4th OPTIMIZE WORKSHOP
USING DAAs IN PATIENTS WITH CIRRHOSIS AND LIVER RECIPIENTS

Treating HCV After Liver Transplantation: What are the Treatment Options?

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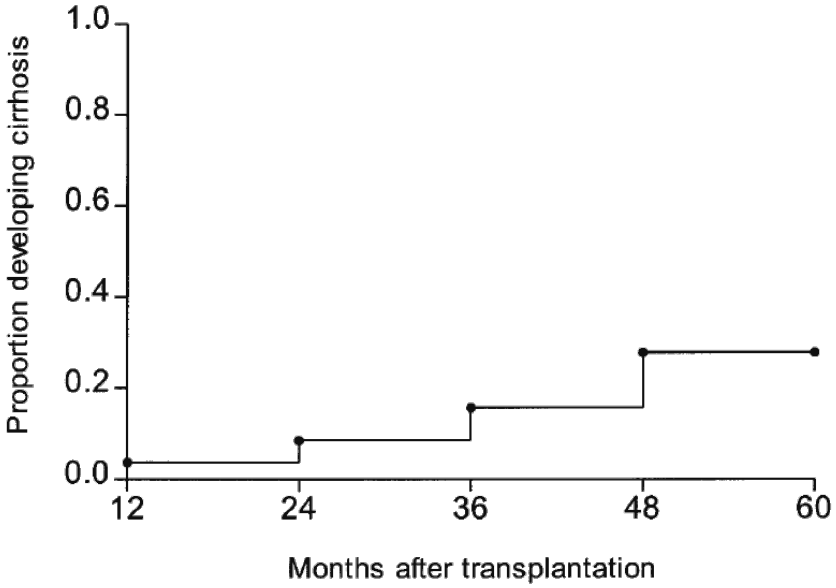
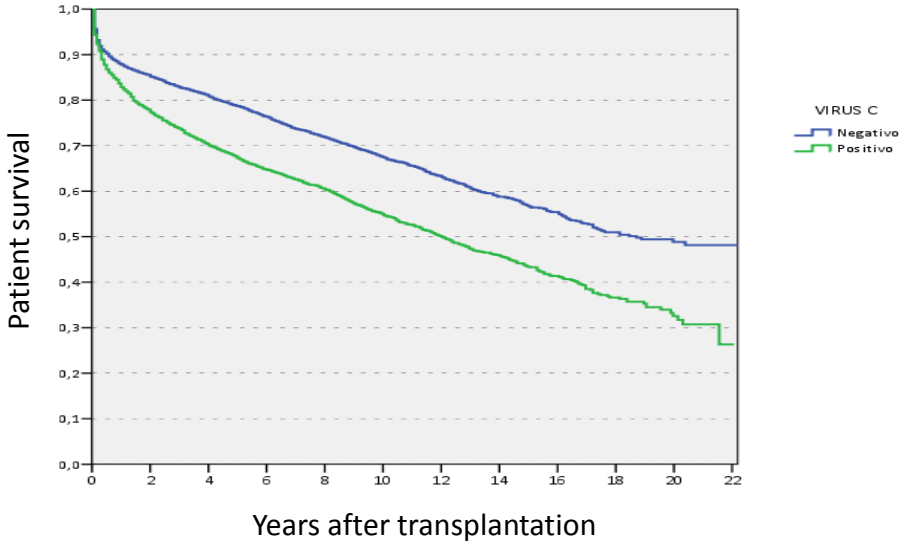
Agenda

- Antiviral options.
- Treatment of patients with mild hepatitis C recurrence or compensated cirrhosis.
- Treatment of patients with decompensated cirrhosis after liver transplant.
- Treatment of patients with fibrosing cholestatic hepatitis.
- Treatment of patients with DAA failures.

Hepatitis C and Liver Transplantation



Prieto et al, Hepatology 1999



Direct-Antiviral Agents

DAA	ADVANCED LIVER DISEASE		ESRD (GFR<30)	DDI	
	CP-B	CP-C		CsA	Tac
SOF	OK	OK	Not recommended	OK	OK
LDV/SOF	OK	OK	Not recommended	OK	OK
SMV	Caution	Not recommended	OK	Not recommended	OK
DCV	OK	OK	OK	OK	OK
3D/2D	Not recommended	Not recommended	OK	Dose adjustment	Dose adjustment
GZV/EBV	Caution	Not recommended	OK	Not recommended	OK
VEL/SOF	OK	OK	Not recommended	OK	OK

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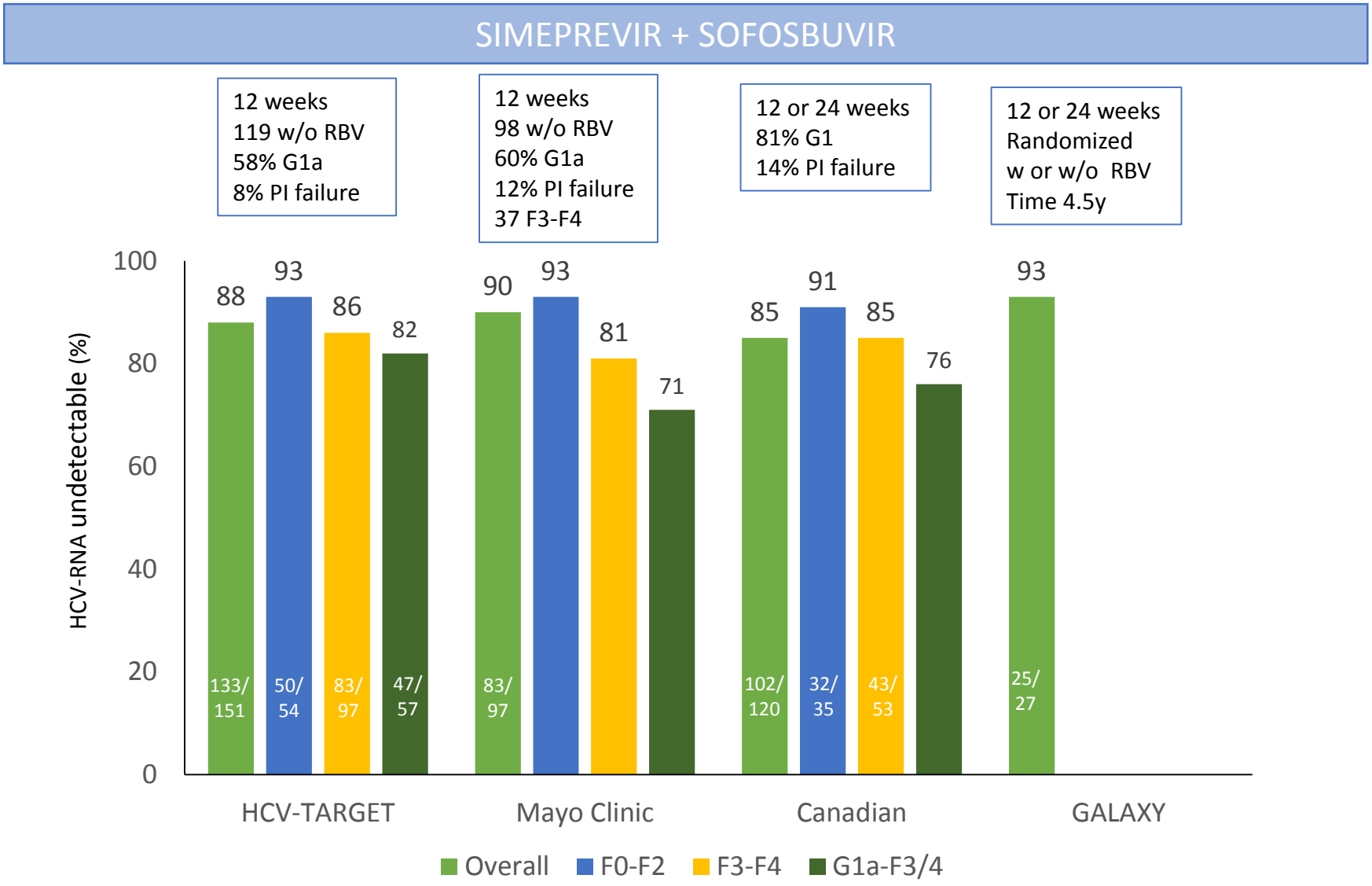
Mild Fibrosis-Compensated Cirrhosis

