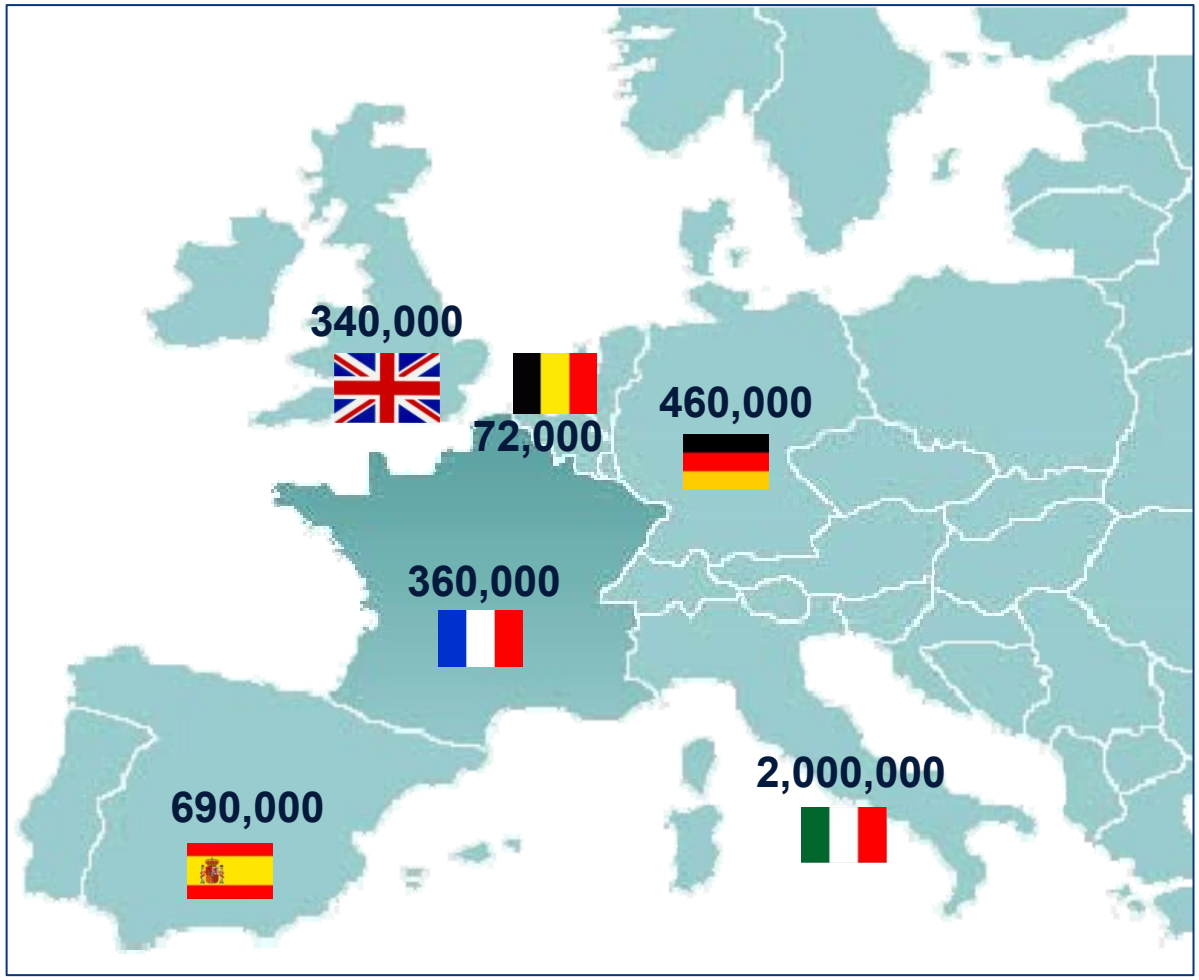
Luci nei nuovi trattamenti per HCV

Mario Angelico
Liver Unit, Università Tor Vergata, Roma

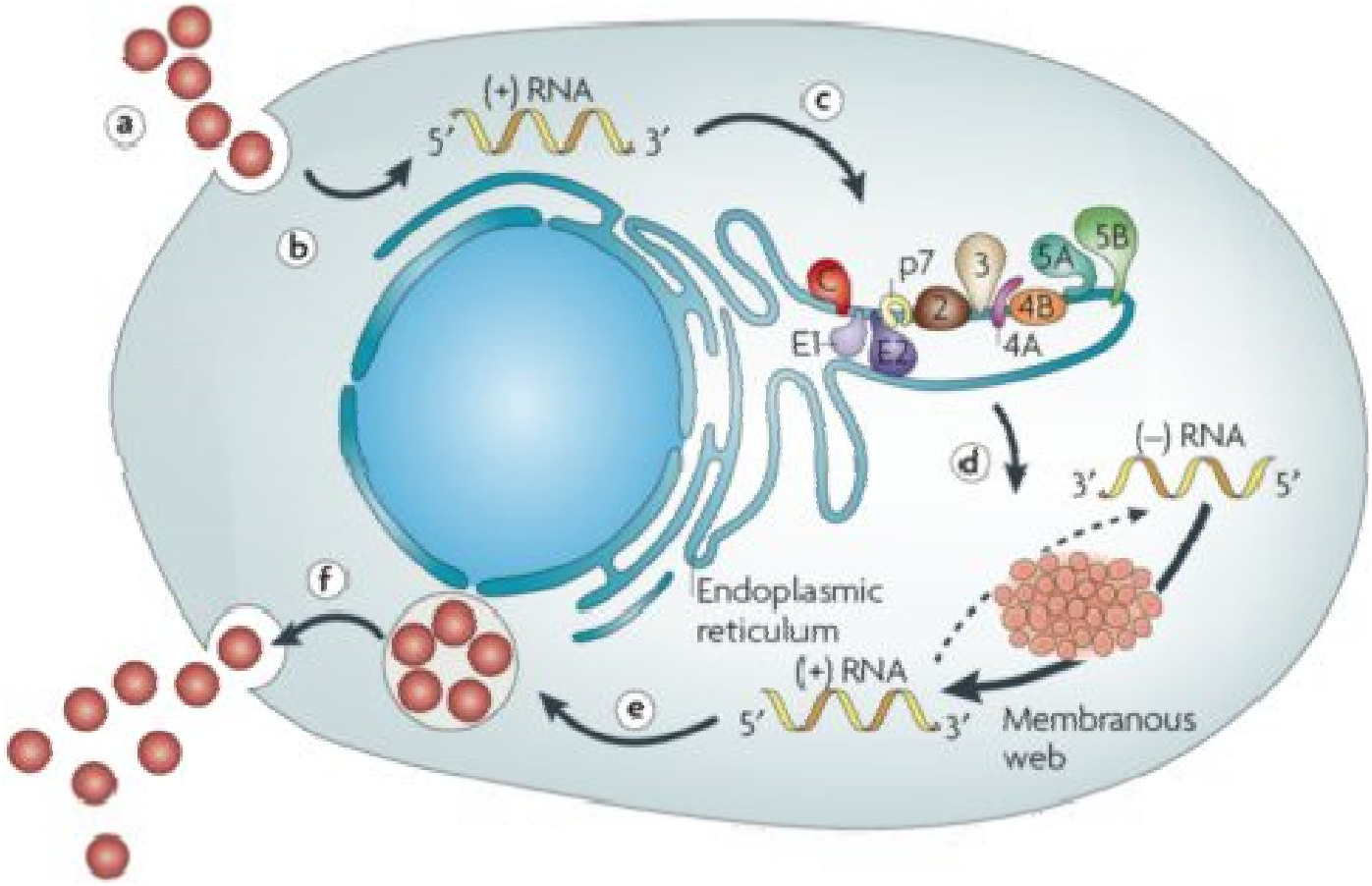
HCV epidemiology in 2011: estimation of number of patients ever infected



HCV: hepatitis C virus

Deuffic-Burban S, et al. Gastroenterology 2012;[ePub ahead of print]

The replicative cycle of HCV



HCV: hepatitis C virus

Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Journal of Hepatology **2011** vol. 55 | 245–264

EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

European Association for the Study of the Liver [1]

4.2. Goals and endpoints of HCV therapy

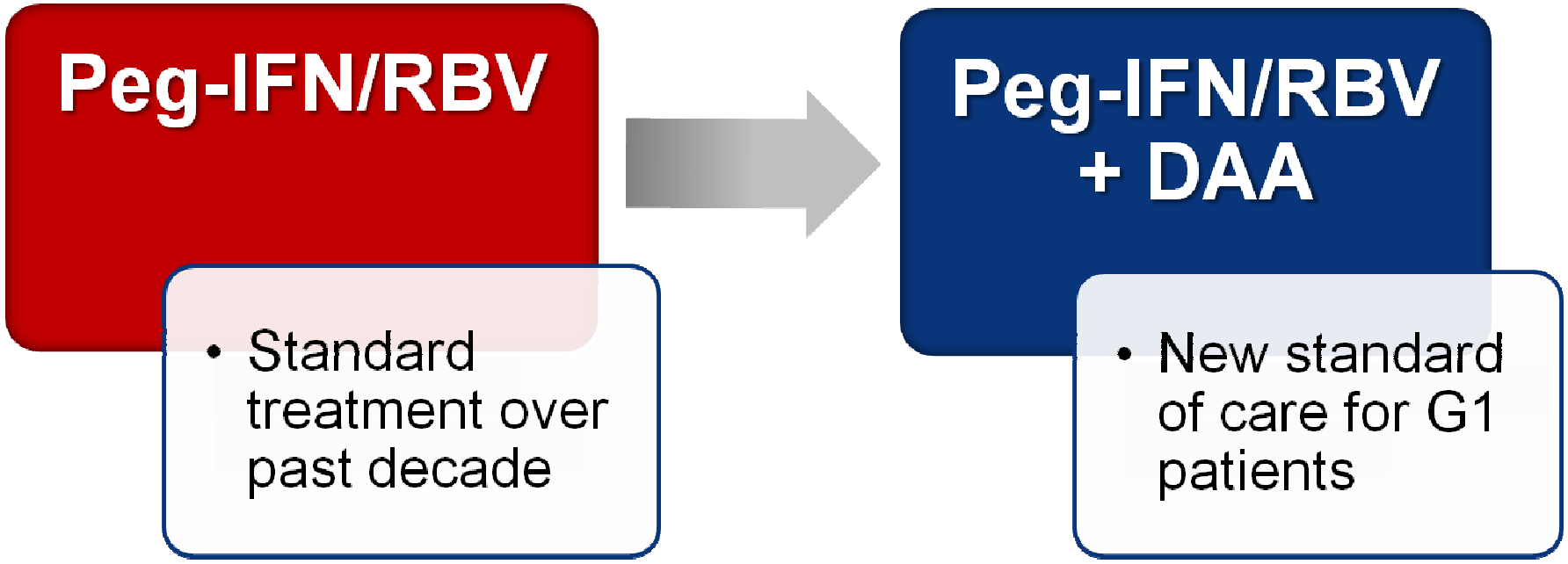
The primary goal of anti-HCV therapy is the eradication of infection

surements at 4, 12, and 24 weeks of therapy, which are interpreted in comparison to the baseline HCV RNA level. When HCV is eradicated, necroinflammation ceases and fibrosis progression is halted in non-cirrhotic patients.

Recommendations

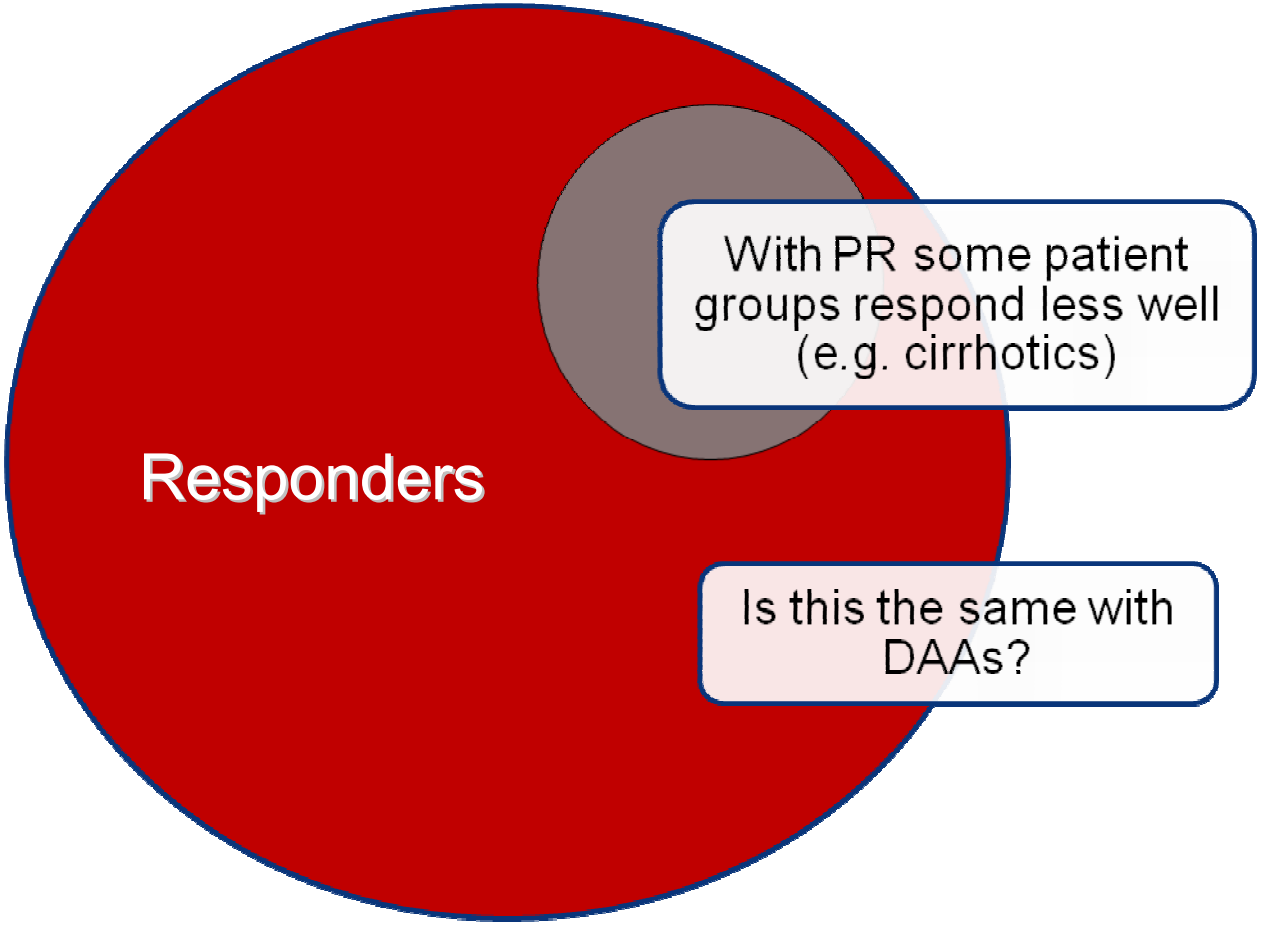
(1) The goal of therapy is to eradicate HCV infection (A1).
(2) The endpoint of therapy is sustained virological response (A1). Once obtained, SVR usually equates to cure of infection in more than 99% of patients (A1).
(3) Intermediate endpoints to assess the likelihood of an SVR are HCV RNA levels at 4, 12, and 24 weeks of therapy (B2).

