RECENT ADVANCES IN THE TREATMENT OF HEPATITIS C

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HCV

The Discovery

HCV: the History

- 1968: Discovery of HBV (Blumberg)
- 1973: Discovery of HAV (Feinstone)
- 1975: Description of non-A, non-B hepatitis (Alter)
- DNA virus (HBV mutant) or RNA virus (Flavivirus)?
- 1989: Sequencing of the HCV RNA and production of specific anti-HCV antibodies (Houghton)

HCV: the History

- 1989: 70% of patients with NANB hepatitis are anti-HCV + (Alter, Marcellin)
- 1990: Screening of blood donors for anti-HCV (Alter)
- 1992: Sensitive anti-HCV assays (100%)
- 1994: First PCR assays (Xu)
- 1995: Genotypes and viral load as predictors of response to therapy (Martinot-Peignoux)

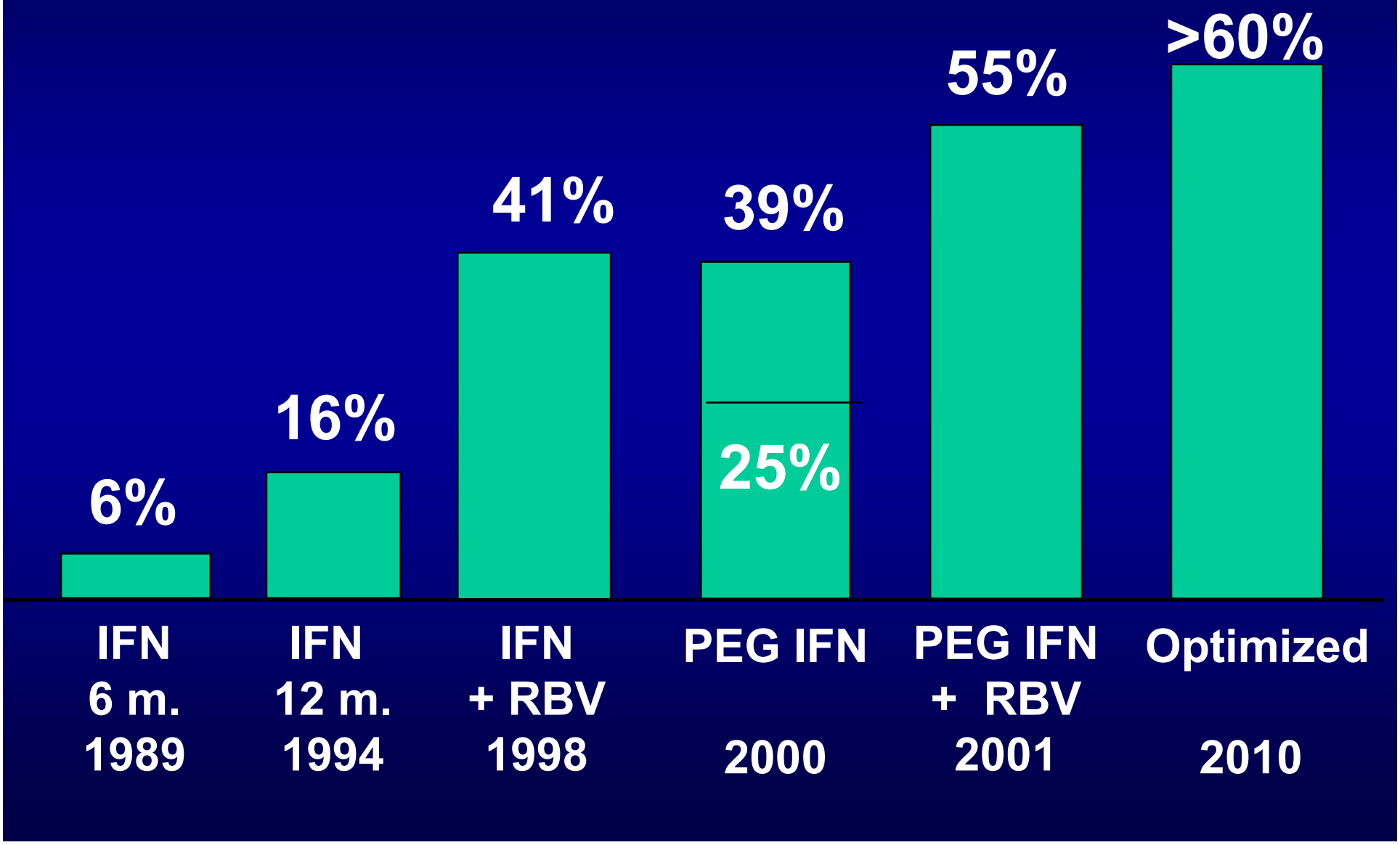
HCV: the History of Treatment

- 1986: IFN can induce a sustained biochemical response (Hoofnagle)
- 1989: Randomized controlled trials of IFN (Di Bisceglie, Marcellin)
- 1991: Ribavirin can induce a biochemical response (Reichard)

HCV: the History

- 1994: Ribavirin doubles the SVR rate of IFN (Brillanti)
- 1999: EASL Consensus Conference: IFN+RBV as the SOC of hepatitis C
- 2000: PEG IFN more effective than IFN (Zeuzem)
- 2001: PEG IFN+RBV more effective than IFN+RBV (Manns, Fried)

RESULTS OF THERAPY
(Sustained Virological Response)



IMPACT OF THERAPY?

Objectives of Therapy:

- Sustained virological response (SVR)
- Arrest progression of liver disease (fibrosis)
- Prevent cirrhosis
- Prevent complications of cirrhosis (HCC)
- Improve survival

SUSTAINED VIROLOGICAL RESPONSE = ERADICATION?

Sustained Virological Response = Viral Eradication

- 80 patients treated in 1987-1992 with SVR
- Follow-up (mean = 3 years)
- Normal ALT = 95%
- Undetectable serum HCV RNA = 97%
- Undetectable liver HCV RNA = 100%

Marcellin et al. Liver 1994

Marcellin et al. Ann Intern med 1997

Sustained Virological Response = Viral Eradication

- 213 patients with SVR
- Most sensitive HCV RNA assay (TMA)
- Follow-up (1-18 years)
- Normal ALT = 95%
- Undetectable serum HCV RNA = 100%
- Undetectable liver HCV RNA = 98%
- Undetectable PBMC HCV RNA = 100%

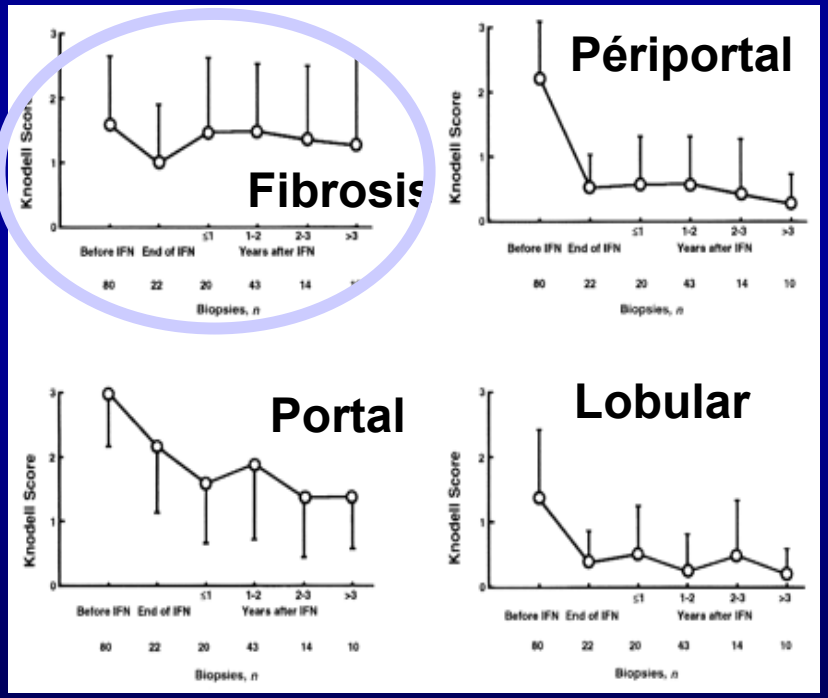
Maylin et al. Gastroenterology 2008

Objectives of Therapy:

- Sustained virological response (SVR)
- Eradication of HCV
- Arrest progression of liver disease (fibrosis)?
- Prevent cirrhosis?
- Prevent complications of cirrhosis (HCC)?
- Improve survival?