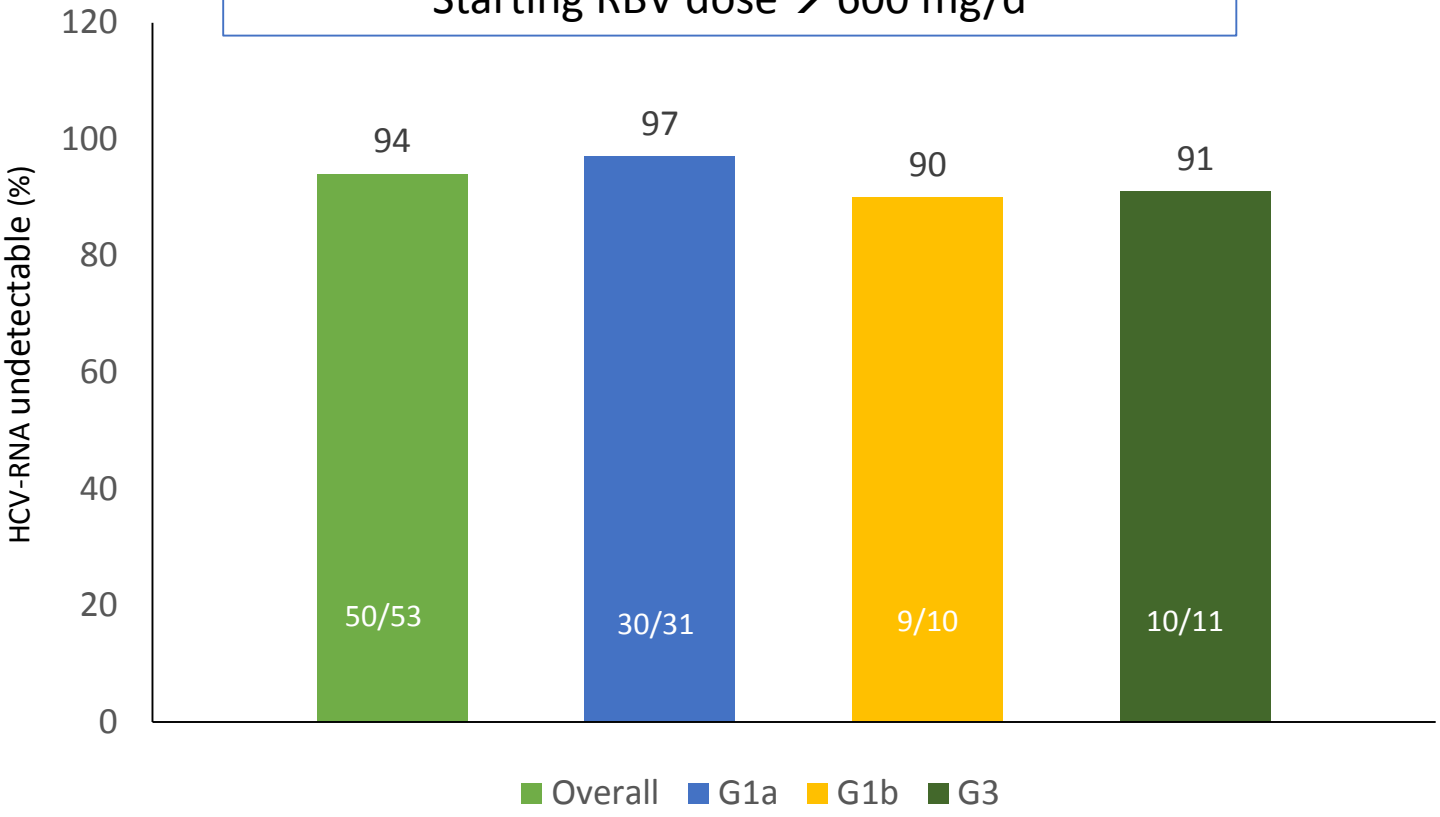


Brown et al. Liver Transpl 2016, Pungpapong et al. Hepatology 2015, Faisal et al Transplantation 2016, O'Leary et al, EASL 2016