Entering a new era in HCV treatment

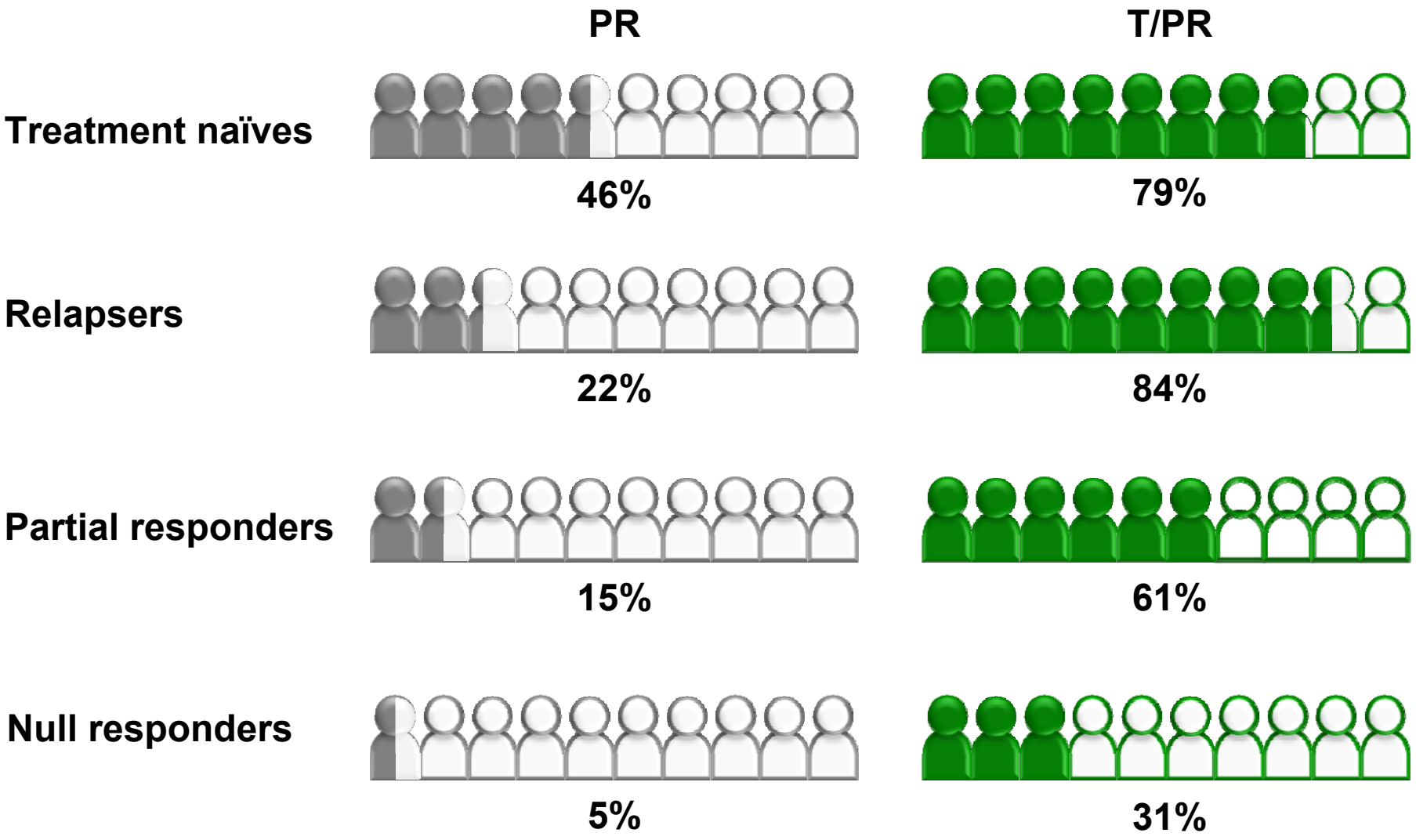


PI: protease inhibitor; G1: genotype 1

Do all patients respond equally well?



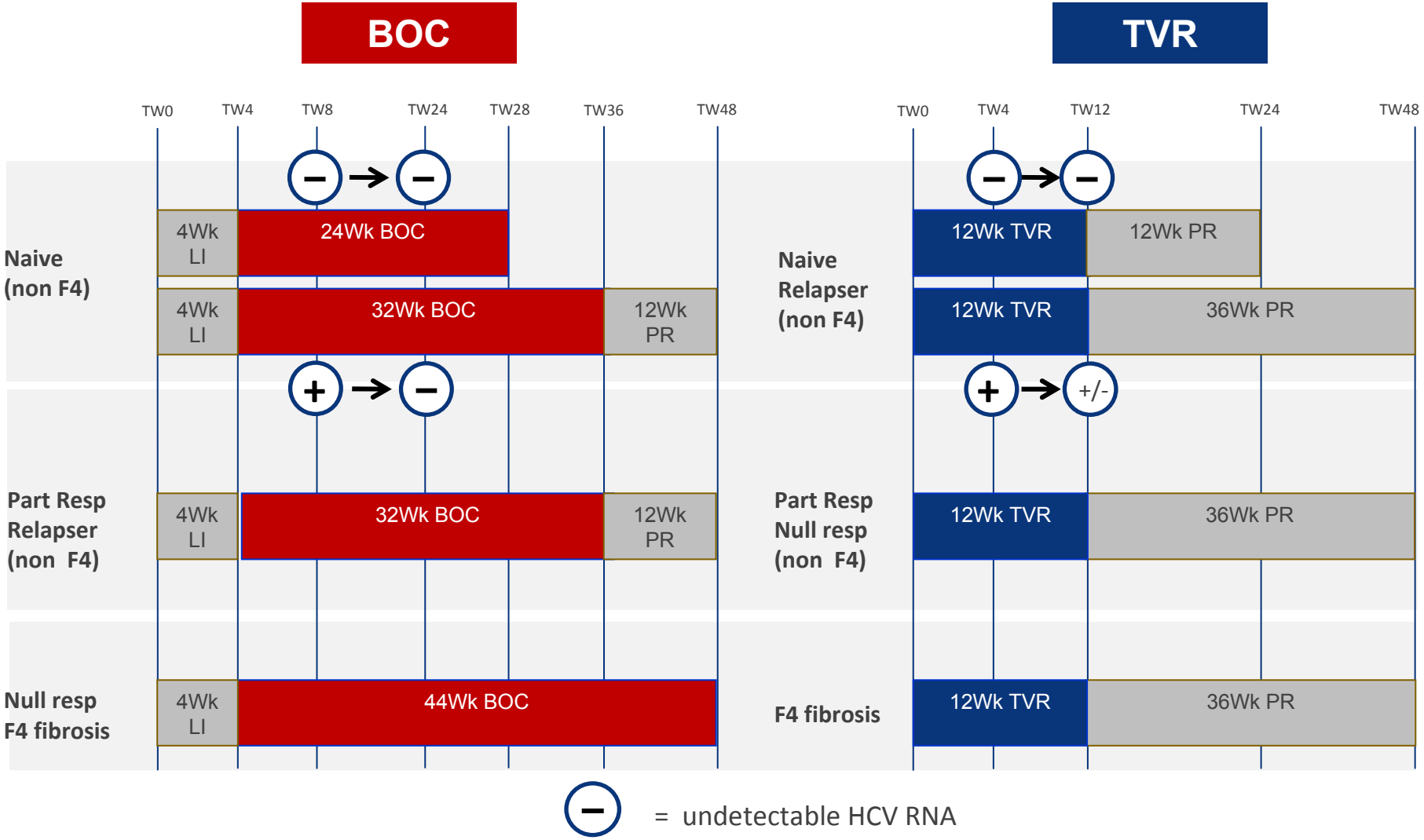
DAAs significantly improve patient outcomes (SVR rates)



T/PR: telaprevir plus PR

Telaprevir EU SmPC

Treatment algorithms with currently licensed DAAs



TW: treatment week; LI: lead-in; Part Resp: partial responders

Boceprevir EU SmPC; Telaprevir EU SmPC

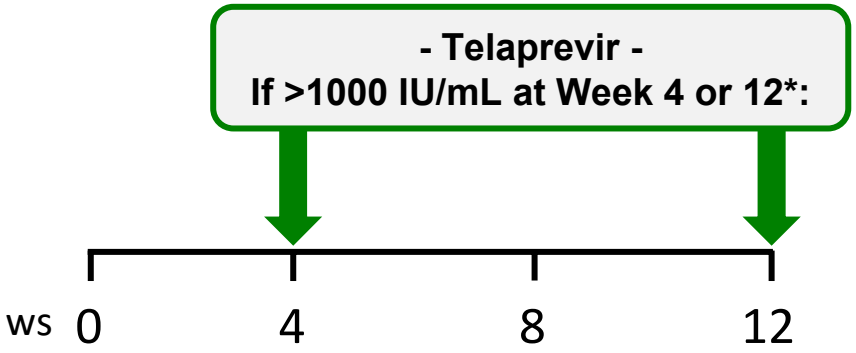
Same principles, but different application of futility rules for boceprevir and telaprevir

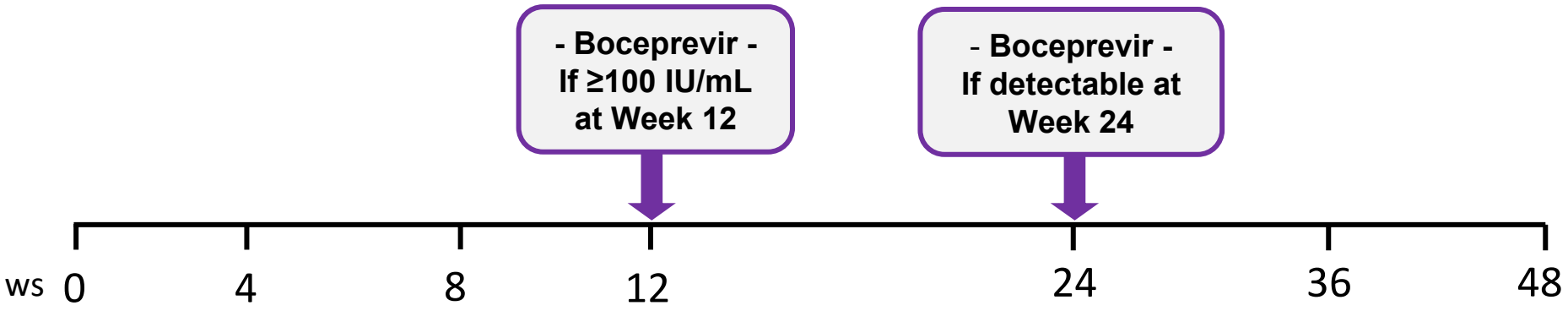
- **TVR**
  - ✓ If HCV RNA is >1000 IU/mL at Week 4 or 12, all three medications should be discontinued
  - ✓ If HCV RNA is confirmed detectable at Week 24 or 36, PR should be discontinued
- **BOC**
  - ✓ If HCV RNA is ≥100 IU/mL at Week 12, all three medications should be discontinued
  - ✓ If HCV RNA is confirmed detectable at Week 24, all three medications should be discontinued

