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Treatment of recurent hepatitis infection after liver transplantation

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Disclosures

International meetings travels
Roche, Gilead, Astellas

Advisory Boards
Astellas, BMS

Conferences, Symposiums
Astellas, Novartis, BMS, MSD, Gilead, Janssen

Research support
Astellas, Novartis

Case report

A 53-year-old man
previous IVDU and heavy alcohol consumption

June 2014: first ascites decompensation
MELD 27, oesophageal varices grade II
HCV : G3a, RNA 1 400 000 UI/L

December 2014: moderate ascites, OH abstinent
MELD 22
MRI: 2 nodules, 12 and 15 mm, αFP 32 ng

Referred for Liver Transplantation

Case report

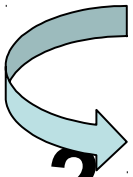
Liver Transplantation april 2015

IS regimen: TAC + MMF + steroids

Post-operative course

- **biopsy-proven mild acute rejection: increase TAC**
- **diabetes mellitus decompensation: insulin**

Discharged at day 28



2 different scenarios

Case report

Scenario 1

At Month 2

US examination: moderate ascites
AST 50 UI/L, ALT 110 UI/L
GGT 250 UI/L, Al Ph 720 UI/L, Bilirubin 90 µM/L

HCV viral load 12 000 000 UI/L

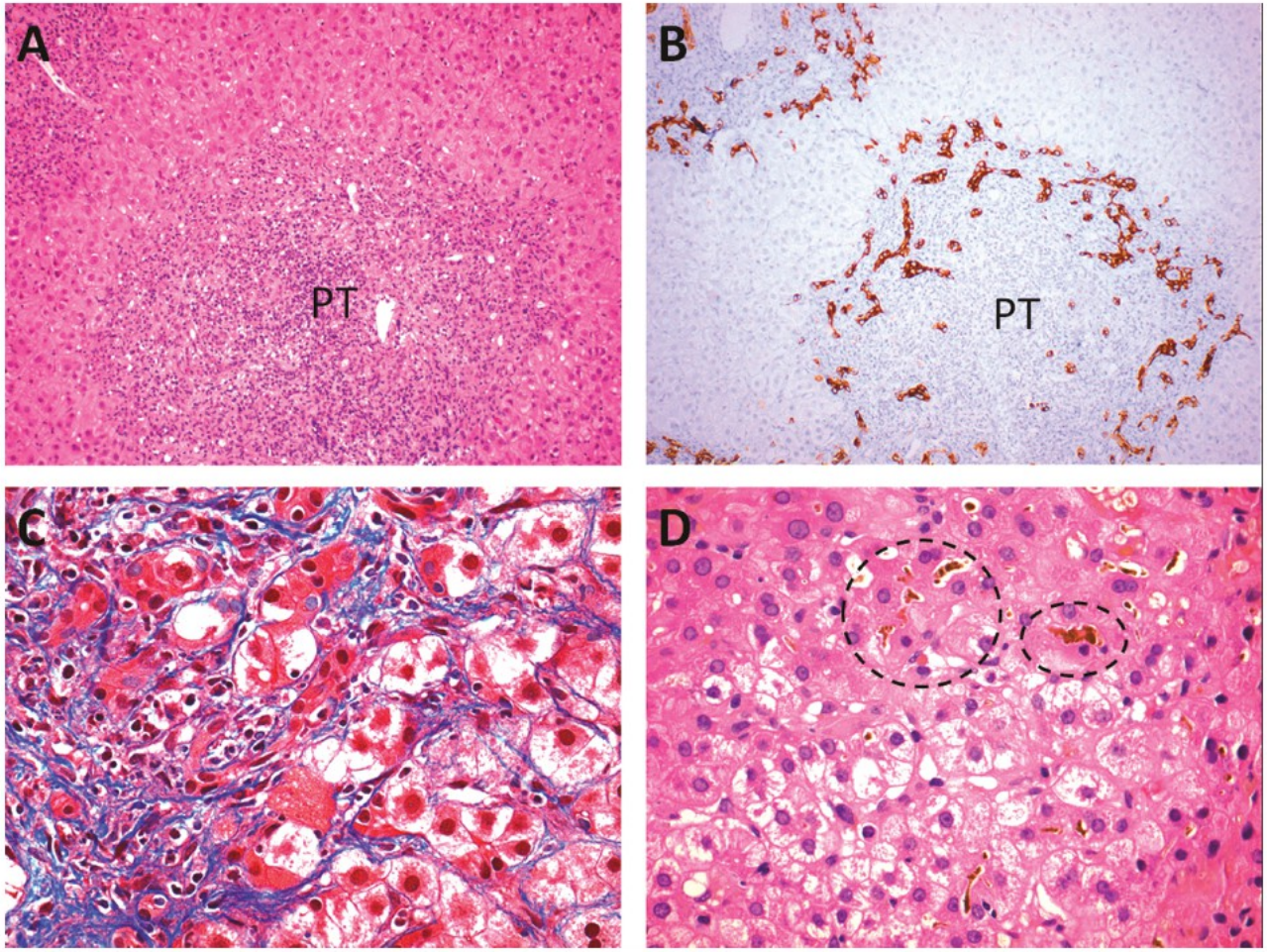
CT scan and MRI
no biliary obstruction, no hepatic artery thrombosis

Graft biopsy

Fibrosing Cholestatic Hepatitis

Portal inflammation

Ductular reaction



Pericellular/sinusoidal fibrosis

Hepatocyte swelling cholestasis

Case report

Scenario 2

At Month 12

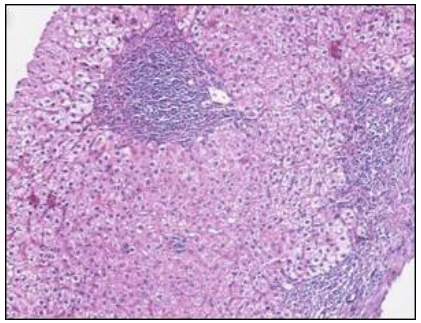
US examination: mild fatty liver
[TAC] 7 ng/L, MMF 1500 mg/d

AST 70 UI/L, ALT 135 UI/L
GGT 105 UI/L, Al Ph 70 UI/L, Bilirubin 14 µM/L
GFR 58 mL/min