Mild Fibrosis-Compensated Cirrhosis

ALLY-1: DACLATASVIR + SOFOSBUVIR

F0=6/ F1=10/ F2=7/ F3=13/ F4=16
Starting RBV dose→ 600 mg/d

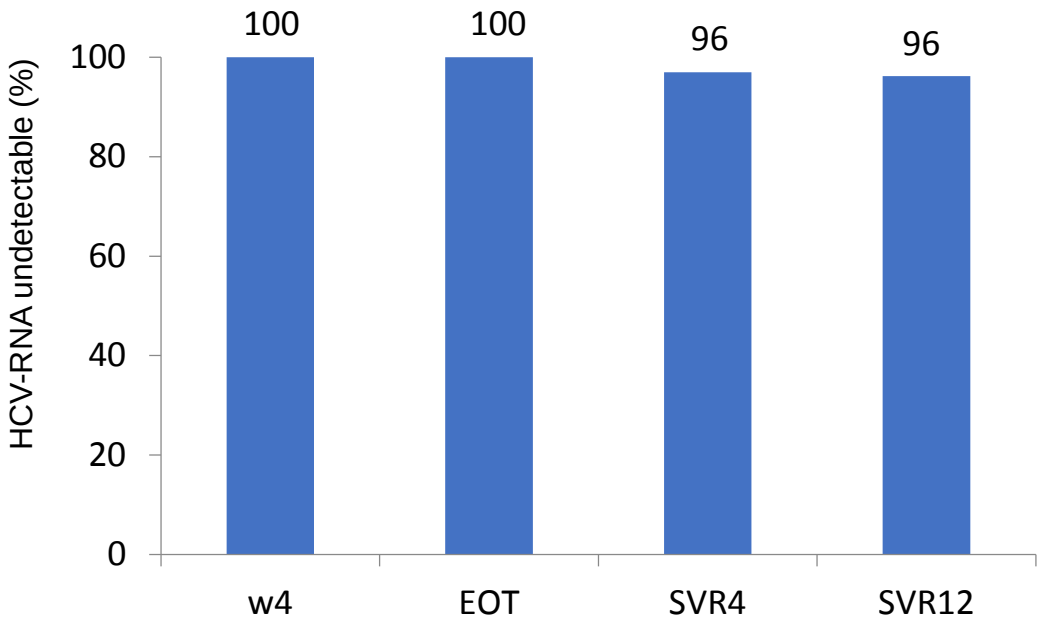


Poordad, Hepatology 2016

Mild Fibrosis-Compensated Cirrhosis

CORAL-1: OMBITASVIR + PARITAPREVIR/r + DASABUVIR + RIBAVIRIN

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



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

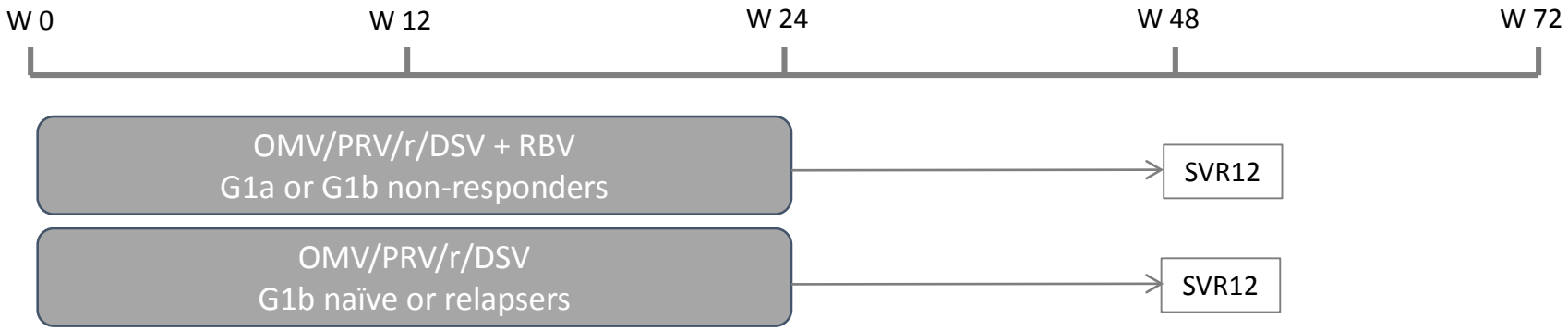
- CNI adjustment (Tac 0.5mg/w and CyA 1/5 of previous dose)

Kwo P, NEJM 2014

Mild Fibrosis-Compensated Cirrhosis

CORAL-1 (Cohort 2): OMBITASVIR + PARITAPREVIR/r + DASABUVIR ± RIBAVIRIN

- Mild-Moderate fibrosis (F0-F3)→ n=40



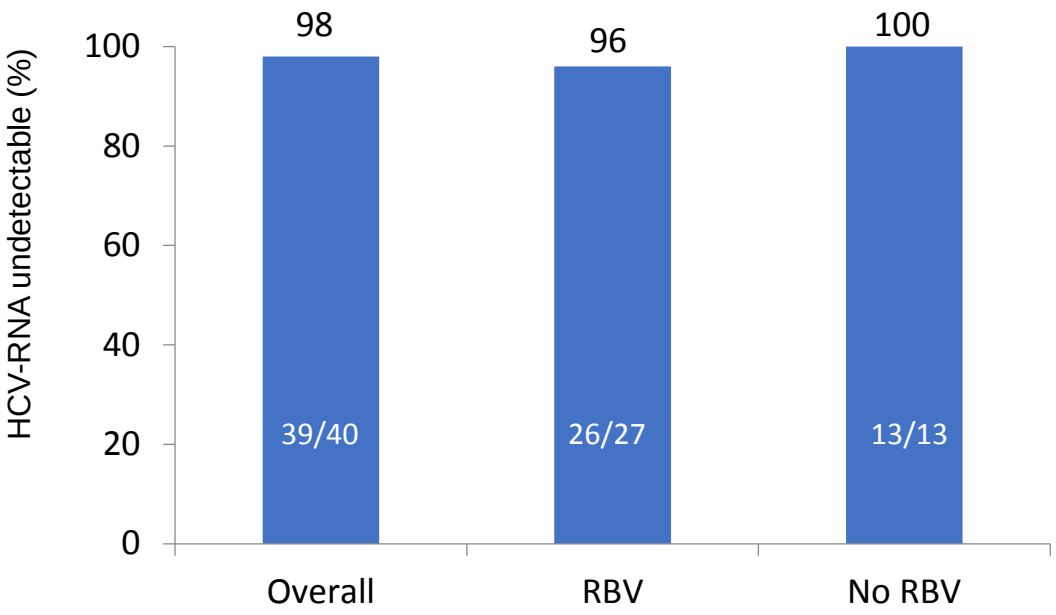
Variable	RBV (n=27)	No RBV (n=13)
Genotype 1a/1b	21 (78%)/6 (22%)	13 (100%)
Post-LT treatment Naïve Relapser Non-responder	 15 (56%) 0 12(44%)	 8 (62%) 5 (38%) 0
Fibrosis F0-1/F2/F3	16(62%)/ 9(35%) / 1(3%)	8/62%)/2 (15%)/3(23%)
Tac/CsA	21 (78%)/6 (22%)	5 (38%)/8 (62%)