Assay should have a LLOQ of ≤25 IU/mL and a LLOD of approximately 10–15 IU/mL

1. BOC [package insert]. May 2011. 2. Ghany MG, et al. Hepatology 2011;54:1433–44
3. TVR [package insert]. May 2011

Stopping rules during DAAs period: stop all drugs

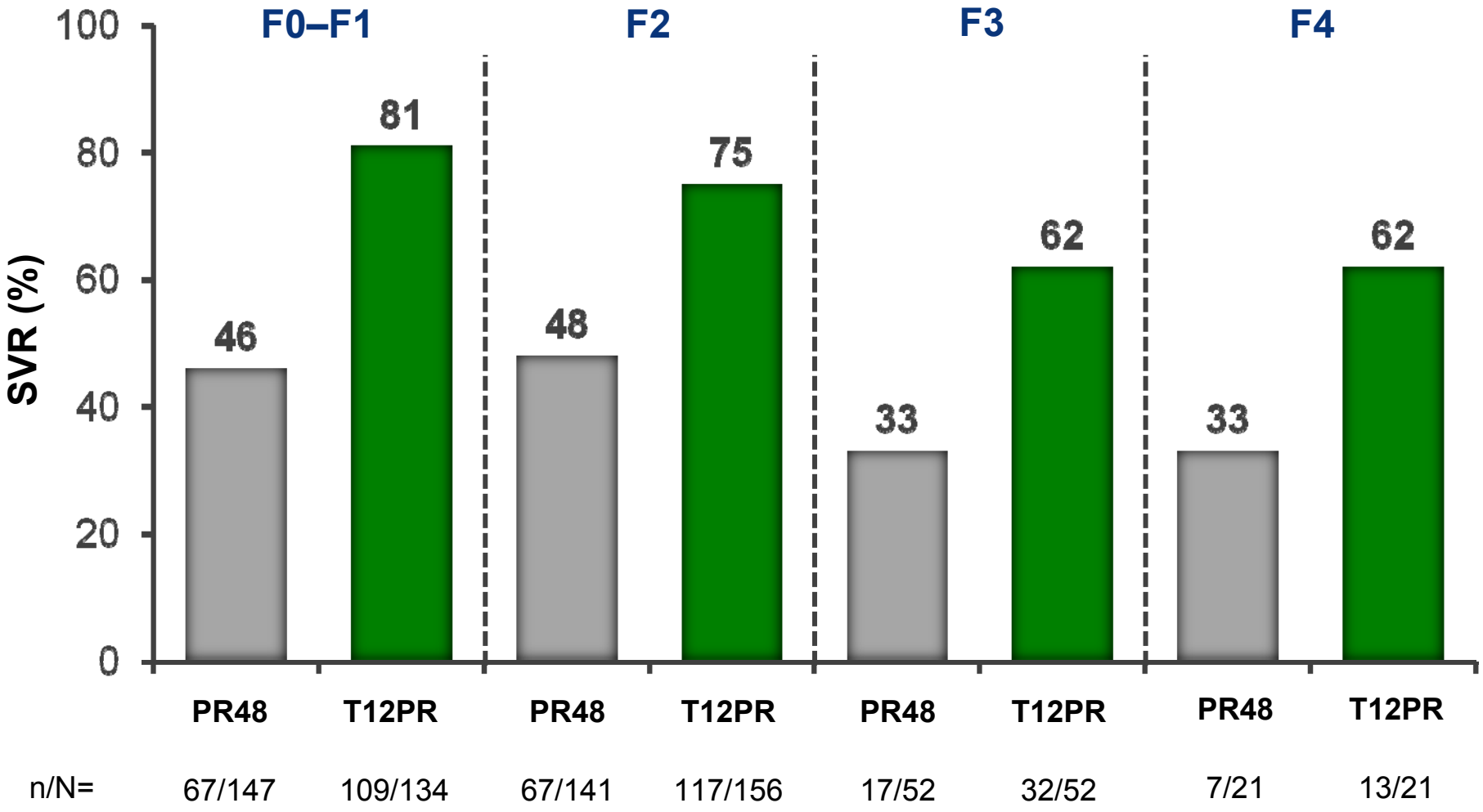




*In prior null responders, consideration should be given to conduct an additional HCV RNA test between Weeks 4 and 12. If the HCV RNA concentration is >1000 IU/mL, telaprevir and PR should be discontinued

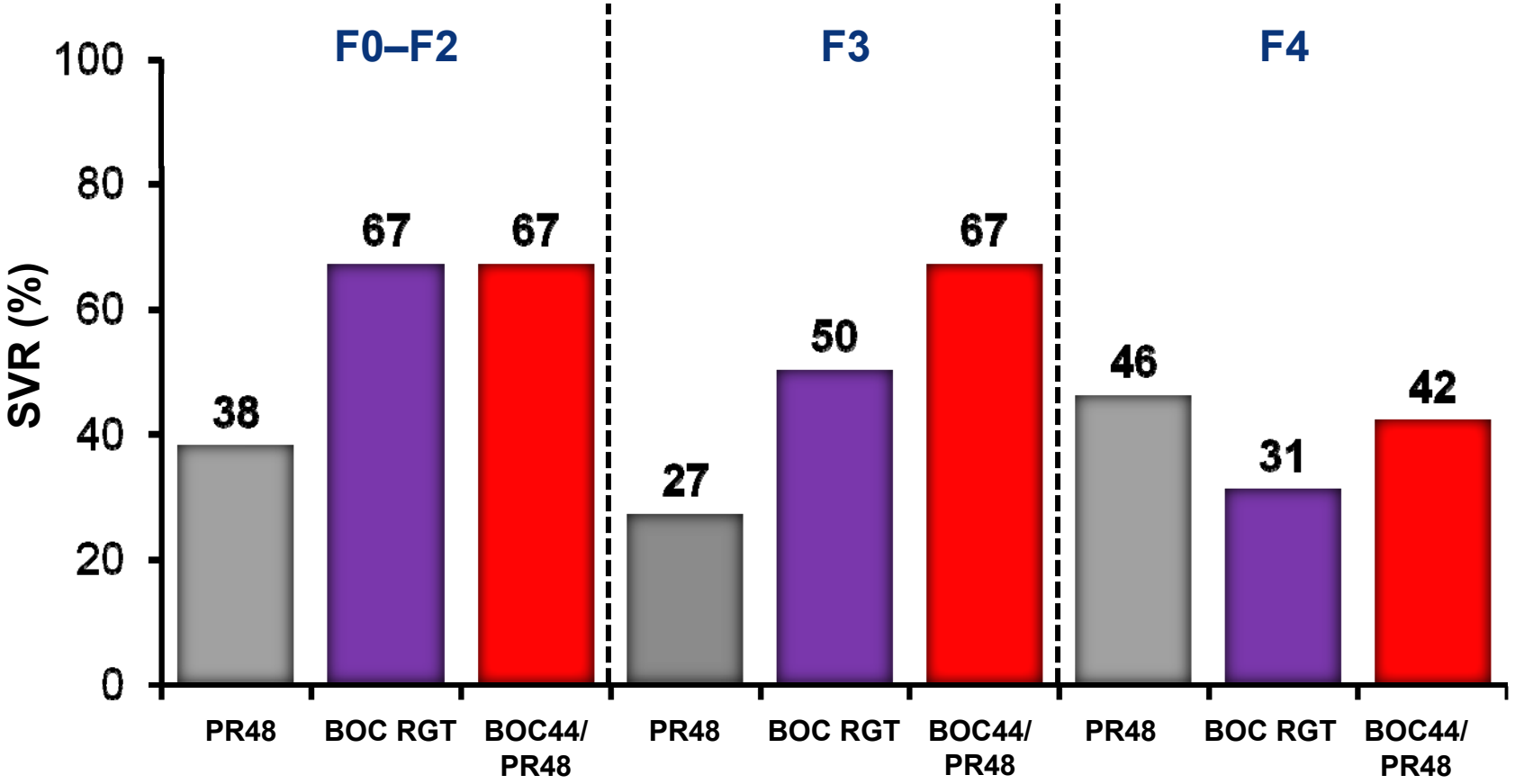
Telaprevir EU SmPC
Boceprevir EU SmPC

ADVANCE (telaprevir): SVR rates by fibrosis stage in treatment-naïve patients



Marcellin P, et al. J Hepatol 2011;54 (Suppl 1): S183

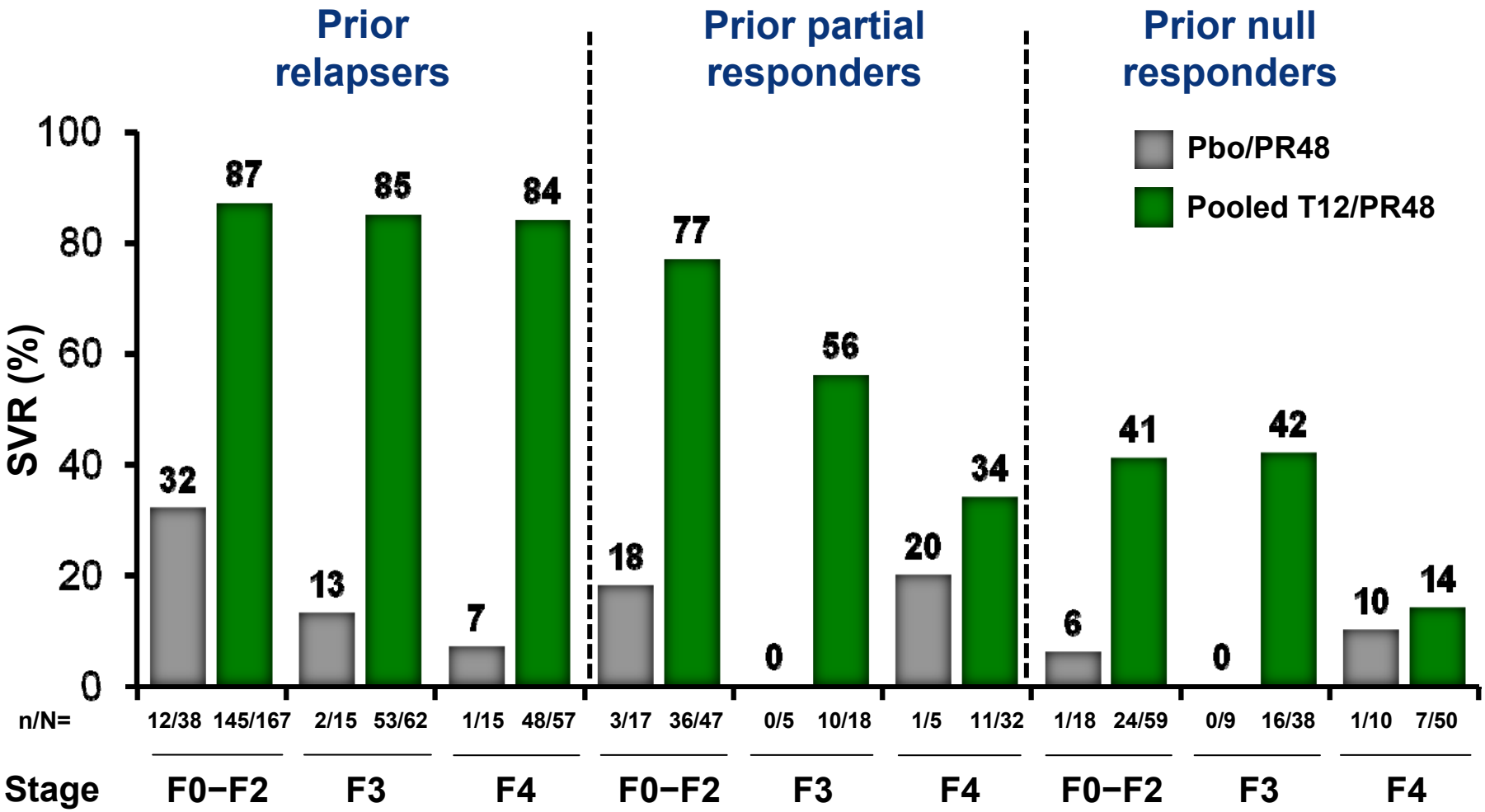
SPRINT-2 (BOC): SVR rates by fibrosis stage in treatment-naïve patients



SVR was defined as undetectable HCV RNA at the last available value in the period at or after follow-up Week 24. If there was no such value, the follow-up Week 12 value was carried forward
BOC: boceprevir

