Treatment of genotype 4 patient

with cirrhosis

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Clinical case

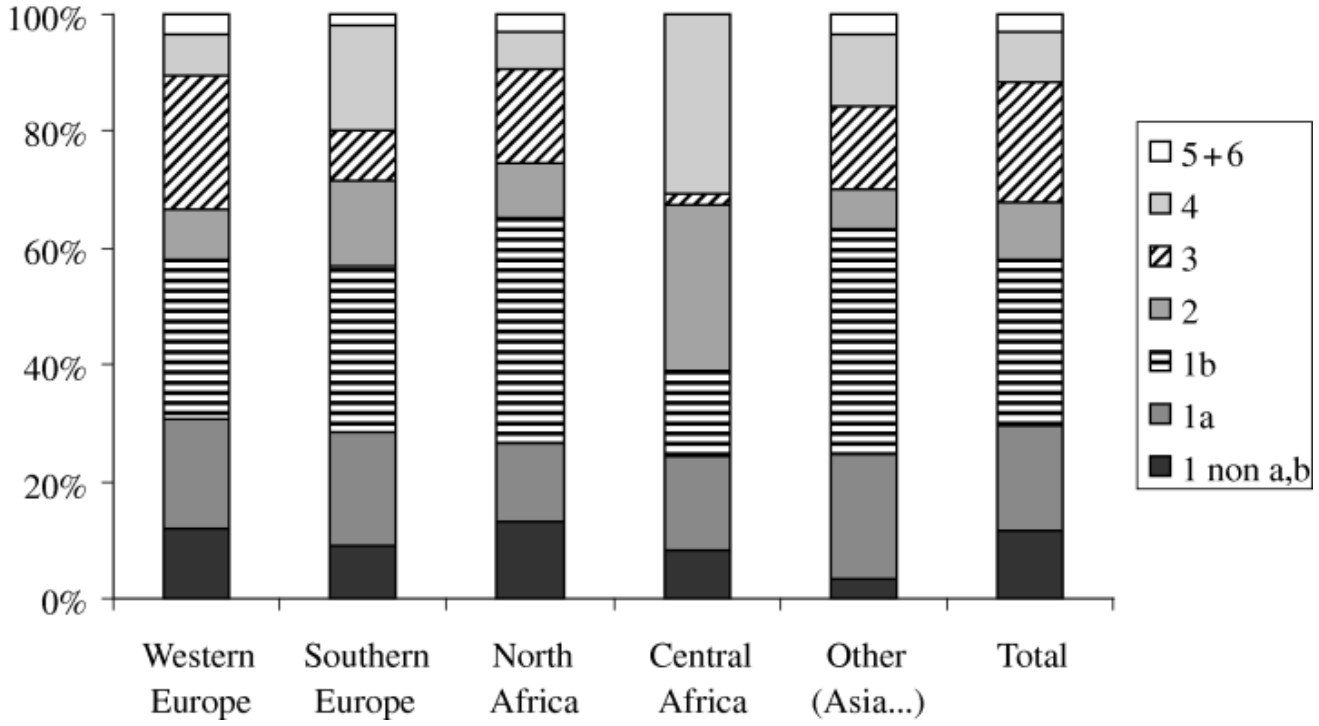
- 52 year-old patient
- Intra-venous drug user 1987-1989
- No other medical history
- Active smoker
- Alcohol consumption : 50 g/d
- No symptom
- Diagnosed with chronic hepatitis C in 2009 (screening)

Clinical case

- Laboratory tests
  - HCV genotype 4d, HCV RNA = 5.7 log IU/ml, no co-infection
  - AST=3ULN, ALT=2ULN, GGT=5ULN
  - Platelets = 70 G/l
  - Albumin = 38 g/L, AFP < 5 IU/ml
- Ultra-sound : hepatomegaly, irregular surface
- Transient elastography : 34.6 kPa
- Gastroscopy : grade I oesophageal varices

→ Compensated cirrhosis, genotype 4

Changing of hepatitis C virus genotype patterns in France at the beginning of the third millenium: The GEMHEP GenoCII Study

