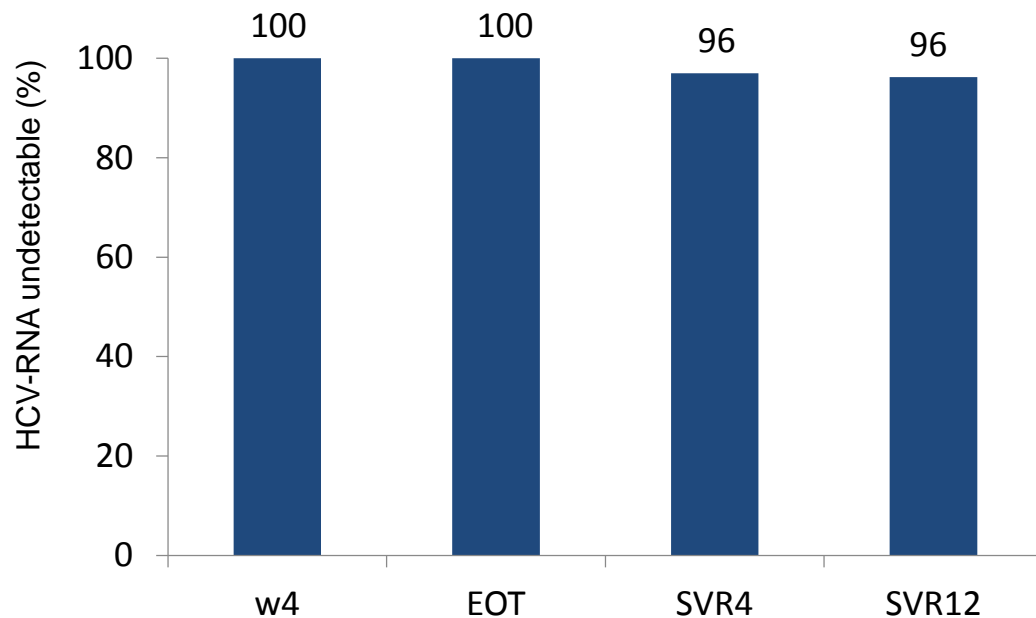
- 40 LT recipients (>6mo)
- 33 were G1
- 16 cirrhotics
- DC due to AE =2
- Relapse 9 patients



After Liver Transplantation

Ombitasvir/Paritaprevir/r + Dasabuvir + Ribavirin

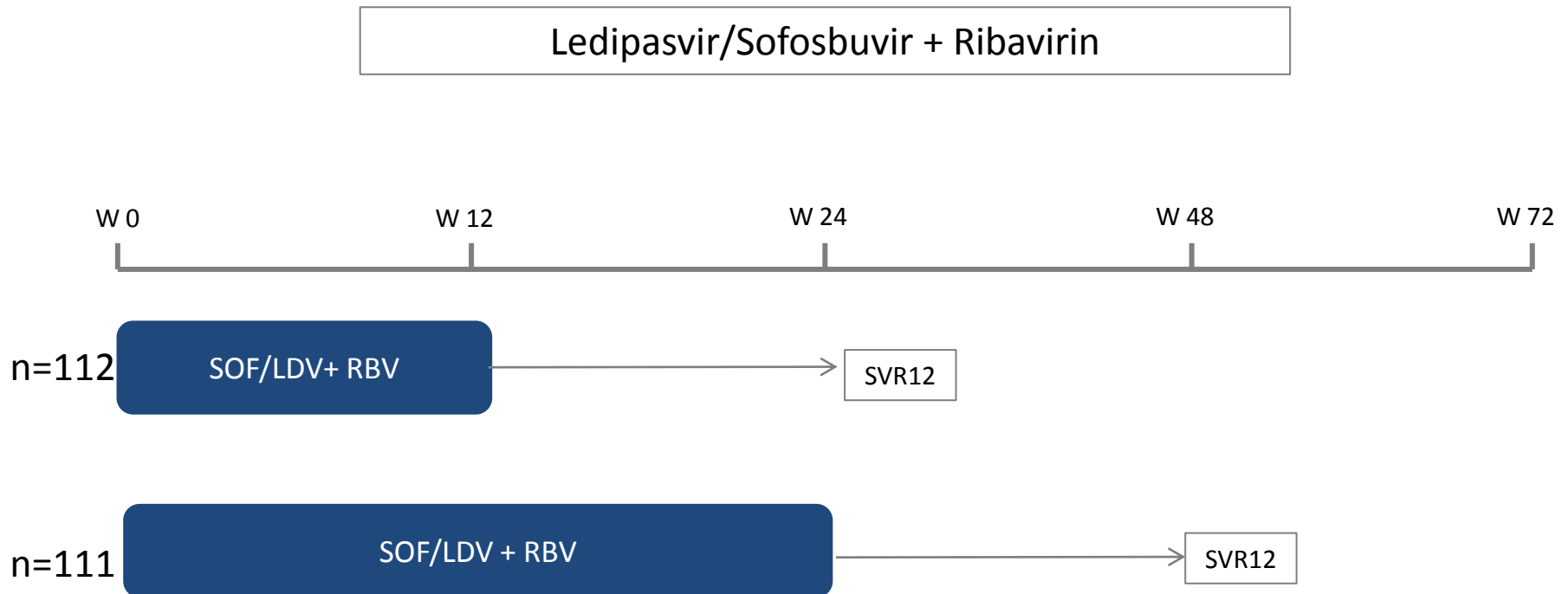
- Mild-Moderate fibrosis (F0-F2) → n=34
- G1a → 85%