Poordad F, et al. N Engl J Med 2011;364:1195–206

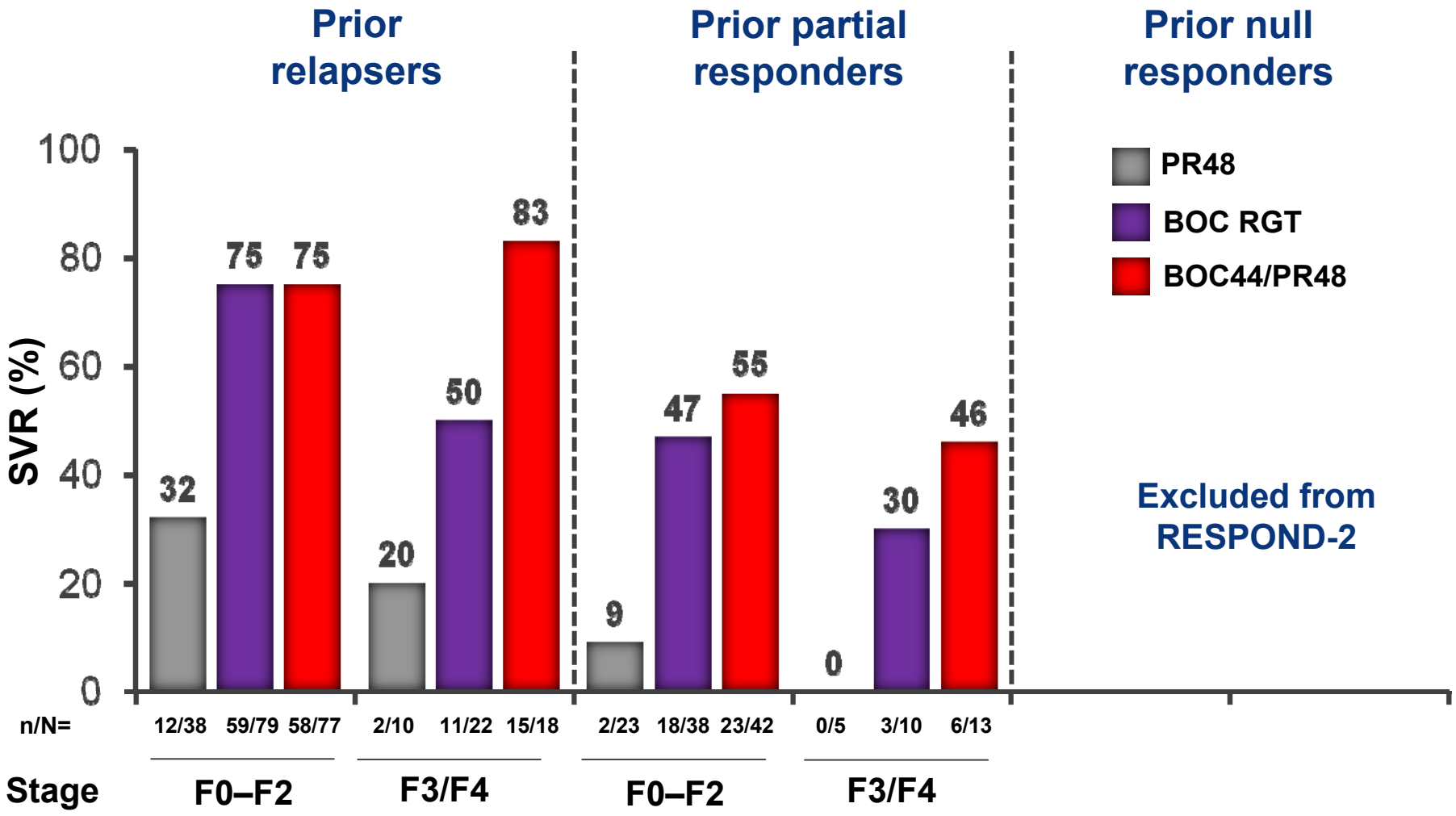
REALIZE (telaprevir): SVR by baseline fibrosis stage and prior response to PR



SVR was defined as HCV RNA <25 IU/mL at last observation within the Week 72 visit window. In case of missing data, the last HCV RNA data point from Week 12 of follow-up onwards was used
Pbo: placebo

Pol S, et al. Hepatology 2011;54(Suppl. S1):374A

RESPOND-2 (boceprevir): SVR by baseline fibrosis stage and prior response to PR



RGT: response-guided therapy

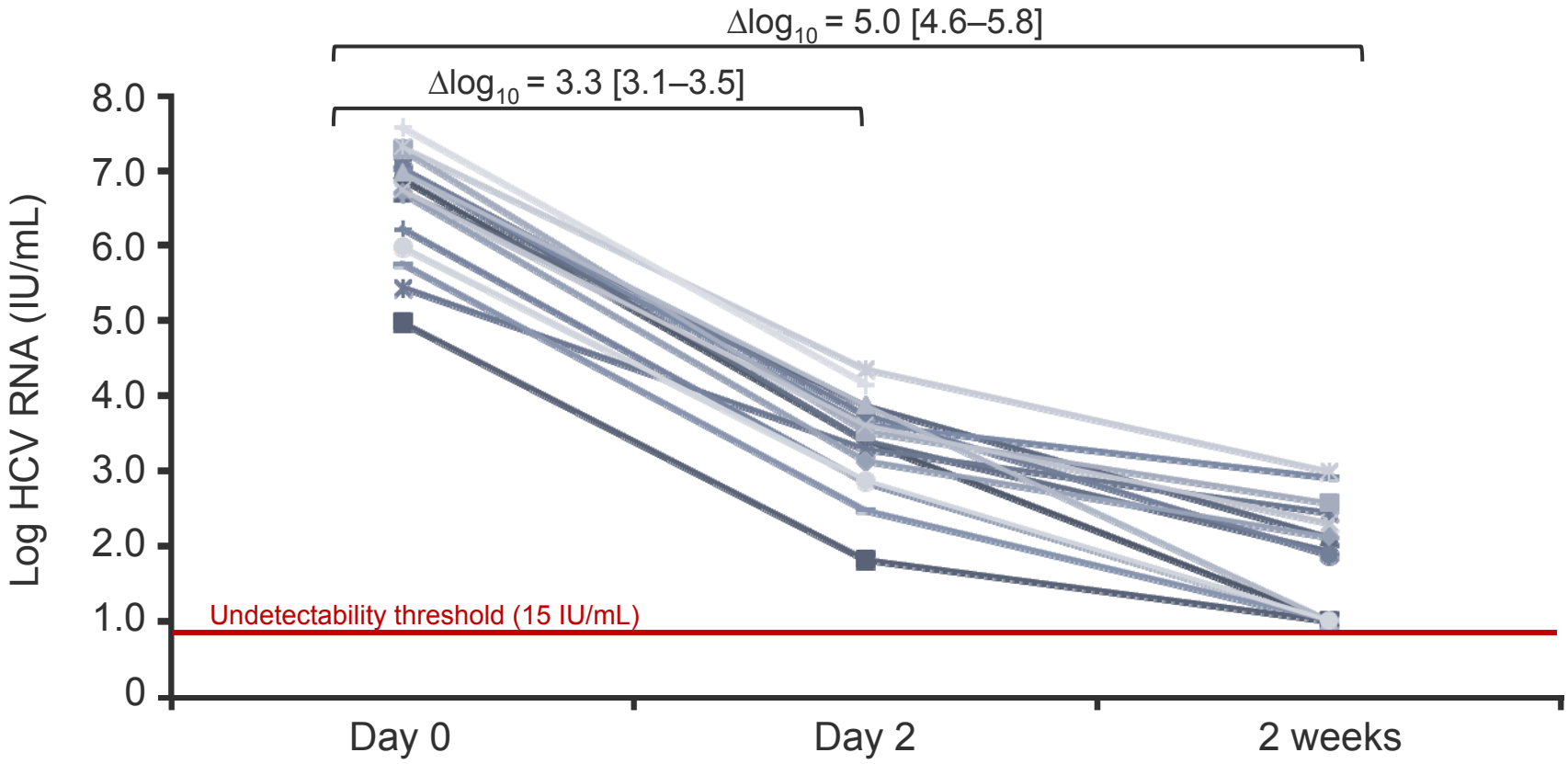
Bruno S, et al. J Hepatol 2011;54(Suppl. 1):S4

Duration of therapy?

With PR we can shorten therapy in some patients

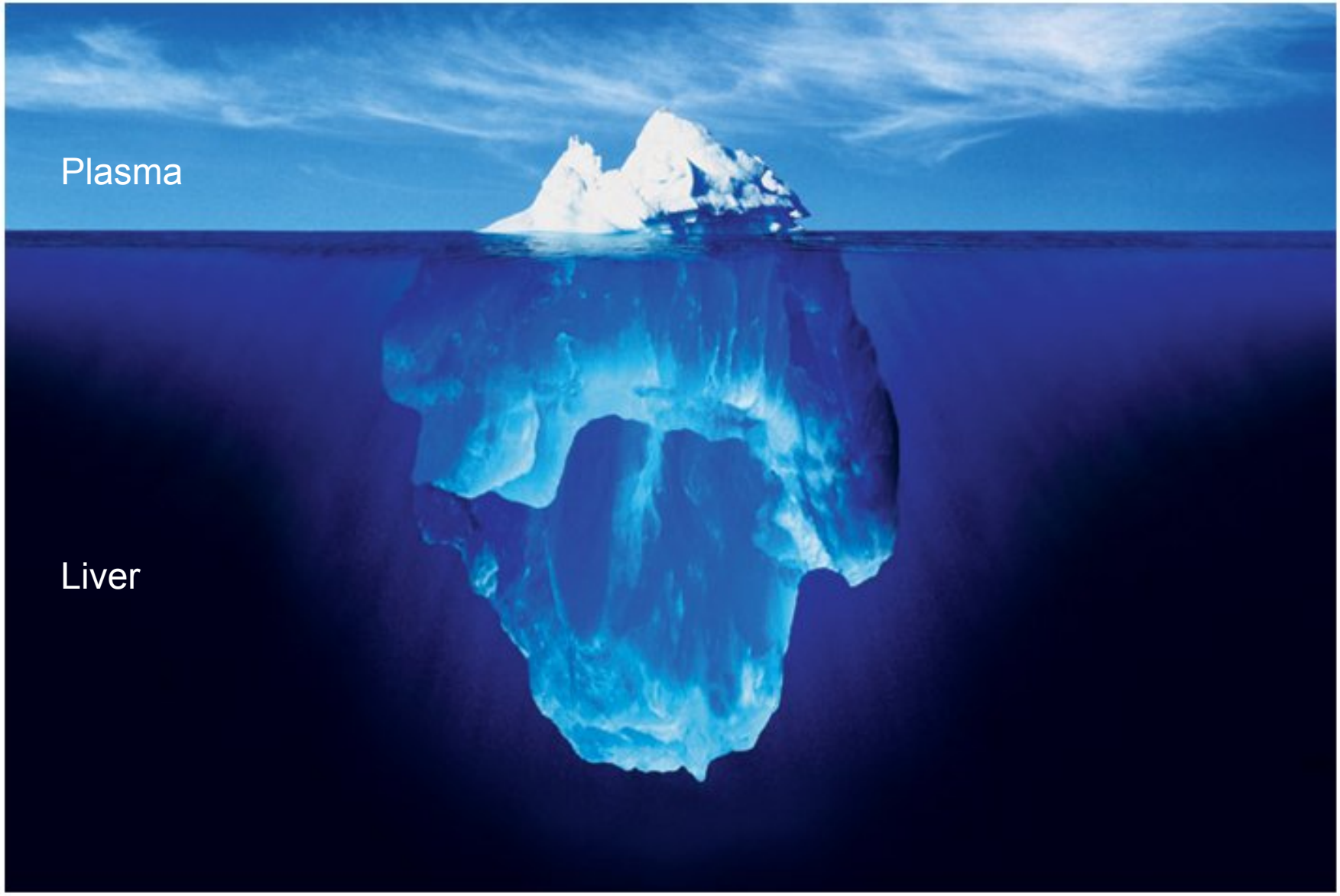
Can we shorten therapy with DAAs?

HCV RNA decay during early phases of telaprevir treatment was extremely fast

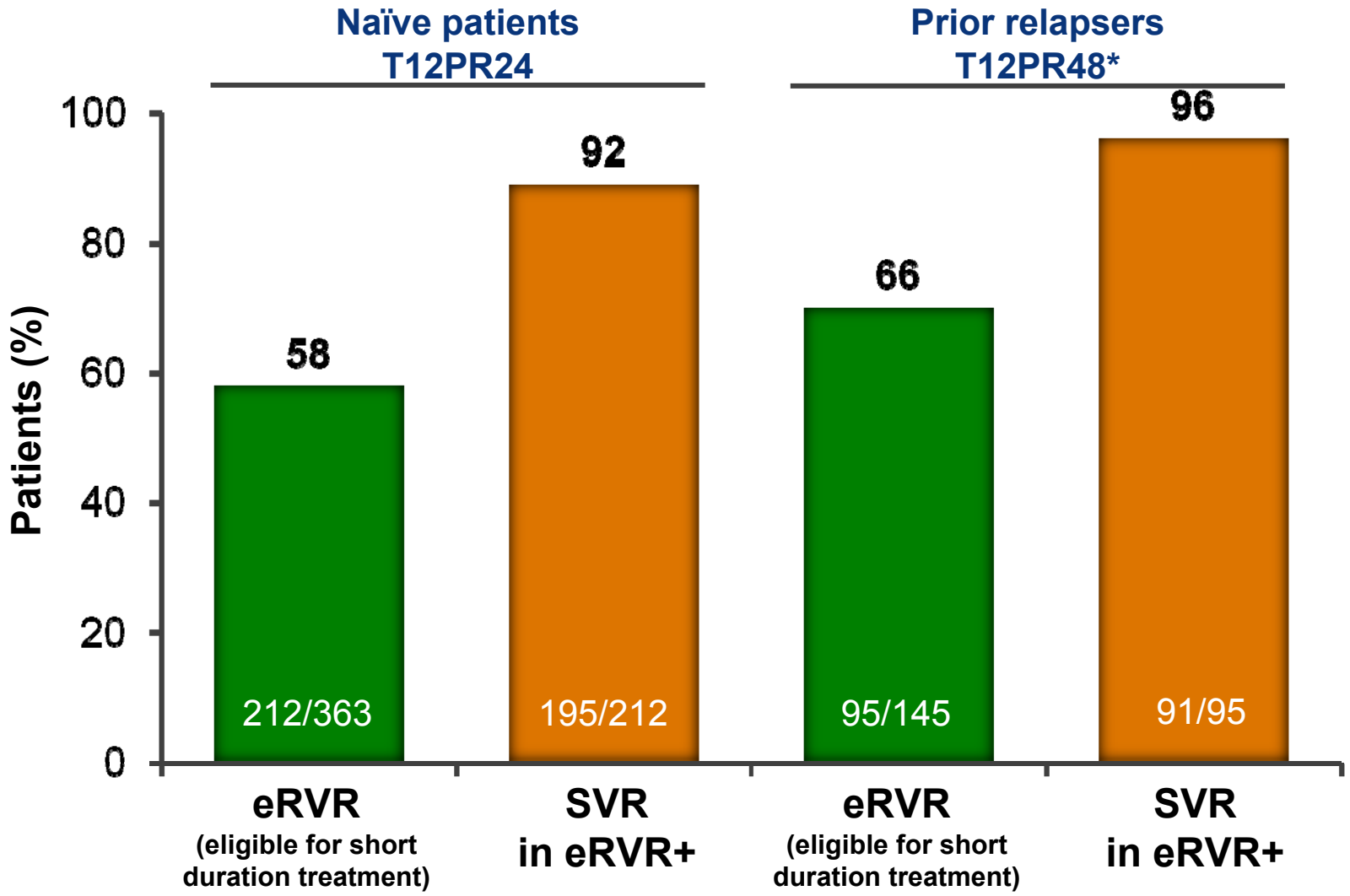


After 2 weeks of TVR treatment, 5/10 (50.0%) genotype 1b patients were undetectable, compared to 1/6 (16.7%) genotype 1a patients