Mantry P, AASLD 2015

Mild Fibrosis-Compensated Cirrhosis

CORAL-1 (Cohort 2): OMBITASVIR + PARITAPREVIR/r + DASABUVIR ± RIBAVIRIN

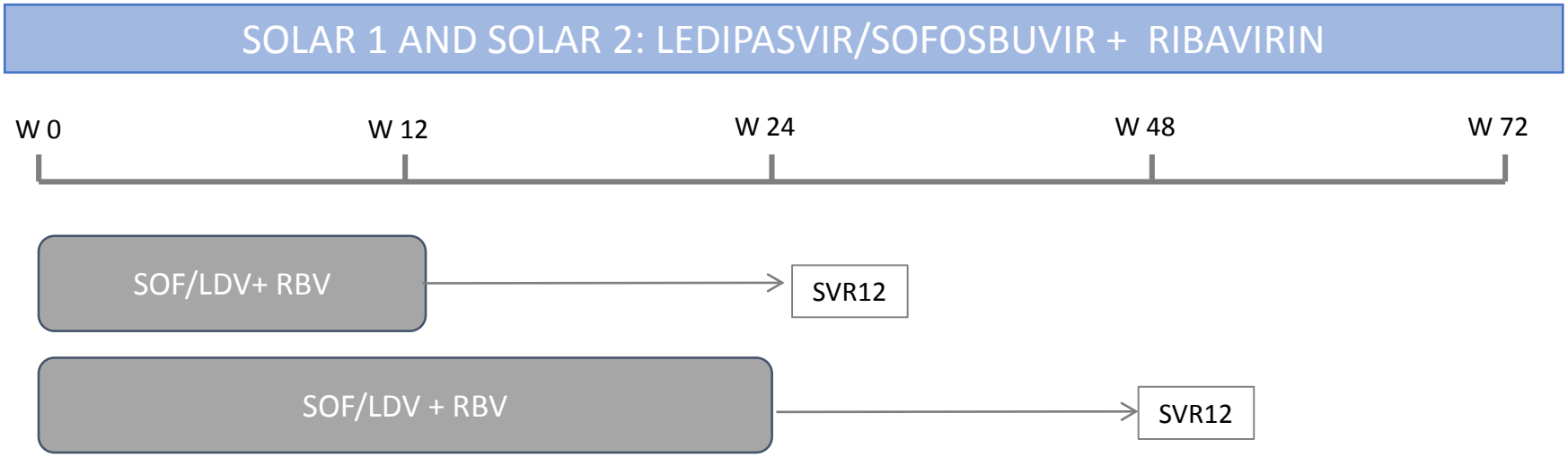
- Mild-Moderate fibrosis (F0-F3)→ n=40



Anemia	**30% of patients with RBV**
Rejection	1
Renal Impairement	0
Hyperbilirrubinemia	**1**
SAEs	**1**
Deaths	0

Mantry P, AASLD 2015

Mild Fibrosis-Compensated Cirrhosis



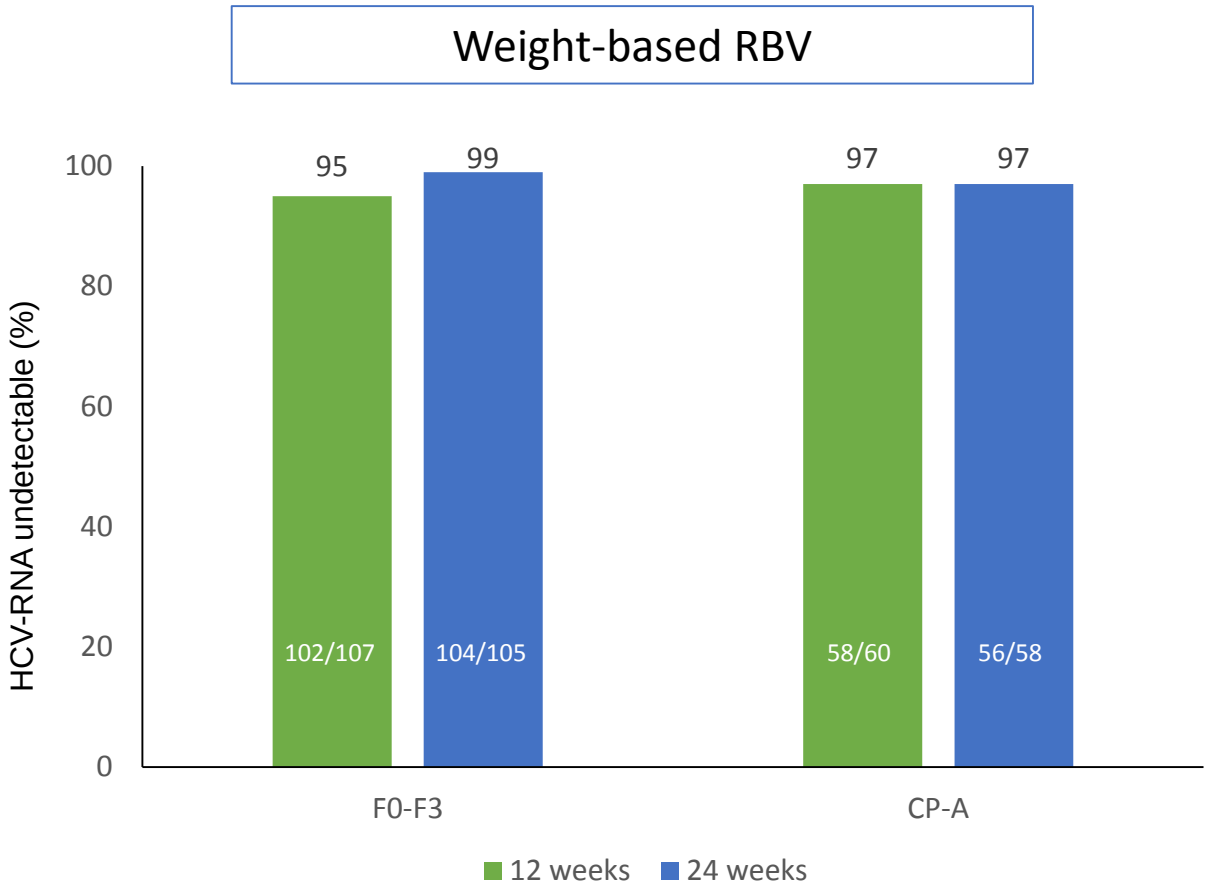
Genotype 1 or 4, F0-F3, CP-A, RBV adjusted by weight

Variable	F0-F3/CP-A (n=330)
Genotype 1a/1b	190 (60%)/111 (34%)
Genotype 4	22 (7%)
Previous treatment	270 (82%)
Cirrhosis	118 (36%)