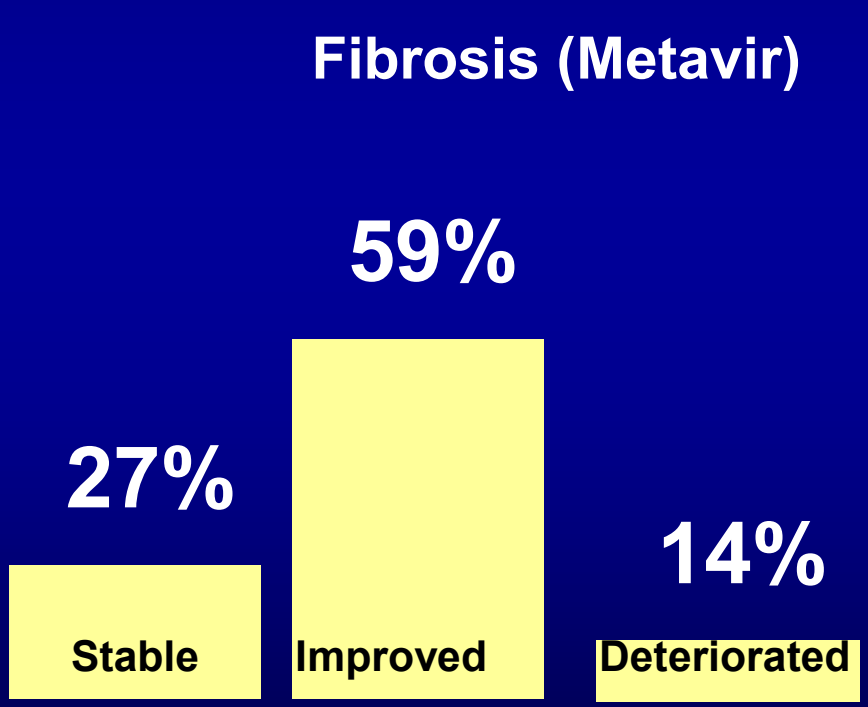
STOP/IMPROVE FIBROSIS

80 responders; 1- 8 years post treatment



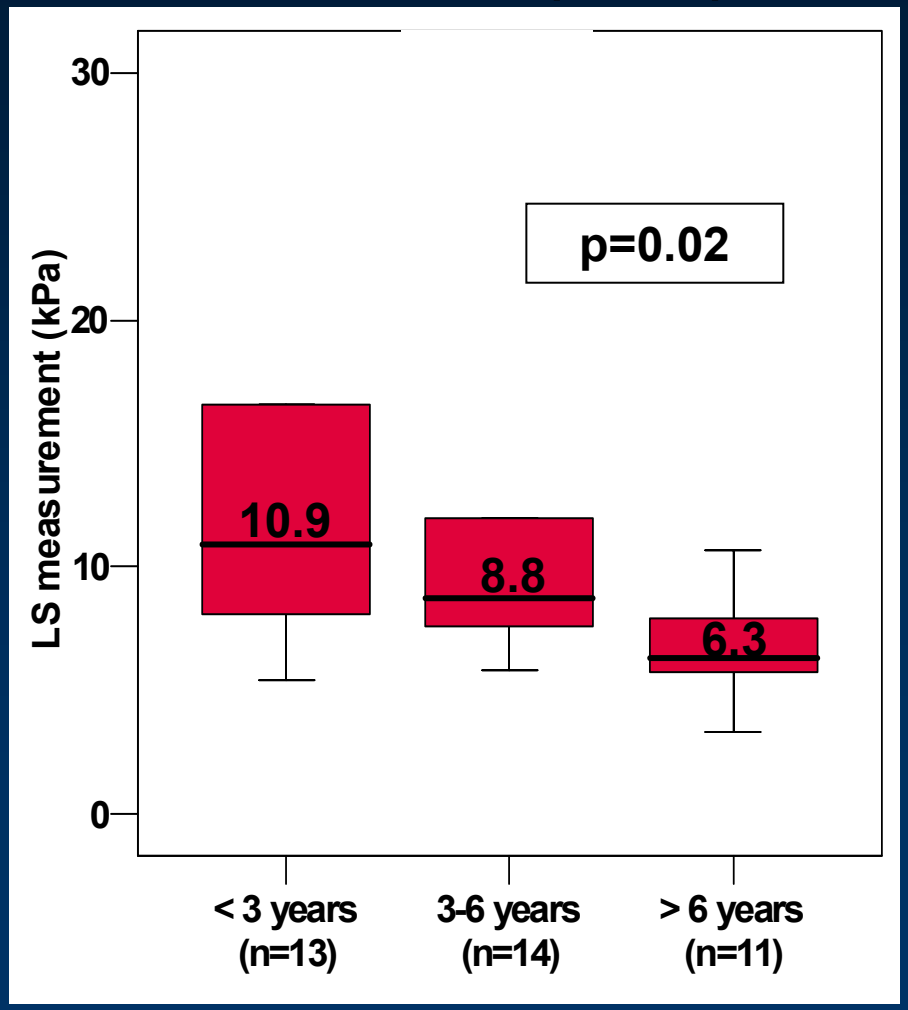
Marcellin et al. Annals of Intern Med 1997

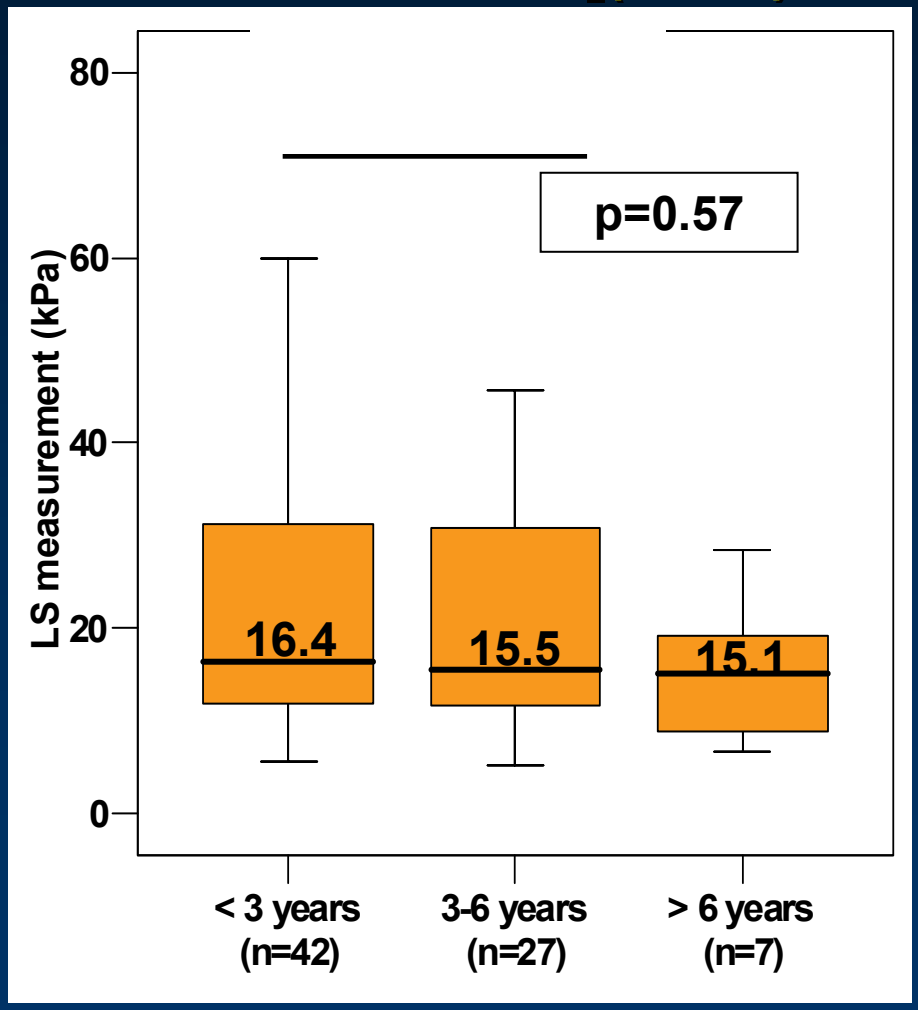
103 responders; 0.5 - 14 years post treatment