Cento V, et al. International Workshop HIV & Hepatitis virus 2012


Plasma
Liver

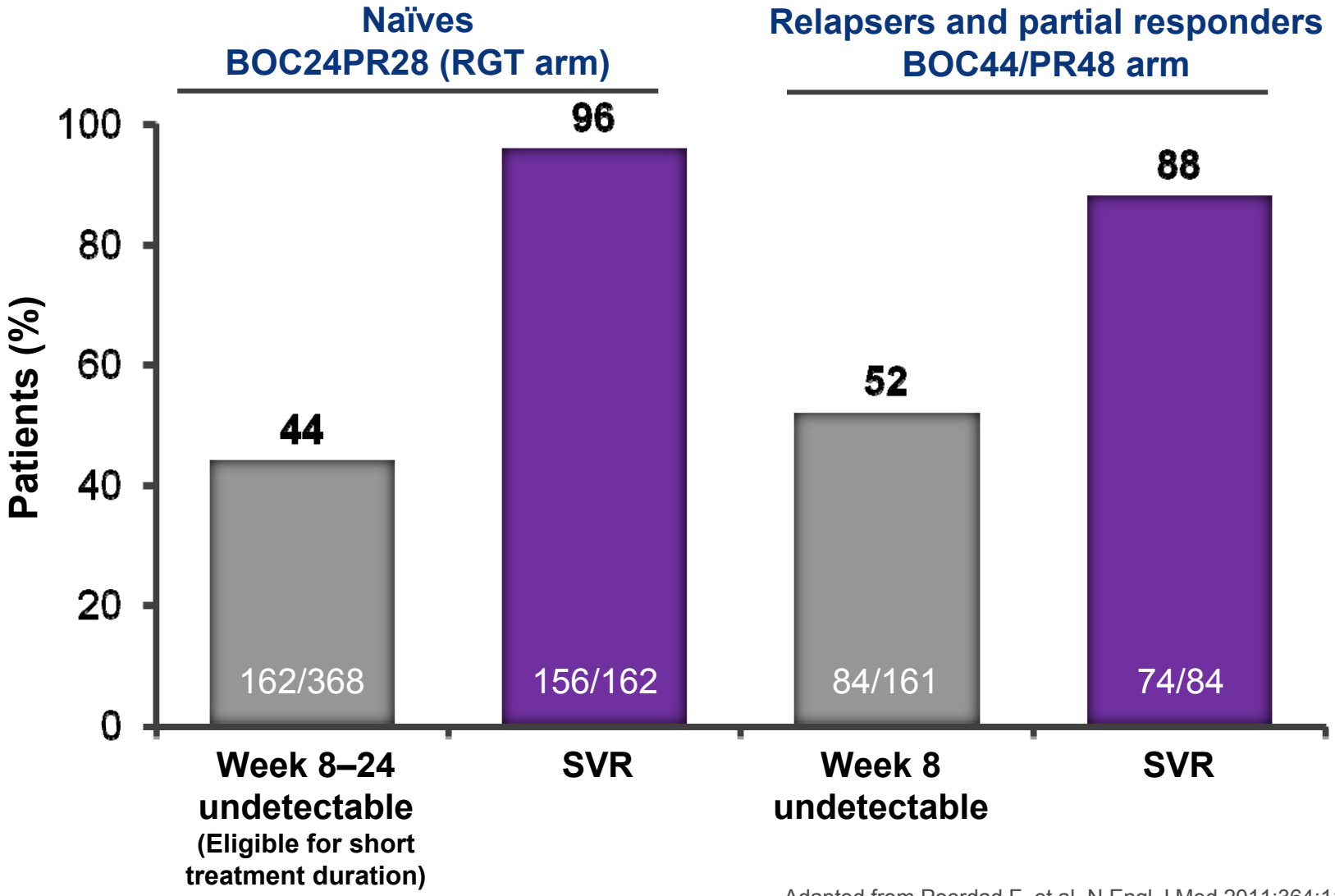
Telaprevir: early viral response can help to motivate patients to stay on therapy (ADVANCE/REALIZE)



RVR: undetectable HCV RNA at Week 4; eRVR: undetectable HCV RNA at Week 4 and Week 12
*SVR rate from REALIZE with 48 weeks of overall treatment; retrospective analysis from the PROVE3 trial and Study 107 showed SVR rates of 89–100% in prior relapsers with undetectable HCV RNA at Weeks 4 and 12 who received 24 weeks of overall treatment

Telaprevir EU SmPC;
Adda N, et al. CDDW/CASL 2012:A26

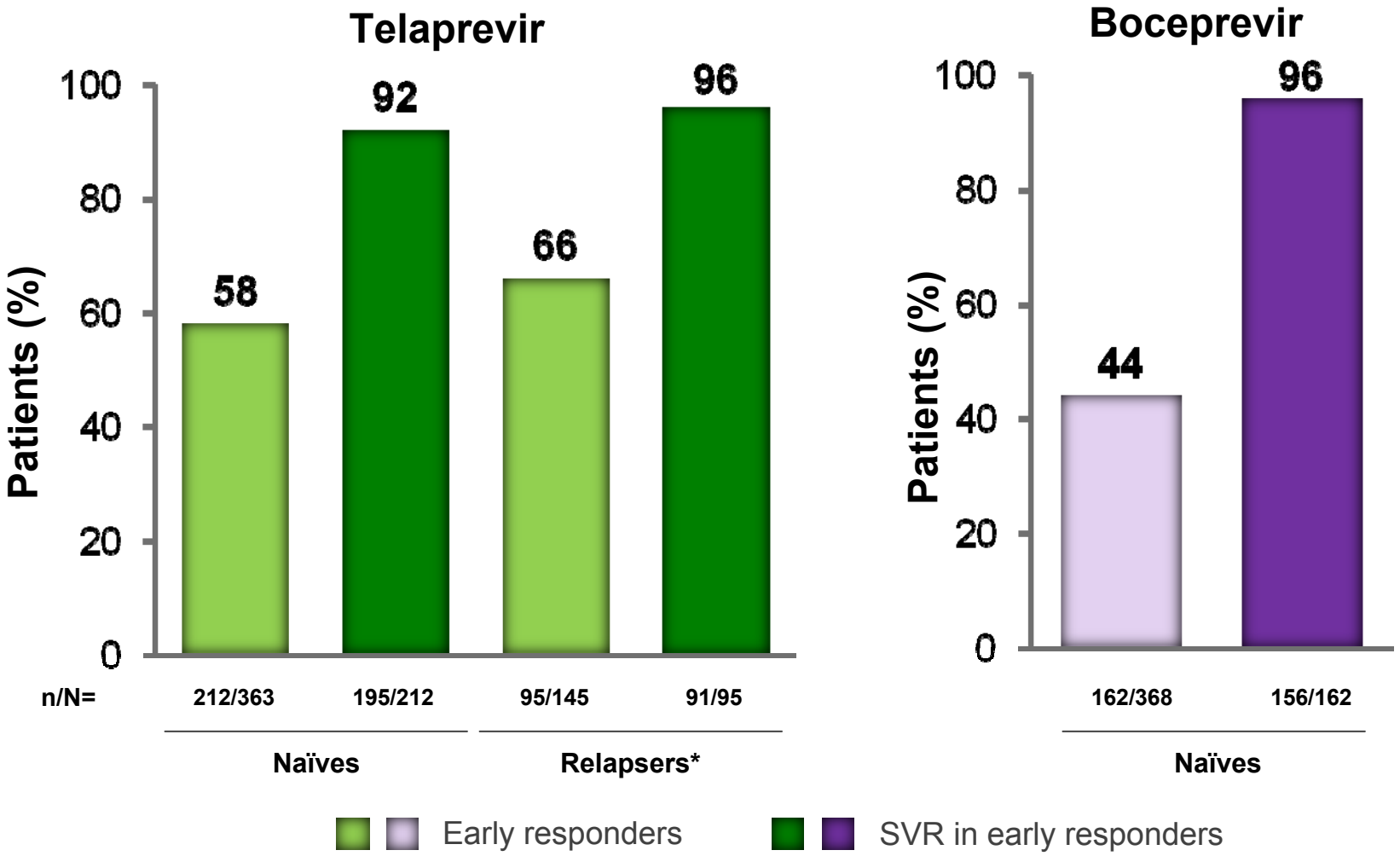
Boceprevir: early viral response can help to motivate patients to stay on therapy (SPRINT-2/RESPOND-2)



RGT: response-guided therapy

Adapted from Poordad F, et al. N Engl J Med 2011;364:1195–206
Bacon BR, et al. N Engl J Med 2011;364:1207–17

SVR rates in patients eligible for shortened treatment duration



Early responder: Telaprevir: undetectable HCV RNA at Weeks 4 and 12; BOC: undetectable HCV RNA at Weeks 8–24
*SVR rate from REALIZE with 48 weeks of overall treatment; retrospective analysis from the PROVE3 trial and Study 107 showed SVR rates of 89–100% in prior relapsers with undetectable HCV RNA at Weeks 4 and 12 who received 24 weeks of overall treatment

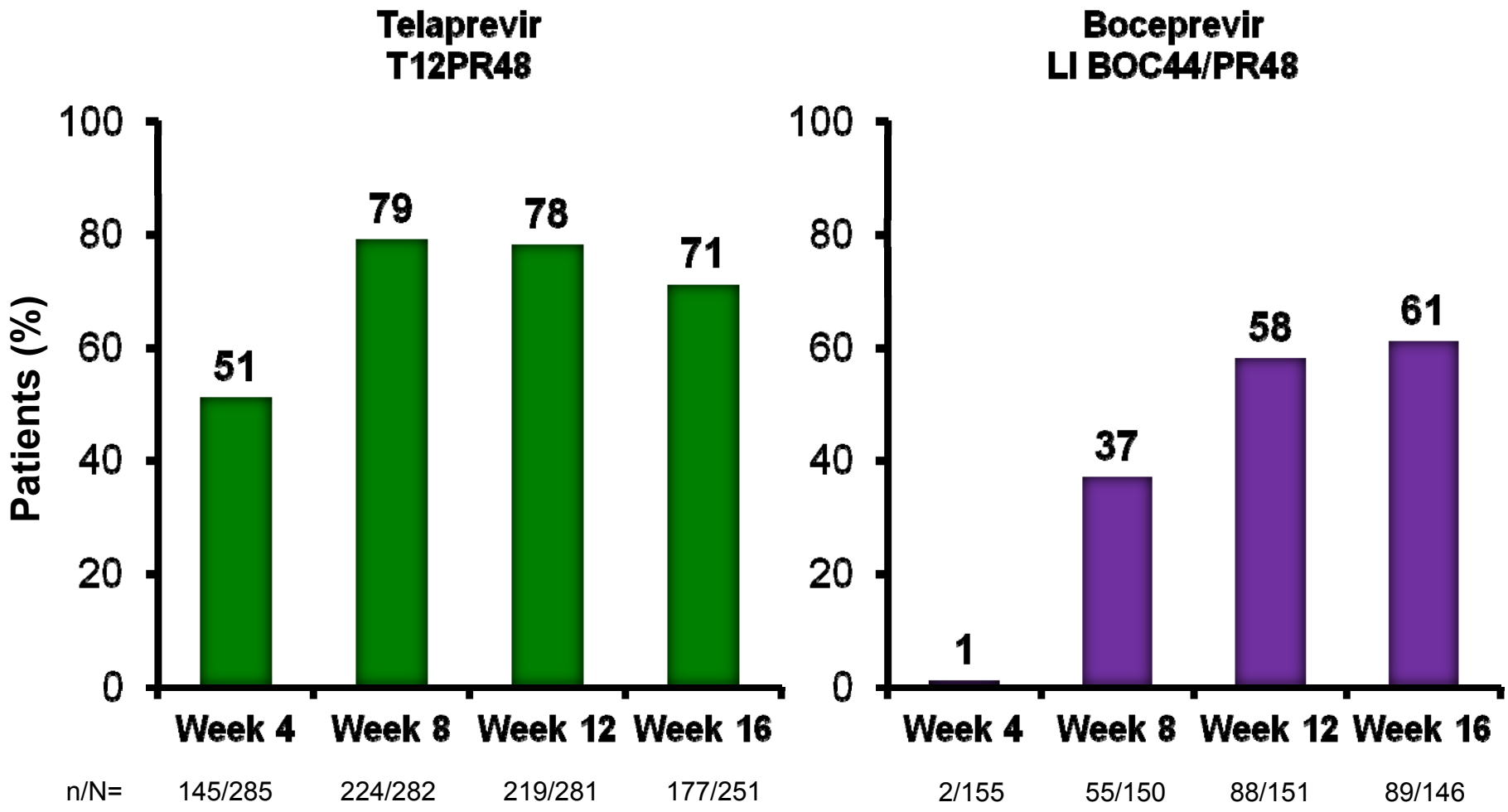
Adda N, et al. CDDW/CASL 2012:A26
Telaprevir EU SmPC; Poordad F, et al. N Engl J Med 2011;364:1195–206