Anemia	17%
Rejection	0
Renal Impairment	0
Early Discontinuation	3%
SAEs	6%
Deaths	0

- CNI adjustment (Tac 0.5mg/w and CyA 1/5 of previous dose)

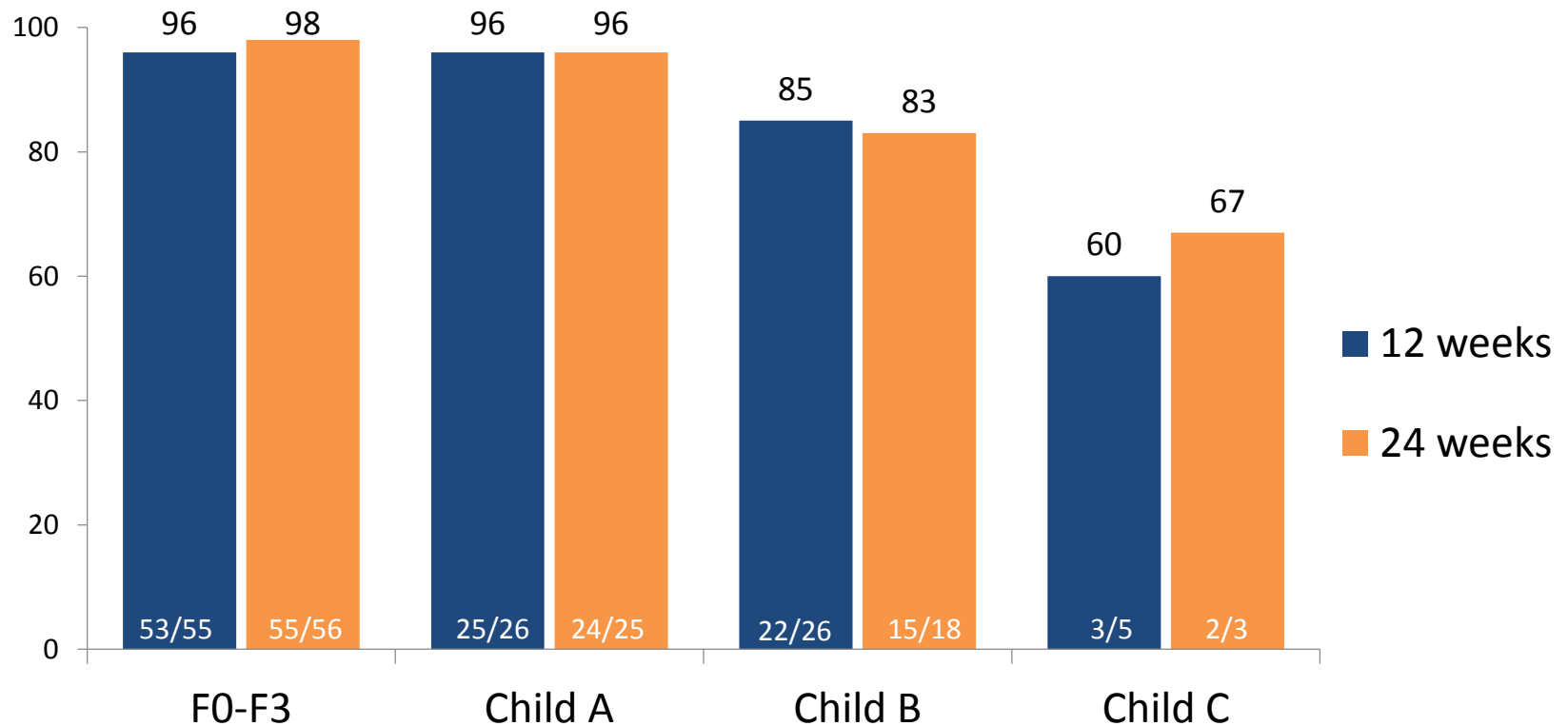
After Liver Transplantation



Randomized trial (1:1), Genotype 1 or 4, naïve or treatment experienced
F0-F3, Child A, B, C