Maylin et al. Gastroenterology 2008

LS (Fibroscan) ACCORDING TO THE DELAY IN PATIENTS WITH AND WITHOUT SVR





Cardoso et al. AASLD 2008

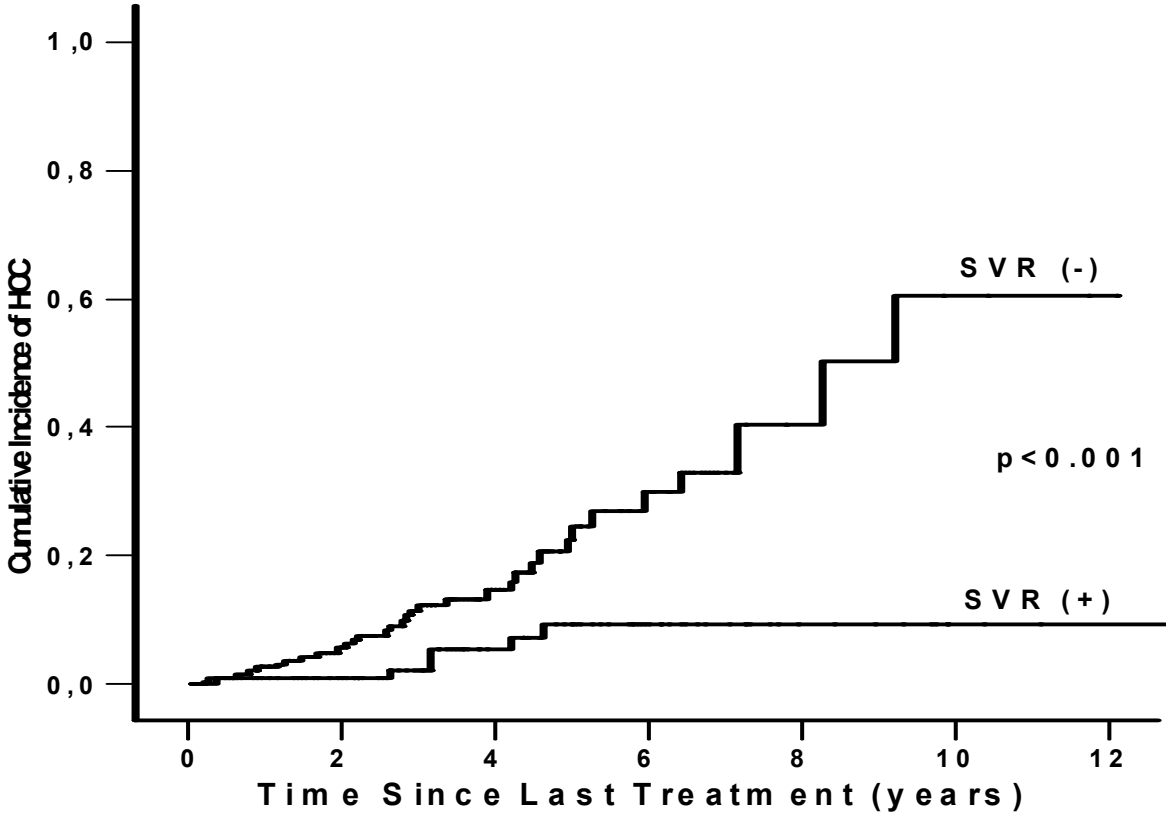
REGRESSION OF CIRRHOSIS?

123 cirrhotics, 2 LBs with median interval of 4 years (1-17)

	F4	F3	F2	F1	*P*
SVR+	54%	25%	13%	8%	<0.01
SVR-	84%	13%	3%	0	

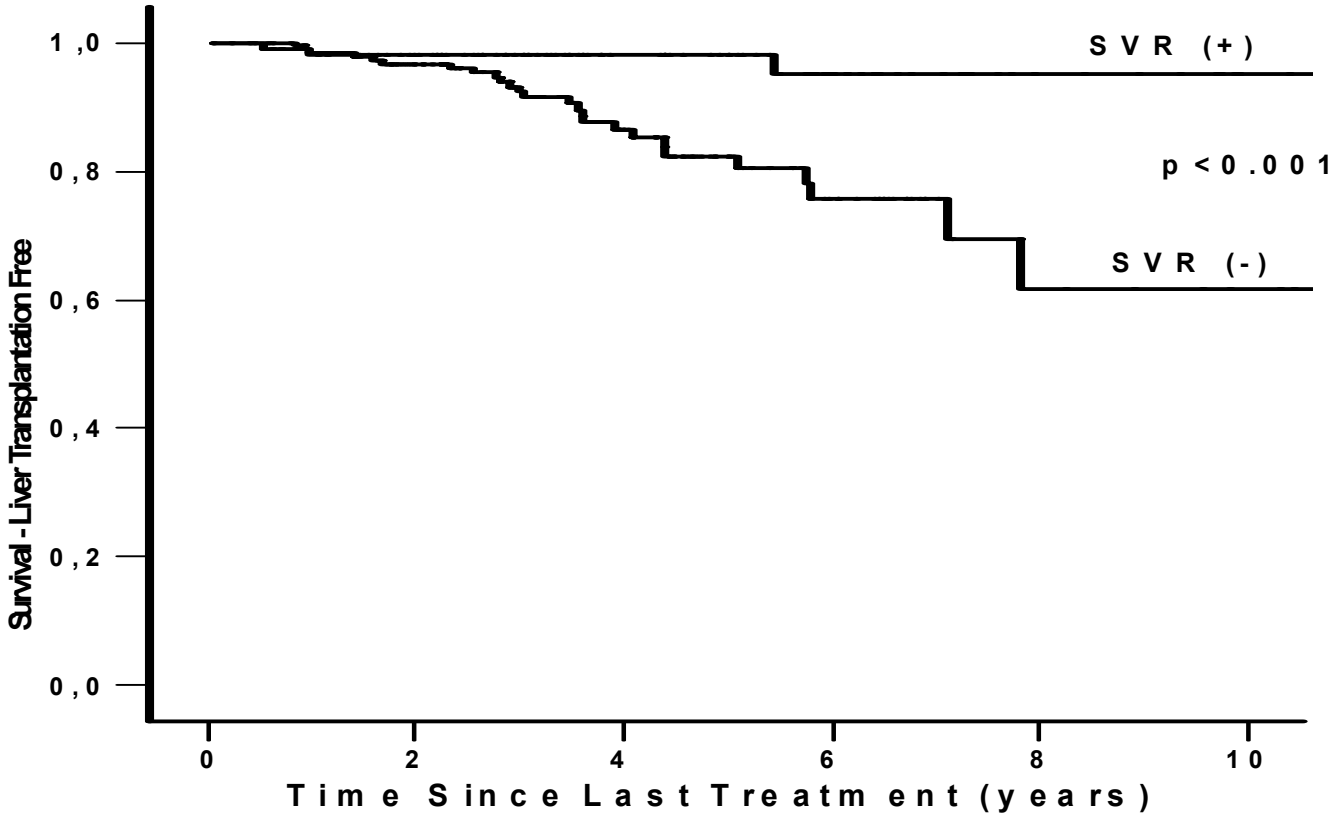
Cardoso et al. J Hepatol 2010

HCC
SVR vs non SVR (in 300 cirrhotics)



Cardoso et al. J Hepatol 2010

SURVIVAL WITHOUT LT
SVR vs non SVR (in 300 cirrhotics)



Cardoso et al. J Hepatol 2010

HOW TO PREDICT RESPONSE?

How to predict response:

- Before treatment

- During treatment

PREDICTION OF SVR BEFORE TREATMENT

VIRUS

- Genotype
- Viral load

HOST

- Ethnicity
- Age
- Gender
- Cirrhosis
- Alcohol
- Weight
- Insulin-Résistance +++

PREDICTION OF SVR BEFORE TREATMENT

Genotype 2, low VL — 90%

Genotype 2, high VL

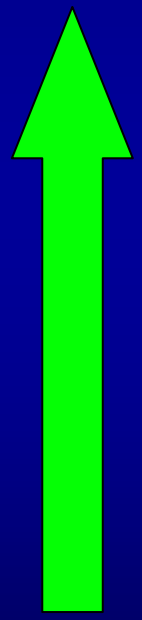
Genotype 3, low VL

Genotype 3, high VL

Genotype 4, VL (?)