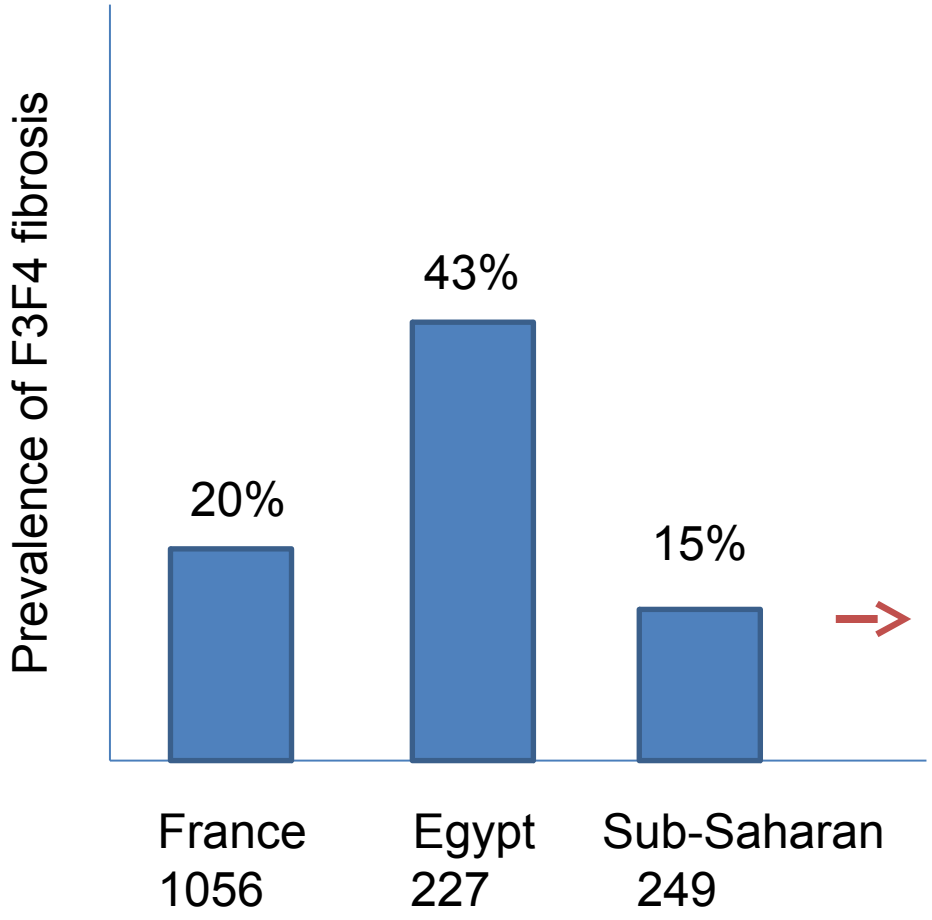


Payan et al, Journal of Viral Hepatitis
Volume 12, Issue 4, pages 405-413, 9 JUN 2005 DOI: 10.1111/j.1365-2893.2005.00605.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2893.2005.00605.x/full#f2

Question to the audience

- Is genotype 4 associated to particular natural history ? (accelerated fibrosis progression, steatosis, role of subtype)
- Yes
- No

Ethnicity, subtype and severe fibrosis



- Role of HCV subtype 4a vs 4d ?
- Cofounding factors ?
  - Metabolic syndrome
  - Shistosomias

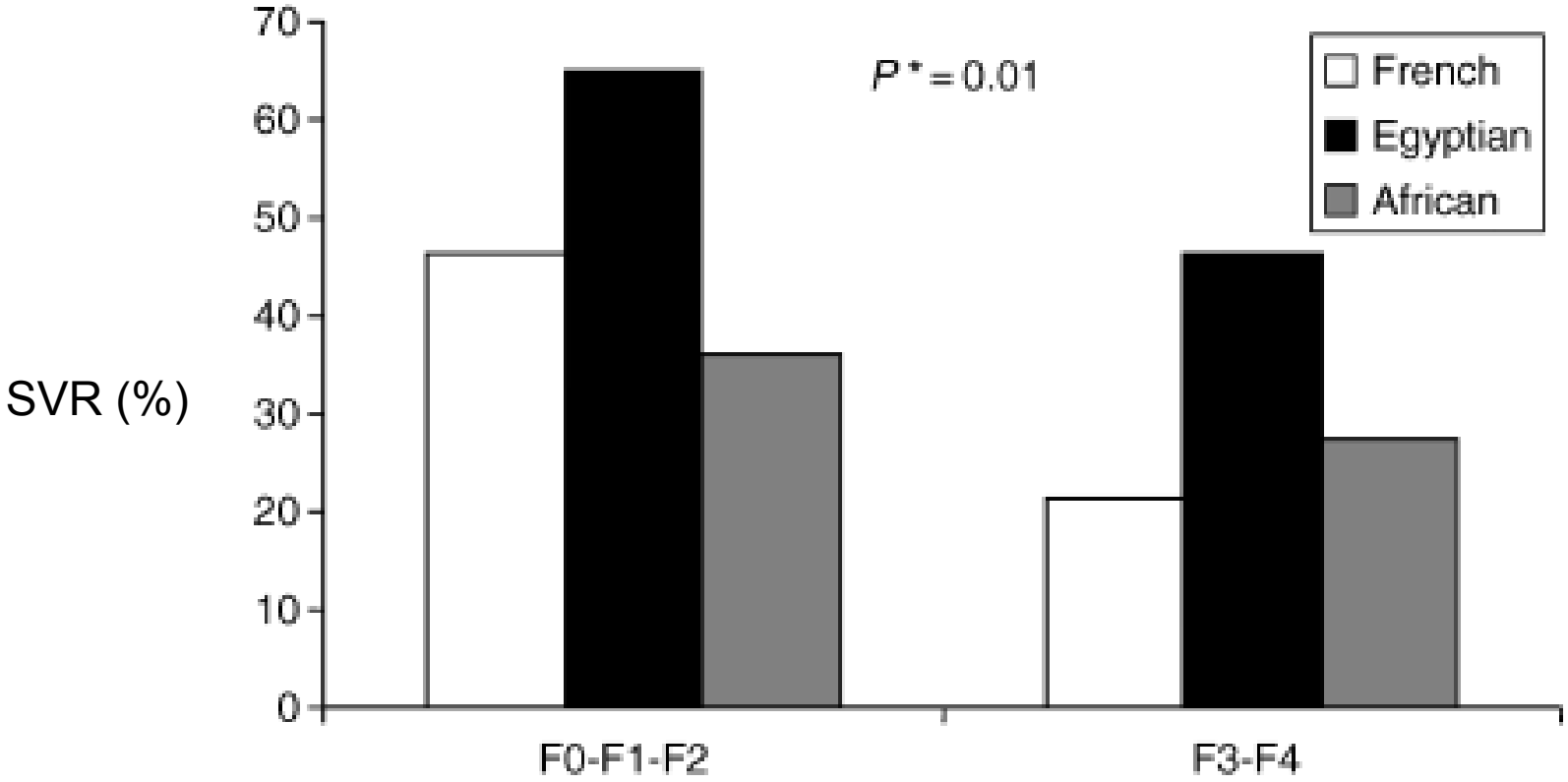
→ Non specific natural history

Roulot et al, J Viral Hepatitis 2007

Questions to the audience

- Due to the severity of lesions a treatement by pegylated interferon + ribavirin was planed. What are the chance to achieve SVR ? Does HCV sub-type has any impact ?