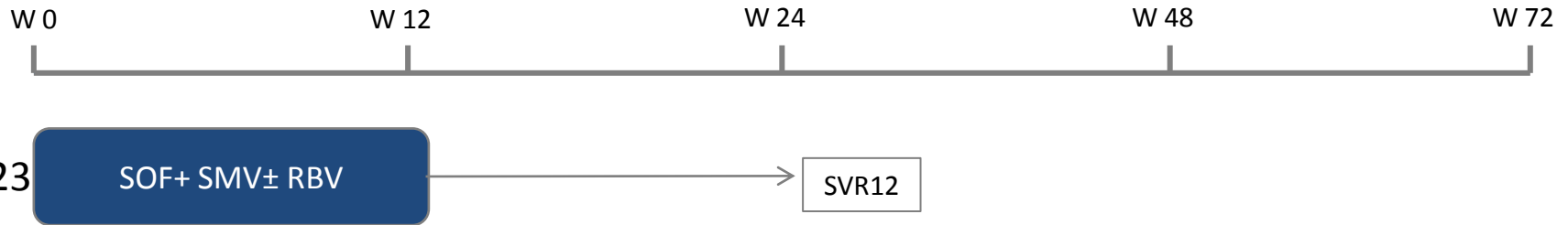
After Liver Transplantation

Ledipasvir/Sofosbuvir + Ribavirin



After Liver Transplantation

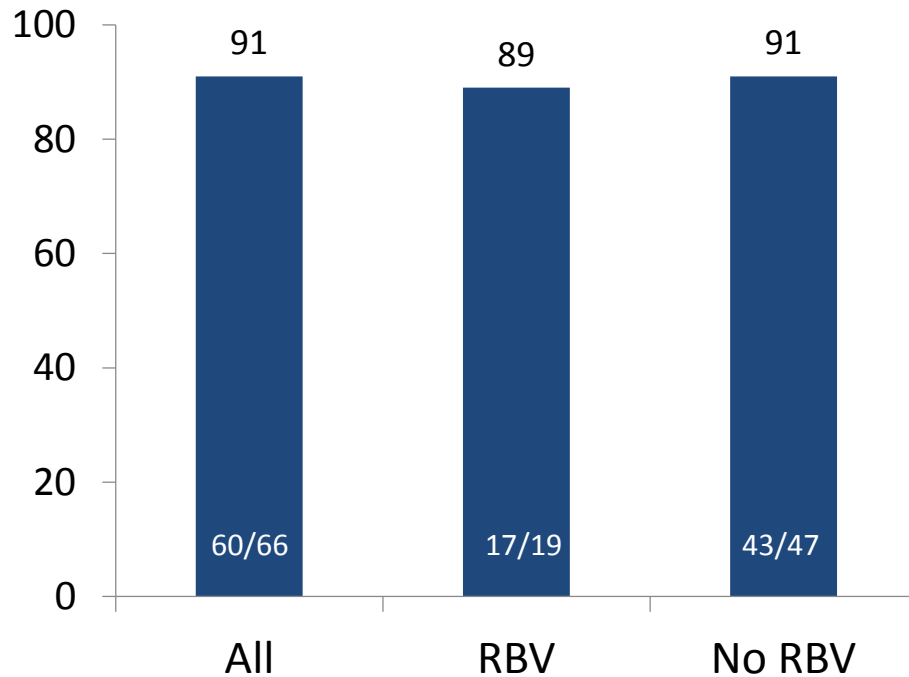
Sofosbuvir+ Simeprevir ± Ribavirin