Genotype 1, low VL

Genotype 1, high VL — 40%



PREDICTION OF SVR BEFORE TREATMENT

Virus

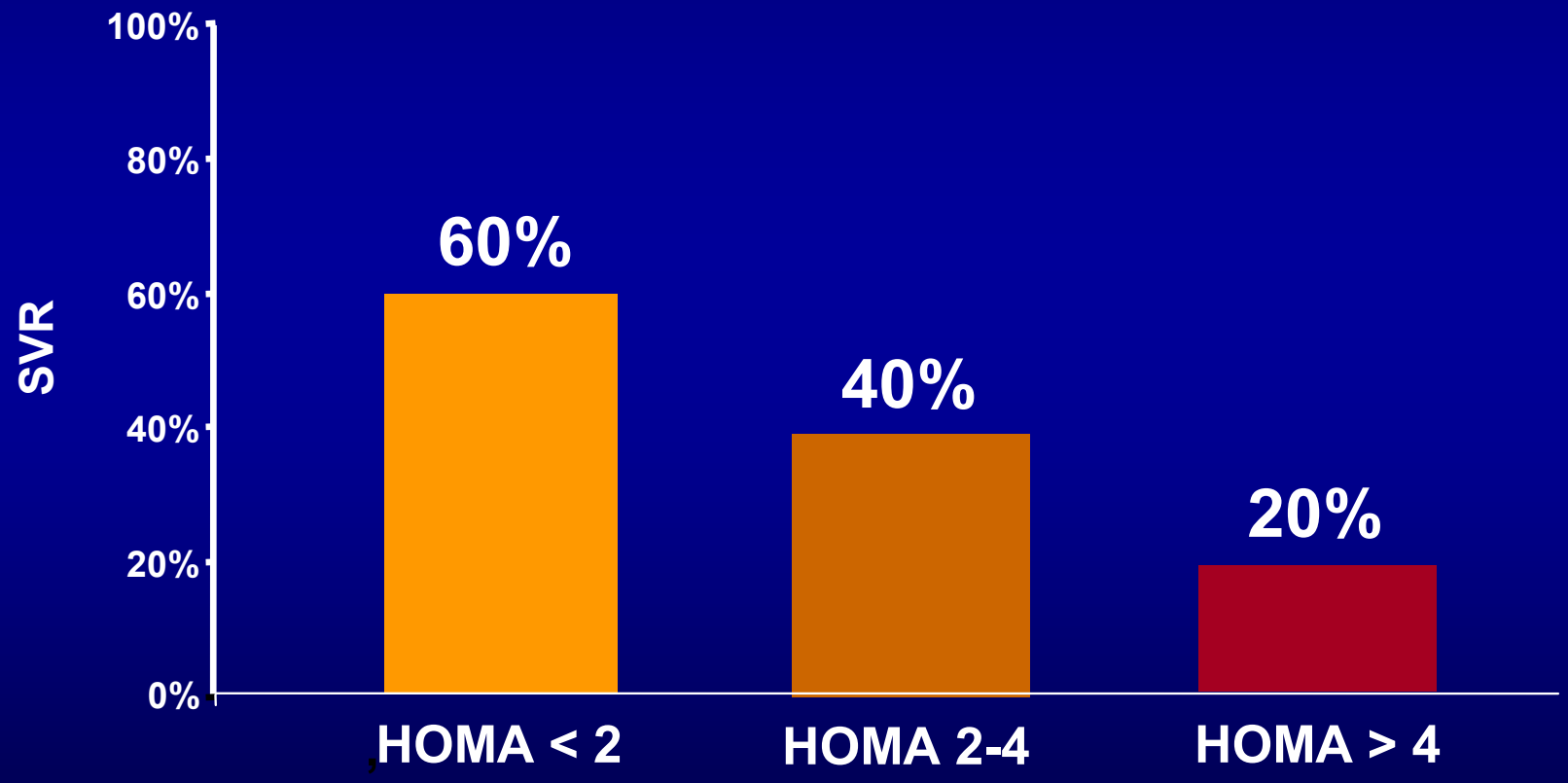
- Genotype
- Viral load

HOST

- Ethnicity
- Age
- Gender
- Cirrhosis
- Alcohol
- Weight
- Insulin-Résistance +++

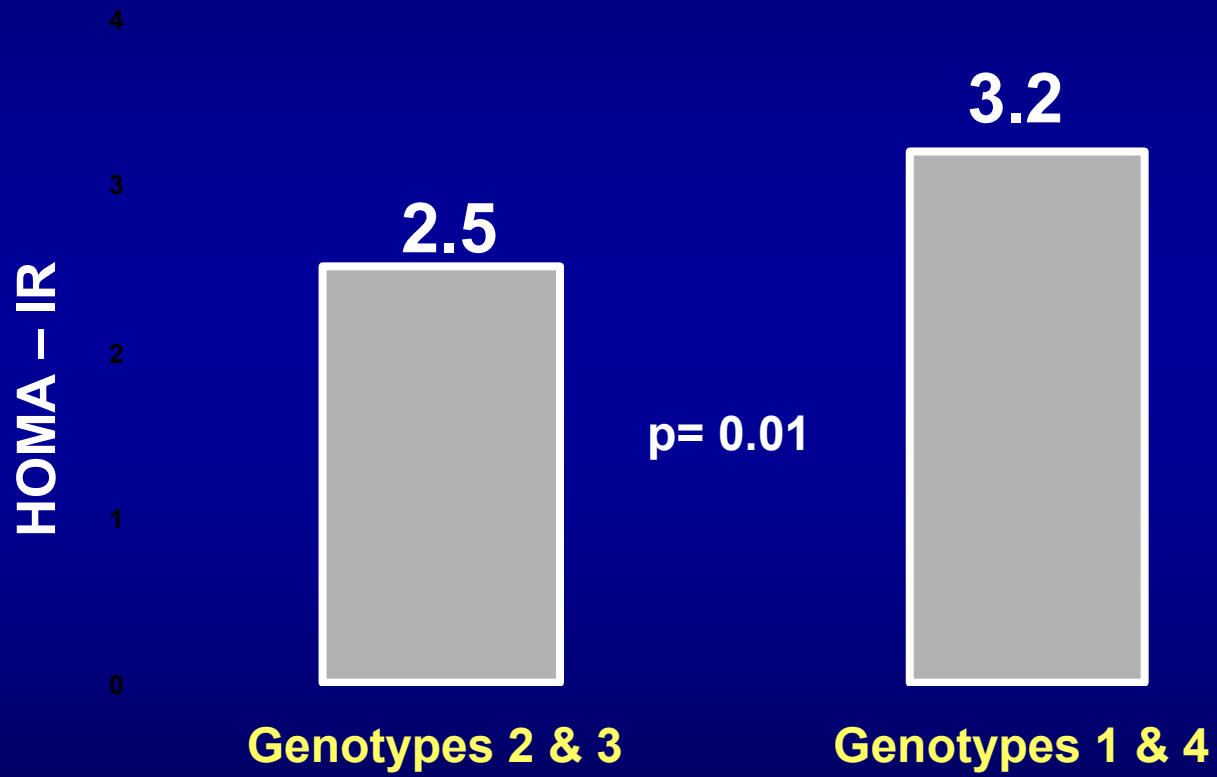
SVR and Insulin-Resistance

113 Patients Genotype 1, PEG IFN + RBV 48 weeks



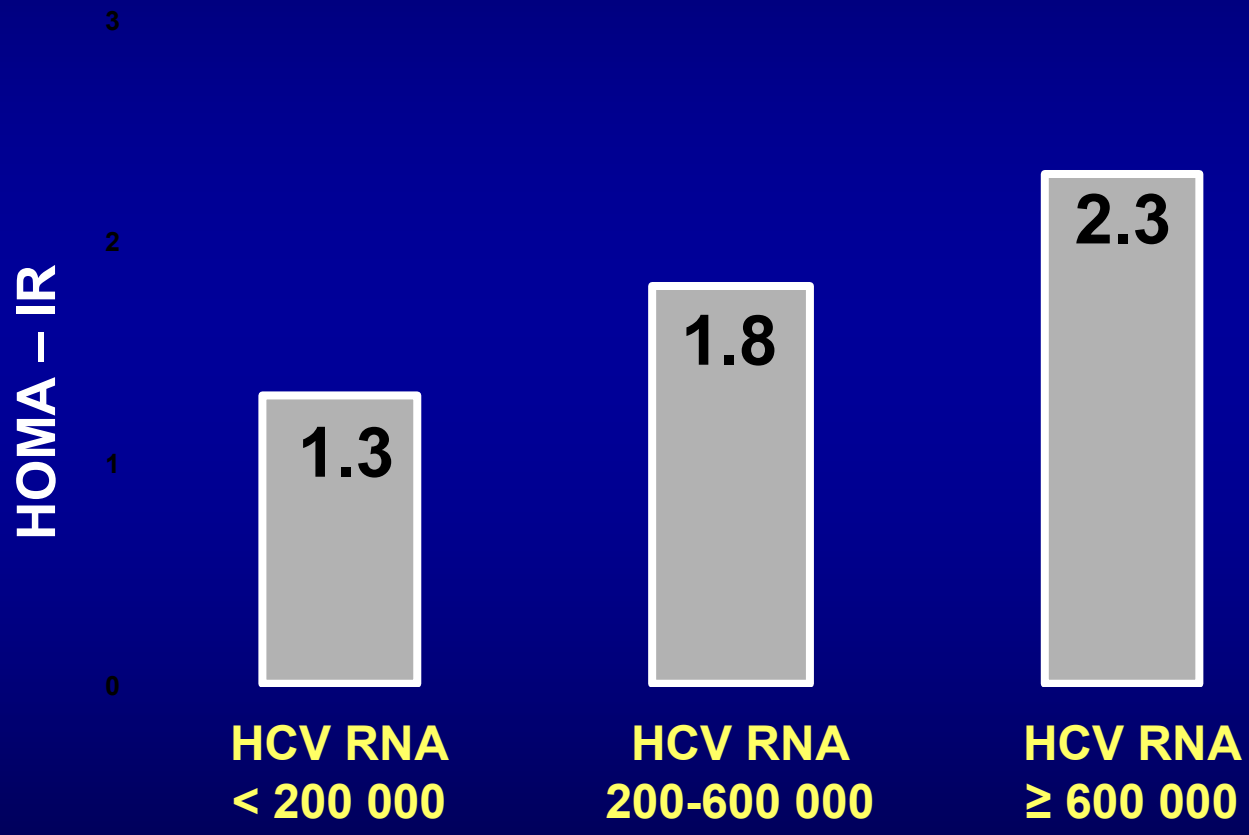
Romero-Gomez et al. Gastroenterology 2005