Epidemiological characteristics and response to peginterferon plus ribavirin treatment of hepatitis C virus genotype 4 infection



HCV subtype not tested in the analysis, IL28B ?

Roulot et al, Journal of Viral Hepatitis
Volume 14, Issue 7, pages 460-467, 20 NOV 2006 DOI: 10.1111/j.1365-2893.2006.00823.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2893.2006.00823.x/full#f1

Treatment by Peg-IFNα + ribavirin

- Treatment conducted in the ENABLE study (Eltrombopag)

	W0	W4	W8	W12	W16	W20	W24
Hb	12.9	11.7	10.8	10.2	10.1	10.3	10.9
Platelets	69	43	37	35	41	38	44
ALT	112	45	42	37	51	48	39
HCV RNA	5.7 log	D < 15	D <15	D <15	ND	D<15	110 IU

→ Optimal treatment, but failure

Clinical case : G4, cirrhosis, PR failure

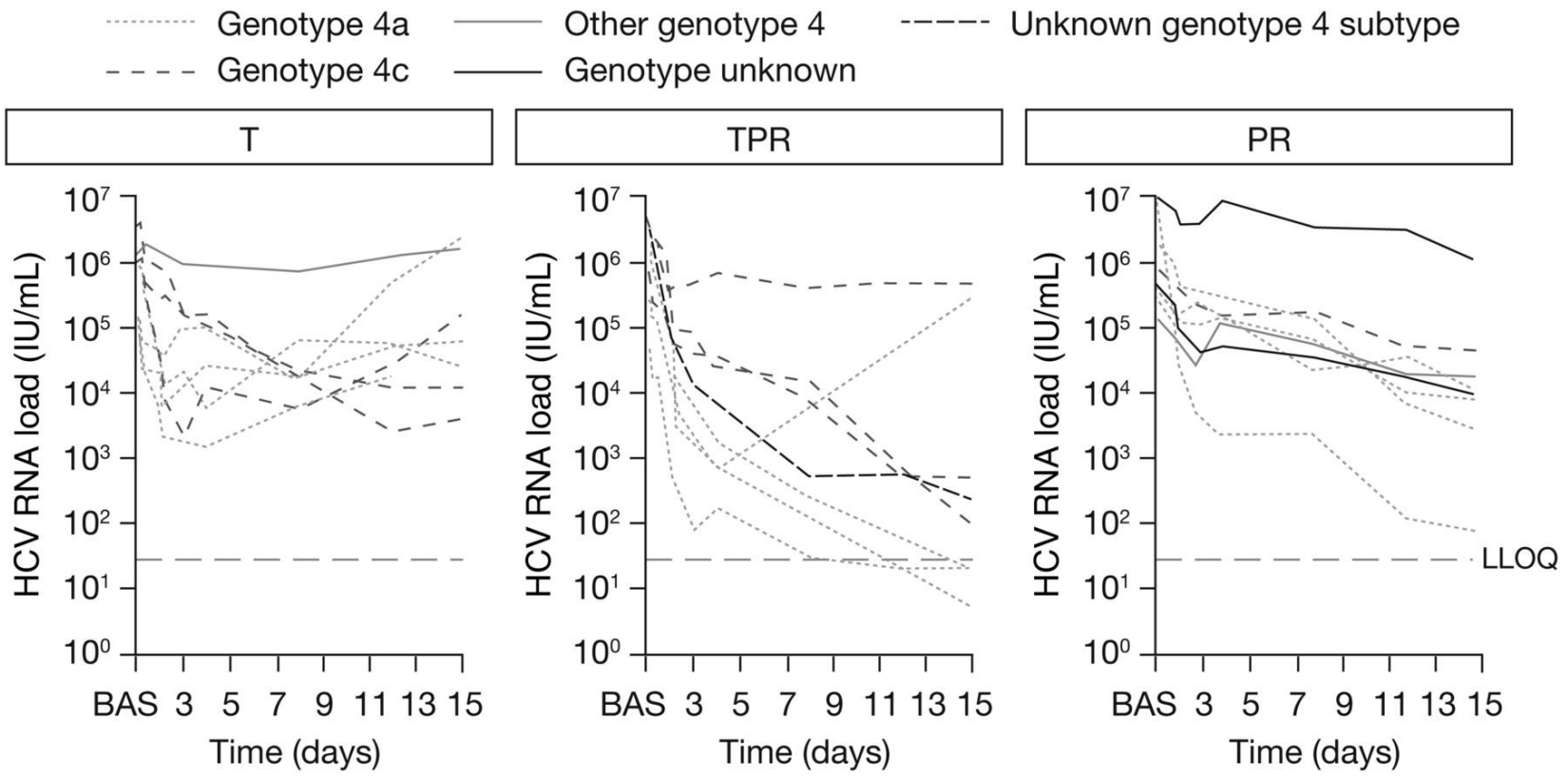
- Improvement of way of life and close follow-up
- Slight deterioration of laboratory tests
  - PT=66%, albumin =32 g/L, platelets = 68 G/l
  - Bilirubin and AFP : normal serum levels
- US every 6 months : no hepato-cellular carcinoma
- Gastroscopy 2011 : grade II varices : propranalol 160 mg/d

- 2011 : availability of first generation protease inhibitors
  - Early access program (cohort ATU : genotype 1)
  - Possibility to apply for « nominative ATU » in other genotypes

Question to the audience

- What would you have done ?
  - Start triple therapy with telaprevir ?
  - Wait for more data on telaprevir in genotype 4 ?
  - Wait for more potent antiviral agents ?