G1 (G1a 62%), F3-F4 30%, Cholestatic recurrence 11%, Failed PR 69%, Failed PR+PI 12%

After Liver Transplantation

Sofosbuvir+ Simeprevir + Ribavirin



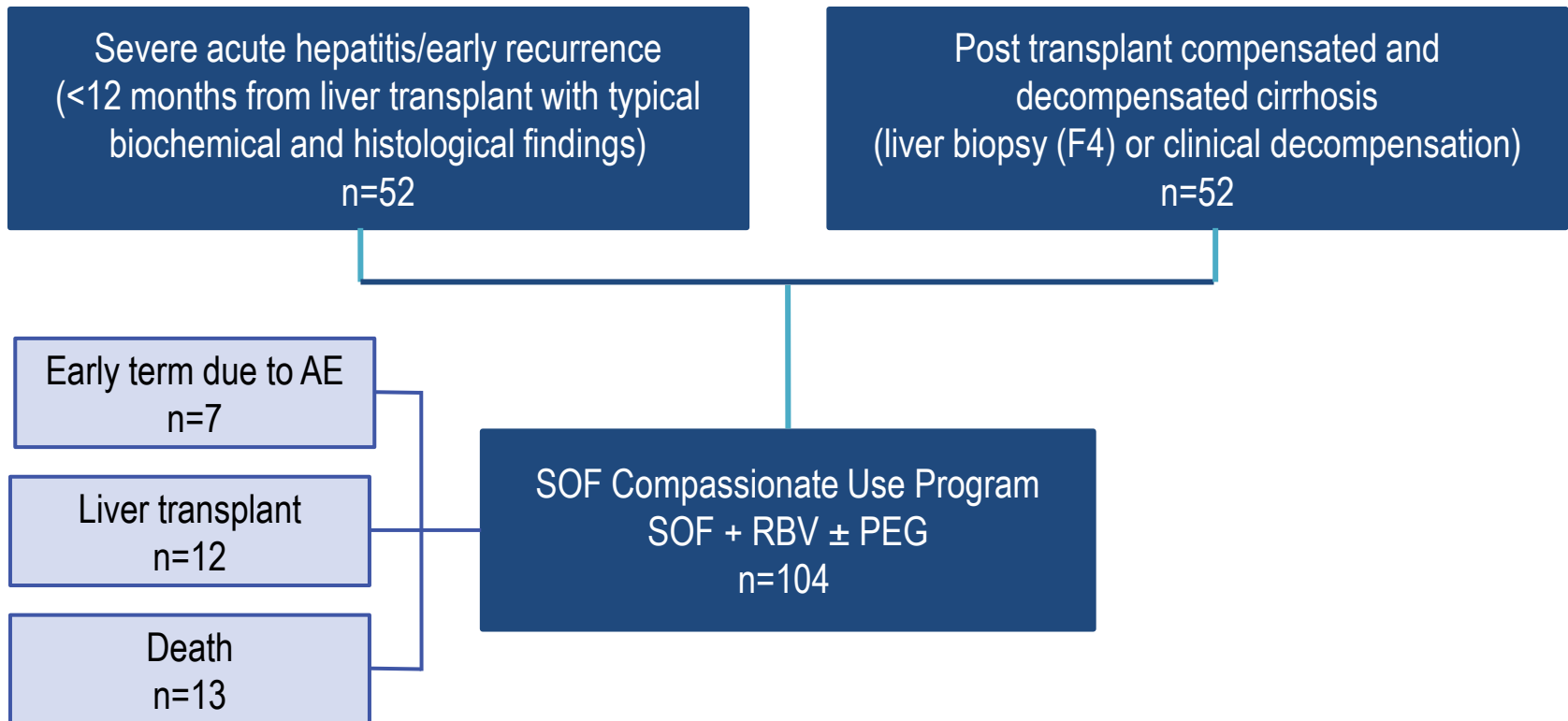
Anemia in RBV group 42% vs.
2% non RBV group

