2015 8th Paris Hepatitis Conference

12 & 13 January 2015

How to optimize treatment in HCV G1 naïve patients?

Raluca Pais, Pitié Salpetrière Hospital, Paris, France

CLINICAL CASE

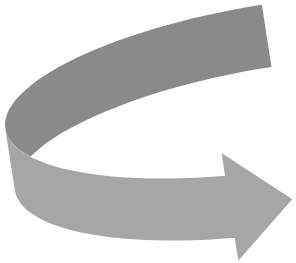
- 62 years old man, BMI = 25.2 kg/m2
- Diagnosed with HCV G1b, IL28B = CT; HCV RNA = 6.5 log.
- Never treated
- Drug user at his age of 20th; HIV negative
- Type 2 diabetes on oral medication, HbA1c = 6.5%
- Drinking less than 30 g/day

Blood group = B +
Hb = 13.5 g/dl; Platelet = 92 000/mm3
AST = 162 IU/l; ALT = 85 IU/l; GGT = 236 IU/l; PAL = 180 IU/l.
Total Bilirubin = 32 mmol/l
Albumin = 34 g/dl; Creatinin = 130 µmol/l
TP = 50%; FV = 55%
AFP = 89 nmol/l

CLINICAL CASE

No hepatic encephalopathy
FT = 0.92; FS = 28 kPa
CT scan – mild ascites; 2 nodules: 2.5 cm and 1 cm, segm. V and VII typical of HCC
Upper gastroscopy: gr. II varices

HCV Cirrhosis, Child B8, MELD = 17
HCC BCLC A, Milan in, AFP Score = 0



Decision:

- **Inscription on the waiting list for OLT**
- **Down staging HCC therapy: TACE**

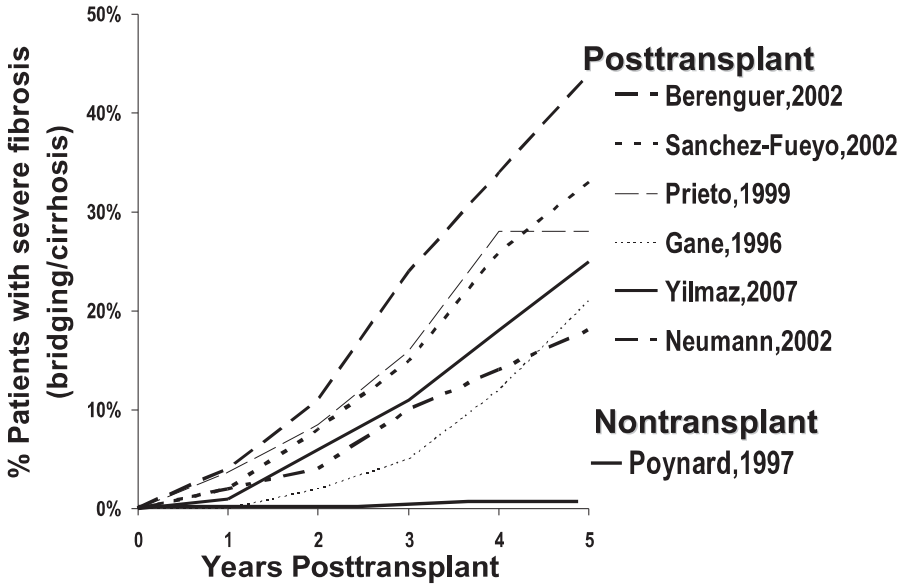
CLINICAL CASE

Q1

Treatment of HCV prior to liver transplantation – Wise or wasteful?

HCV Recurrence post OLT

Cumulative rate of progression to HCV cirrhosis

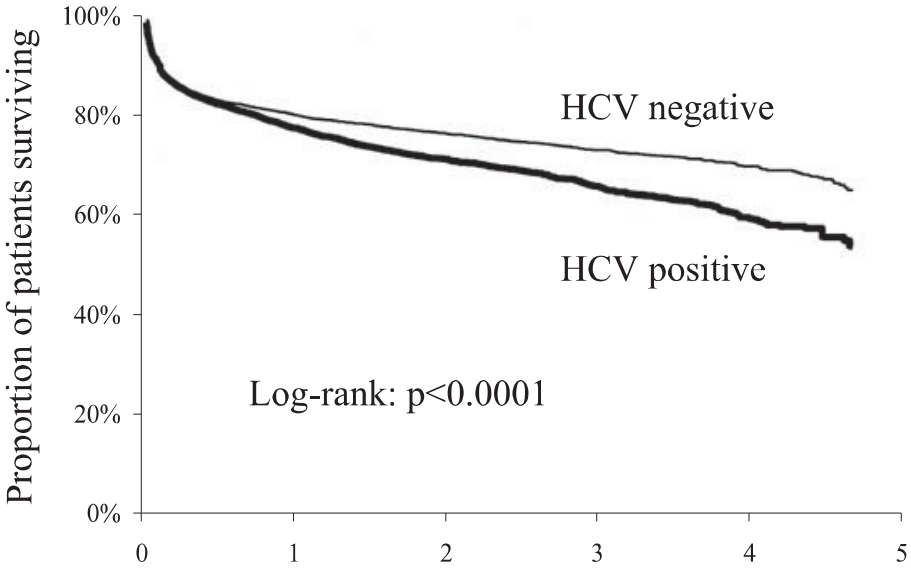


- Reduced patient and graft survival
- Poor outcomes of re-transplantation (50 – 80% mortality on waiting list)

Gane, Liver Int. 2014

5 Years post OLT:

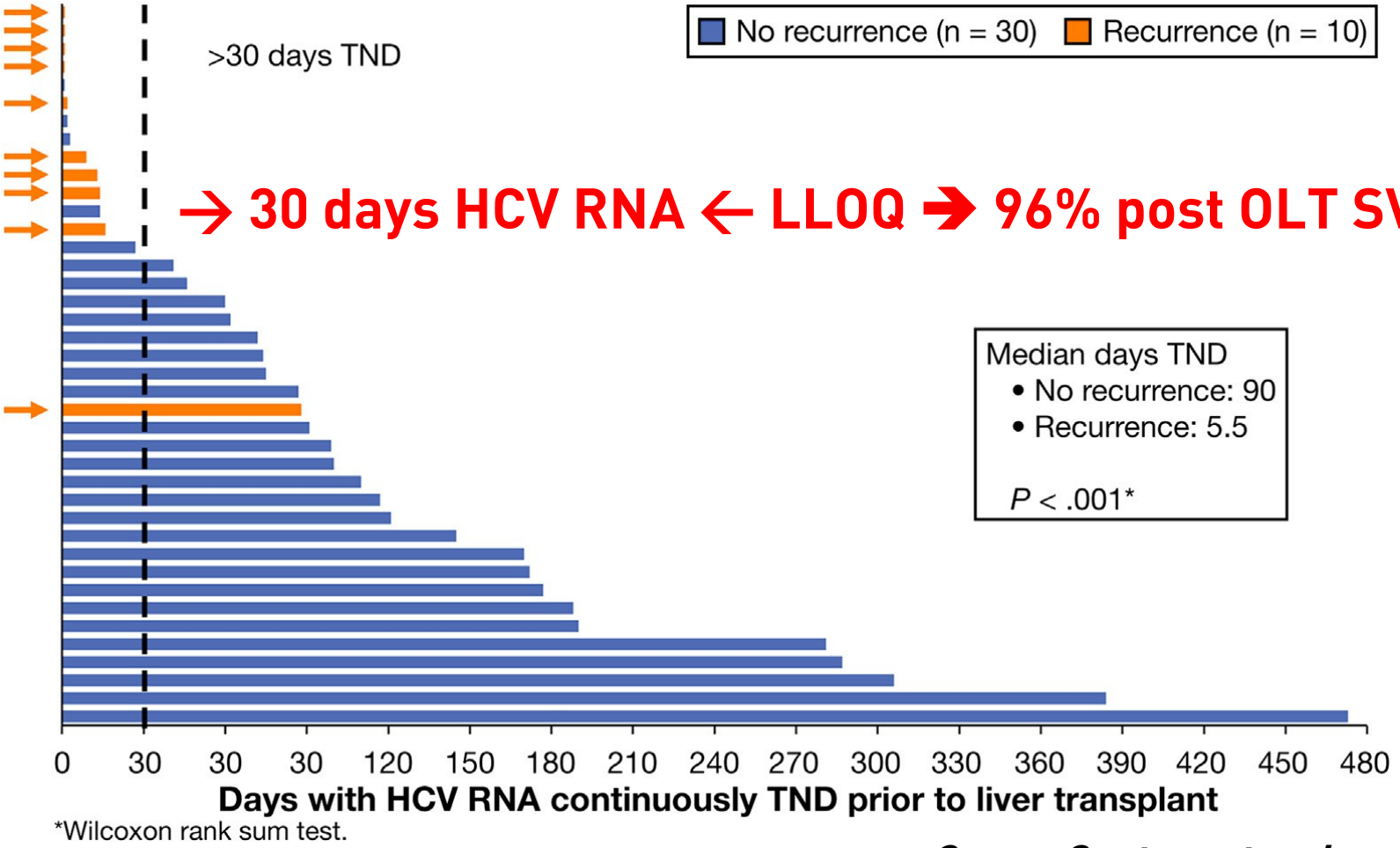
- → 90% recipients have histological features of chronic HCV
- 10 – 30% progress to cirrhosis
- Median interval OLT → cirrhosis = 9.5 y Post OLT HCV cirrhosis – 40% decomp. 1 year