HCV viral load 1 400 000 UI/L

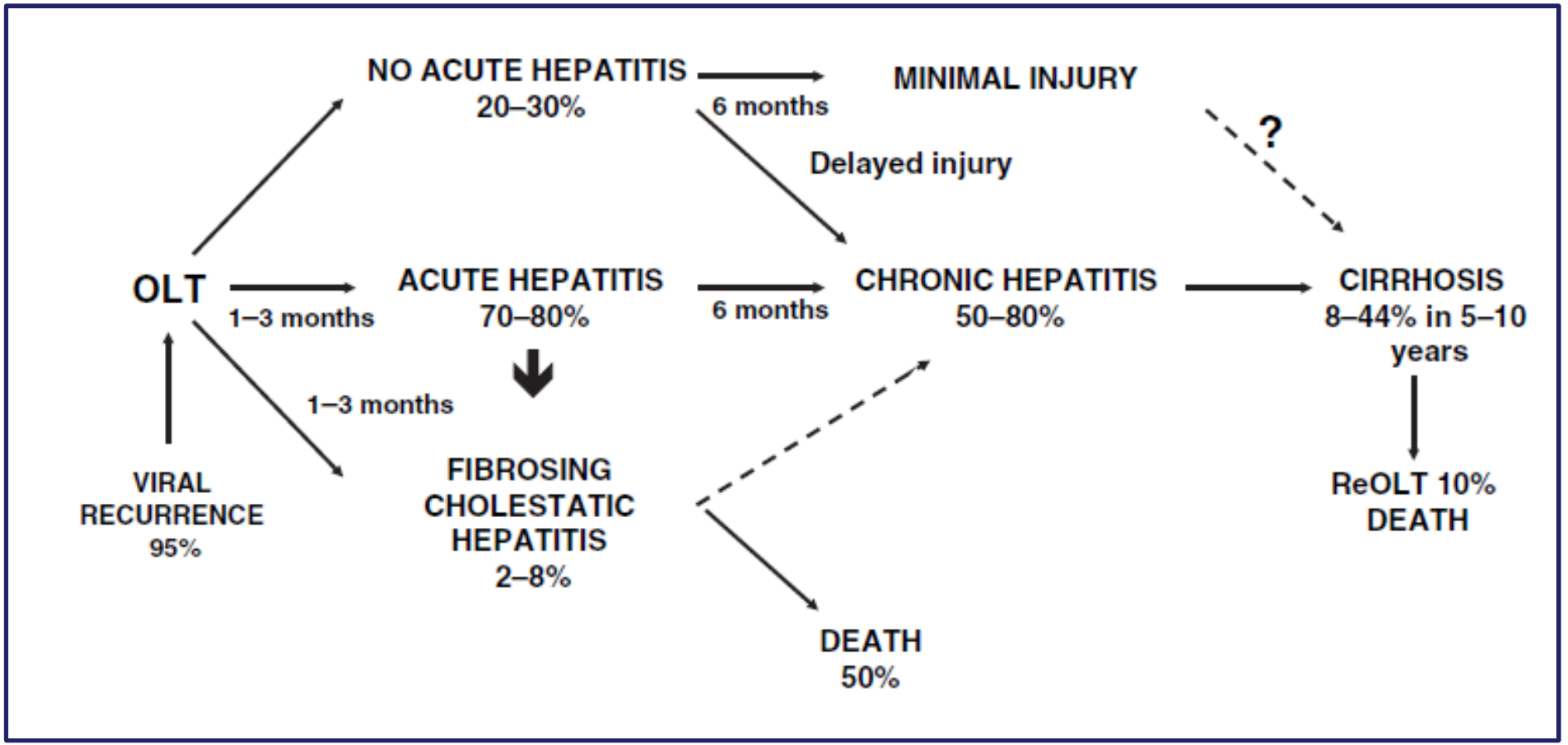
CT scan: normal

Graft biopsy →



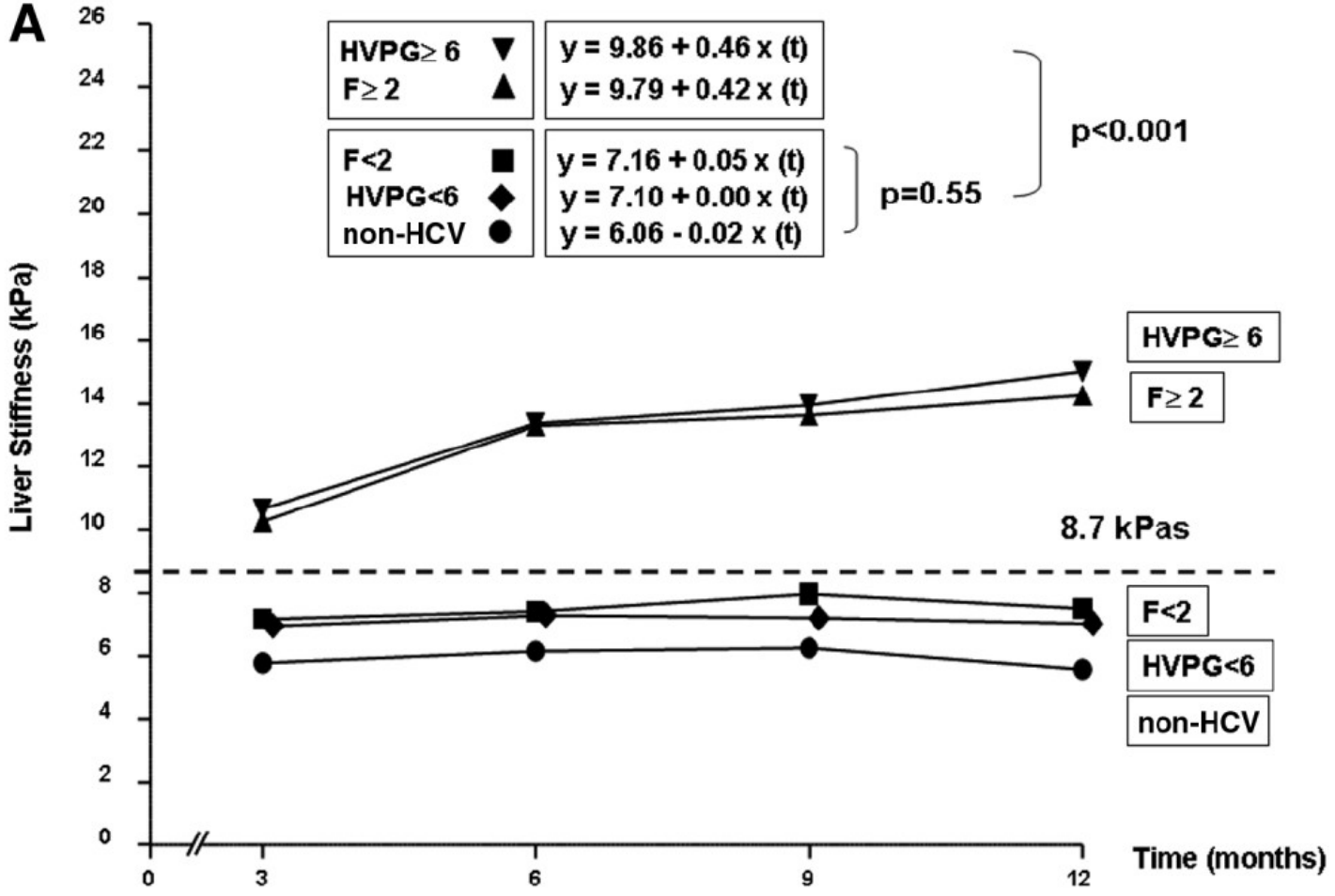
A2F2

Natural history of HCV recurrence



Roche B et Samuel D, J Viral Hepat 2007

40% patients ≥ F2 at 1 year



Carrion JA, Hepatology 2010

To treat as soon as possible

Accelerated fibrosis progression rate

More aggressive course

Better results in patients with compensated disease

Deterioration of renal function over time

Many co-morbidities in liver transplant recipients

Shortage of grafts

I want to change job…

		HCV NS34 PIs			HCV NS5A inhibitors		HCV NS5B polymerase inhibitor
	Ribavirin	Boceprevir 800 mg tid	Telaprevir 750 mg tid	Simeprevir 150 mg qd	Daclatasvir 60 mg qd	Ledipasvir 90 mg qd	Sofosbuvir 400 mg qd
Route of metabolism or excretion	Hepatic (deribosylation and hydrolysis) Renal excretion	CYP3A4, CYP3A5 AKR	CYP3A4	CYP3A4	CYP3A4	Not a substrate, of CYP 450/UGT Excreted in faeces (>98%)	Not substrate of CYP 450/UGT Renal excretion
HIV PIs							
Lopinavir/r	Recommended	Not recommended	Not recommended	Not recommended	No data	No data	Recommended
Darunavir/r	Recommended	Not recommended	Not recommended	Not recommended	No data	No data	Recommended
Atazanavir/r	Close monitoring	Consider on an individual basis	Recommended	Not recommended	Recommended at 30 mg qd	No data	Recommended
HIV NNRTIs							
Efavirenz	Recommended	Not recommended	Recommeded at 1125 mg tid	Not recommended	Recommended at 90 mg qd	Recommended	Recommended