Gane E. AASLD 2015, Charlon M. Gastroenterology 2015, Manns M. Lancet 2016

Mild Fibrosis-Compensated Cirrhosis

SOLAR 1 AND SOLAR 2: LEDIPASVIR/SOFOSBUVIR + RIBAVIRIN



Gane E. AASLD 2015, Charlon M. Gastroenterology 2015, Manns M. Lancet 2016

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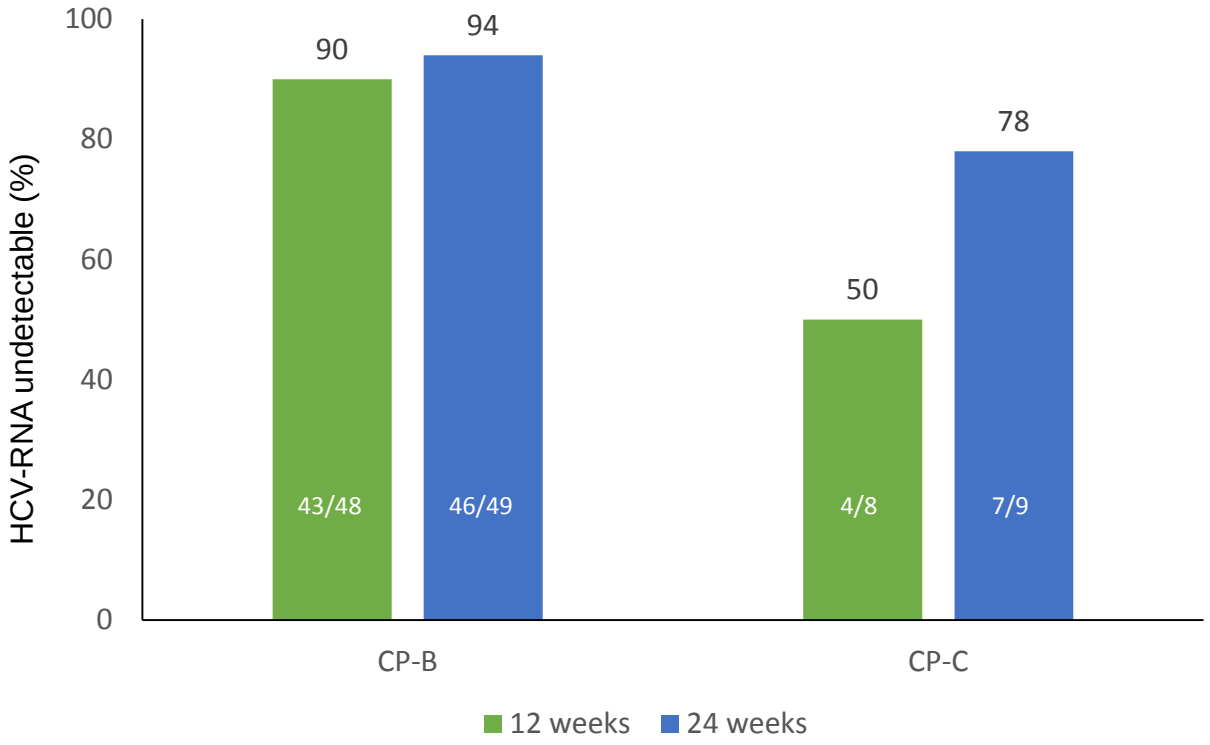
Decompensated Cirrhosis