Changes in the hepatitis C virus (HCV) RNA load over the investigational treatment phase for each patient, by G4 HCV subtype and treatment group.



Benhamou Y et al. J Infect Dis. 2013;208:1000-1007

The Journal of Infectious Diseases

Results in the real life setting : CUPIC G1

SVR12

SVR12 according to PR response	Bocéprevir n=212	Télaprevir n=299
Relapsers	54	74
Partial responders	38	40
Nul responders	0	19

- But no data in genotype 4 !

Fontaine H, et al. EASL 2013. Amsterdam, The Netherlands. #60 actualisé
Fontaine H, et al. AFEF 2013, CO-26
BOC= Bocéprevir; TVP= Télaprévir, PEG-IFN= interféron pegylé; RBV= Ribavirine

Treatment by peg-IFNα + ribavirin + telaprevir

- Telaprevir 750 mg every 8 hours 12 weeks
- Treatment from may 2011 to april 2012

	W0	W2	W4	W12	W24	W48	W72
Hb	12.5	11.7	8.7	9.2	10.1	10.3	11.8
Platelets	72	52	43	35	47	38	61
ALT	112	45	42	37	30	26	78
HCV RNA	5.6 log	D < 15	ND	ND	ND	ND	5.8 log

→ Better initial response but relapse…

Case : G4, cirrhosis, triple therapy failure

- Follow-up
- Variceal bleeding in january 2013 (band ligation)
- Still in good general condition
- Slight deterioration of liver tests
  - PT=58%, platelets = 55 G/l, albumin = 30 g/L
- US : no hepato-cellular carcinoma, portal hypertension

- January 2014 : simeprevir and sofosbuvir available in the early access program (cohort ATU) for cirrhotics with G4

Question to the audience

- What would you do ?
  - Start triple therapy with simeprevir ?
  - Start triple therapy with sofosbuvir ?
  - Start dual therapy sofosbuvir + ribavirin ?
  - Start simeprevir + sofosbuvir, with or without ribavirin ?

Triple therapy PR + sofosbuvir : Neutrino

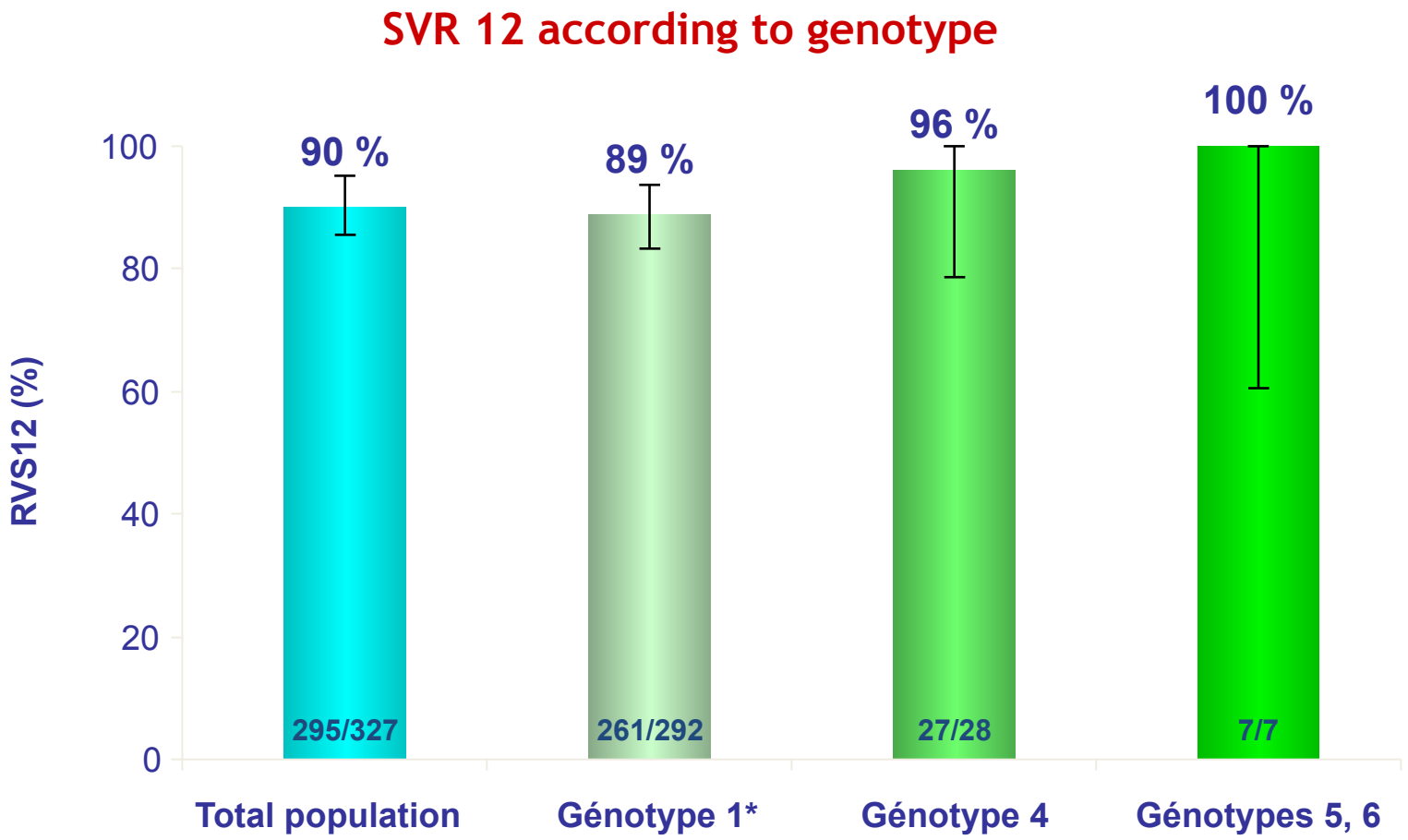
- Multicentric non randomised phase III study
- Naive patients of genotype 1, 4, 5 et 6
- Cirrhotics included (17%)