Rilpivirine	Recommended	Recommended	Caution for QT prolongation	Recommended	No data	Recommended	Recommended
Etravirine	Recommended	Recommended	Recommended	No data	No data	No data	No data
HIV InSTIs							
Dolutegravir	Recommended	Recommended	Recommended	No data	No data	No data	No data
Raltegravir	Recommended	Recommended	Recommended	Recommended	No data	Recommended	Recommended
Elvitegravir/ cobicistat	Recommended	No data	Recommended	Not recommended	No data	No data	No data
HIV NtRTI							
Tenofovir	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended
CCR5 inhibitor							
Maraviroc	Recommended	Reduce maraviroc to 150 mg bid	Reduce maraviroc to 150 mg bid	No data	No data	No data	No data
IS drugs							
Calcineurin inhibitors							
Cyclosporin	No data	↓Ciclosporin dose	↓↓Ciclosporin dose	Not recommended	No data	No data	No dose adjustment
Tacrolimus (FK)	Recommended	↓FK dose	↓↓↓FK dose	No dose adjustmet Close monitoring	No data	No data	No dose adjustment
mTOR inhibitors							
Sirolimus	Close monitoring	↓↓Sirolimus dose	↓↓Sirolimus dose	↓↓Sirolimus dose	No data	No data	Recommended
Prednisone	No data	No dose adjustmet Close monitoring	No data	No data	No data	No data	Recommended
Anti-HCV therapies							
Pegylated interferon	Recommended	Recommended	Recommended	Recommended	Recommended	No data	Recommended
Ribavirin		Recommended	Increasing ribavirin concentration. Close monitoring	Recommended	Recommended	No data	Recommended