Prevent post OLT HCV Recurrence

Phase II Study
N = 61 Patients, CP A
46 LT, 43 undetectable HCV RNA at LT

Post OLT SVR 12 = 70%



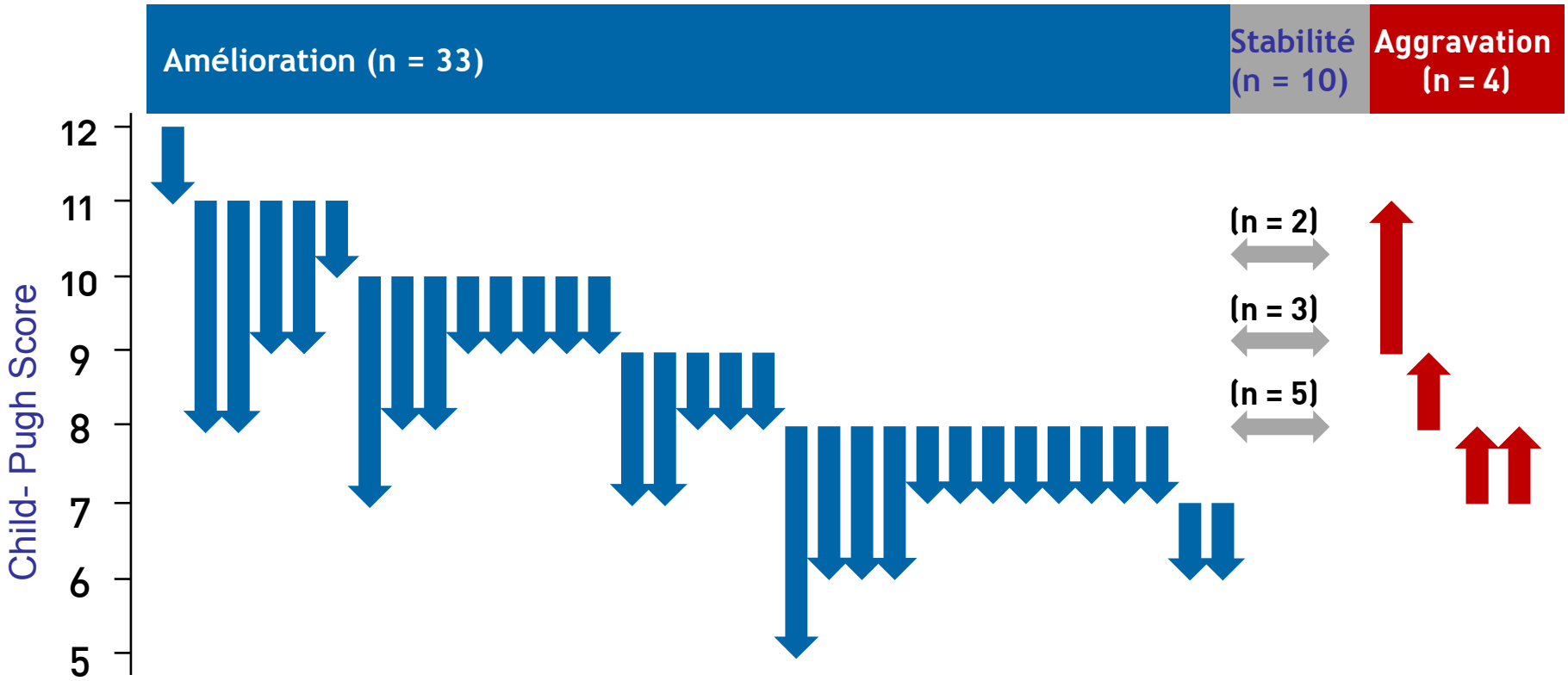
→ 30 days HCV RNA ← LLOQ ➔ 96% post OLT SVR

Curry, Gastroenterology 2015

Significant reduction in CHILD Score

OF/LDV + RBV for 12 weeks in patients with decompensated cirrhos

Changes in Child-Pugh Score at post treatment W4



Flamm SL, Etats Unis, AASLD 2014, Abs. 239 actualise

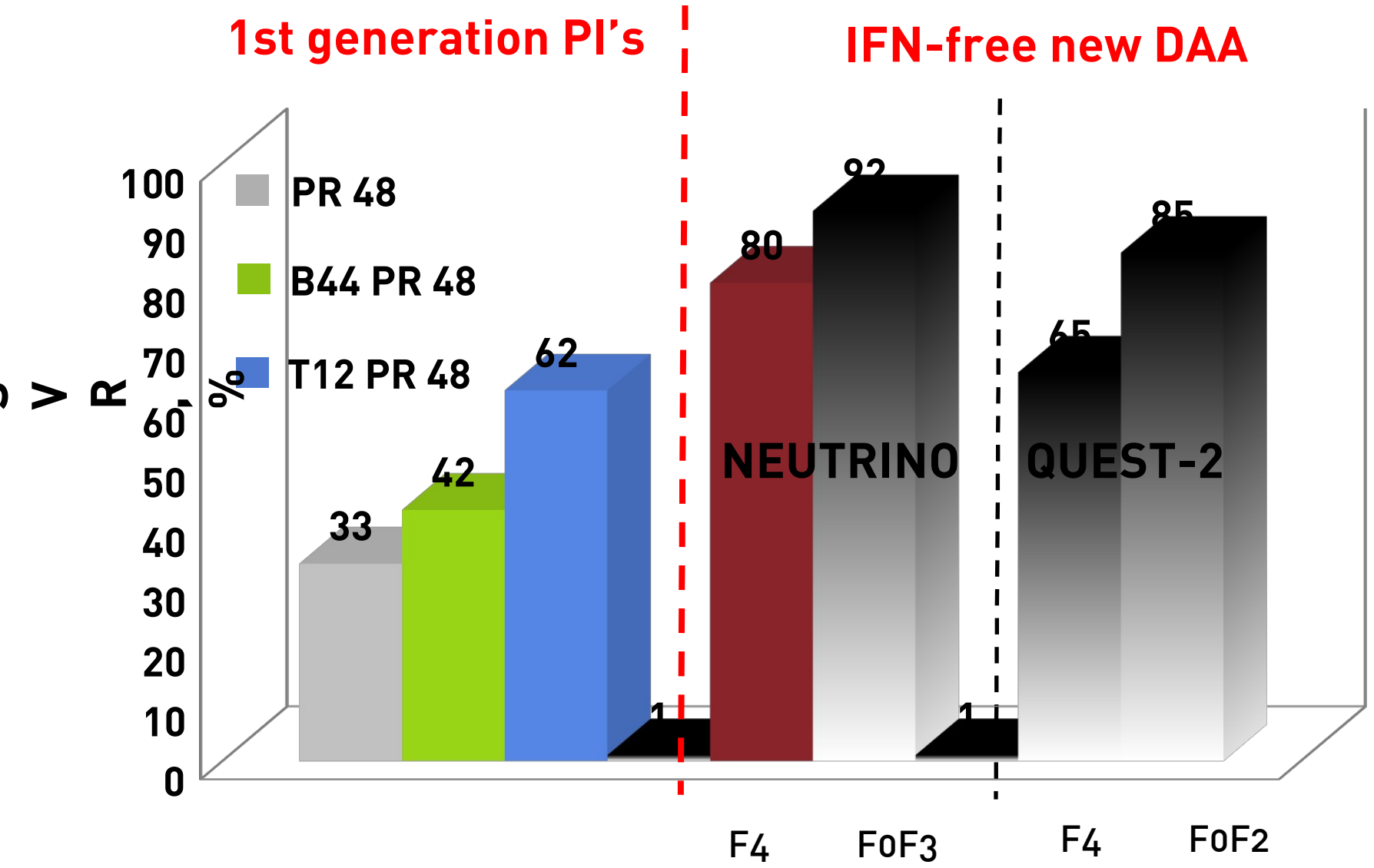
CLINICAL CASE

Q2

Choice of the treatment regimen:

- ✓ IFN based 1st generation PI's
- ✓ IFN based new DAA
- ✓ IFN- free DAA

SVR with IFN based regimens in cirrhotic patients

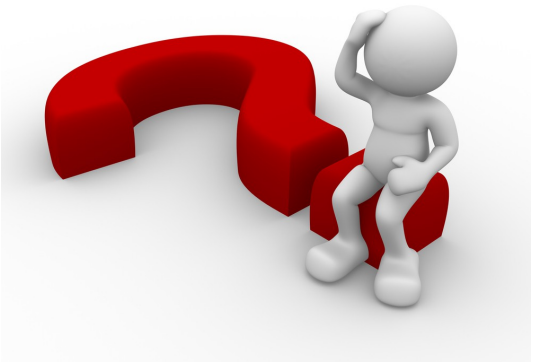


Poordad, NEJM 2011
Jacobson, NEJM 2011

Lawitz, NEJM 2014
Manns, Lancet 2014

CLINICAL CASE

Q3 IFN-free DAA:



Treatment duration in cirrhotic patients?