SOLAR 1 AND SOLAR 2: LEDIPASVIR/SOFOSBUVIR + RIBAVIRIN

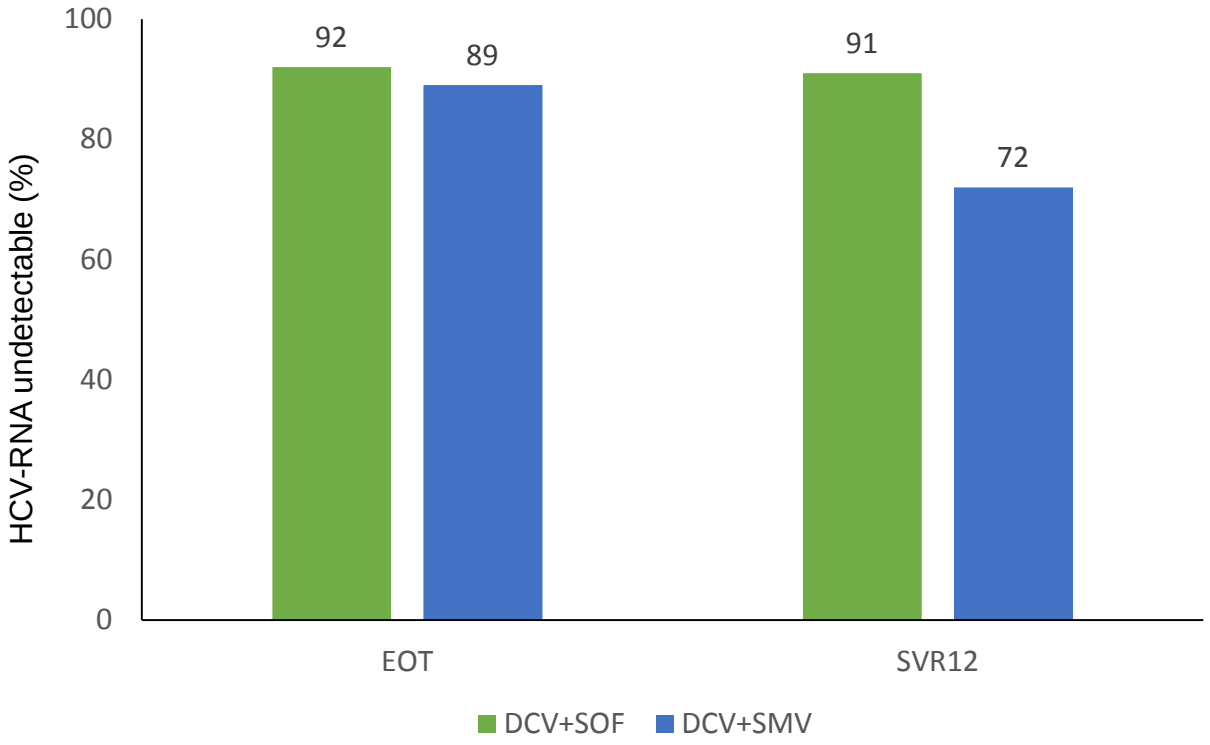
Starting RBV dose →600mg/d



Gane E. AASLD 2015, Charlon M. Gastroenterology 2015, Manns M. Lancet 2016

Decompensated Cirrhosis

DACLATASVIR COMPASSIONATE USE



DCV+SOF→77
DCV+SMV→18
39% G1a
49% CP-B or CP-C
MELD→13
RBV→35%

Fontana R. Liver Transplant 2016

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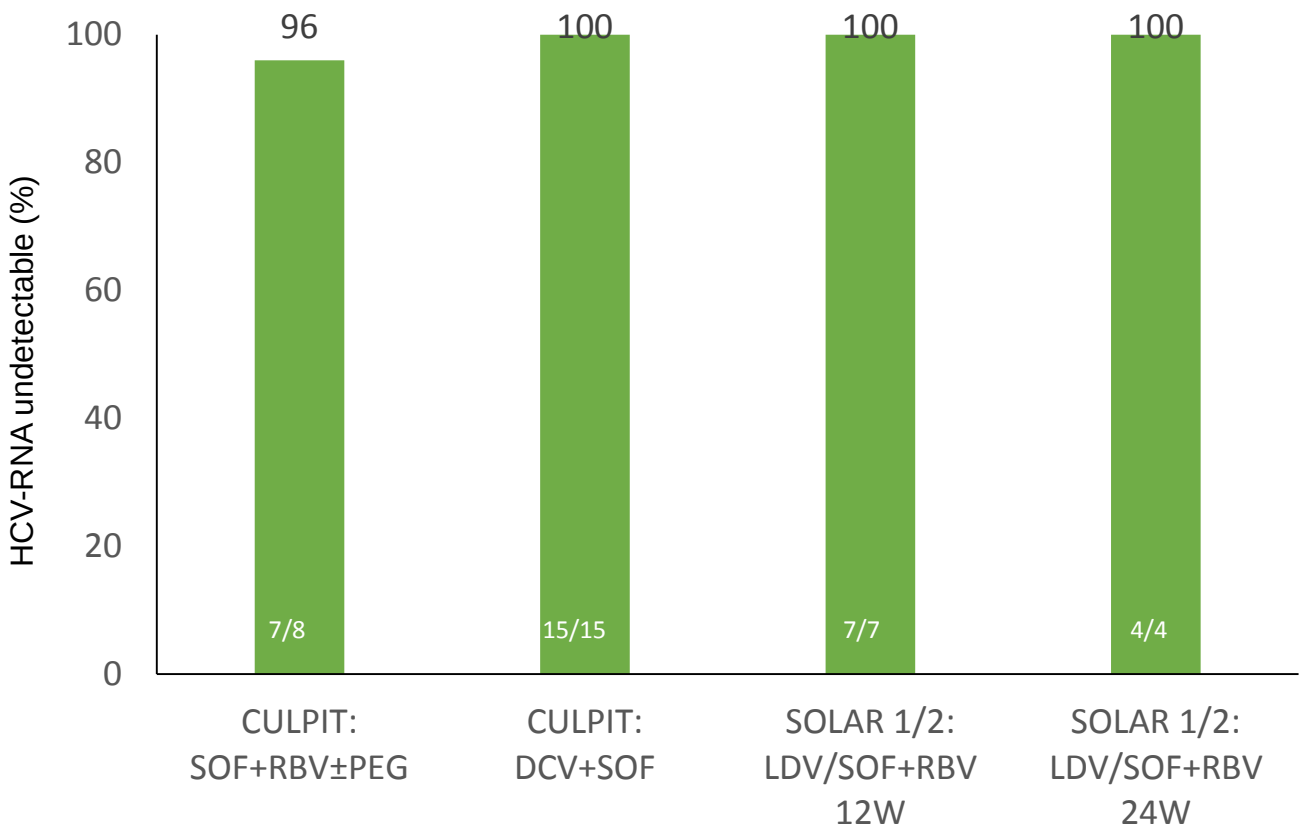
Fibrosing Cholestatic Hepatitis



Leroy V. Clin Gastroenterol and Hepatol 2015, Forns X. EASL 2015, Gane E. AASLD 2015

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DAAs Failures

Failed treatment	Genotype	LDV/SOF	3D	2D	SOF+SMV	SOF+DCV
SOF+SMV	1 or 4	12w+RBV or 24w+RBV if F3 or F4				12w+RBV or 24w+RBV if F3 or F4
SOF+DCV or LDV/SOF	1				12w+RBV or 24w+RBV if F3 or F4	
	2 or 3					12w+RBV or 24w+RBV if F3 or F4
	4				12w+RBV or 24w+RBV if F3 or F4	
	5 or 6	12w+RBV or 24w+RBV if F3 or F4				12w+RBV or 24w+RBV if F3 or F4
3D or 2D	1 or 4	12w+RBV or 24w+RBV if F3 or F4			12w+RBV or 24w+RBV if F3 or F4	12w+RBV or 24w+RBV if F3 or F4

DAAs Failures

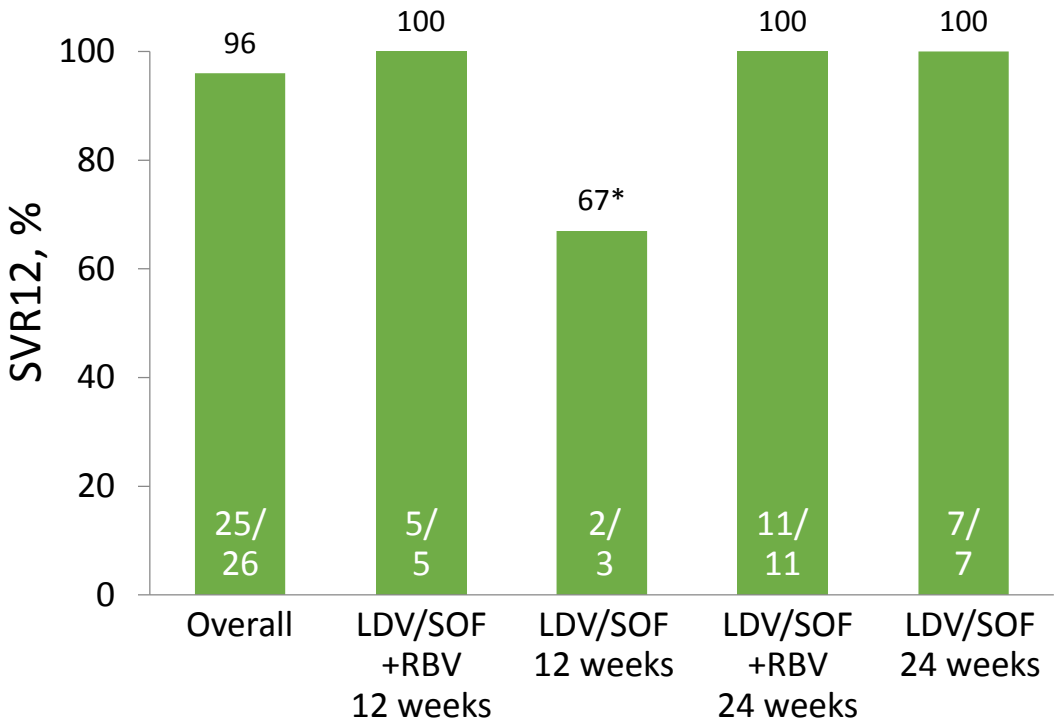
- Deferral of treatment

- NS5A and NS3-associated RAVs testing
  - No NS5A RAVs→ LDV/SOF+RBV for 24 w
  - NS5A but no NS3 RAVs→ SMV+SOF+RBV for 24 w
  - Both→ 3D+SOF+RBV or GZV/EBV+SOF+RBV 12 or 24 weeks

DAAs Failures

FAILURES TO SOF+SMV→ RETREATMENT WITH LDV/SOF

Patients	n=34
Average age, years (range)	59 (49–76)
Male, n (%)	28 (82)
Non-white, n (%)	5 (15)
GT 1a, n (%)	24 (71)
IL28B CT/TT, n (%)	21 (88)
Metavir F3–F4, n (%)	27 (79)
CTP Class B/C, n (%)	11 (32)
Post-liver transplant, n (%)	10 (29)
Median time since last dose of SMV+SOF, weeks (range)	23 (7–55)