CUPIC: patient baseline characteristics

	Telaprevir (n=296)	Boceprevir (n=159)
Male, %	68	67.5
Mean age, years	57.0	56.8
G1b/1a, %	61/39	60/40
Mean baseline HCV RNA, log_{10} IU/mL	6.5	6.5
Previous treatment response, %		
Partial responders	52	49
Relapsers	40	48
Null responders	8	3
Patients with Phase III exclusion criteria, %	34	26

Hézode C, et al. J Hepatol 2012;56 (Suppl 2):S4

French CUPIC cohort: patients with undetectable HCV RNA (ITT)



LI: lead in
ITT: intent-to-treat population

Hézode C, et al. Oral presentation at EASL 2012. Abstract 8

Treatment of Hepatitis C Genotype 1 Patients with Severe Fibrosis or Compensated Cirrhosis: The International Telaprevir Early Access Program

AUTORI : Massimo Colombo[1], Inmaculada Fernández[2], Djamal Abdurakhmanov[3], Paulo R. Abrão Ferreira[4], Simone I. Strasser[5], Petr Urbanek[6], Christophe Moreno[7], Adrian Streinu-Cercel[8], Anke Verheyen[9], Wafae Iraqi[10], Ralph DeMasi[11], Andrew Hill[12], Joerg Läuffer[13], Isabelle Lonjon-Domanec[10], Heiner Wedemeyer[14]

Time on treatment	Week 4		Week 12	
HCV RNA suppression	<25 IU/mL	Not detected	<25 IU/mL	Not detected
Naïve (n=124)	86%	59%	88%	85%
Relapser (n=171)	80%	63%	87%	85%
Partial responder (n=94)	80%	52%	85%	77%
Null responder (n=176)	68%	41%	76%	68%
Viral breakthrough (n=28)	82%	68%	89%	86%
Overall (n=609)	77%	54%	83%	79%

- 66% aveva livelli di HCV RNA ≥ 800.000 UI / mL
- il **45% aveva fibrosi severa e il 55% cirrosi**
- il 28% presentava HCV genotipo 1a.

Potential adverse events that may occur

Telaprevir:

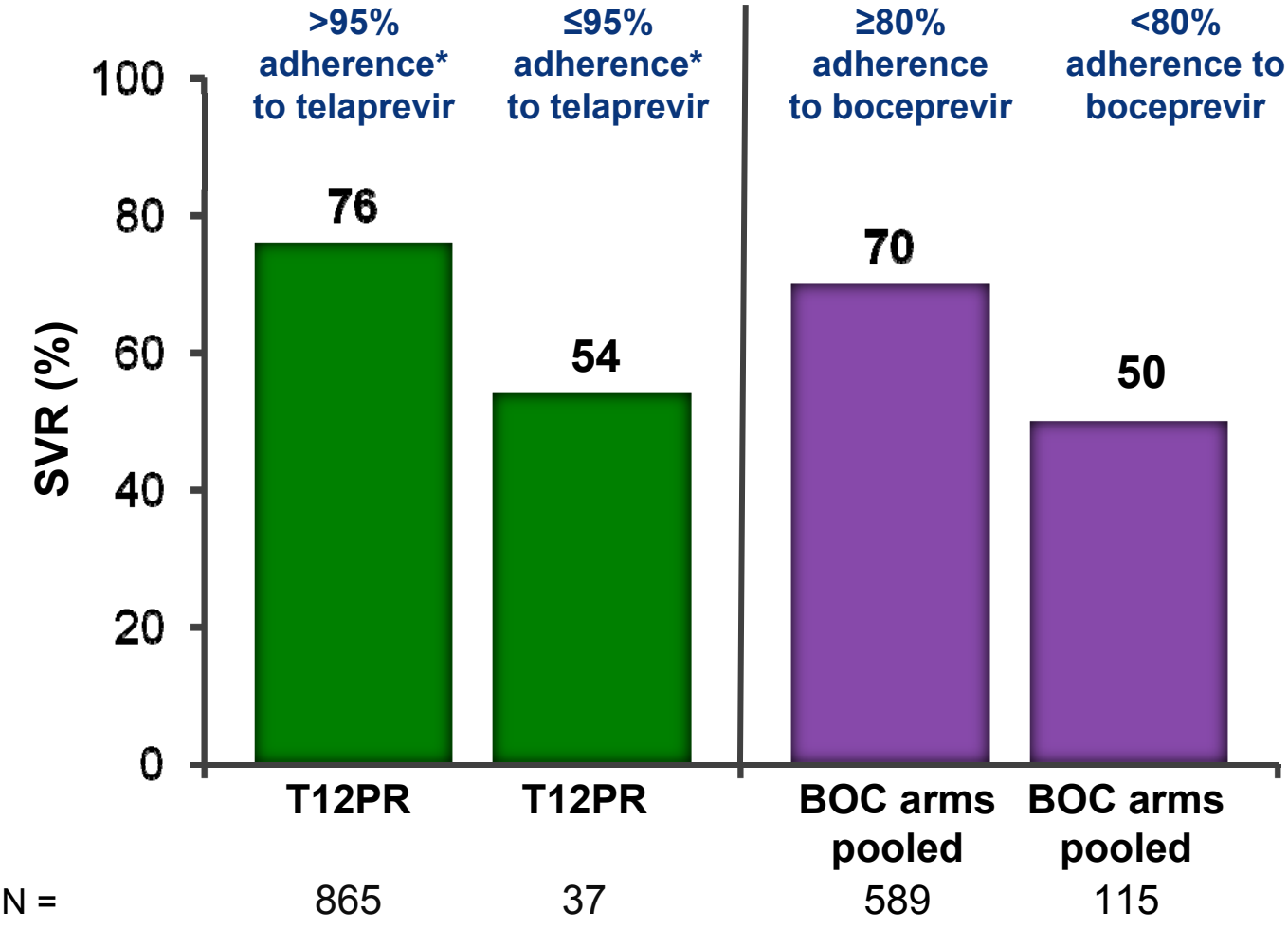
- Rash, pruritus
- Anemia
- Nausea
- Anorectal signs/symptoms
- Diarrhoea

Boceprevir:

- Anemia
- Dysgeusia
- Nausea
- Neutropenia
- Headache

1. Telaprevir EU SmPC; 2. Boceprevir EU SmPC

SVR rates by degree of adherence in treatment-naïve patients



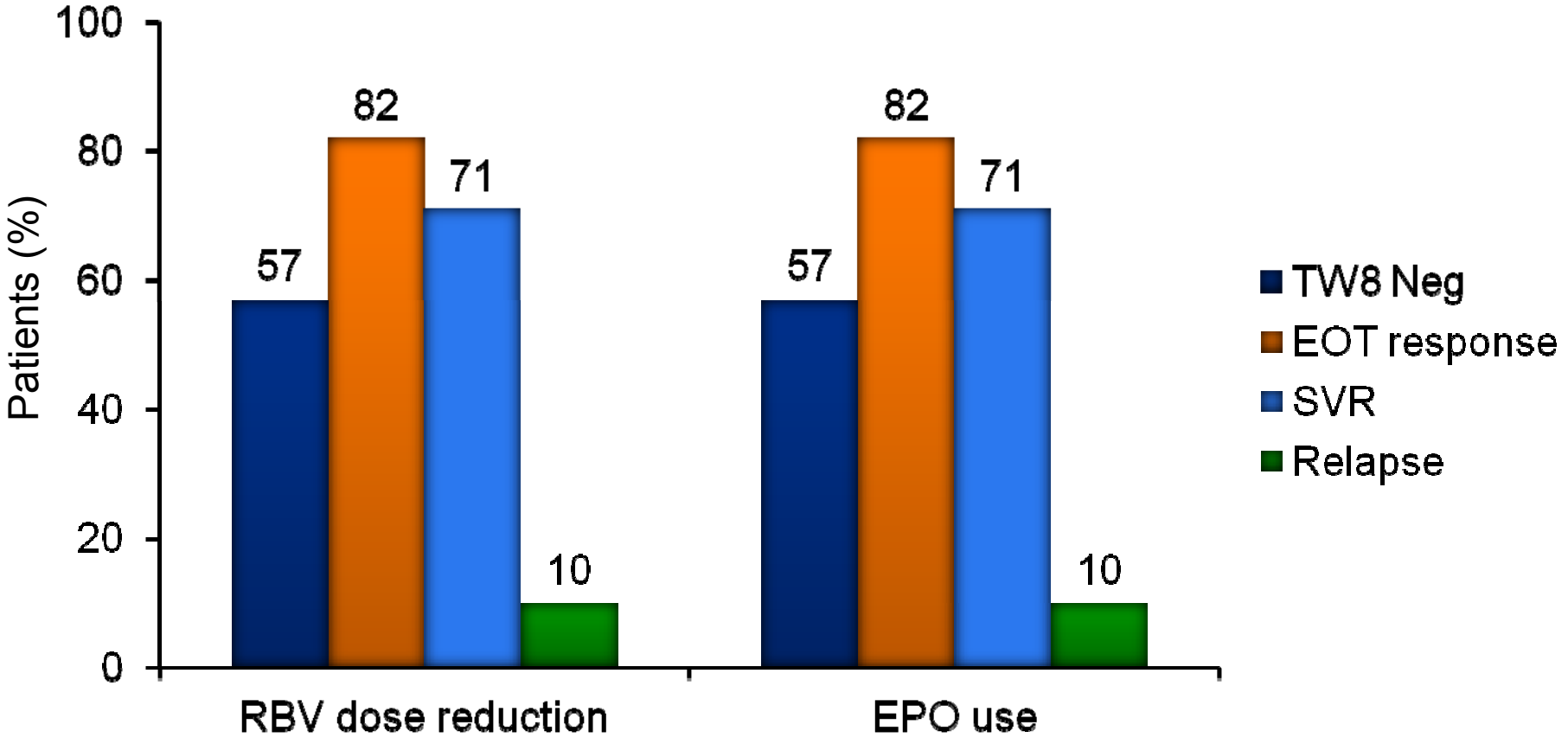
*95% adherence corresponds to 4.2 days' missed doses

Data is shown for combined boceprevir arms of SPRINT-2 (n=704);
Only patients who took at least one boceprevir dose
are included; patients who discontinued during the lead-in were excluded.

Adiwijaya BS, et al. HepDART 2011. Poster 53
Gordon SC, et al. J Hepatol 2011;54(Suppl. 1):S173