- ✓ 12 weeks
- ✓ 24 weeks

Our patient:

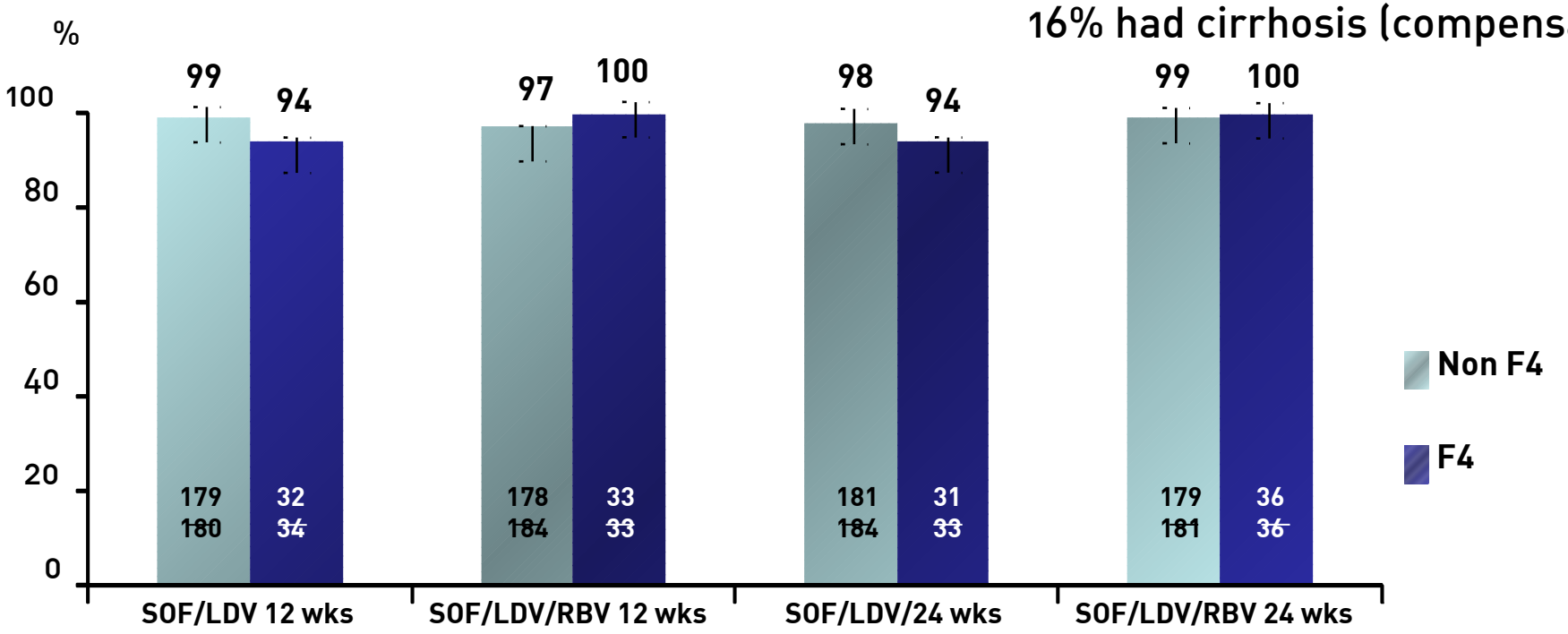
Child B8, MELD 17
Naive
G1b, IL28B = CT
Hb = 13.5 g/dl

RBV:

- ✓ With RBV
- ✓ Without RBV

ION – 1: SOF/LDV in G1 untreated patients with or without cirrhosis

Phase III, N = 865 patients
16% had cirrhosis (compensated)



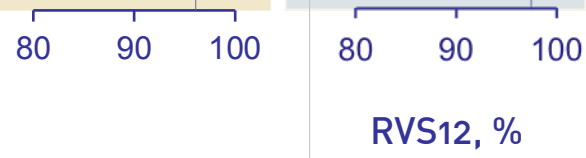
	SOF/LDV 12 wks.	SOF/LDV/RBV 12 wks.	SOF/LDV 24 wks.	SOF/LDV/RBV 24 wks.
Breackthrough	0	0	1 (↓ 1 %)	0
Relapse	1 (↓ 1 %)	0	1 (↓ 1 %)	0
Lost of f/u	2 (↓ 1 %)	6 (3 %)	3 (1 %)	2 (1 %)

Afdhal, NEJM 2014

SOF/LDV ± RBV in G1 patients with cirrhosis

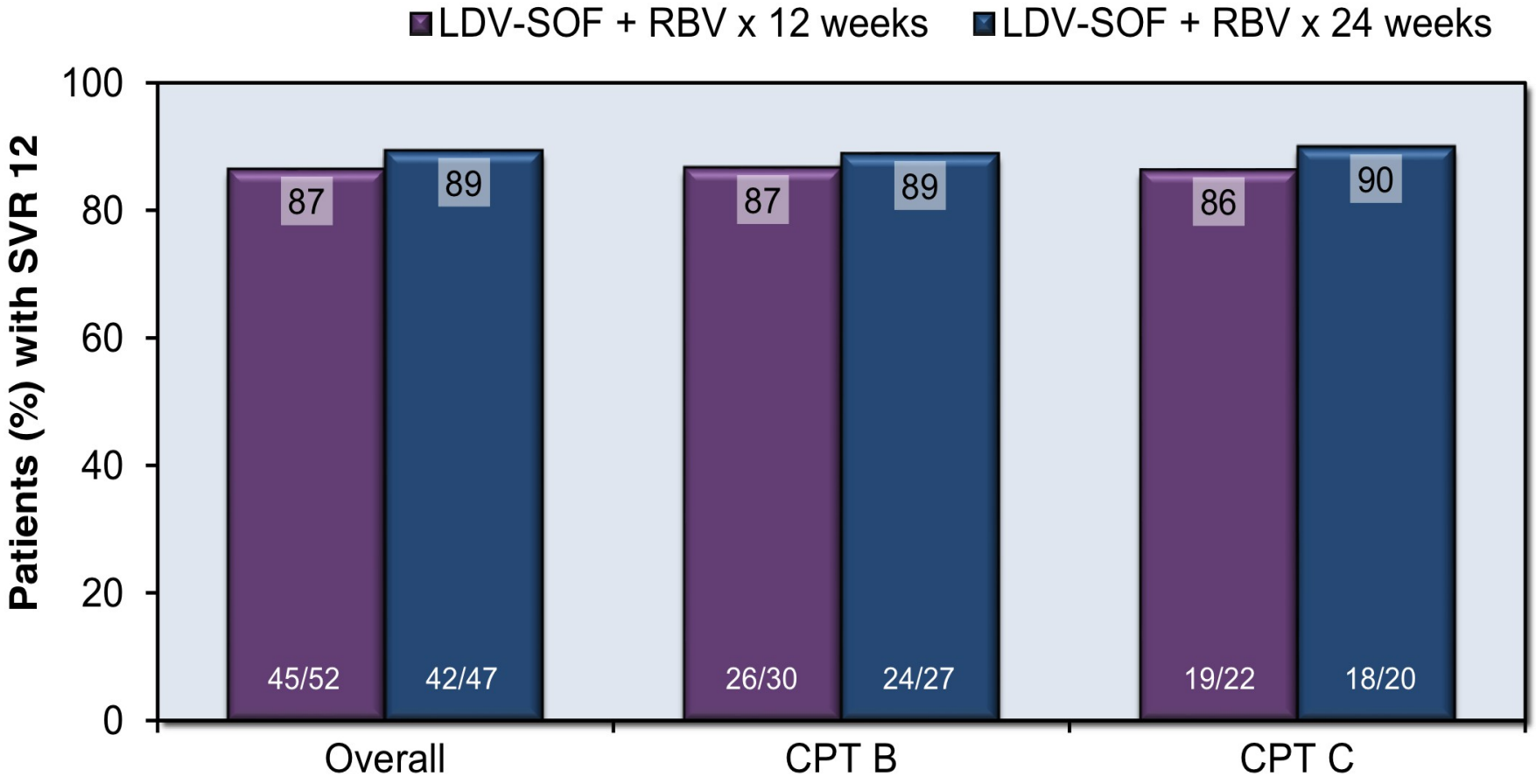
N = 513 patients with compensated cirrhosis; 31% naïve.

		Total	Naïfs de traitement	En échec de traitement
RVS12 globale		96 %	98 %	95 %
Durée	12 sem.	95 %	97 %	94 %
	24 sem.	98 %	99 %	98 %
Régime	LDV/SOF	95 %	96 %	95 %
	LDV/SOF + RBV	97 %	99 %	96 %
Durée ± RBV	LDV/SOF 12 sem	92 %	96 %	90 %
	LDV/SOF + RBV 12 sem	96 %	98 %	96 %
	LDV/SOF 24 sem	98 %	97 %	98 %
	LDV/SOF + RBV 24 sem	100 %	100 %	100 %