Miro JM, J Hepatol 2015

Treatment of recurrence after LT

Sofosbuvir + RBV

Charlton M, Gastroenterology 2015

Sofosbuvir + Simeprevir ± RBV

Pungpapong S, Hepatology 2015; TARGET, Liver Transplant 2016

SOLAR-1: Sofosbuvir + Ledipasvir + RBV

Charlton M, Gastroenterology 2015

Sofosbuvir + Daclatasvir ± RBV

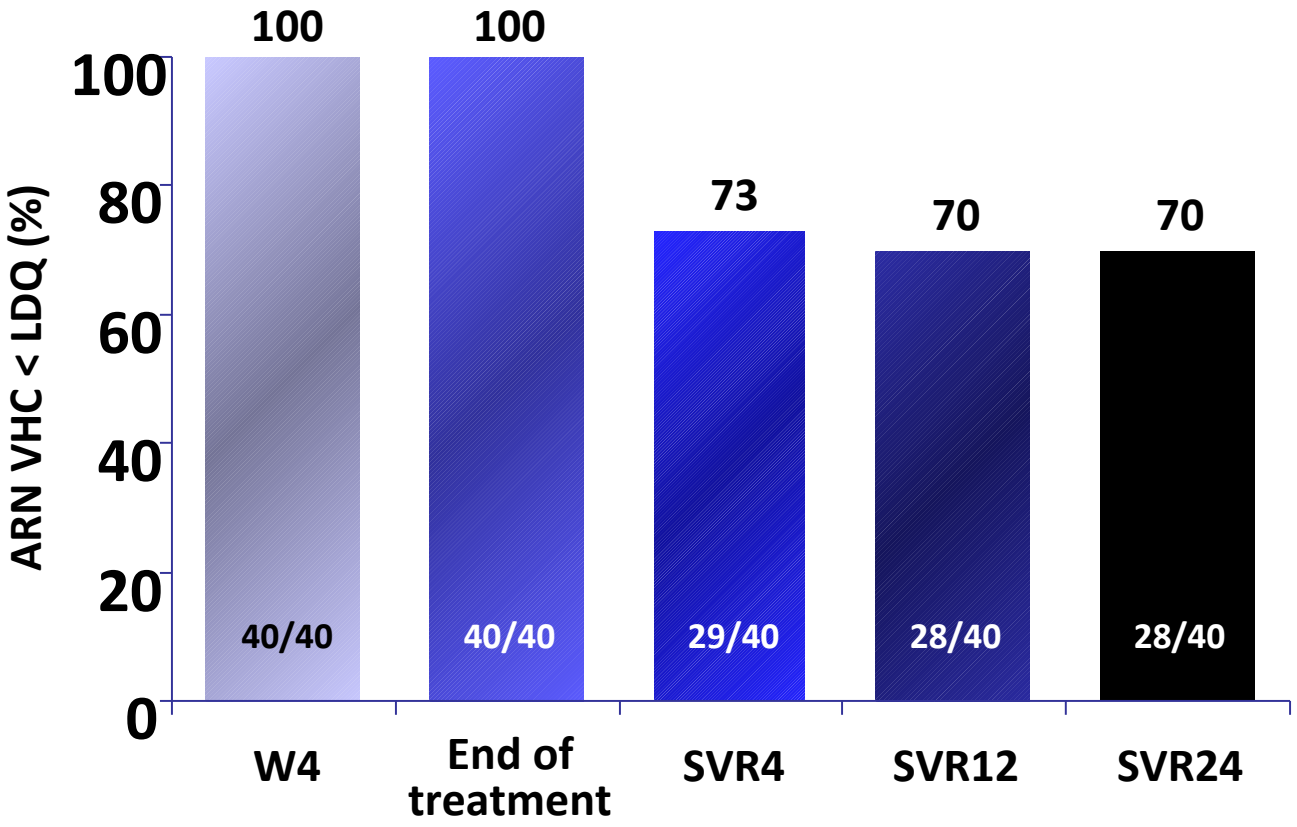
ALLY-1; CUPILT

Ombitasvir + ABT-450/r + Dasabuvir + RBV

Kwo PY, N Engl J Med 2014

Sofosbuvir + RBV

40 patients, 83% G1, 40% F4
SOF + RBV 24 weeks

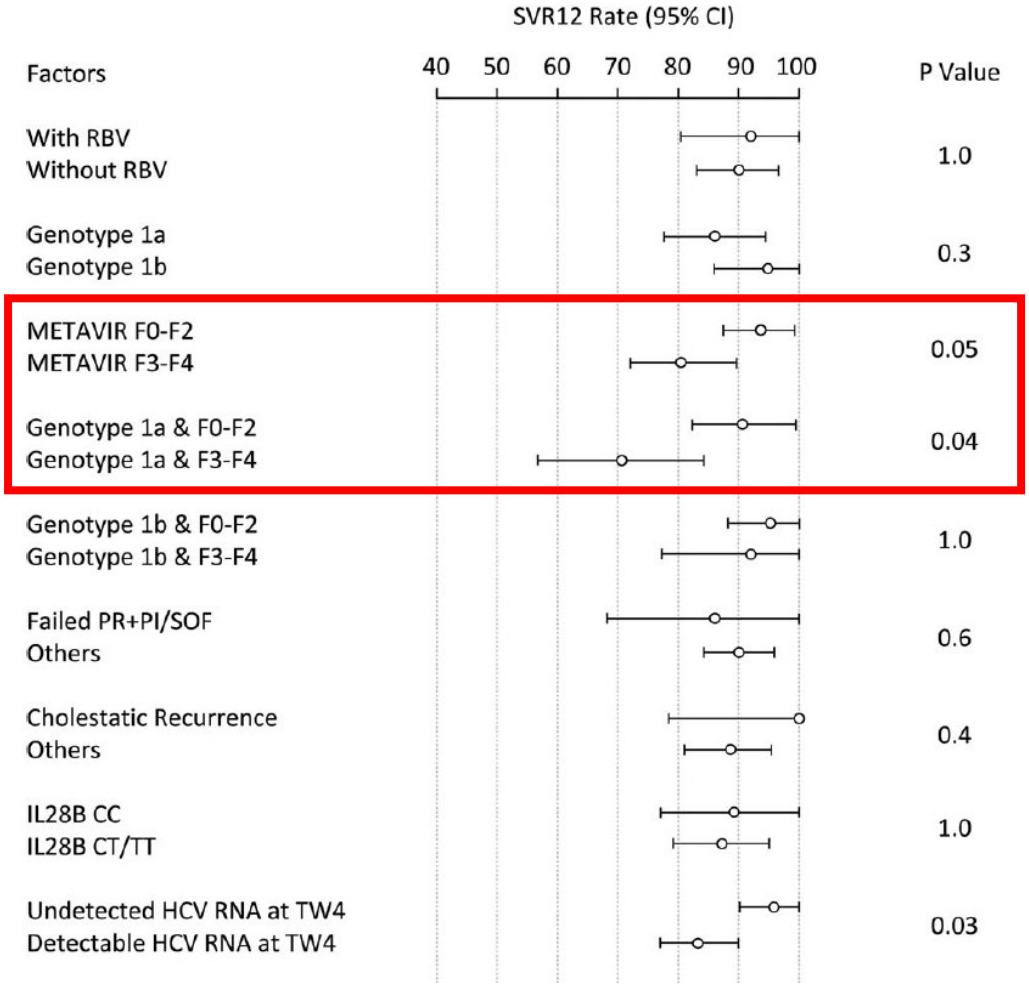


Charlton M, Gastroenterology 2015

Sofosbuvir + Simeprevir ± RBV

Multicenter, 123 patients LT, FCH 11%, F3/4 30%

SVR12 90%

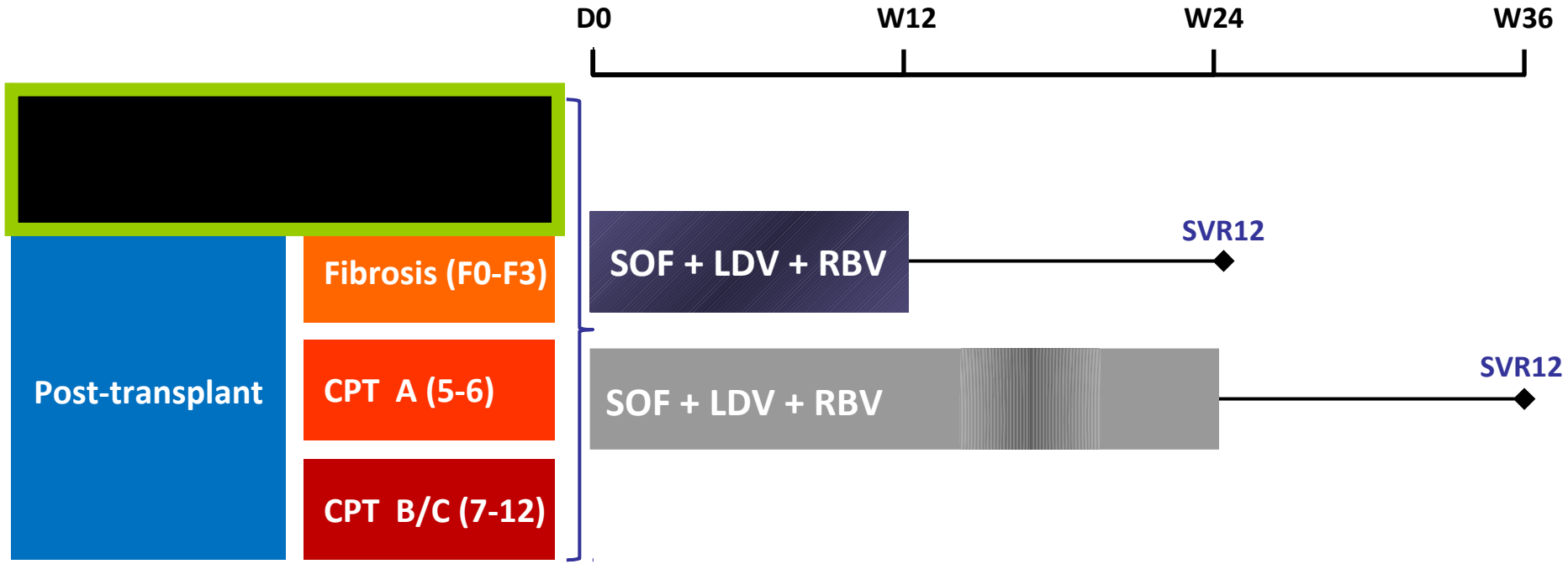


CsA + SMV

Pungpapong S, Hepatology 2015

Sofosbuvir + Ledipasvir + RBV

SOLAR-1



Charlton M, Gastroenterology 2015

Sofosbuvir + Ledipasvir + RBV

SOLAR-1

Cohort B: post-transplantation

	Group 3 No cirrhosis		Group 4 CTP A		Group 5 CTP B		Group 6 CTP C		Group 7 FCH	
	12 wk (n = 55)	24 wk (n = 56)	12 wk (n = 26)	24 wk (n = 25)	12 wk (n = 26)	24 wk (n = 26)	12 wk (n = 5)	24 wk (n = 4)	12 wk (n = 4)	24 wk (n = 2)
HCV RNA <LLOQ on treatment										
At week 2	27/55 (49)	23/55 (42)	9/26 (35)	7/25 (28)	2/25 (8)	11/26 (42)	2/5 (40)	1/4 (25)	2/4 (50)	0/2
At week 4	48/55 (87)	50/55 (91)	23/26 (88)	20/25 (80)	18/25 (72)	23/26 (88)	5/5 (100)	4/4 (100)	4/4 (100)	1/2 (50)