Regimen

400mg/j: 1 prise
Cirrhose:17%
Génotype1:89%

Lawitz E et al, NEJM 2013

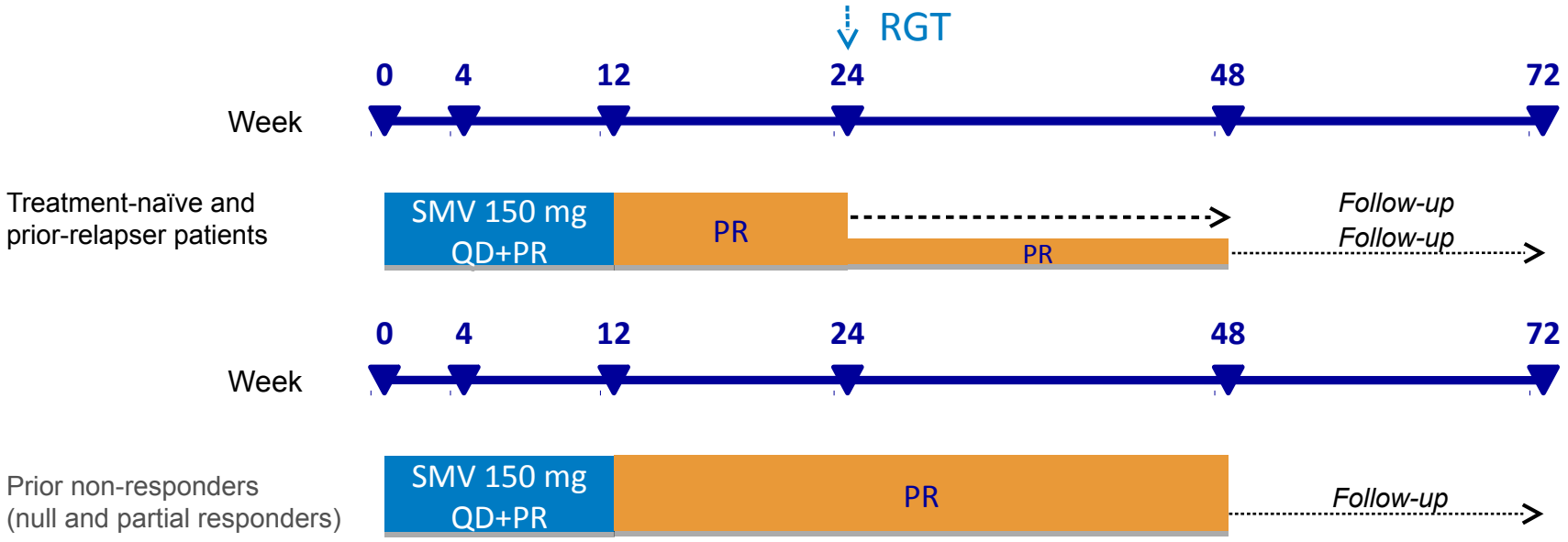
Triple therapy PR + sofosbuvir : Neutrino



*1a:92%
1b:82%

Lawitz E et al, NEJM 2013

Triple therapy PR + simeprevir : RESTORE (G4)