Bourlière M, France, AASLD 2014, Abs. 82 actualis

SOLAR -1: LDV-SOF + RBV in patients with decompensated cirrhosis listed for OLT

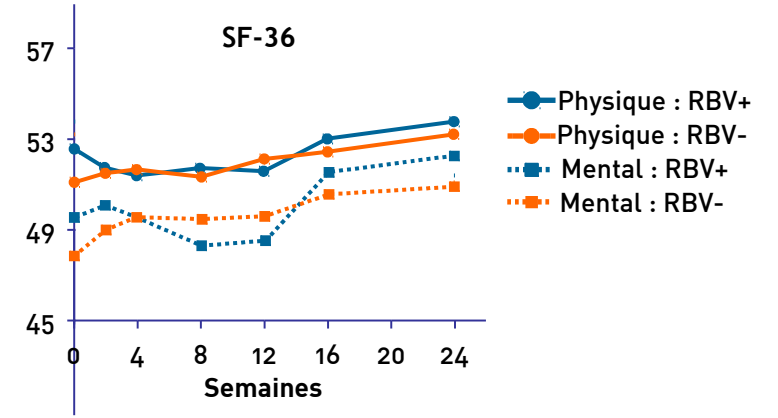


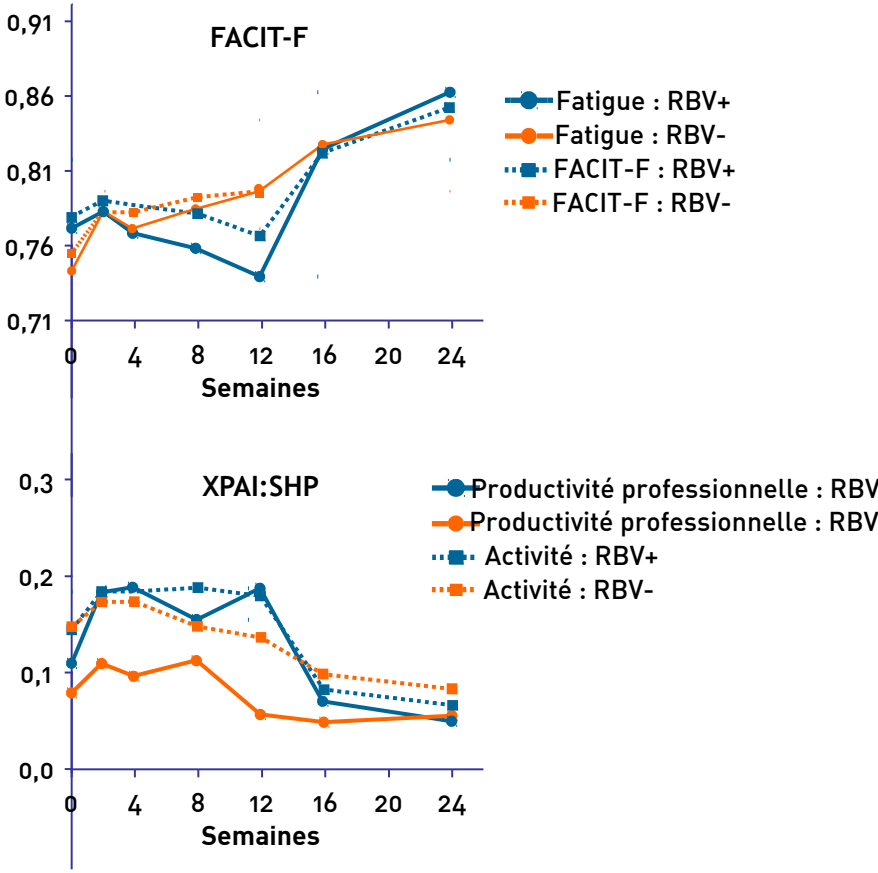
6 subjects excluded because received transplant while on study: (2 CPT B/24 week; 1 CPT 2/12 week; 3 CPT C/24 week
3 subjects had not reached SVR12 timepoint