At week 6	53/55 (96)	55/55 (100)	25/25 (100)	25/25 (100)	25/25 (100)	26/26 (100)	5/5 (100)	4/4 (100)	4/4 (100)	1/2 (50)
HCV RNA <LLOQ after treatment										
At week 4 (SVR4)	53/55 (96)	55/56 (98)	25/26 (96)	25/25 (100)	23/26 (88)	24/26 (92)	5/5 (100)	3/4 (75)	4/4 (100)	2/2 (100)
At week 12 (SVR12)	53/55 (96)	55/56 (98)	25/26 (96)	24/25 (96)	22/26 (85)	23/26 (88)	3/5 (60)	3/4 (75)	4/4 (100)	2/2 (100)
90% CI	89–99	92–100	83–100	82–100	68–95	73–97	19–92	25–99	47–100	22–100
Virologic failure										
Breakthrough	0	0	0	0	0	0	0	0	0	0
Relapse	2	0	0	0	1	0	2	1	0	0

Charlton M, Gastroenterology 2015

Sofosbuvir + Ledipasvir + RBV

Safety

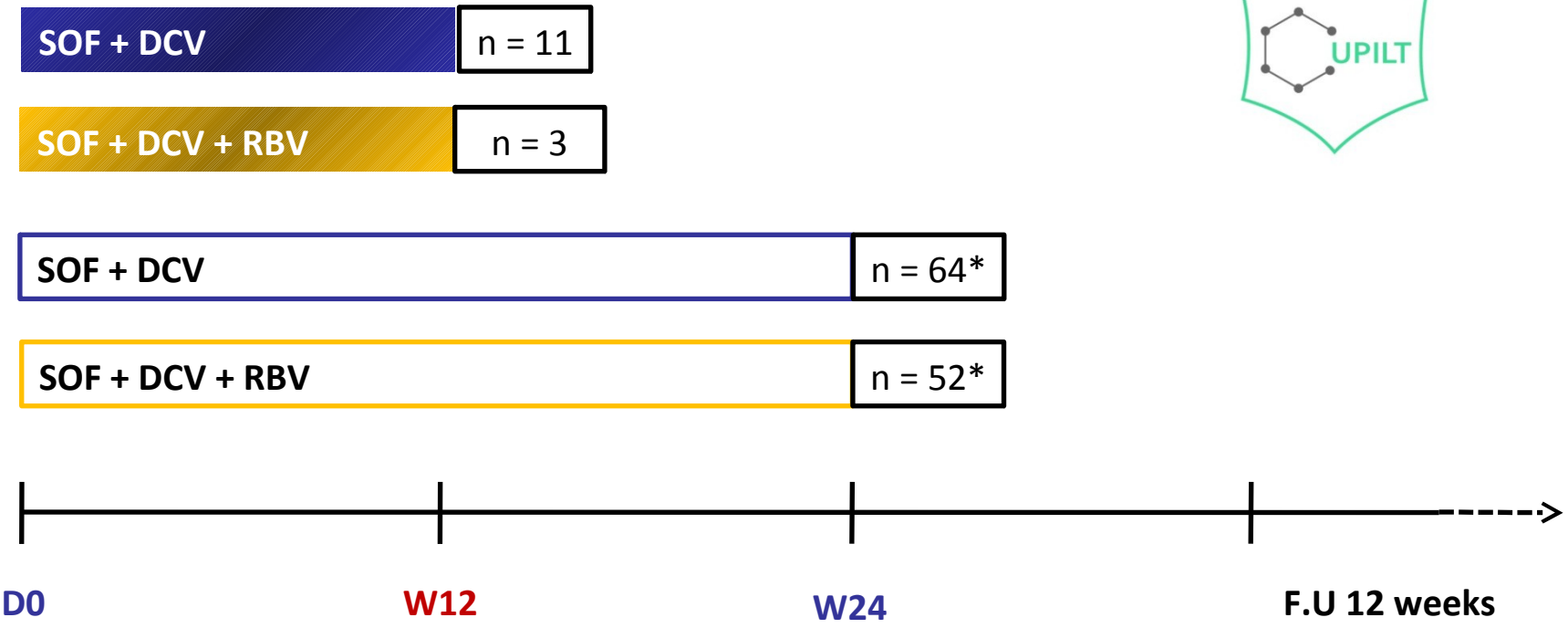
	F0-F3		Child-Pugh A		Child-Pugh B		Child-Pugh C	
Patients	W12 (n = 55)	W24 (n = 56)	W12 (n = 26)	W24 (n = 25)	W12 (n = 26)	W24 (n = 26)	W12 (n = 5)	W24 (n = 4)
Adverse events grade 3-4	15 27 %	14 25 %	4 15 %	7 28 %	6 23 %	9 35 %	1 20 %	1 25 %
Severe adverse events (SAE)	6 11 %	12 21 %	3 12 %	4 16 %	5 19 %	11 42 %	1 20 %	4 100 %
SAE related to the study	2 4 %	1 2 %	2 8 %	2 8 %	0 0 %	1 4 %	0 0 %	0 0 %
Discontinuation/AE	0	2	1	0	0	3	0	0
Death during treatment*	0	0	1	0	1	2	0	0

AEG leading to death: respiratory distress, haemoperitoneum, thoracic artery anevrysma, seizures, cytolysis, dyspnea

***Death during treatment: progressive multivocal encephalopathy, thoracic artery anevrysma, hemorraghe, cirrhosis complications**