Triple therapy: RBV dose reduction vs EPO use

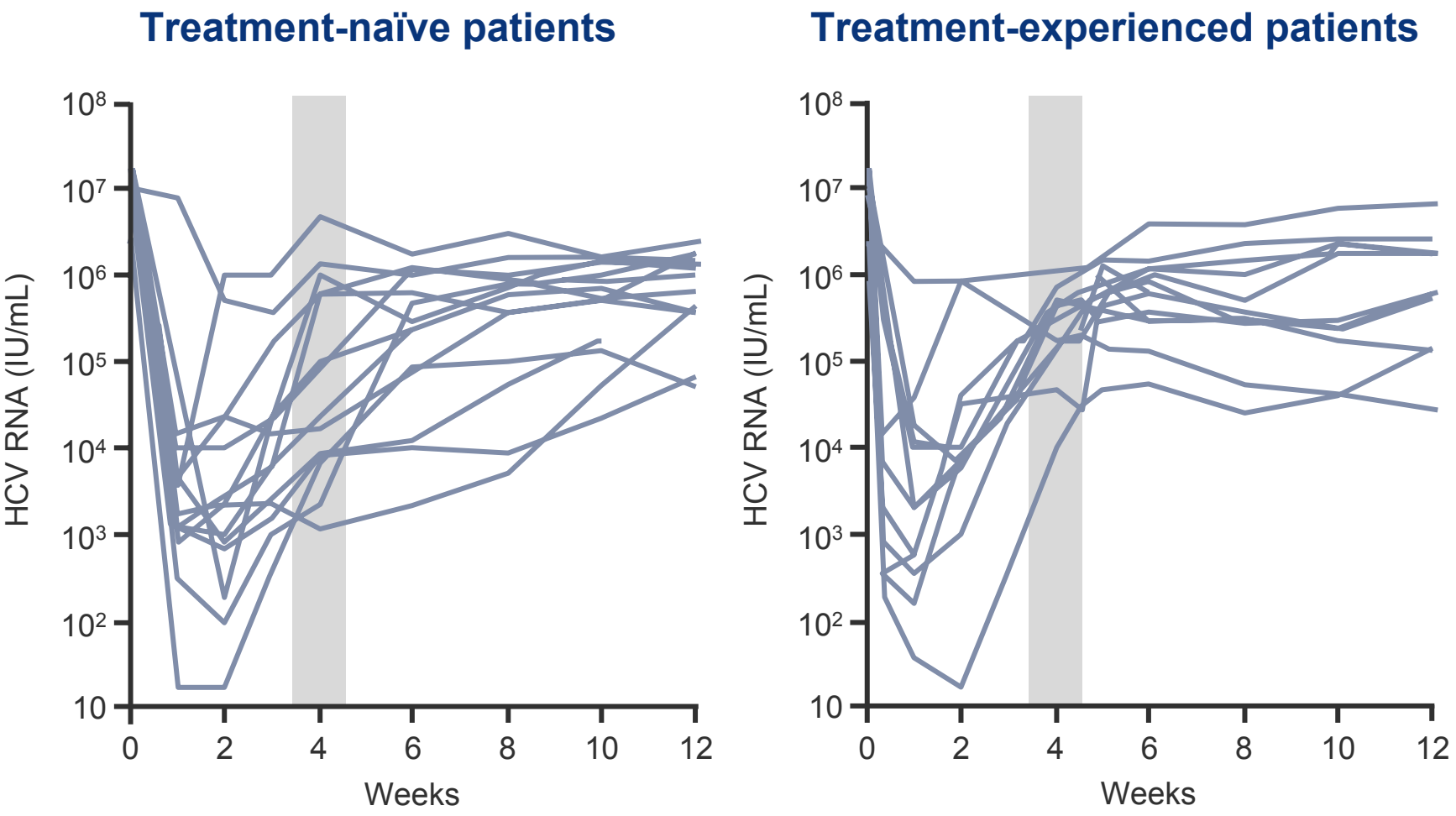
687 G1 patients treated with boceprevir RGT, *randomized when Hb <10g/dL any time*



EPO: epoetin, EOT: end of treatment, TW: treatment week; Neg: negative;

Poordad FF, et al. J Hepatol 2012;56 (Suppl 2):S559

HCV RNA profiles in patients with HCV RNA >1000 IU/mL at Week 4



Jacobson IM, et al. J Hepatol 2012;56(Suppl. 2):S24

Viral resistance profile in patients with HCV RNA >1000 IU/mL at Week 4

Variant, n	Level of resistance	Treatment-naïve (ADVANCE/ILLUMINATE) N=14	Treatment-experienced (REALIZE) N=11
V36M + R155K	High	12	8
A156S/T/V	High	1	0
R155K	Low	0	2
WT	WT	1	1

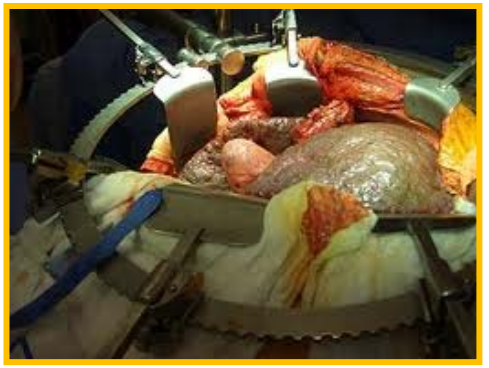
- None of the 25 patients with HCV-RNA levels >1000 IU/mL at Week 4 achieved SVR with continued PR treatment
- 4/16 treatment-naïve and 1/7 treatment-experienced patients achieved SVR after having HCV RNA between 100 and 1000 IU/mL at Week 4
- No patient with HCV RNA >1000 IU/mL at Week 12 achieved SVR

Jacobson IM, et al. J Hepatol 2012;56(Suppl. 2):S24

Conclusions

- Response-guided therapy in treatment-naïve (TVR and BOC) or relapsing (TVR) patients
- High rate of RVR
- Eligibility for short-duration treatment
- Predictor of SVR
- Similar adverse events but more frequent and more severe (anemia, rash)
- Importance of adherence to DAAs
- New DAA in the horizon

Il paziente in lista di trapianto di fegato



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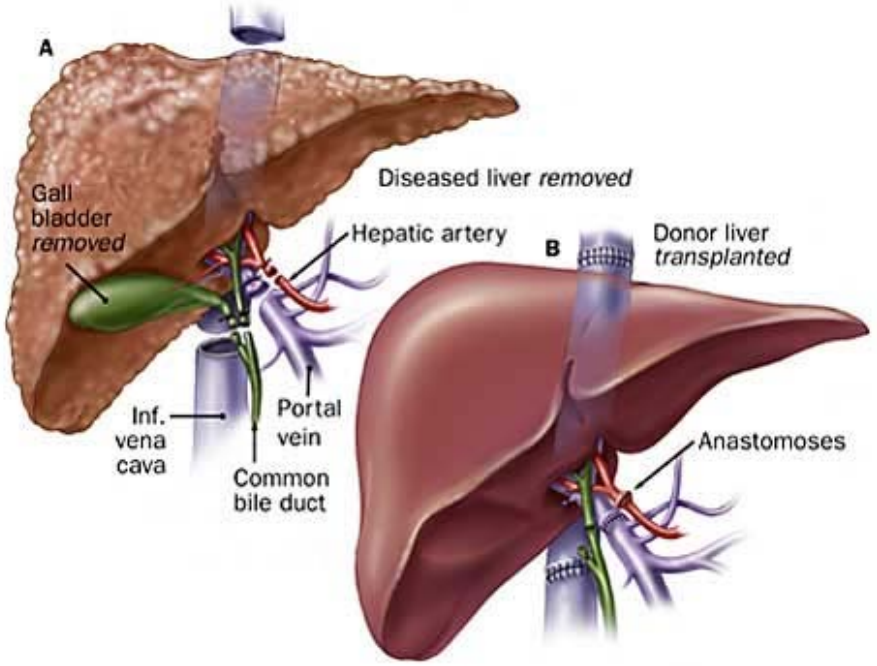
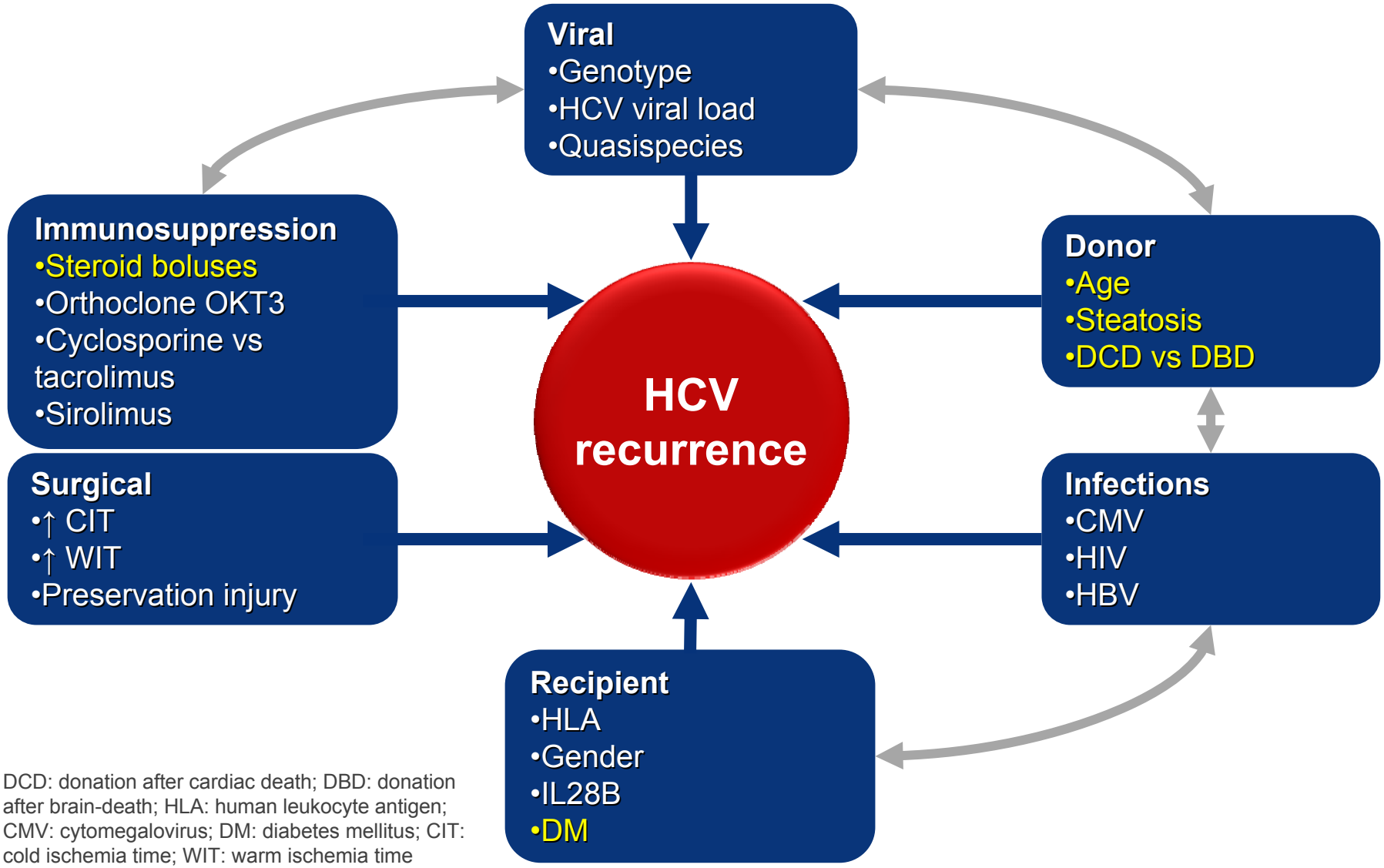


PTV
Azienda Ospedaliera Universitaria
POLICLINICO TOR VERGATA

Università di Roma
Tor Vergata
Facoltà di Medicina e Chirurgia

Factors that influence HCV recurrence post transplant

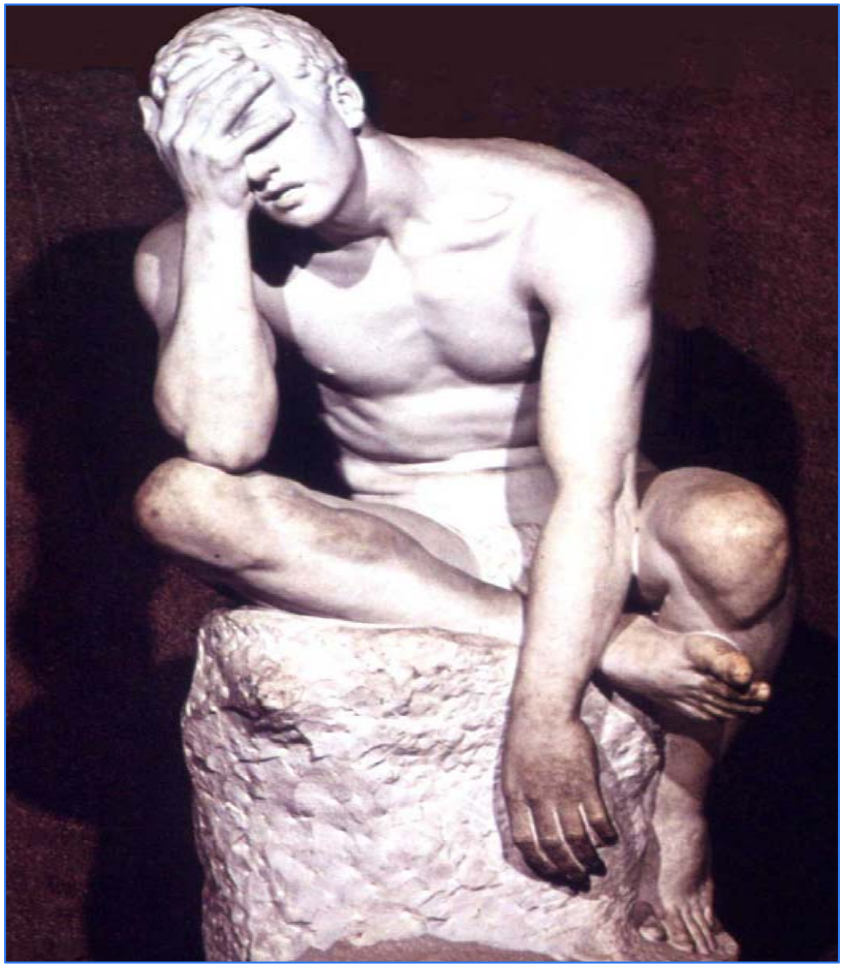


DCD: donation after cardiac death; DBD: donation after brain-death; HLA: human leukocyte antigen; CMV: cytomegalovirus; DM: diabetes mellitus; CIT: cold ischemia time; WIT: warm ischemia time

HCV treatment (PR) post LT

A prototype of a 'difficult to treat' population

- Whole different set of issues
- Many patients are not eligible (41%)
- Anemia in ≥40% of patients
- Discontinuation in 40% - tolerability
- 15% receive full dose; 23% receive >80% treatment dose/duration
- Renal and diabetes issues/ co-morbidities
- Rejection problem overstated but autoimmune (immune mediated graft dysfunction in 5%)



EDITORIALS

Telaprevir, Boceprevir, Cytochrome P450 and Immunosuppressive Agents – A Potentially Lethal Cocktail

Should any liver transplant recipients receive these HCV protease inhibitors? I would counsel that three criteria should be met by any recipient who for whom telaprevir or boceprevir is prescribed:

1. There should be evidence of aggressive histological recurrence of HCV (e.g. $\leq$ stage 3 fibrosis) in the absence of hepatic decompensation;
2. The patient should be treated by physicians experienced in managing complex drug-drug interactions; and
3. Treatment should be in the context of informed consent by the recipient to participate in a protocol reviewed and approved by the appropriate Insititutional Review Board/Ethics Committee.