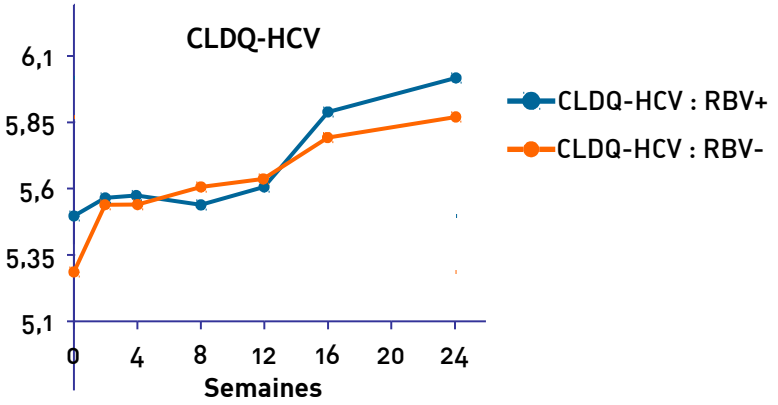
Flamm, Abstr 239, AASLD 2014

Impact of RBV on quality of life

On treatment and EOT quality of life: SOF/LDV± RBV

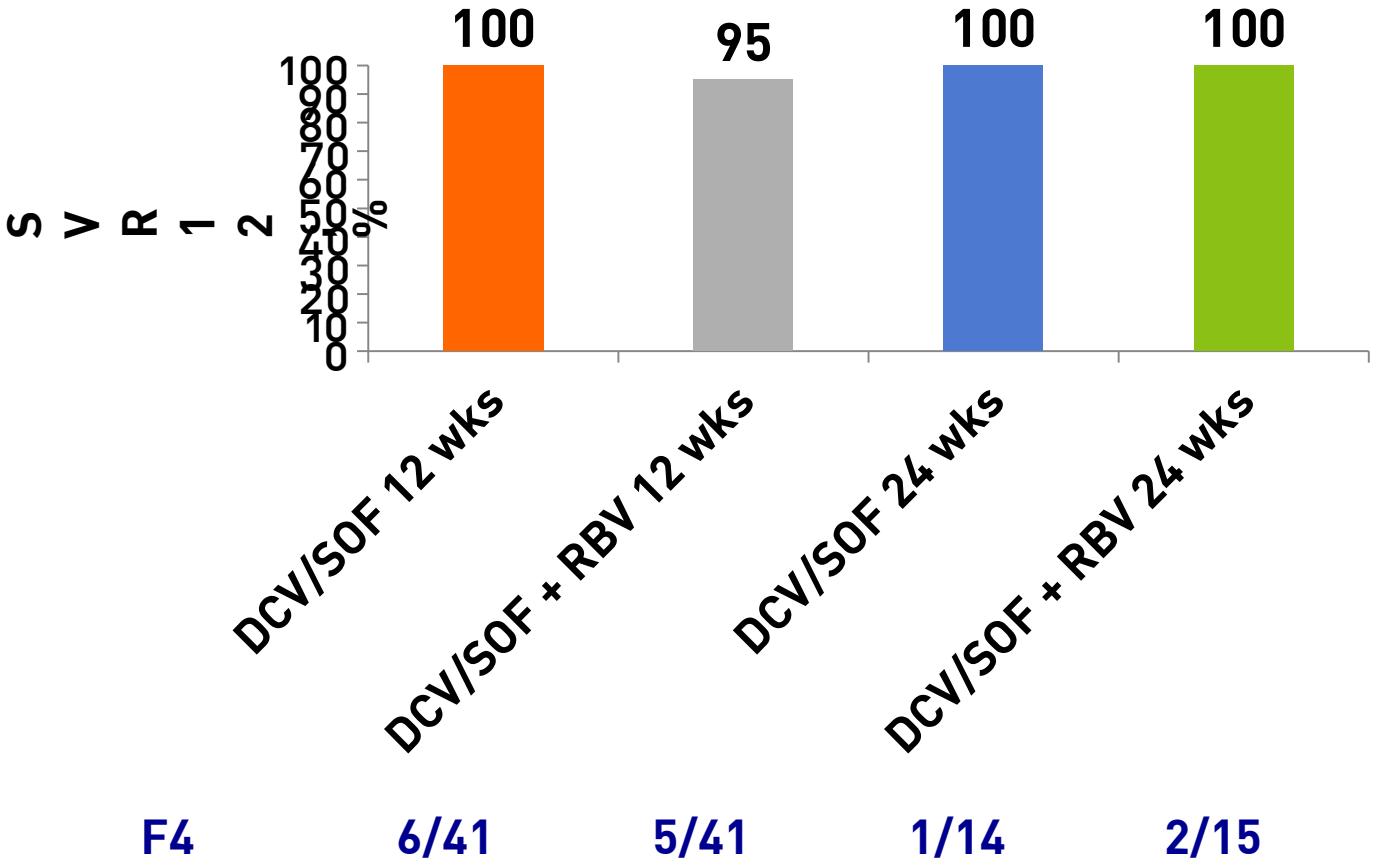






Younossi Z, Etats-Unis, EASL 2014, Abs. P1324 actualis

Sofosbuvir + Daclatasvir in previously untreated G1 patients

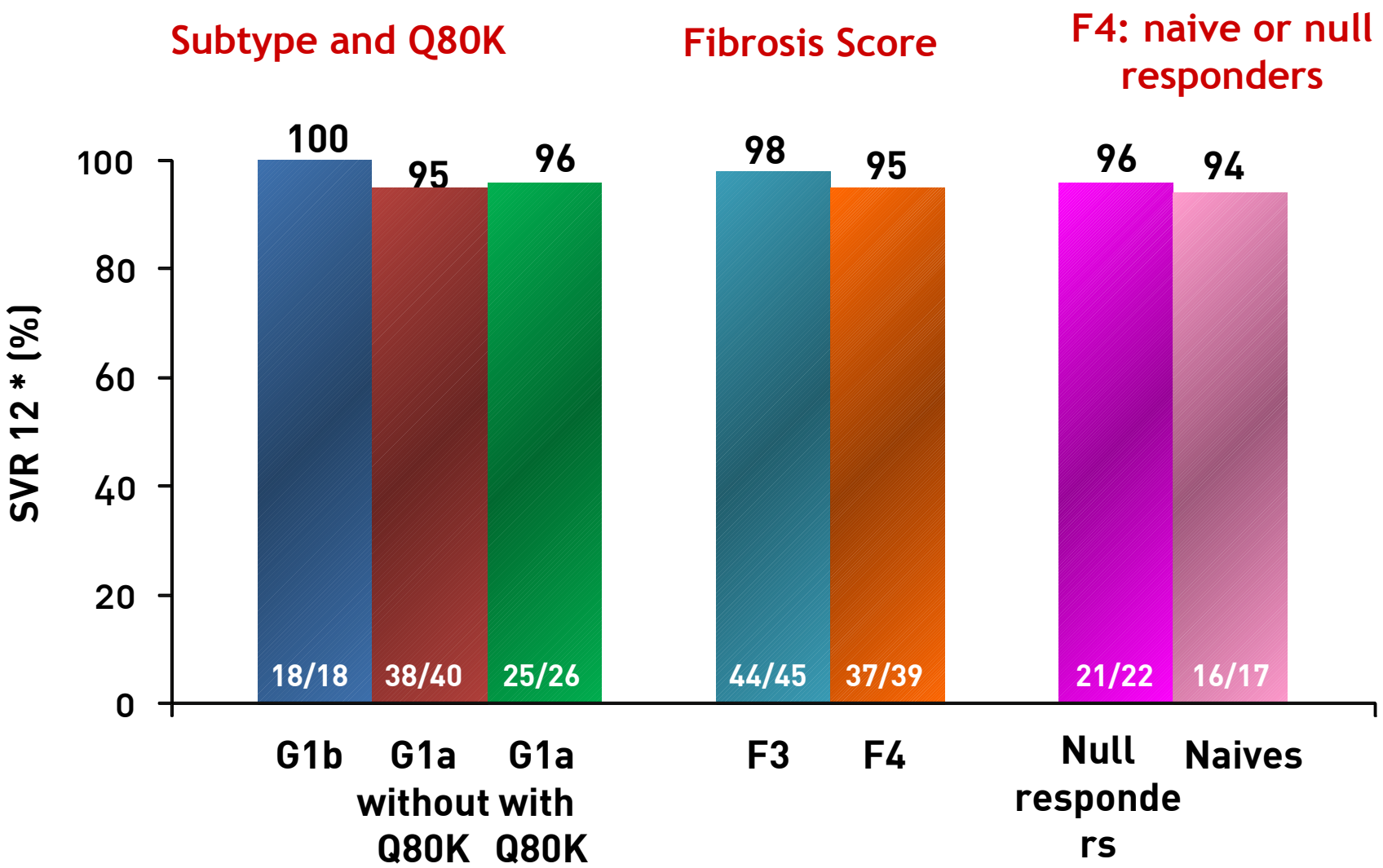


F4	6/41	5/41	1/14	2/15

Sulkowski, NEJM 2014

Phase III ALLY 1 trial: ongoing (cirrhosis and post OLT)

COSMOS (cohort 2) : sofosbuvir/simeprevir ± RBV in F3F4 G1 naïve and non responders

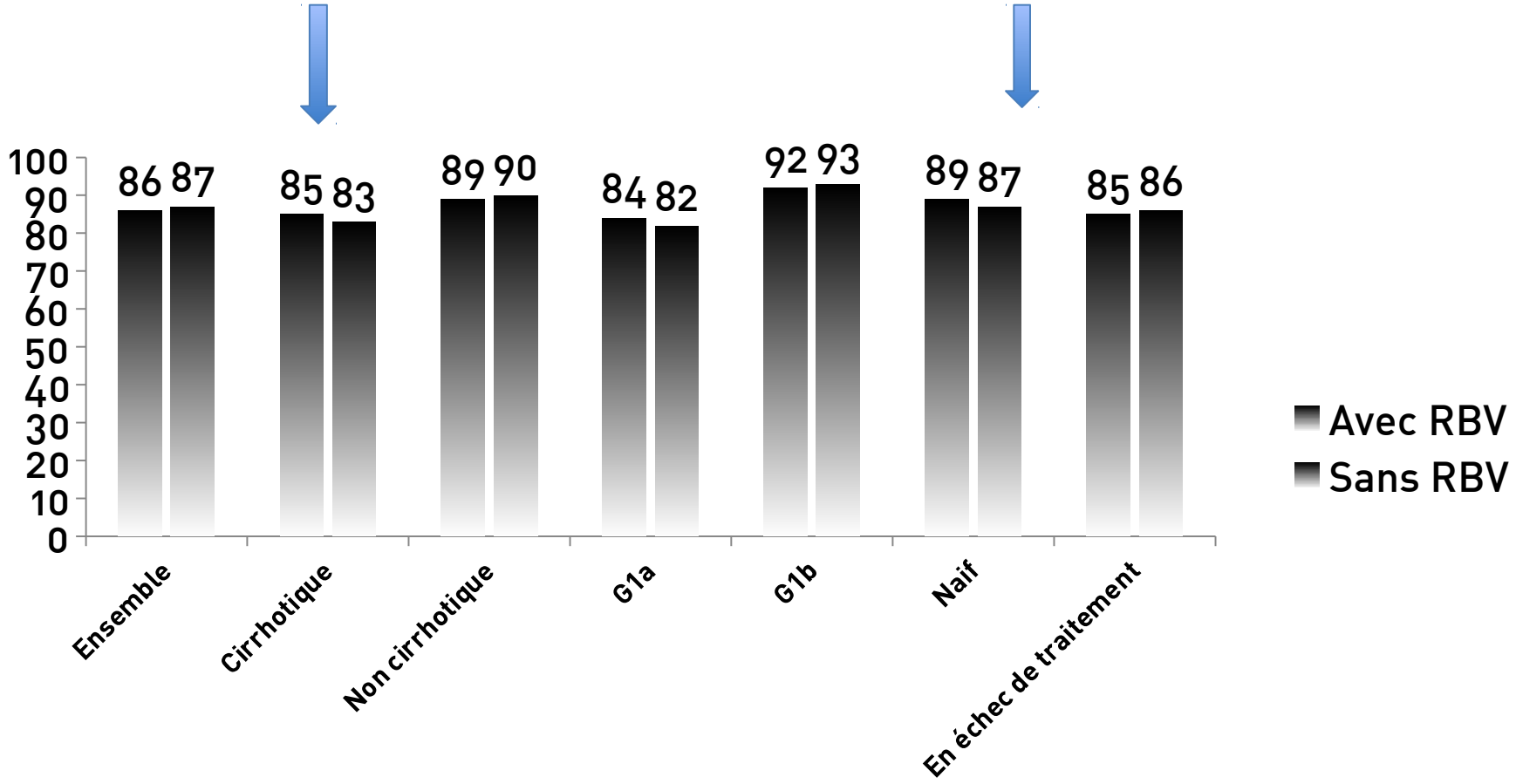


* Patients sans RVS12 pour raison non virologique exclus de l'analyse

Lawitz E, Etats-Unis, EASL 2014, Abs. 0165 actualis

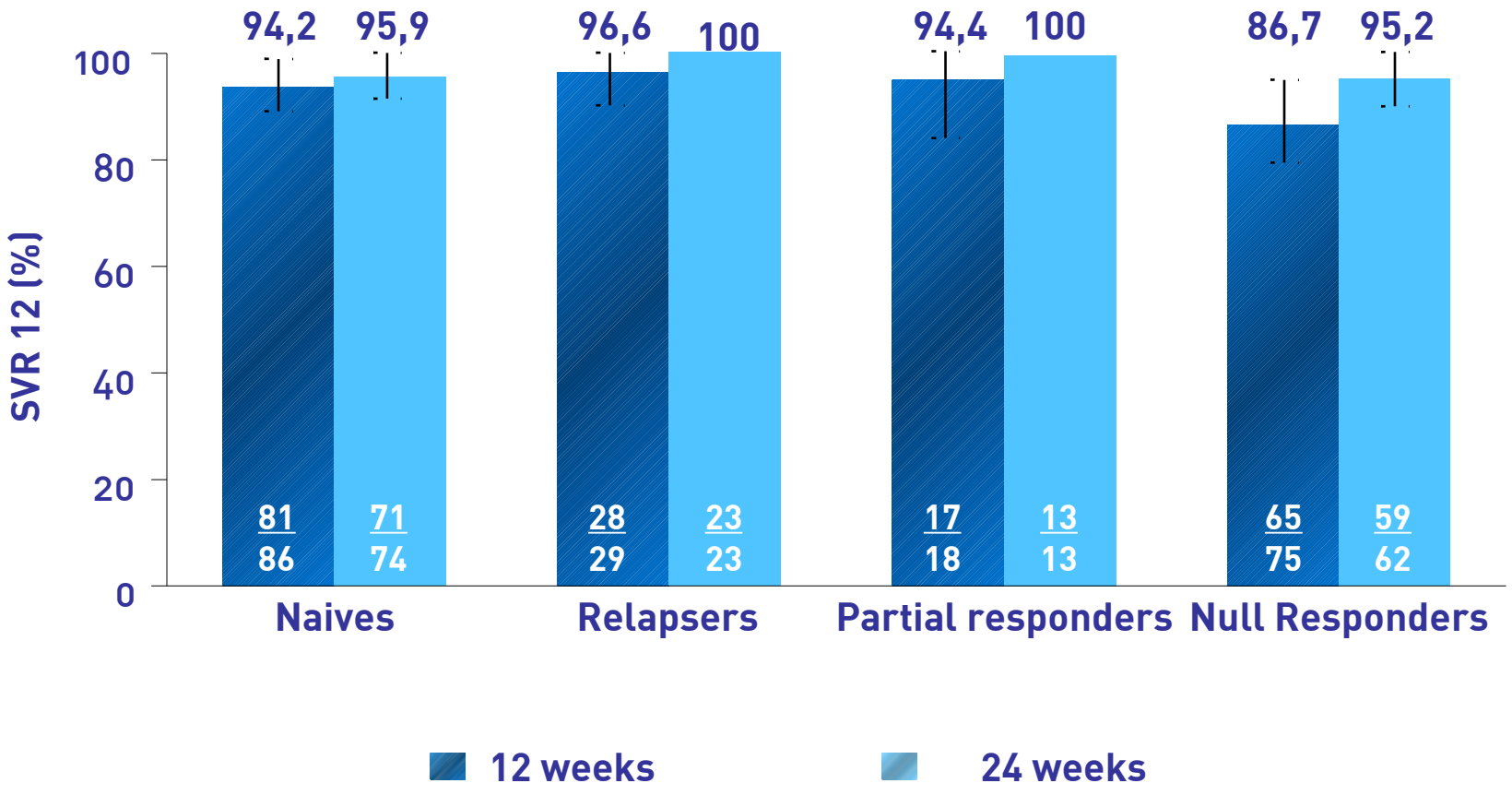
SOF/SMV ± RBV – Real Life Data
HCV TARGET