GENOTYPE AND IR



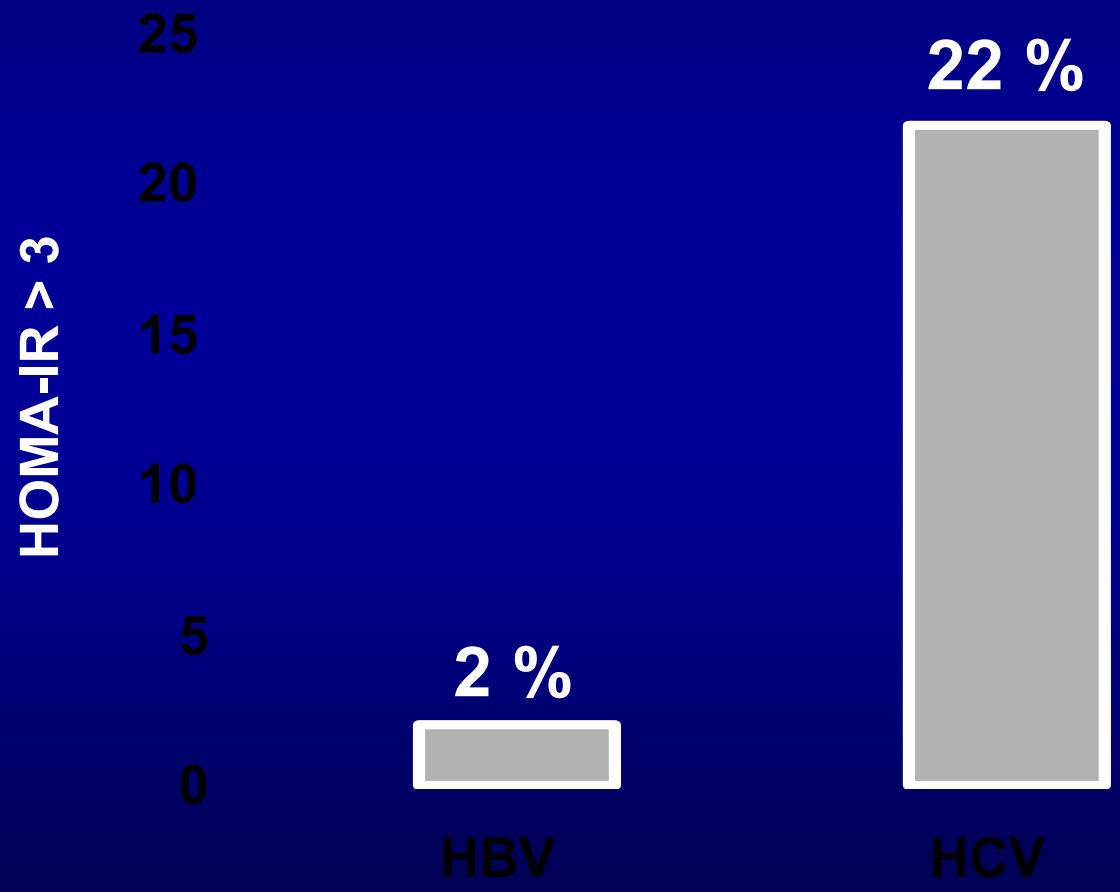
Moucari et al. Gastroenterology 2008

HCV RNA LEVEL AND IR



Moucari et al. Gastroenterology 2008

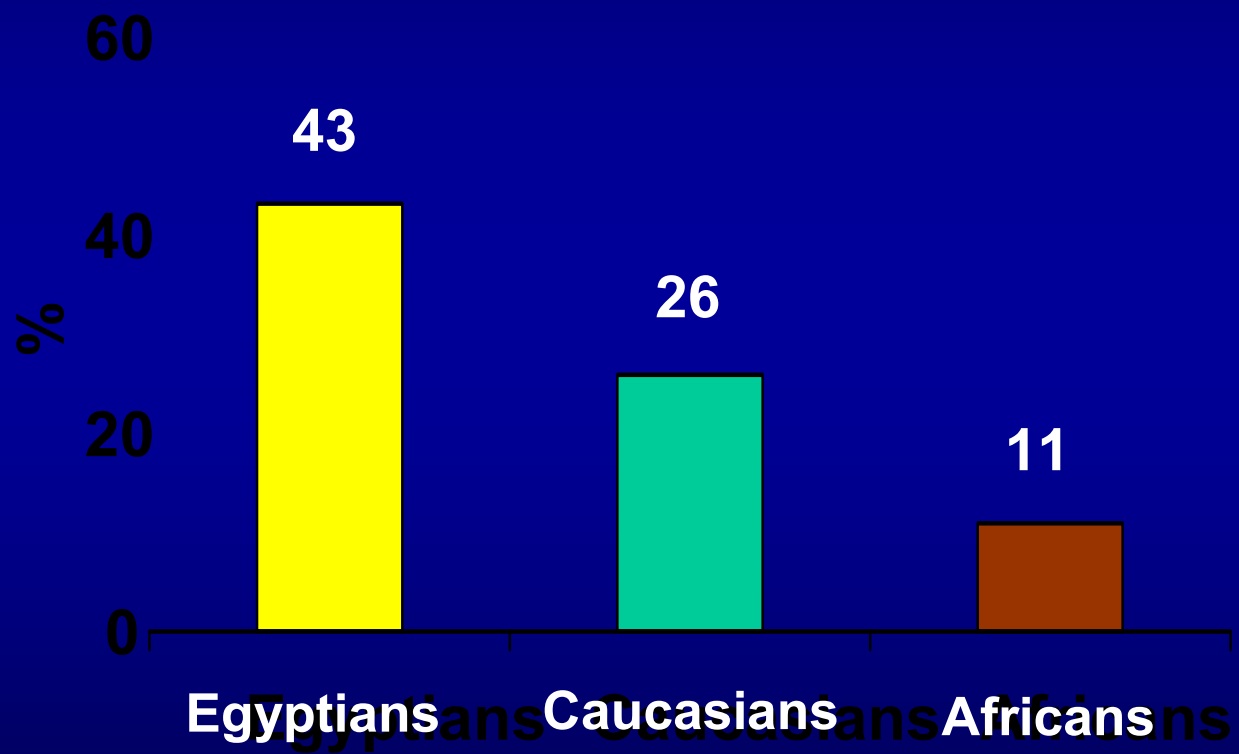
Insulin Resistance: HCV versus HBV



Moucari et al. Gastroenterology 2008

ROLE OF GEOGRAPHiCAL ORIGIN IN HCV G4 PATIENTS?