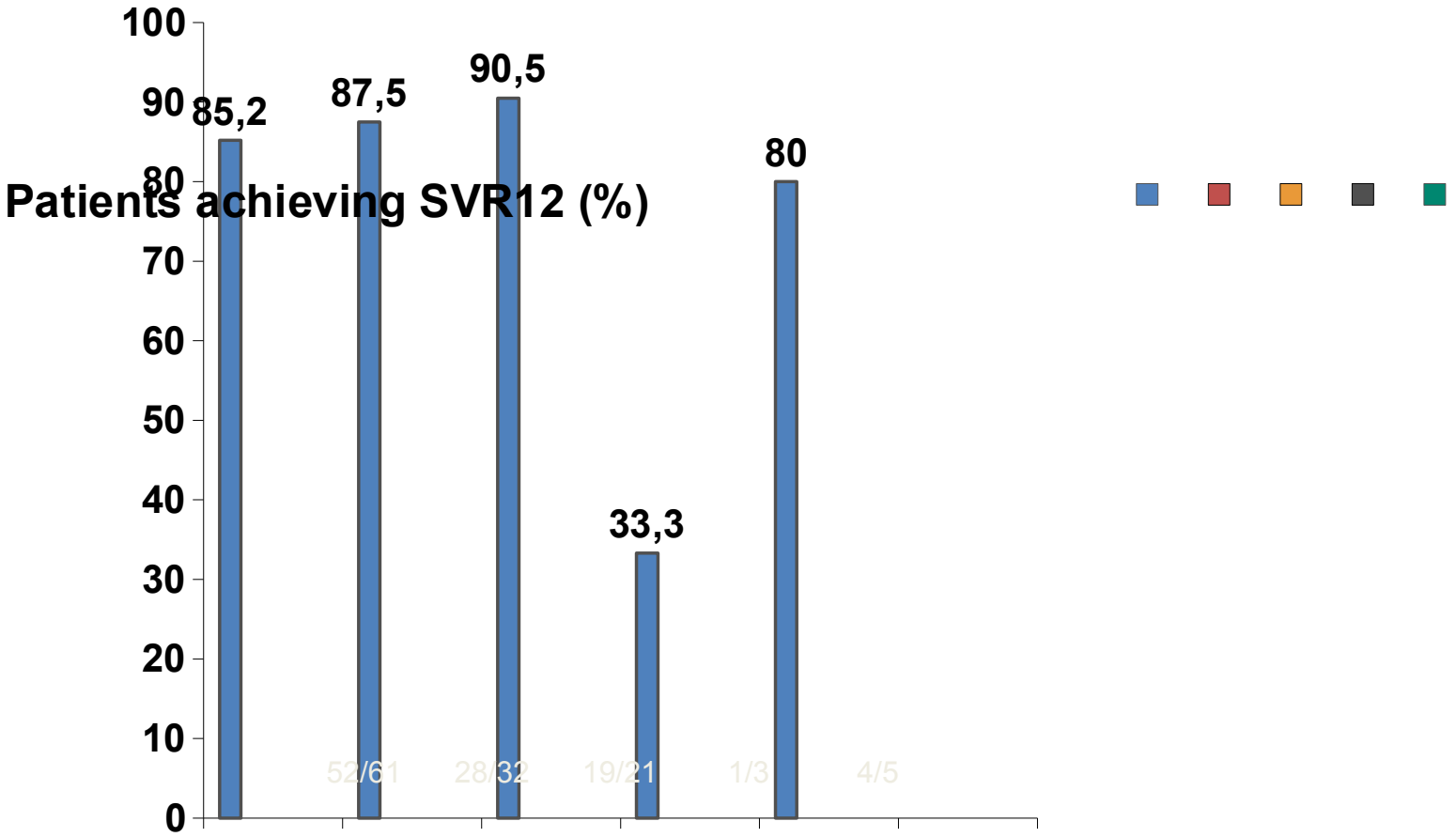


- Phase III, multicenter, open-label, single-arm study
- Aim: to evaluate efficacy / safety of SMV with PR in treatment-naïve or -experienced patients with chronic HCV genotype 4 infection and compensated liver disease
- Primary efficacy endpoint: rate of SVR 12 weeks after planned EOT (SVR12)
- Treatment completed at Week 24 if RGT criteria met: Week 4 HCV RNA <25 IU/mL detectable / undetectable and Week 12 HCV RNA <25 IU/mL undetectable
- Stopping rules: HCV RNA >1000 IU/mL at Week 4, HCV RNA >1000 IU/mL at Week12, confirmed detectable and HCV RNA level ≥25 IU/mL at Week 24 or 36

HCV RNA plasma concentration was determined using the Roche COBAS Taqman HCV/HPS v2.0 assay (lower limit of quantification 25 IU/mL)
EOT, end of treatment; QD, once daily; RGT, response-guided therapy; SMV, simeprevir;

RESTORE: NCT01567735

Patients achieving SVR12



Question to the audience

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  - Start triple therapy with sofosbuvir ?
  - Start dual therapy sofosbuvir + ribavirin ?
  - Start simeprevir + sofosbuvir, with or without ribavirin ?

Tolerance of triple therapy : CUPIC

Patients, n (% patients with at least one event)	Telaprevir n=292	Boceprevir n=205
Serious adverse events (SAEs)	132 (45.2%)*	67 (32.7%)**
Premature discontinuation Due to SAEs	66 (22.6%) 43 (14.7%)	54 (26.3%) 15 (7.3%)
Death *Septicemia (2) Pneumonia (2), Endocarditis, Oesophageal varices Bleeding,*	5 (2.6%)	1 (0.5%)
Infection (Grade 3/4)	19 (6.5%)	5 (2.4%)
Hepatic decompensation (Grade 3/4)	6 (2.0%)	6 (2.9%)
Asthenia (Grade 3/4)	16 (5.5%)	12 (5.8%)
Rash Grade 3/SCAR	14 (4.8%)	0
Renal failure	5 (1.7%)	0

*334 SAEs in 132 patients / **159 SAEs in 67 patients

Hézode C, et al. Hepatology 2012;56(Suppl.):217A

Predictive facors of severe complications

Factors	Platelets count >100,000/mm3	Platelets count ≤100,000/mm3
Albumin 35 g/L	3.4% (10/298)	4.3% (3/69)
Albumin <35 g/L	7.1% (2/28)	44.1% (15/34)

Hézode C, et al. J Hepatol. Accepted for publication

Question to the audience

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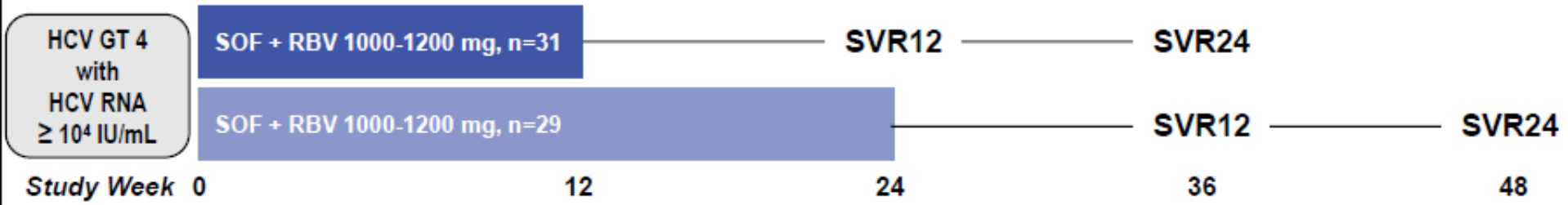
Contra-indication to IFN ?