Treatment After Liver Transplant: Unsolved Issues

- Which is the right time to start antiviral therapy? Early? When fibrosis is established?
- Is there a point where we might be able to eradicate HCV but not to revert liver cirrhosis (liver function, portal hypertension)?
- Which one is the best regimen? Drug-drug interactions?

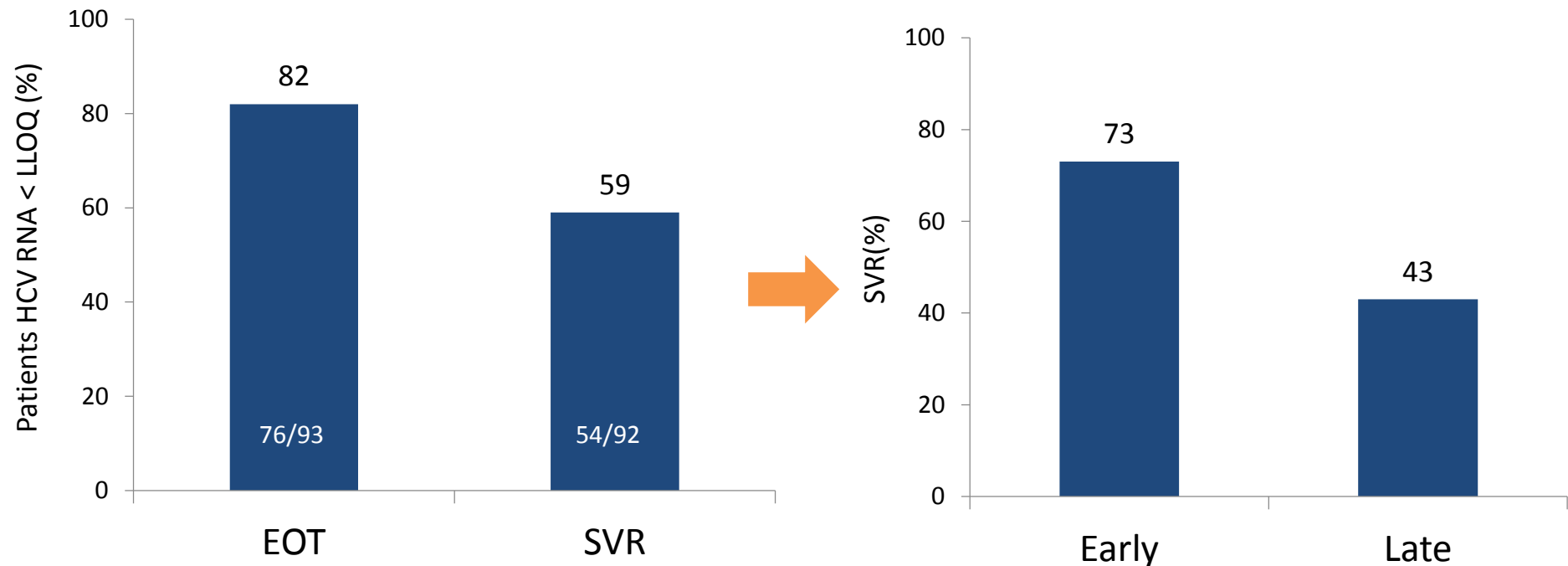
Treatment After Liver Transplant: Unsolved Issues