- **Genotype 1 :** SOF + SIM ± RBV 12 weeks - 378 patients



Jensen DM, Etats-Unis, AASLD 2014, Abs. 45 actualis

Turquoise 2 : ABT-450/r/ombitasvir + dasabuvir + RBV in G1 patients with cirrhosis



Fried M, Etats-Unis, AASLD 2014, Abs. 81 actualisé

CLINICAL CASE

Q4

Predictors of SVR/AE's

Does Albumin level and platelets count impact outcomes of patients with cirrhosis treated with the new DAA?

- ✓ YES
- ✓ NO

Our patient:

Child B8, MELD 17
Naïve, G1b, IL28B = CT
Hb = 13.5 g/dl
Albumin = 34 g/l
Platelet = 92 000/mm3

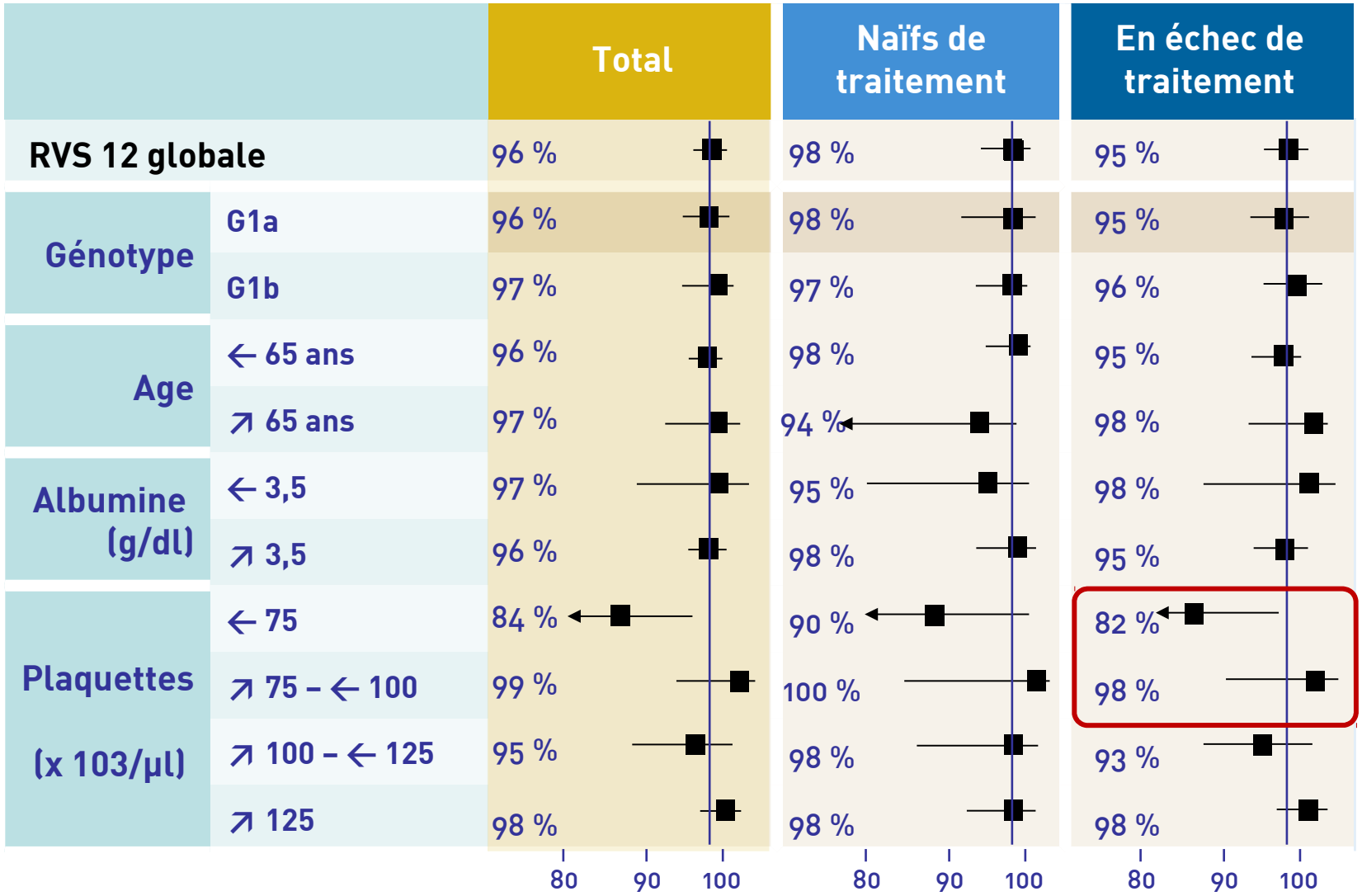
Predictors of SVR and AE's with 1st generation PI's

		Platelets count ≤ 100,000/mm3	Platelets count > 100,000/mm3
Albumin < 35 g/L	N Complications, n (%) SVR12, n (%)	37 19 (51.4%) 10 (27.0%)	31 5 (16.1%) 9 (29.0%)
Albumin 35 g/L	N Complications, n (%) SVR12, n (%)	74 9 (12.2%) 27 (36.5%)	306 19 (6.2%) 168 (54.9%)