Sofosbuvir + Daclatasvir ± RBV

130 patients LT



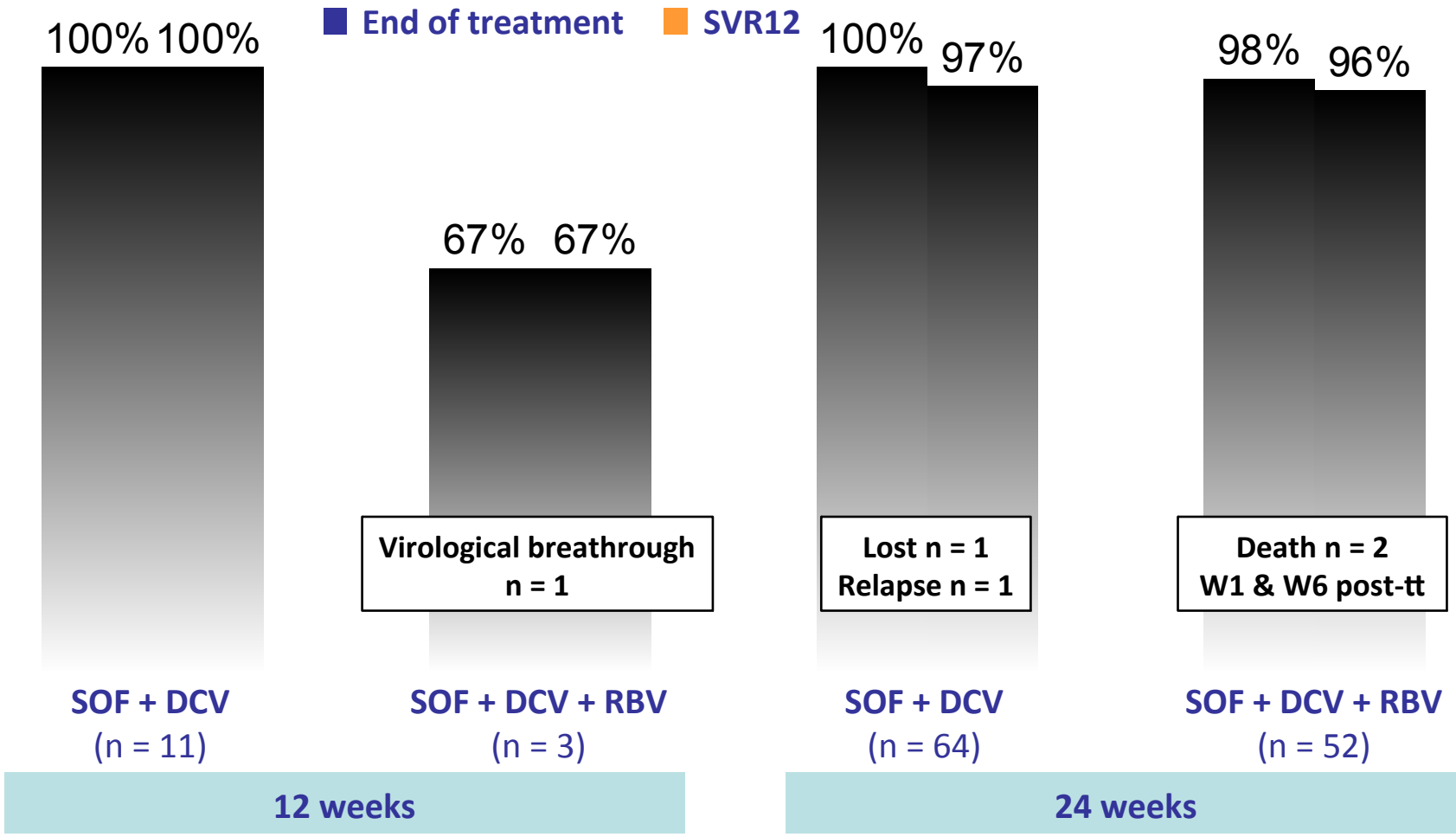
SOF = 400 mg/d ; DCV = 60 mg/d ; RBV = according to investigator

*In 3 patients, le traitement a été prolongé jusqu'à S36 (n = 2) et S48 (n = 1)