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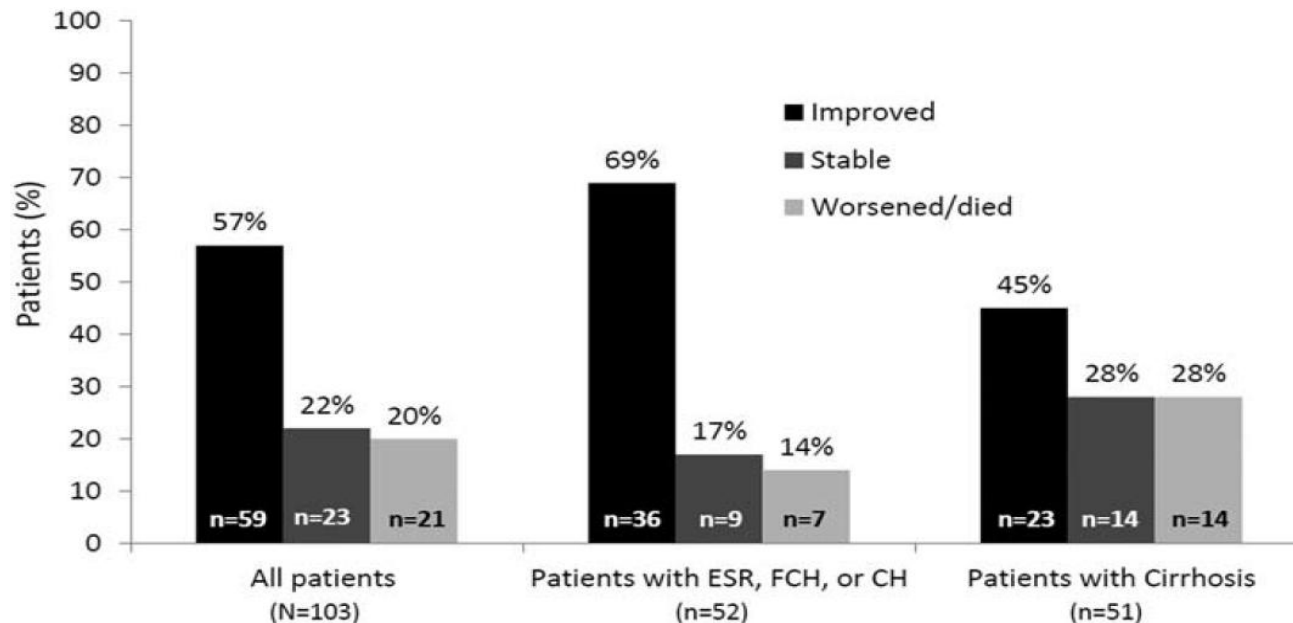
Treatment After Liver Transplant: Unsolved Issues

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Treatment After Liver Transplant: Unsolved Issues

- Is there a point where we might be able to eradicate HCV but not to revert liver cirrhosis (liver function, portal hypertension)?



* Significant decrease in hepatic encephalopathy, improvement or disappearance of ascites, or improvement in liver-related laboratory values.

Treatment After Liver Transplant: Unsolved Issues

- Which one is the best regimen? Drug-drug interactions?

	Cyclosporine		Tacrolimus	
	Healthy volunteers	Dose adjustment	Healthy volunteers	Dose adjustment
Sofosbuvir	No change	Not necessary	No change	Not necessary
Simeprevir	↑ SMV 19%	Under investigation	↓17%	Not necessary
Daclatasvir	No change	Not necessary	No change	Not necessary
Ledipasvir	No change	Not necessary	No change	Not necessary
Paritaprevir/r	↑ 5.8 fold	↓ 5 fold	↑ 58 fold	↓ 100 fold

Conclusions

- Antiviral therapy with an interferon-free regimen is effective and safe in the liver transplant setting.
- Viral eradication should be attempted before liver transplantation in order to prevent the infection of the new liver (depending on status of the patient and the prioritization system).
- After liver transplantation, antiviral therapy administered in patients with mild fibrosis stages achieves higher response rates as compared to patients with cirrhosis and decompensation.
- It is currently unknown if there is a no-return point in which antiviral therapy should not be administered.