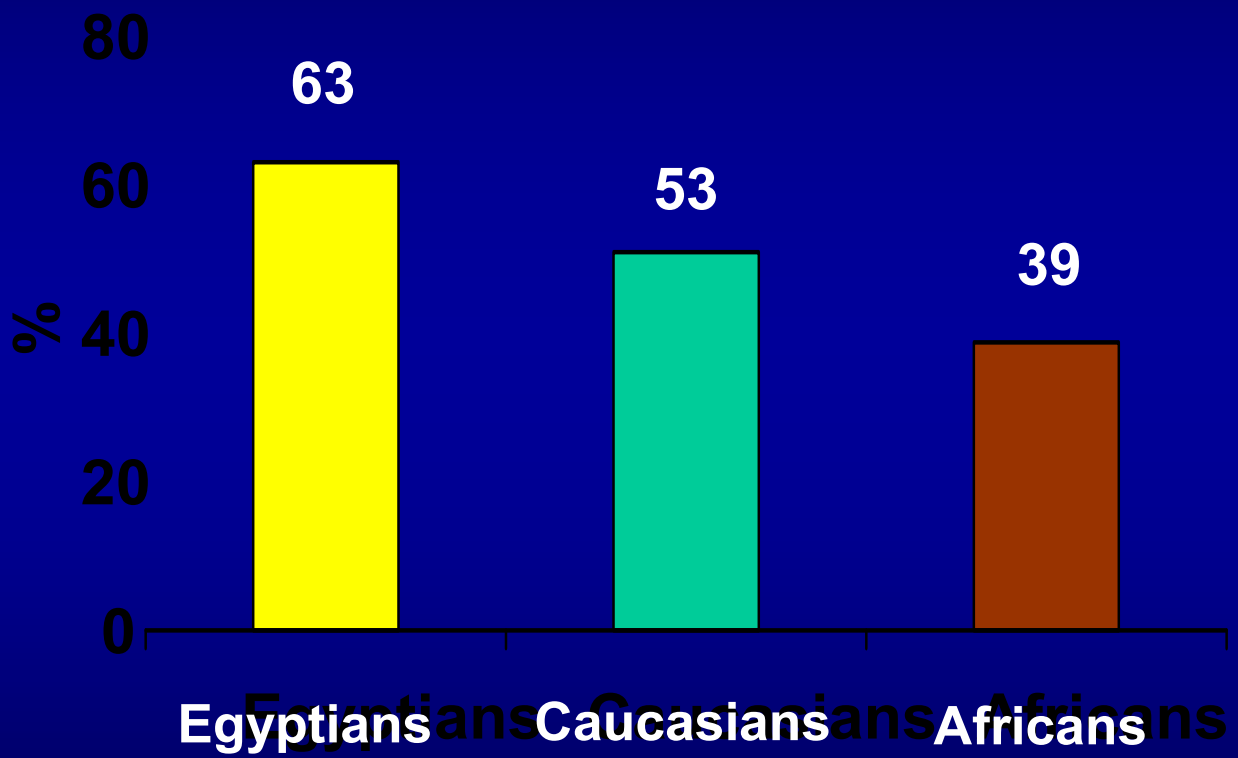
SEVERE FIBROSIS ACCORDING TO GEOGRAPHICAL ORIGIN IN G4



Geographical origin and IR are independent factors ($p<0.001$)

Moucari et al. GUT 2009

SVR ACCORDING TO GEOGRAPHICAL ORIGIN IN G4



Geographical origin and IR are independent factors of SVR (p<0.001)

Moucari et al. GUT 2009

How to predict response:

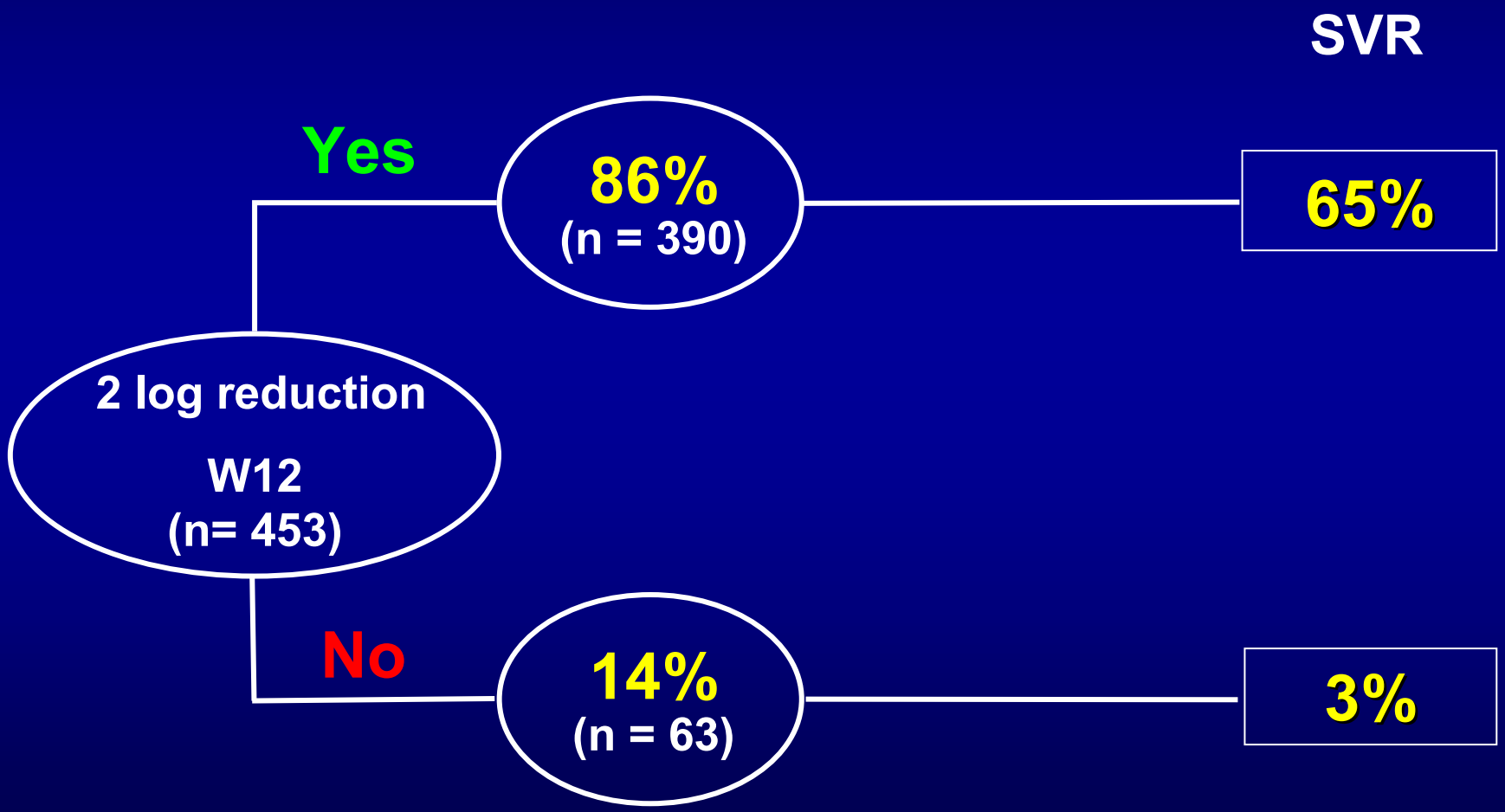
- **Before treatment**

- **During treatment**

PREDICTIVE VALUE OF

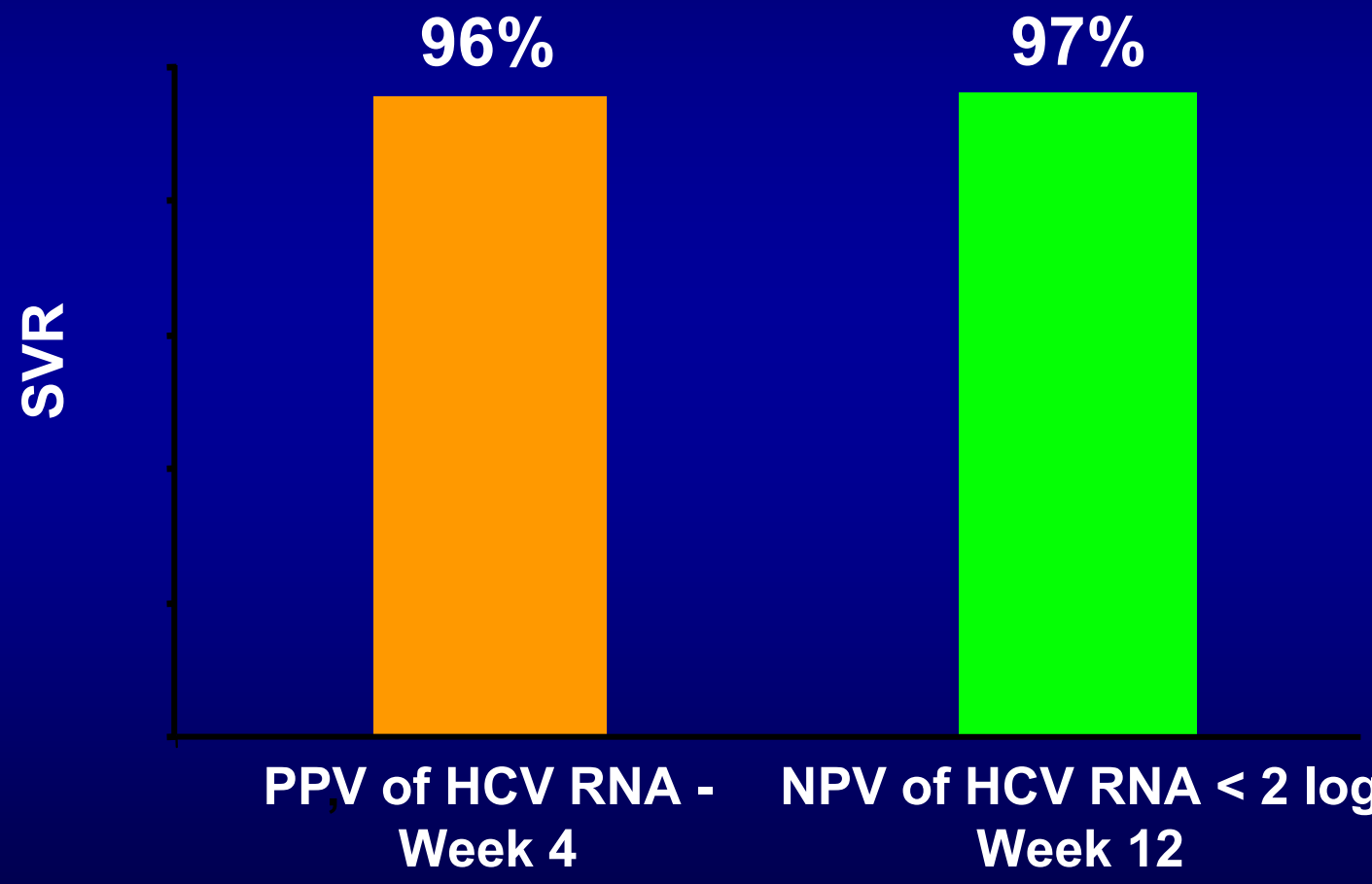
EARLY VIRAL KINETIC

Predictive Value of Early Virological Response in HCV G1 patients



Fried et al. N Engl J Med 2002

Predictive value of Rapid Virological Response
RVR = 4 weeks (N = 400 naive, NR, RR)

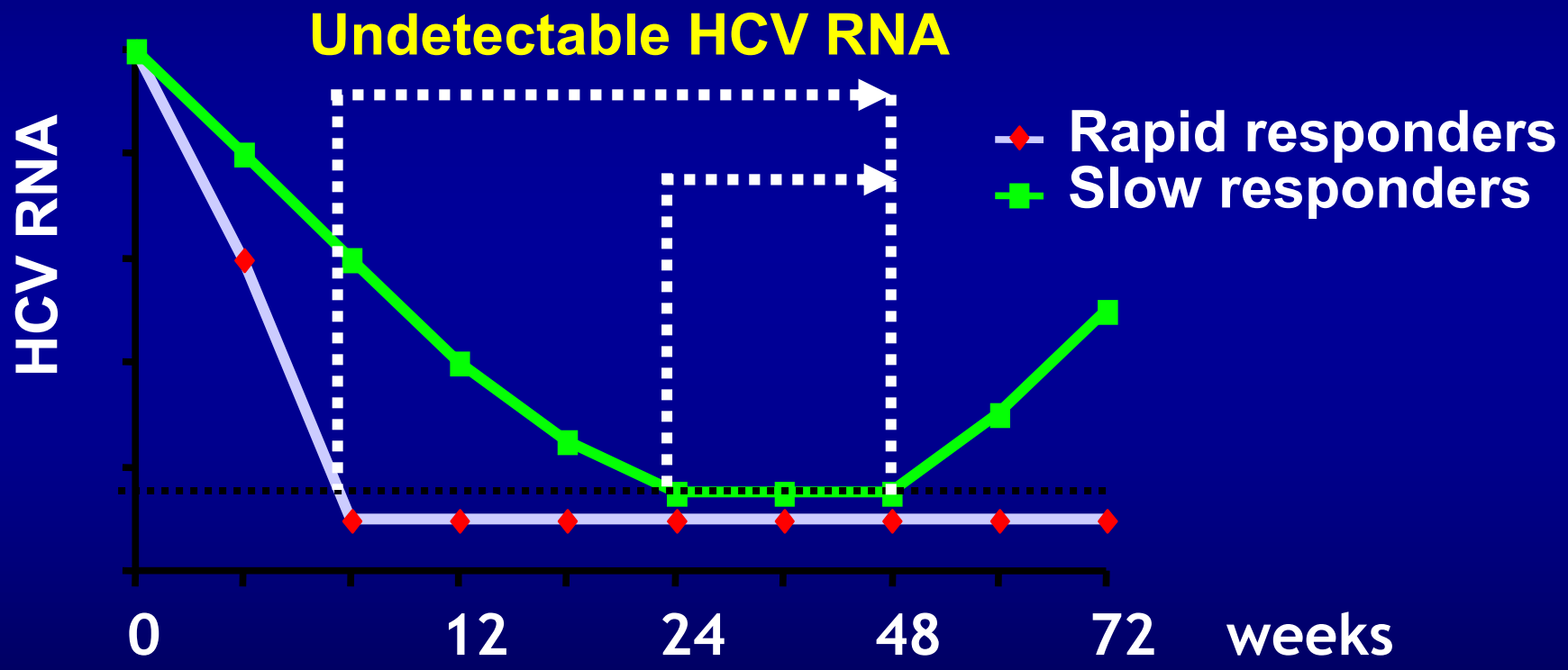


Martinot et al. Antiviral Therapy 2009

HOW TO OPTIMIZE TREATMENT?

The concept of response guided therapy

THE « ACCORDION » CONCEPT



Marcellin et al. J Hepatol 2007

Definitions of on-treatment response

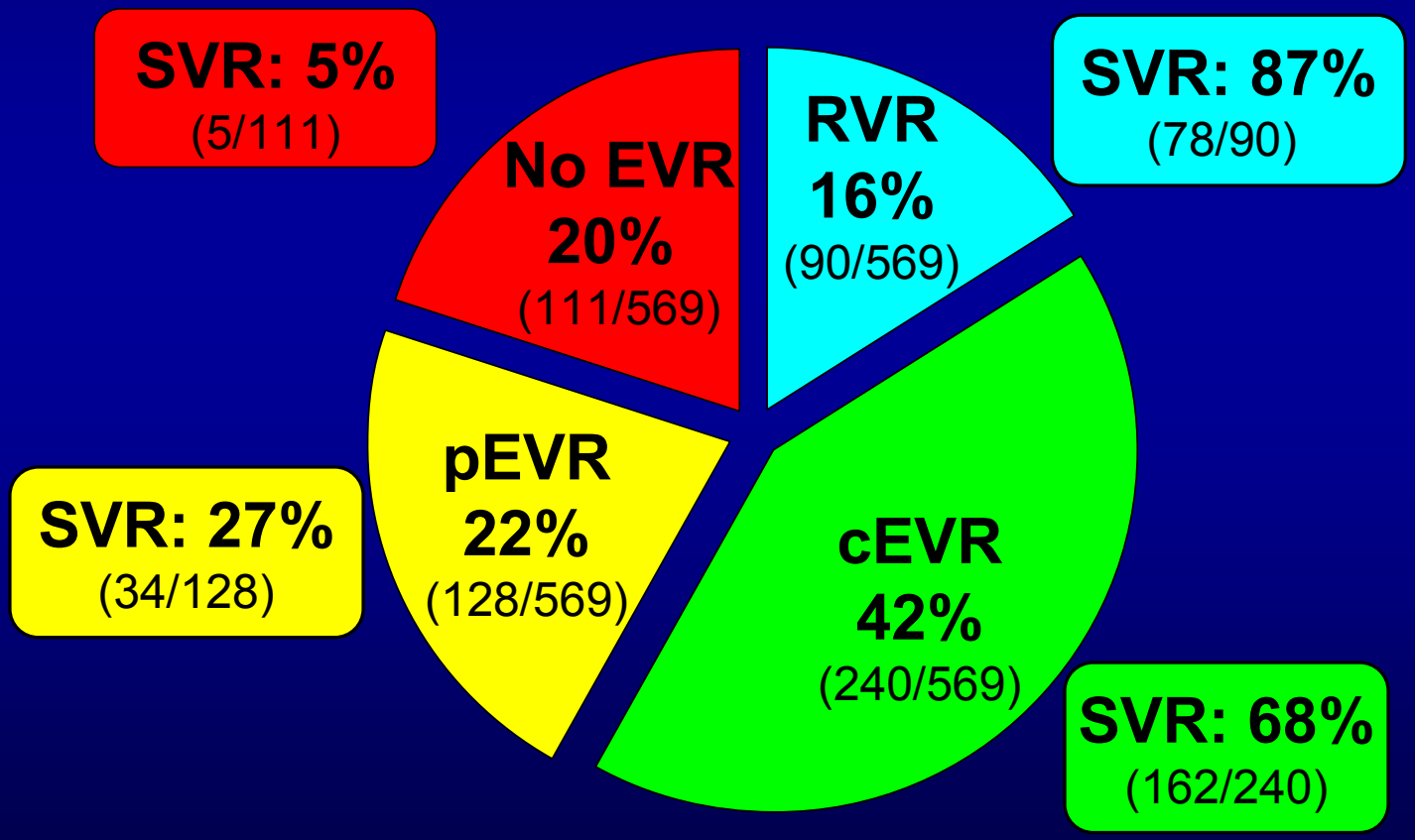
Response		Definition
RVR*		HCV RNA negative at week 4
EVR**	Complete EVR	HCV RNA positive at week 4 but negative at week 12
	Partial EVR	HCV RNA positive but ≥2 $\log_{10}$ drop at week 12
Non-EVR		<2 $\log_{10}$ drop from at week 12