SOF + RBV in Treatment of HCV GT 4 in Patients of Egyptian Ancestry ‡

Study Design

Randomized, open-label, single-center study conducted in the US of the safety and efficacy of all-oral SOF + RBV in patients of Egyptian ancestry with HCV GT 4

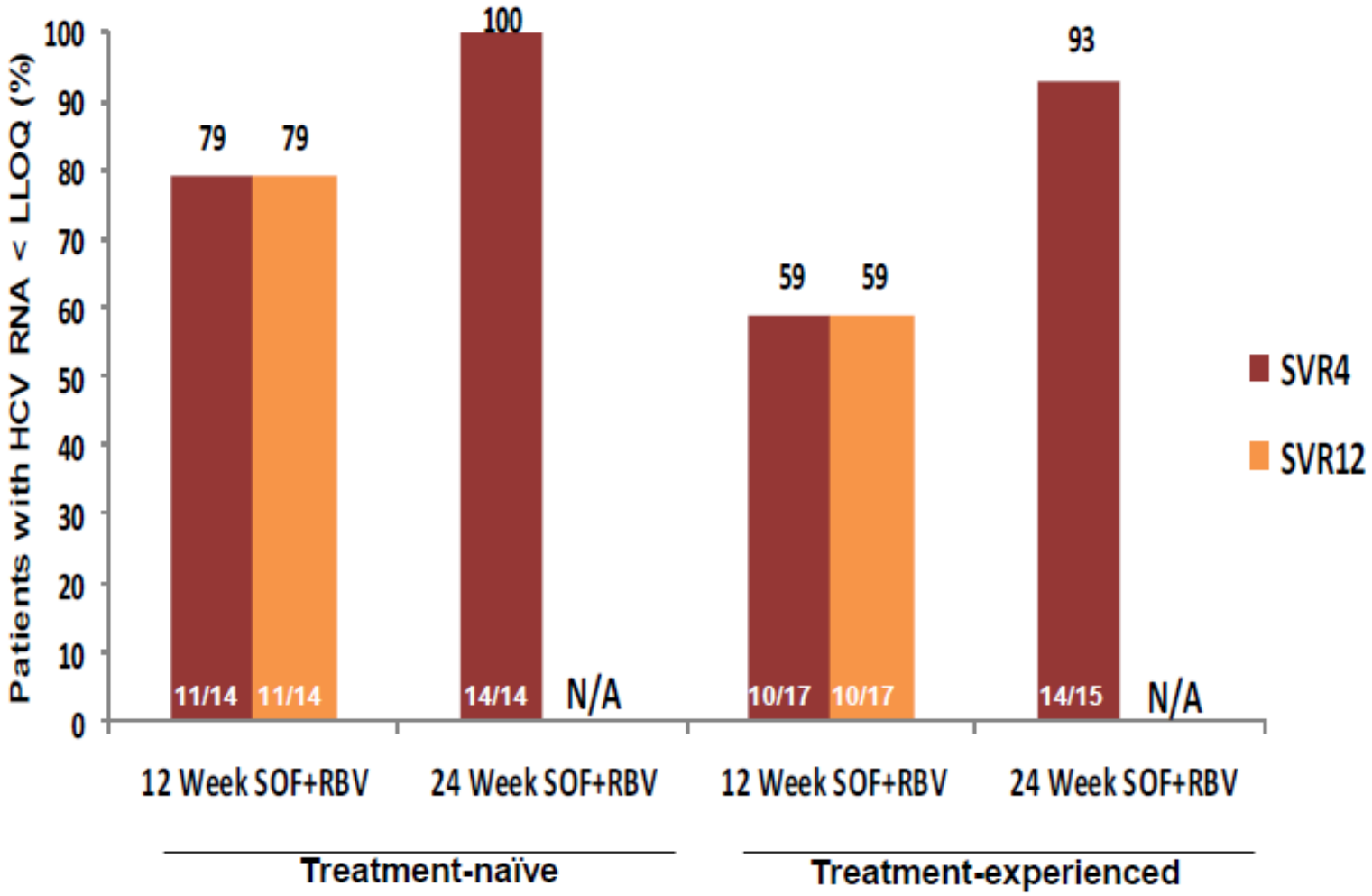


- Key eligibility criteria
  - Chronic HCV GT 4 with HCV RNA ≥10^4 IU/mL
  - Treatment naïve or experienced
  - Up to 20% of patients with compensated cirrhosis
  - Born in Egypt and both parents of Egyptian ancestry