Coilly A, Villejuif, EASL 2015, Abs. G15 actualisé

Sofosbuvir + Daclatasvir ± RBV

SVR according to treatment duration

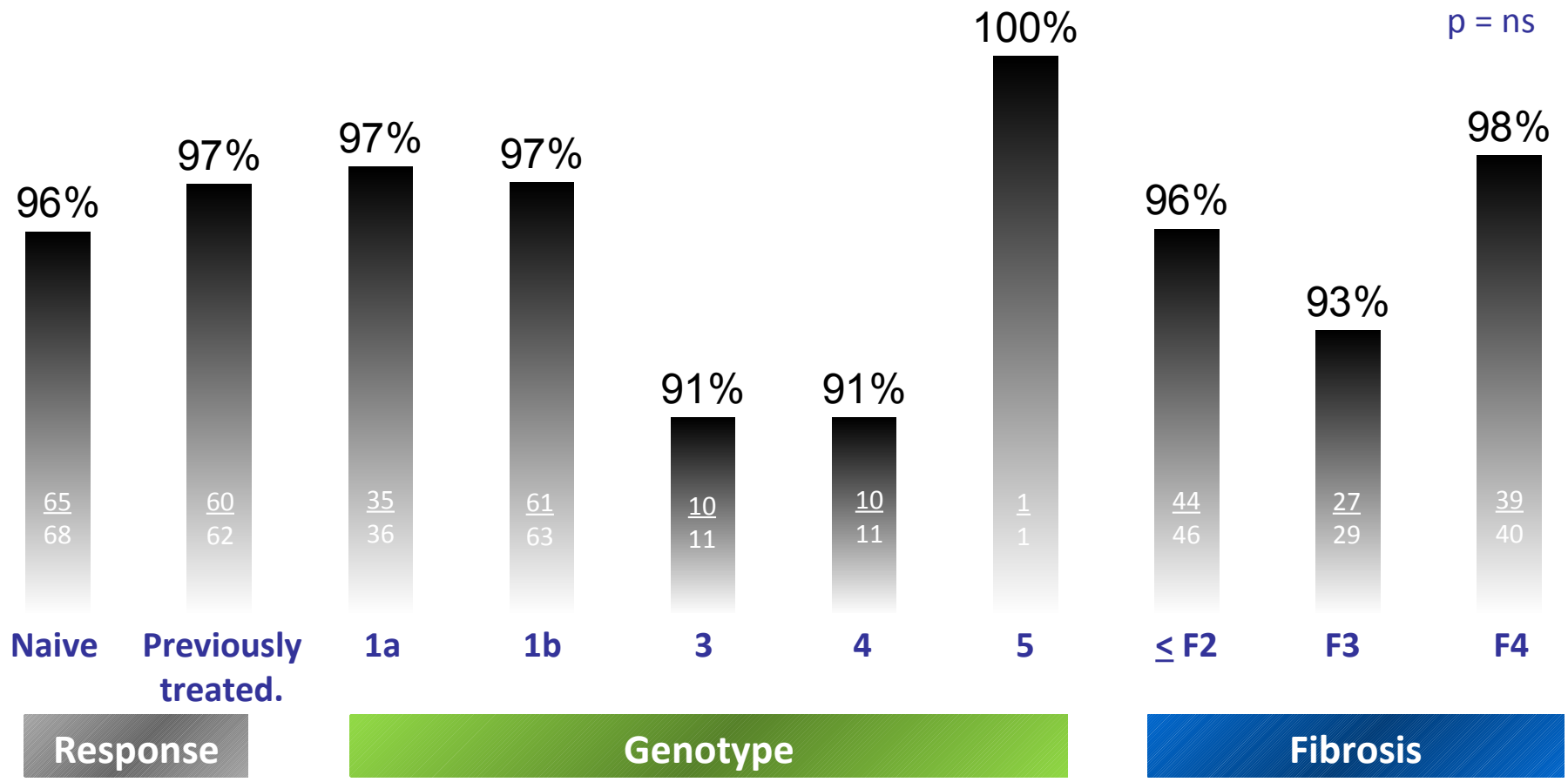


Résultats en ITT

Coilly A, Villejuif, EASL 2015, Abs. G15 actualisé

Sofosbuvir + Daclatasvir ± RBV

SVR according to genotype, fibrosis, previous treatment

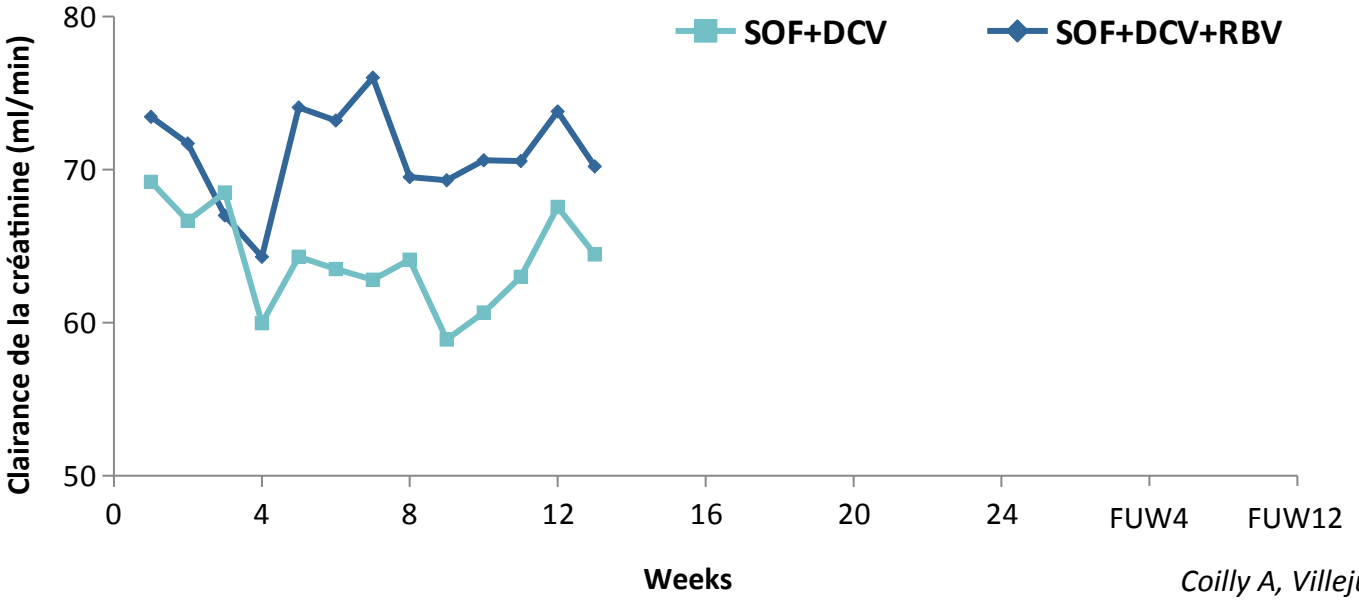


Coilly A, Villejuif, EASL 2015, Abs. G15 actualisé

Sofosbuvir + Daclatasvir ± RBV

Renal function

	Overall (n = 130) n (%)	SOF + DCV (n = 75) n (%)	SOF + DCV + RBV (n = 55) n (%)
Renal failure(declared)	6 (4,6)	4 (5,3)	2 (3,6)
Renal failure (calculated)	79 (60,1)	47 (62,7)	32 (58,2)
Cr Cl ≤ 60	67 (51,5)	37 (49,3)	30 (54,5)
Cr Cl ≤ 30	10 (7,7)	8 (10,7)	2 (3,7)
Cr Cl ≤ 10	2 (1,5)	2 (2,7)	0