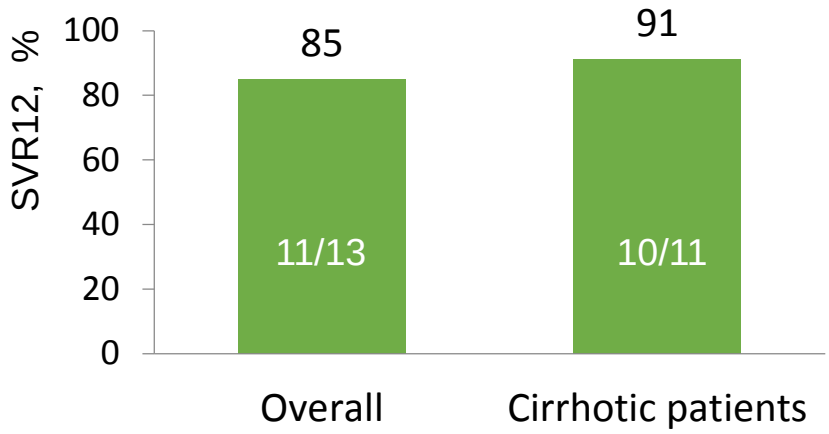


Pungpapong AASLD 2015

DAAs Failures

FAILURES TO SOF+SMV→ RETREATMENT WITH LDV/SOF

Patients	n=31
Male, n (%)	24 (77)
Median age, years (range)	58 (44–66)
GT 1a, n (%)	29 (93)
Compensated cirrhosis, n (%)	15 (48)
Decompensated cirrhosis, n (%)	10 (32)
Post-liver transplant, n (%)	3 (10)
LDV/SOF 12 weeks, n (%)	1 (3)
LDV/SOF+RBV 12 weeks, n (%)	11 (35)
LDV/SOF 24 weeks, n (%)	16 (52)
LDV/SOF+RBV 24 weeks, n (%)	3 (10)

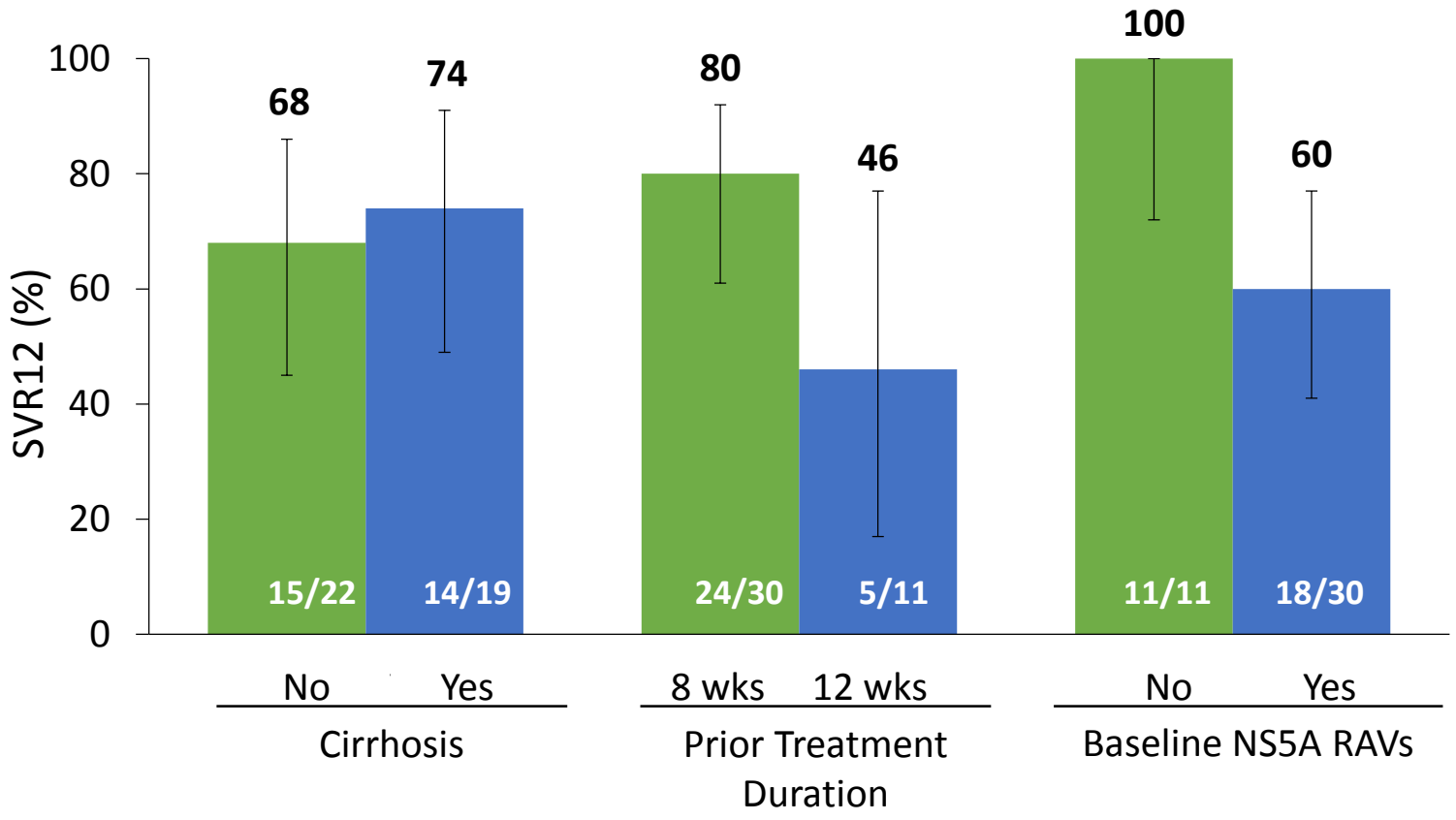


- 2 patients did not achieve SVR due to relapse
- 31% reported no AEs
- Most common AEs: fatigue, headache, insomnia, nausea, diarrhea
- 1 episode of decompensation with bleeding esophageal varices during treatment (patient on LDV/SOF 24 weeks who achieved SVR12)

Gonzalez AASLD 2015

DAAs Failures

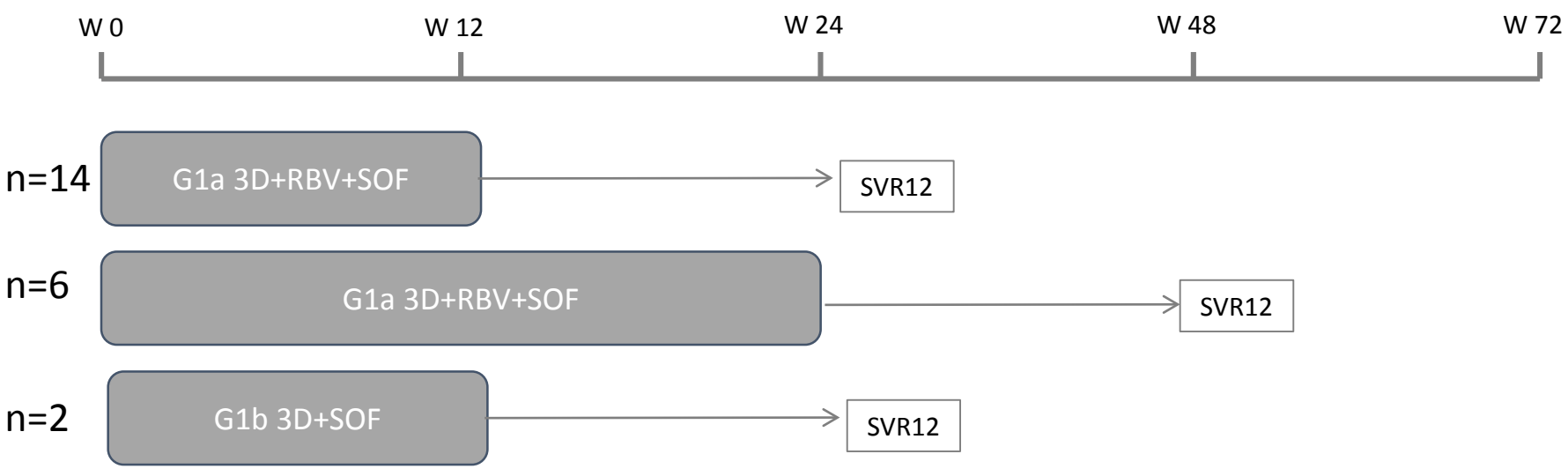
FAILURES TO LDV/SOF→ RETREATMENT WITH LDV/SOF