Ruane PJ, et al. AASLD 2013. Washington, DC. #1090

SOF + RBV in Treatment of HCV GT 4 in Patients of Egyptian Ancestry

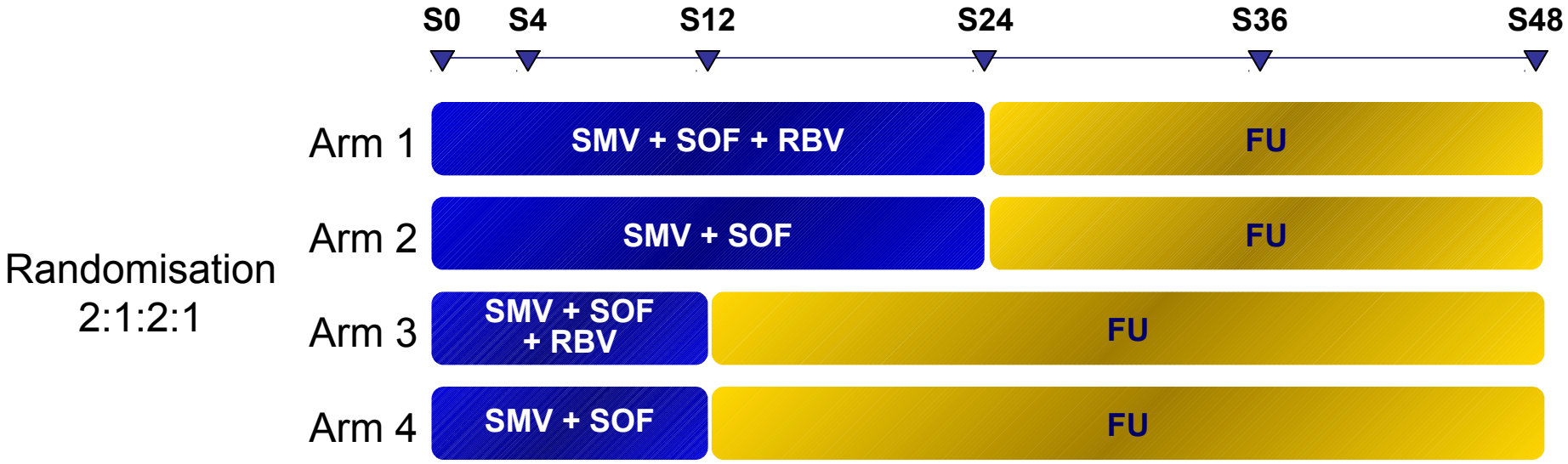
Virologic Response



Ruane PJ, et al. AASLD 2013. Washington, DC. #1090

Cosmos : sofosbuvir + simeprevir genotype 1

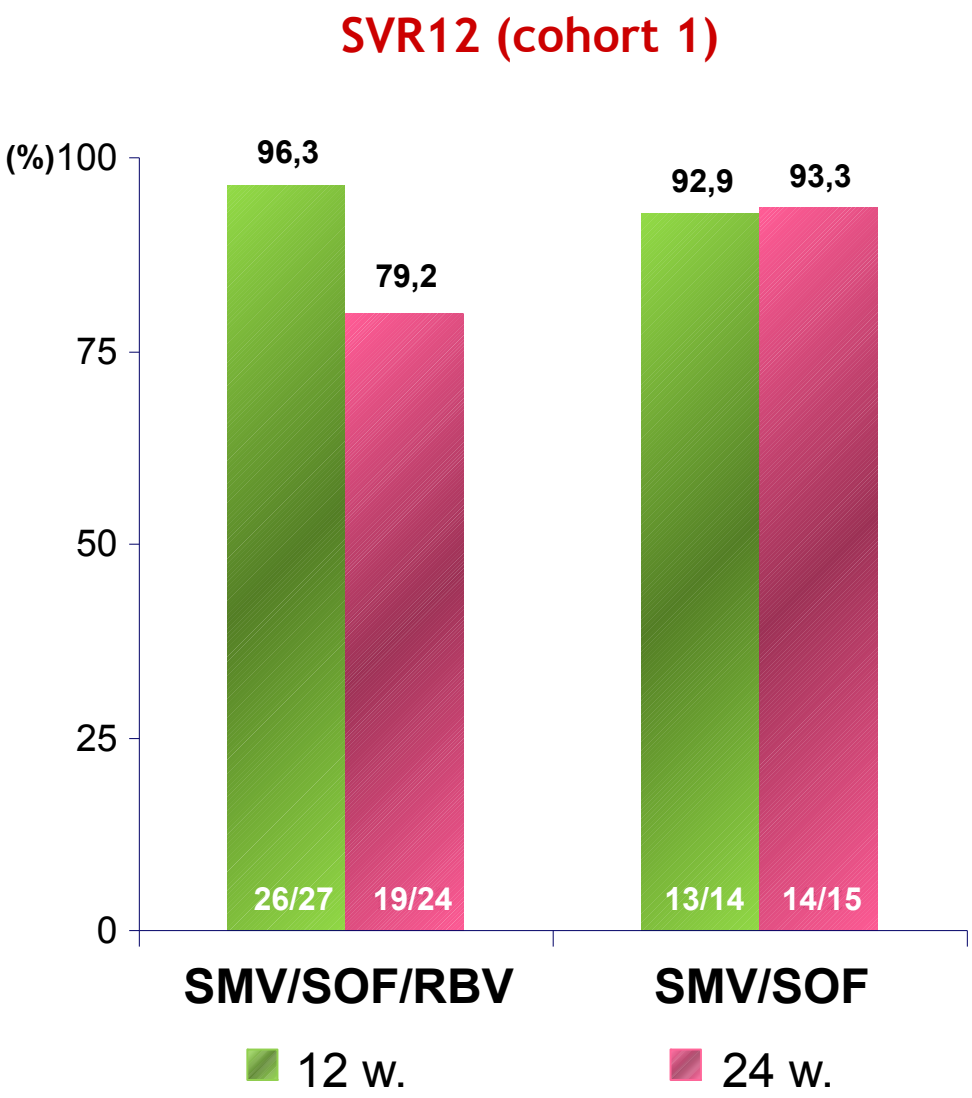
- Cohort 1 : 80 patients nul responders (METAVIR F0-F2)
- Cohort 2 : 87 patients naive and null responders (METAVIR F3-F4)



SMV 150 mg/j + SOF 400 mg/j ± RBV 1 000-1 200 mg/j

Jacobson IM, Etats-Unis, AASLD 2013, Abs. LB3, actualisé

Cosmos : sofosbuvir + simeprevir genotype 1



- But no data in genotype 4 !

Jacobson IM, Etats-Unis, AASLD 2013, Abs. LB3, actualisé

Case : G4, cirrhosis, triple therapy failure

- No mutation of resistance detected at time of relapse with telaprevir-based triple therapy
- Risk of severe complications with IFN (CUPIC criteria)
- Sofosbuvir + ribavirin : risk of relapse in this difficult to treat patient?
- Regimen chosen : simeprevir + sofosbuvir + ribavirin, treatement started last week…