Hézode C, et al. J Hepatol 2013;59:434-441

Fontaine H, et al. AFEF2013

SOF/LDV ± RBV in G1 patients with cirrhosis

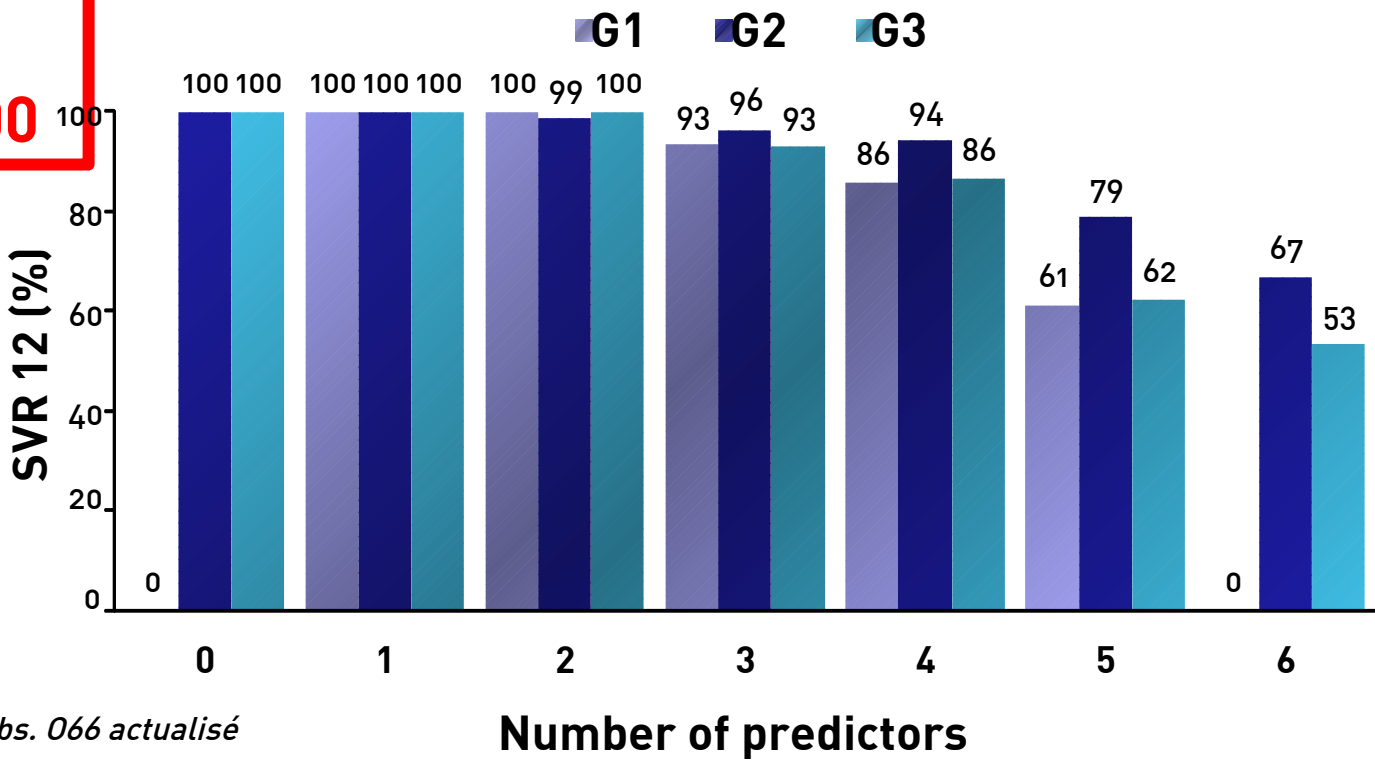


Bourlière M, France, AASLD 2014, Abs. 82 actualis

Negative predictors with SOF-based regimens

Previous treatment
Male
Weight ↗ 75 kg
IL28B non CC
Cirrhosis
HCV RNA → 800 000

SVR 12 according to the number of negative predictors and viral genotype



Foster G, Royaume-Uni, EASL 2014, Abs. 066 actualisé

CLINICAL CASE

Q5

DAA and renal impairment

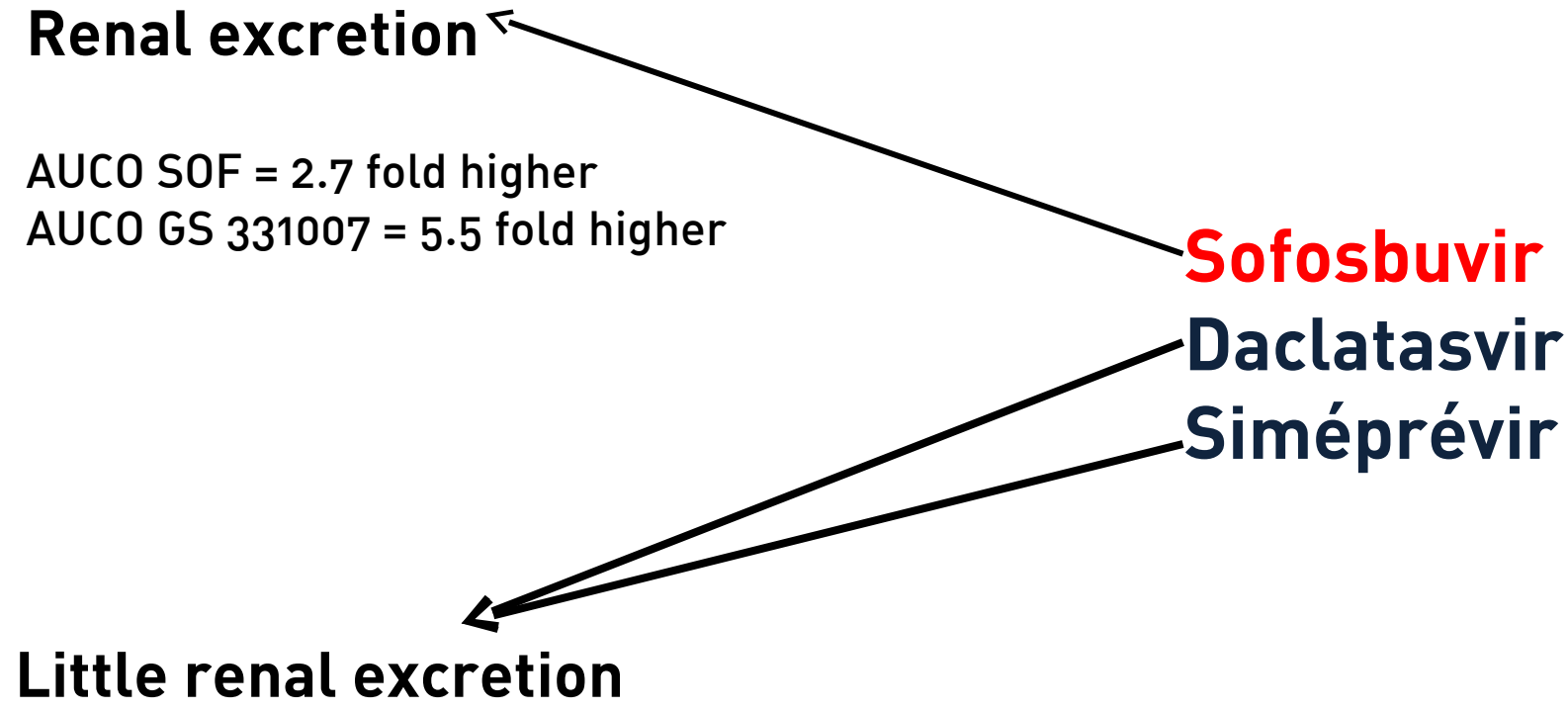
Dose adaptation according to renal function?

- ✓ YES
- ✓ NO

Our patient:

Child B8, MELD 17
Naive
G1b, IL28B = CT
Hb = 13.5 g/dl
Creatinin = 130 µmol/l; Clearence = 53 ml/min

In november 2014...



In 2015, Lédipasvir

Less than 1%
renal excretion

Safety, Efficacy and PK of SOF and LDV in patients with renal impairment

SOFOSBUVIR

10 patients
Without cirrhosis
CrCl ↓ 30 ml/min
SOF/RBV 24 wks

Efficacy →

W4 HCV RNA under LLOQ = 9/10

Safety ↓

- ✓ 1 RBV STOP at W8
- ✓ 4 RBVdose reduction
- ✓ 2/3 increased dose EPO
- ✓ 3 introductions EPO
- ✓ 1 angor instable

Gane, AASLD 2014 Abstr. 966

LEDIPASVIR

Same PK as patients with normal RF
No dose adaptation

Mogalian, AASLD 2014 Abstr. 1952

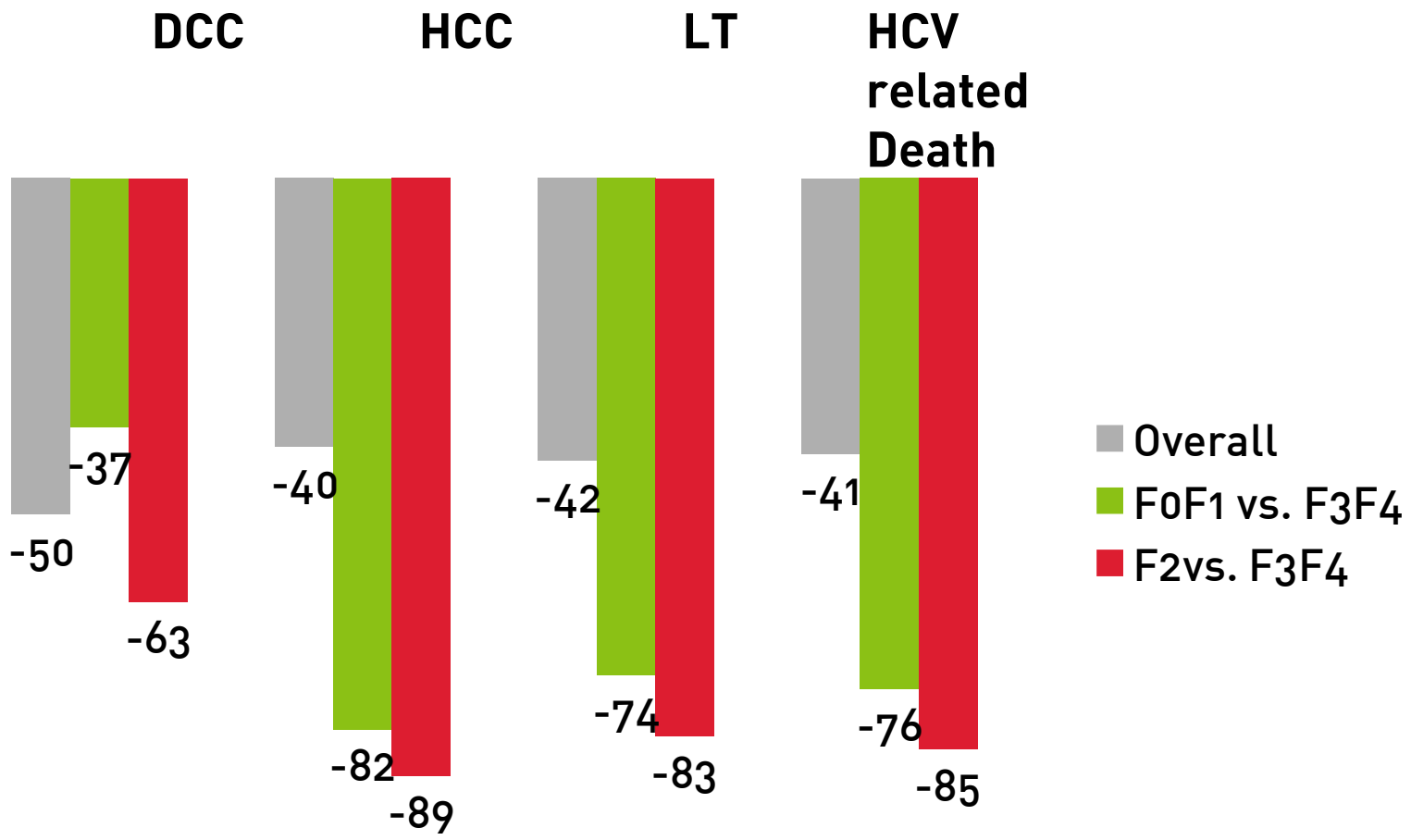
CLINICAL CASE

Q6

Health outcomes and benefits with DAA?