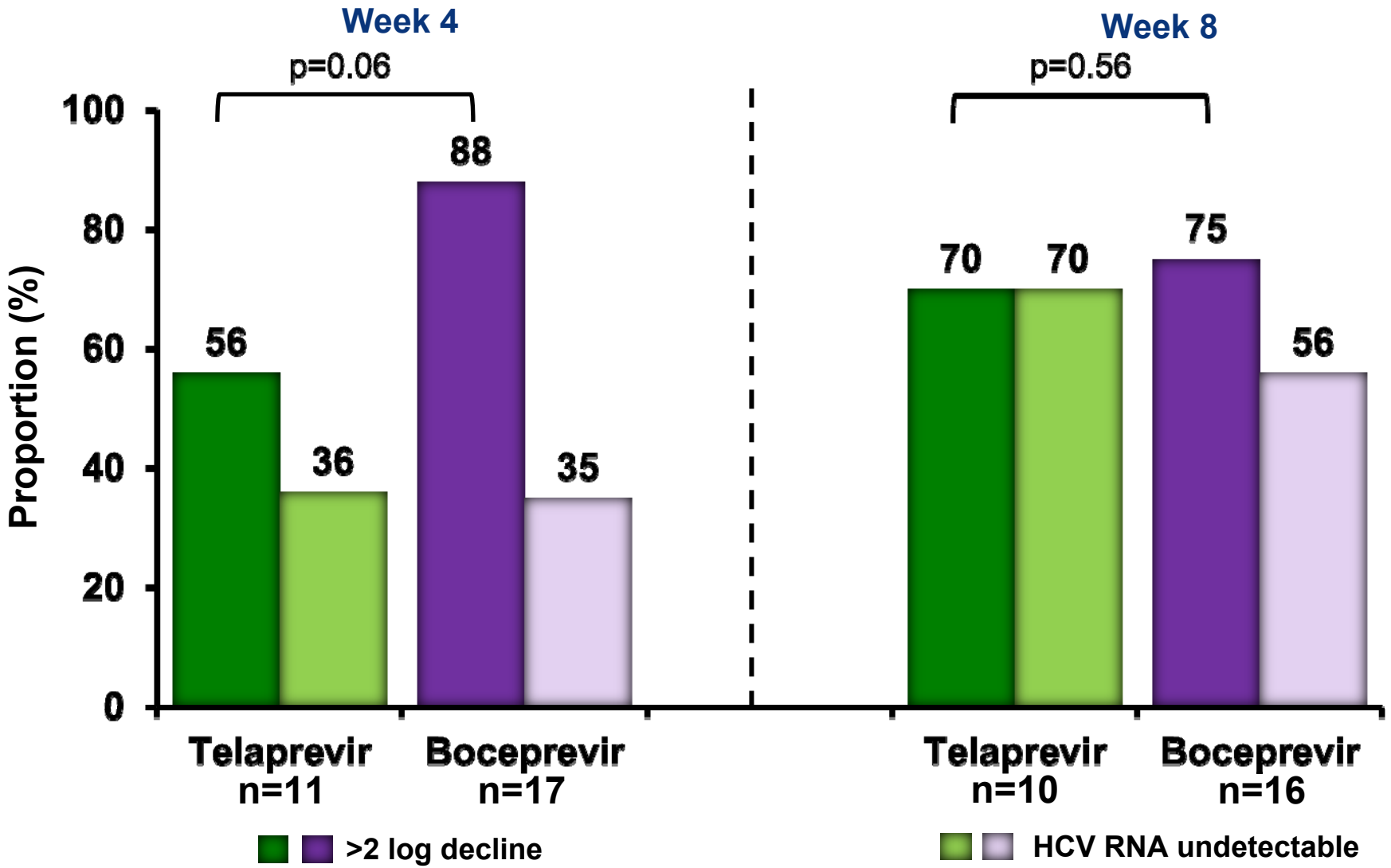
MICHAEL CHARLTON, MD, FRCP
Department of Gastroenterology and Hepatology
Mayo Clinic, Rochester, MN

Efficacy and safety of protease inhibitors for severe Hepatitis C recurrence after liver transplantation: a first multicentric experience

A Coilly, B Roche, J Dumortier, D Botta-Fridlund, V Leroy,
GP Pageaux, SN Si-Ahmed, TM Antonini, D Samuel,
J -C Duclos-Vallée

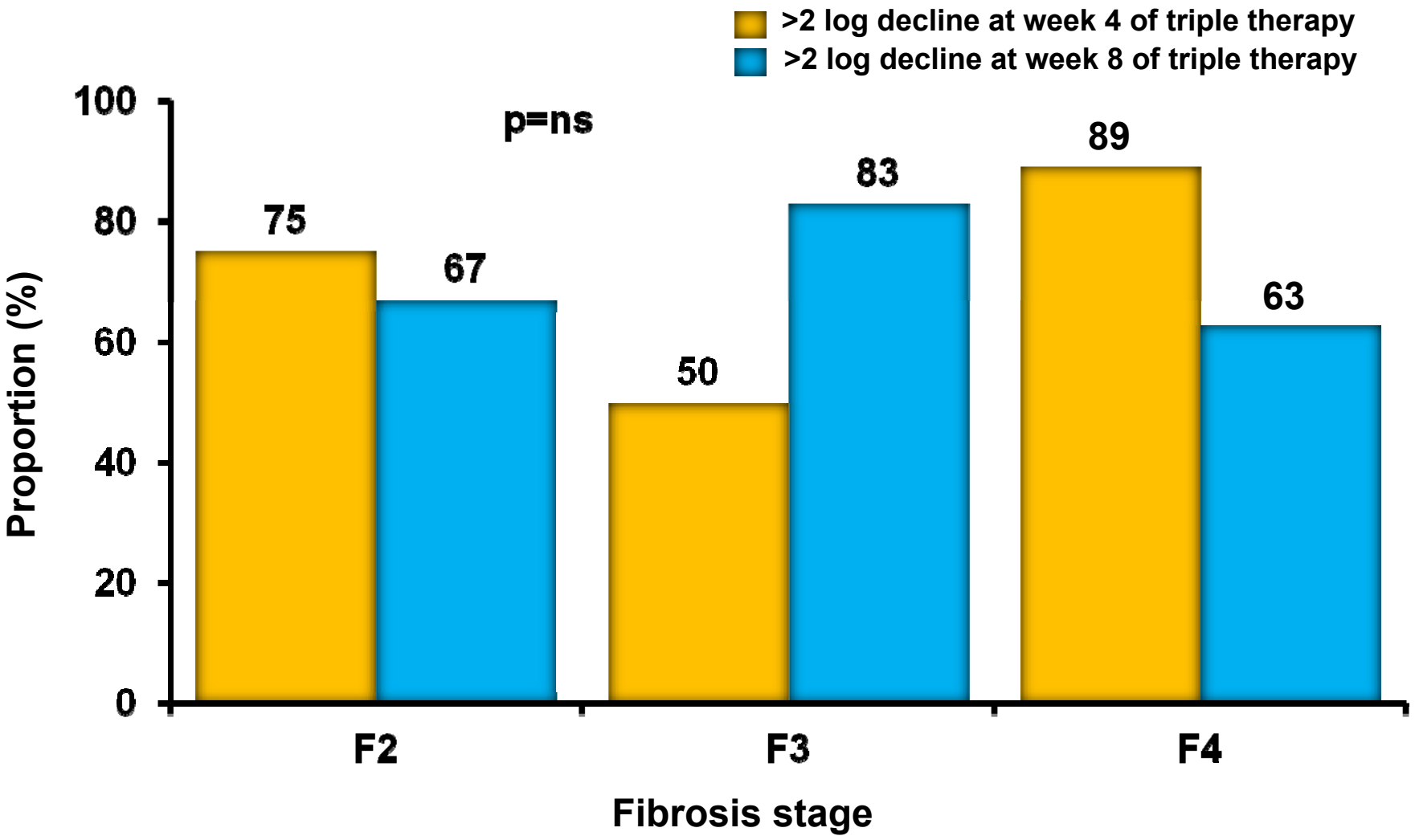
Mantry PR, et al. HepDART 2011. Abstract 90

Virologic response



Coilly A, et al. J Hepatol 2012;56 (Suppl 2):S21

Virologic response according to fibrosis stage



Coilly A, et al. J Hepatol 2012;56 (Suppl 2):S21

Adverse events

	Boceprevir (n=17)	Telaprevir (n=11)	*p*
Death	0 (0%)	1 (9%)	ns
Infections	2 (12%)	2 (18%)	ns
Myelotoxicity			
Anemia			
<10 g/dL	12 (71%)	6 (55%)	ns
<8 g/dL	3 (18%)	1 (9%)	
Neutropenia (<1 G/L)	4 (24%)	2 (18%)	
Thrombocytopenia (<50 G/L)	0 (0%)	1 (9%)	
Dermatological AE	1 (6%)	1 (9%)	ns
Renal failure	0 (0%)	1 (9%)	ns
Diabetes mellitus	2 (12%)	0 (0%)	ns

Coilly A, et al. J Hepatol 2012;56 (Suppl 2):S21

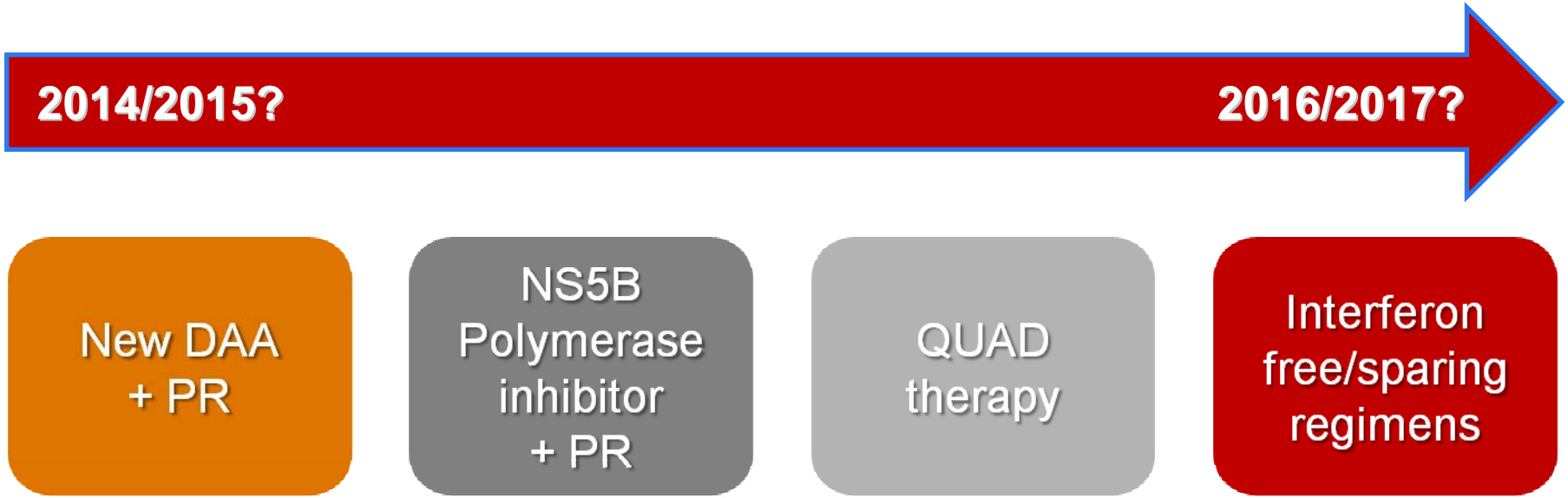
A look to the (near ?) future

- 2*nd* generation DAAs should enter the transplant arena as soon as possible !!!!
  - ✓ *Safety and efficacy should be tested in decompensated cirrhotic patients to be listed for LT*
  - ✓ *Patients should ideally be transplanted with undetectable viremia*
  - *IFN-free regimens are eagerly awaited in this setting !*

- Availability of new DAAs will likely result into dramatic favorable changes:
  - ✓ *in reducing the number of transplant candidates*
  - ✓ *in the preparation of patients to be transplanted*
  - ✓ *in the treatment of recurrent disease*

AASLD 2012, Boston: 18 abstracts on the use of 1st and 2nd generation

HCV treatments potentially available from 2014/2015 onwards



- Future regimens depend on the success of current clinical trial programs
- Drugs whose clinical development has been halted include
  - IDX184 and IDX320 (Idenix) – liver toxicity (halted Sep 2010)
  - PSI-938 (Gilead-Pharmasset) – liver toxicity (halted Dec 2011)
  - Alisporivir (Novartis) – acute pancreatitis (halted Apr 2012)
  - BMS-986094/INX189 (Bristol-Myers Squibb) – heart and kidney toxicity (halted Aug 2012)

NS: non-structural