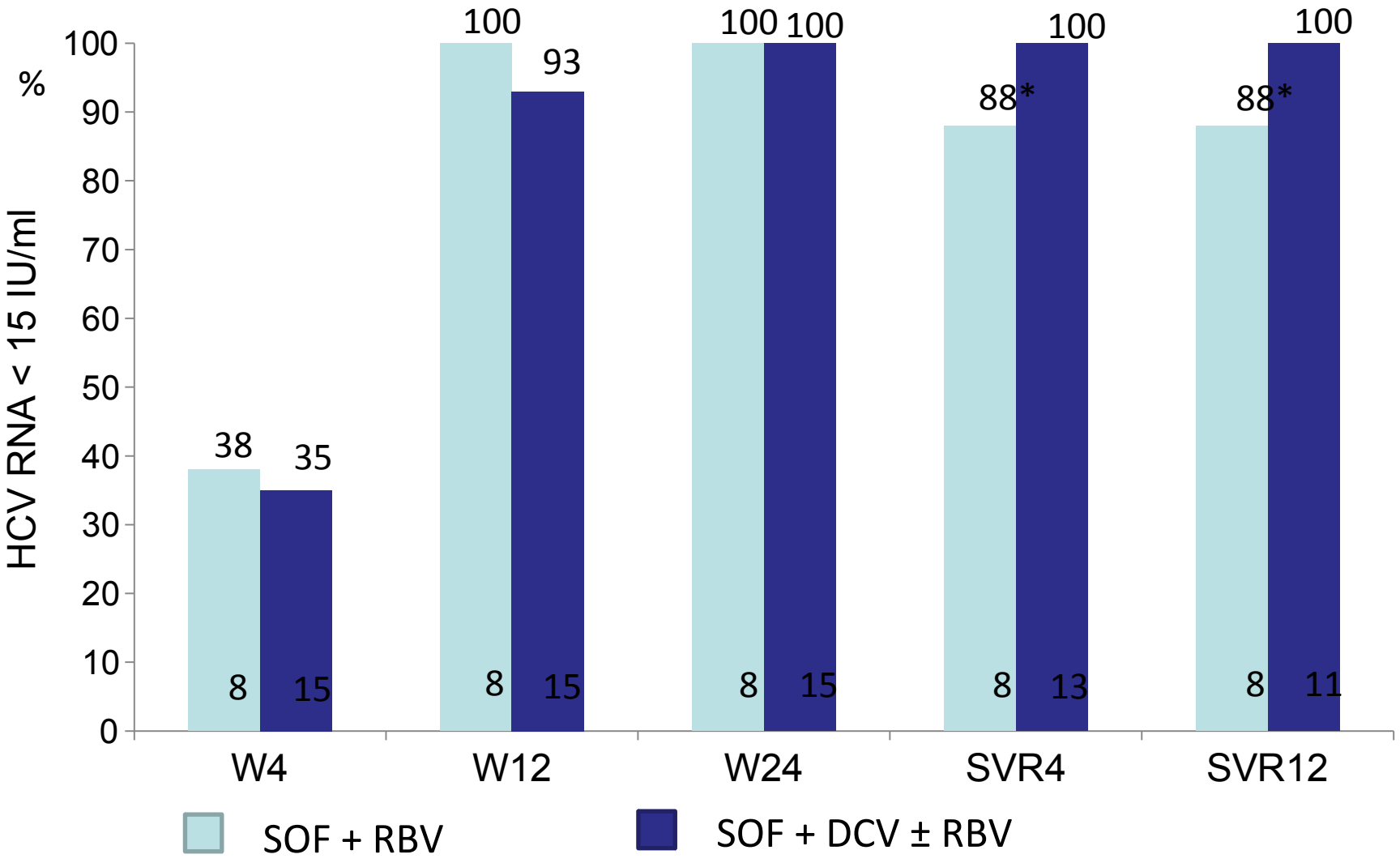


Mean decrease=
72,7 ± 29,0 à
68,7 ± 26,1 ml/min,
p < 0,0001

Coilly A, Villejuif, EASL 2015, Abs. G15 actualisé

Sofosbuvir + Daclatasvir ± RBV

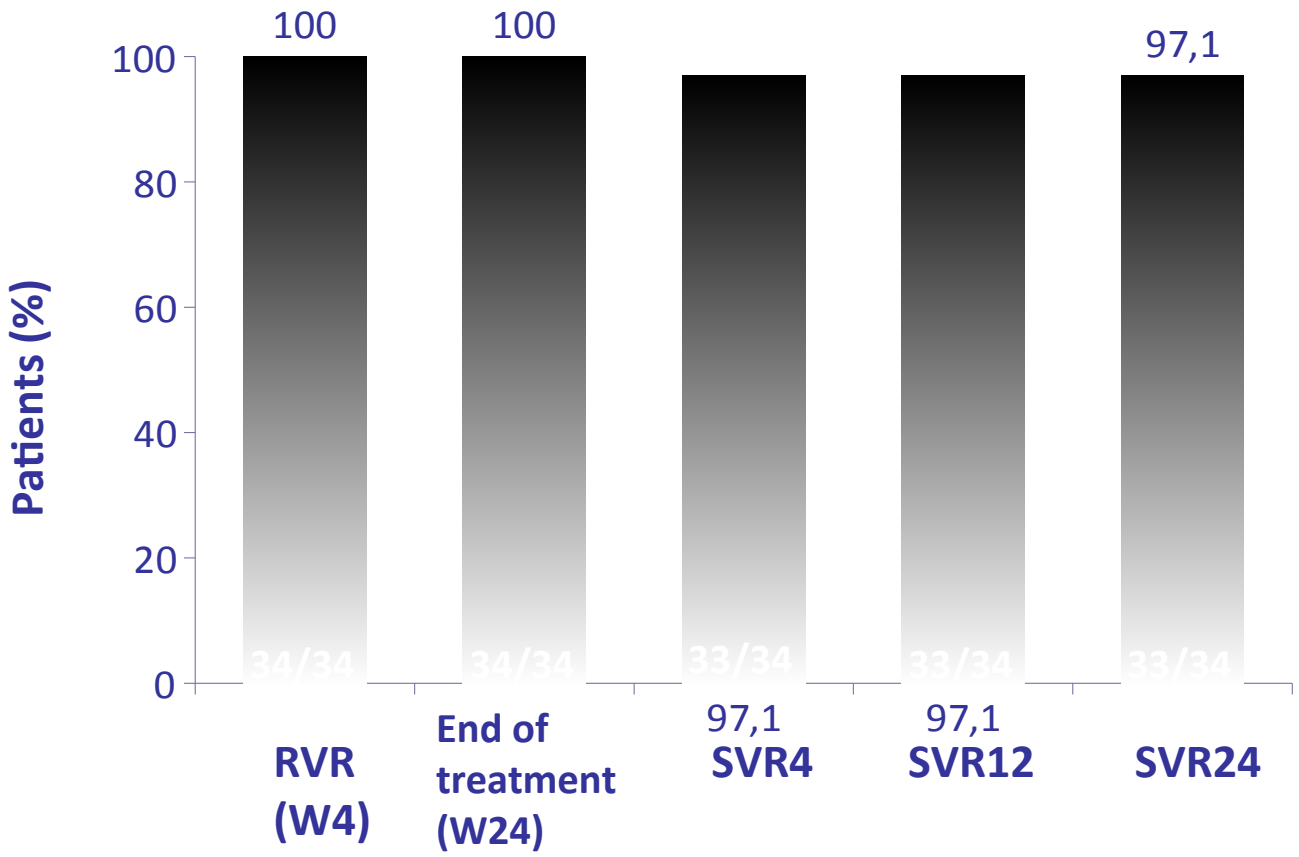
Fibrosing cholestatic hepatitis



* : 1 relapse in HIV co-infected patients, G1b, F4

Ombitasvir + ABT-450/r + Dasabuvir + RBV

34 patients G1, ≤ F2, naive post TH
Tacrolimus 0,5mg/w or 0,2mg/3d; Ciclo 1/5 initial dose



Kwo PY, N Engl J Med 2014

Ombitasvir + ABT-450/r + Dasabuvir + RBV

RBV dosage

n (%)	D0 (n = 34)	End TTT (n = 34)
400 mg/j	3 (9)	4 (12)
600-800 mg/j	19 (56)	23 (68)
1 000-1 200 mg/j	12 (35)	7 (20)

- 1 premature discontinuation for AE (rash, anxiety)
- Immunosuppressive drugs :
  - No rejection
  - 5 patients with [TAC] > 15 ng/ml (15,7-34)→ reversible ↑ of creatinine in 2 patients
  - Stable [ciclosporin] (1/5 initial dose)

EI, n (%)	3D + RBV (n = 34)
Fatigue	17 (50)
Headache	15 (44)
Cough	11 (32)
Anemia	10 (29)
Diarrhea	9 (27)
Insomnia	9 (27)
Asthenia	8 (24)
Nausea	8 (24)
Muscle spasm	7 (21)
Rash	7 (21)
Back pain	6 (18)
Dizziness	6 (18)
Peripheral oedema	6 (18)
Rhinorrhea	6 (18)

Kwo PY, N Engl J Med 2014

Conclusion

Liver transplant recipients are no more longer a difficult-to-treat population

The timing of post-LT treatment has to be better defined:
pre-emptive or curative as soon as possible?

The best DAAs strategy after liver transplantation:
efficacy > 90%, safety, non nephrotoxic,
as few as possible drug-drug interactions