- ✓ Most benefit with IFN-based DAA
- ✓ Most benefit with IFN-free DAA

Delaying treatment initiation in HCV G1 treatment naive patients would lead to a substantially more cases of CLD complications ....

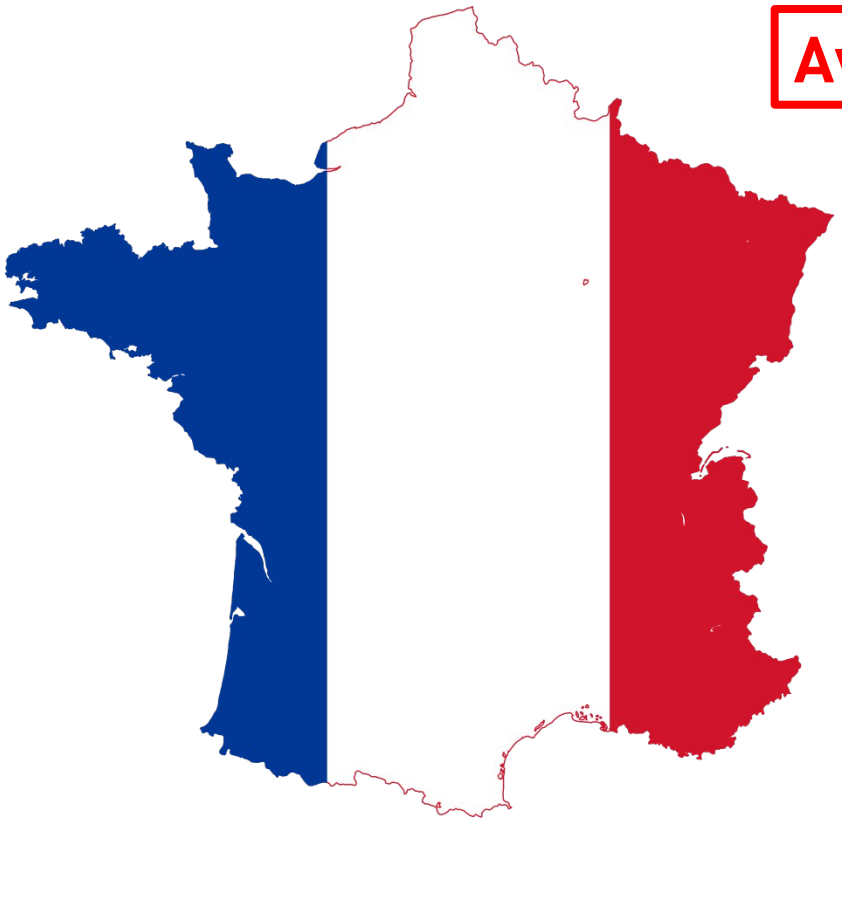


Greatest benefit of treating F2 vs. F3F4

Ahmed, Younossi, AASLD 2014, Abstr. 175

Impact of future HCV treatment on LT

2013 – 2022



Avoid LT in 4425 potential candidates

Reduction in gap between the needs of LT and graft availability:

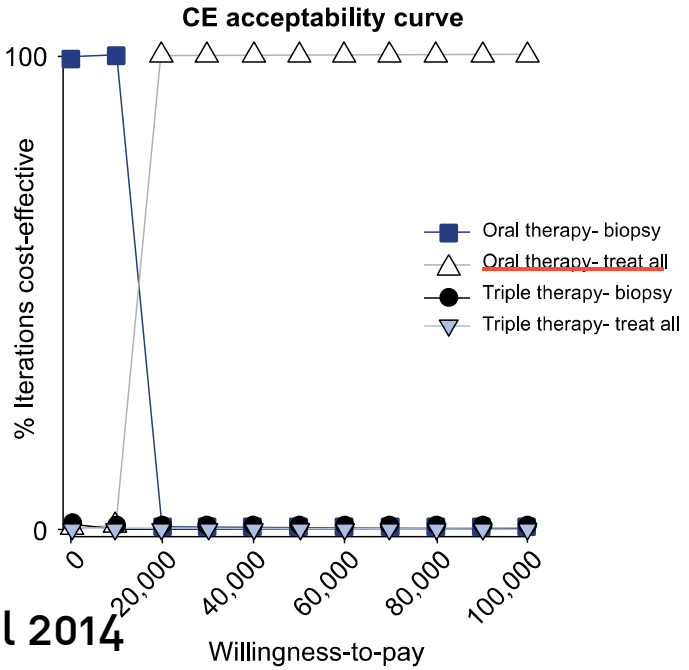
- 88% for HCC
- 42% for decompensated cirrhosis

Deuffic-Burban, Dig. Liv. Dis. 2014

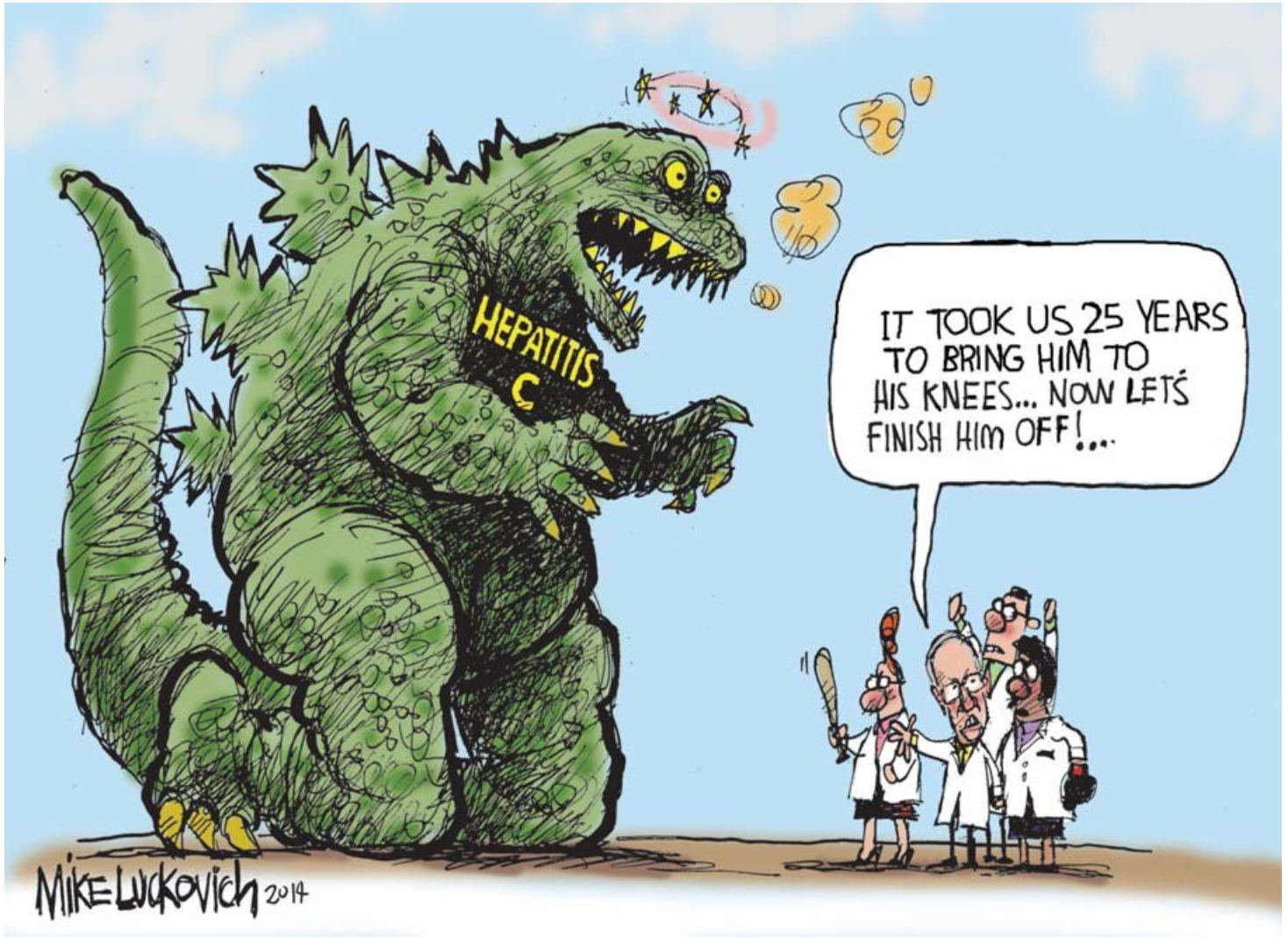
Cost effectiveness in G1 patients

	Triple therapy		Oral interferon-free therapy	
	Staging	Treat all	Staging	Treat all
Life expectancy (yr)	28.324	28.520	29.827	29.978
Progression to:				
Cirrhosis (%)	29.4	23.6	10.6	6.5
Decompensated (%)	13.4	11.8	5.9	4.9
HCC (%)	12.0	10.5	7.3	6.4
Decompensated or HCC (%)	24.2	21.3	12.7	10.9
Transplant (%)	5.2	4.6	3.1	2.7

	Unit price
Unit price of molecules, €/week	
Combination of pegylated interferon and ribavirin	312
Telaprevir	2210
Boceprevir	796
IFN-based new DAAs*	5062
Unit price of severe adverse events, €†	
Anemia	2564
Depression	1619
Rash	2942
Unit price of moderate anemia, €‡	4200



ounossi, J Hepatol. 2014; Deuffic-Burban, J Hepatol 2014



»There are decades where nothing happens; and there are weeks where decades happen«

Scott Freedman, J Hepatol. 2014


Thank you!