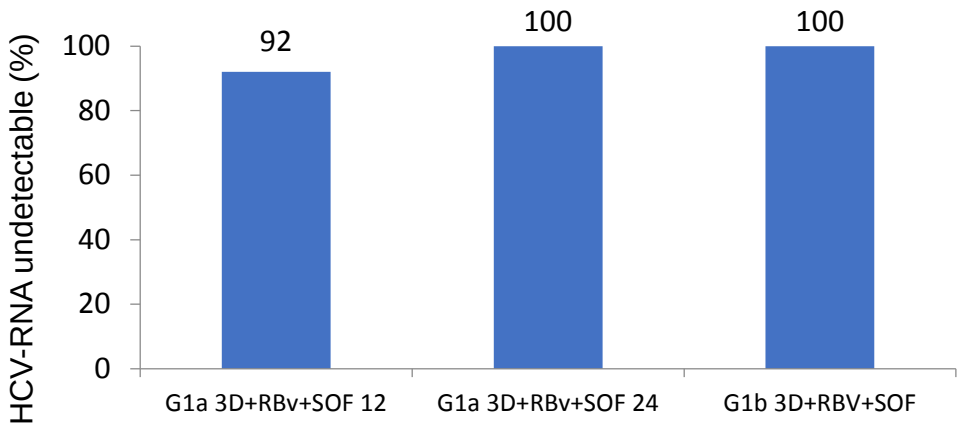


Lawitz et al EASL 2015

DAAs Failures

3D FAILURES→ RETREATMENT WITH 3D+SOF

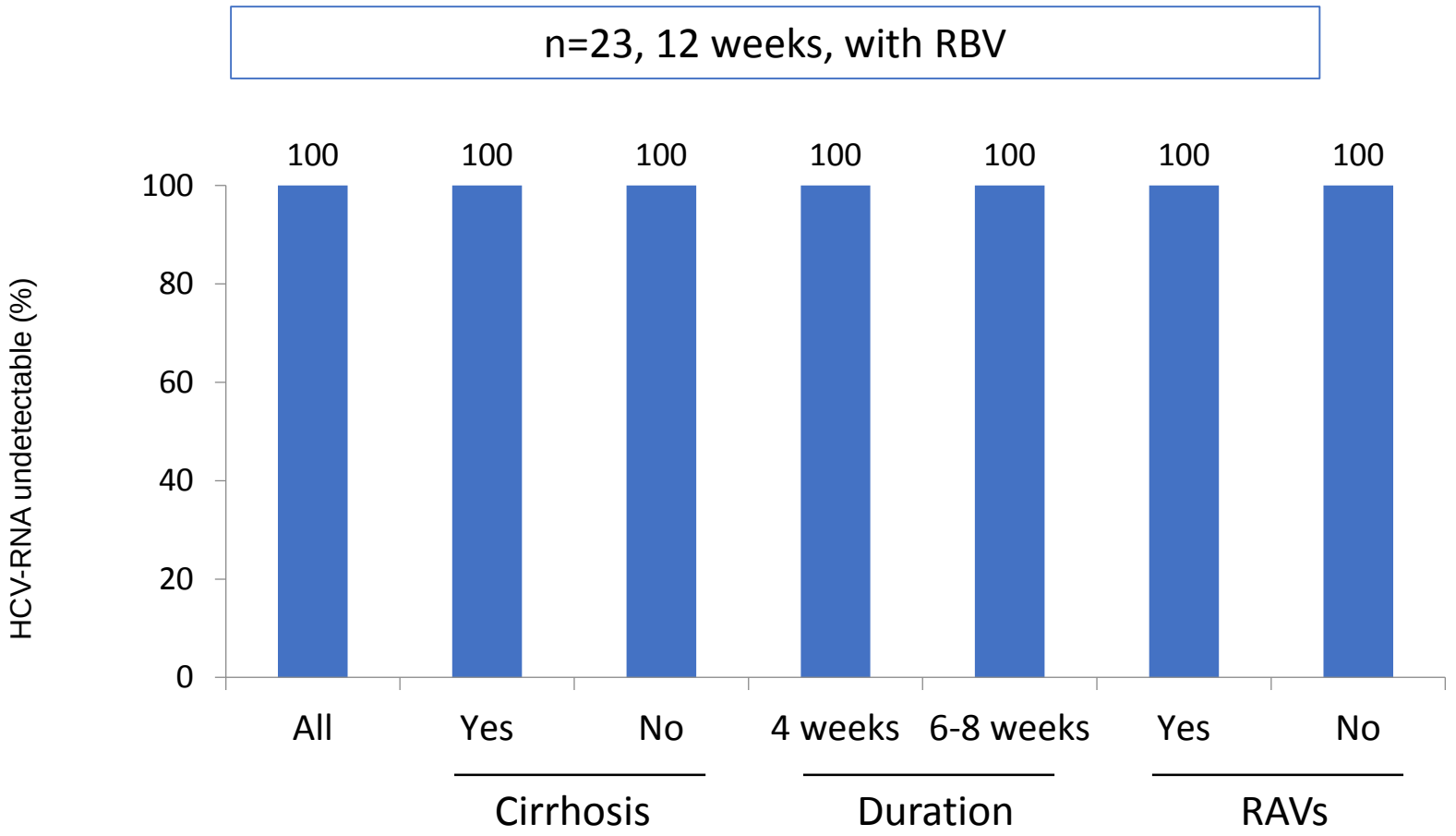




Poordad F. AASLD 2015

DAAs Failures

FAILURES TO GZV/EBV+SOF→ RETREATMENT WITH GZV/EBV+SOF+RBV



Lawitz. AASLD 2015

Conclusions

- After liver transplantation, antiviral therapy administered in patients with mild fibrosis stages achieve higher response rates as compared to patients with cirrhosis and decompensation.

- The election of antiviral regimen should be based on patients characteristics (liver function, immunosuppression, renal function).

- The need of RBV, the optimal treatment duration and the treatment of DAA failures need further studies.