* RVR = rapid virological response
** EVR = early virological response

Marcellin et al. APASL 2008

SVR rates in G 1 patients according to RVR or EVR

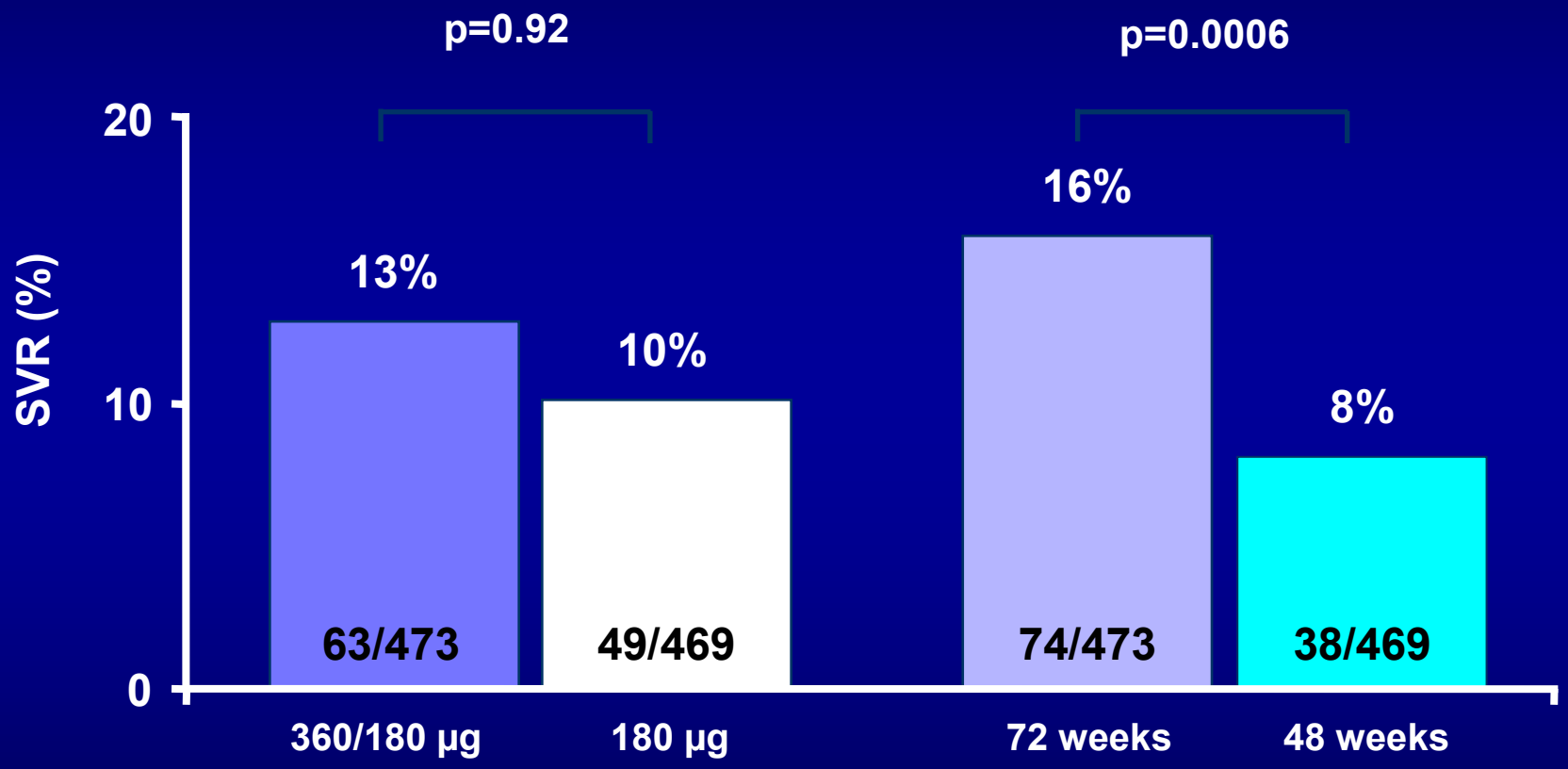
PEG IFN 180 μg/wk plus RBV 1000/1200 mg/day for 48 weeks; n=569



Marcellin et al. APASL 2008

TREATMENT OF NON RESPONDERS

Induction dosing had less impact than treatment duration on rate of SVR



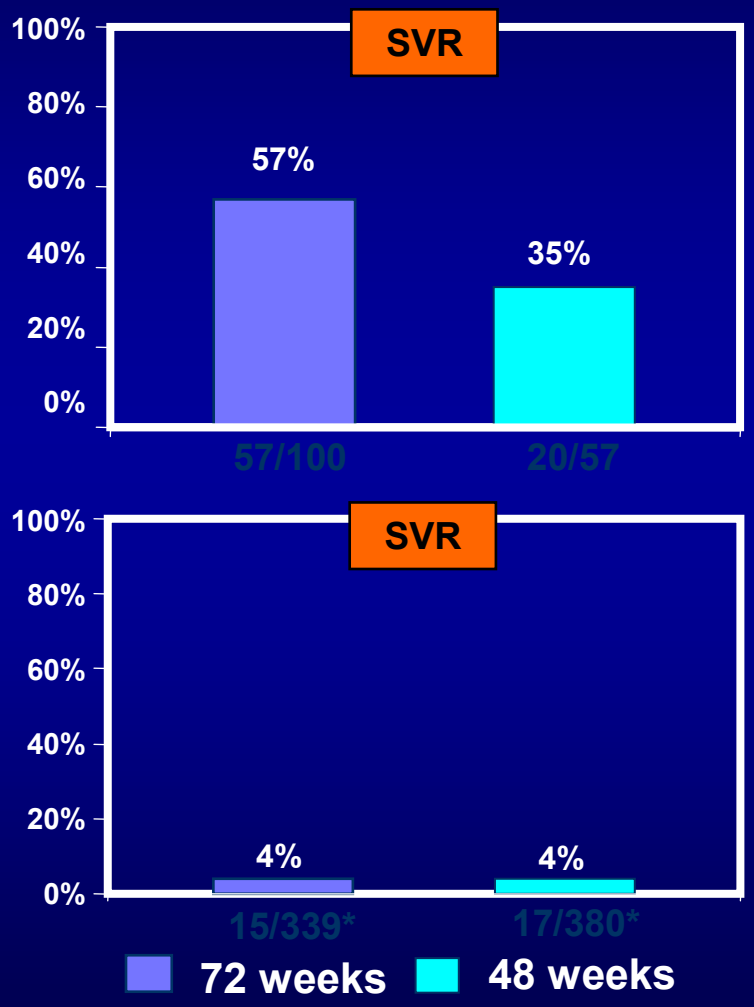
Jensen and Marcellin et al. Annals Intern Med 2009

HCV RNA - at week 12 is a strong predictor of SVR with 72 weeks treatment

All patients (n=942)

HCV RNA - at week 12: YES 17%

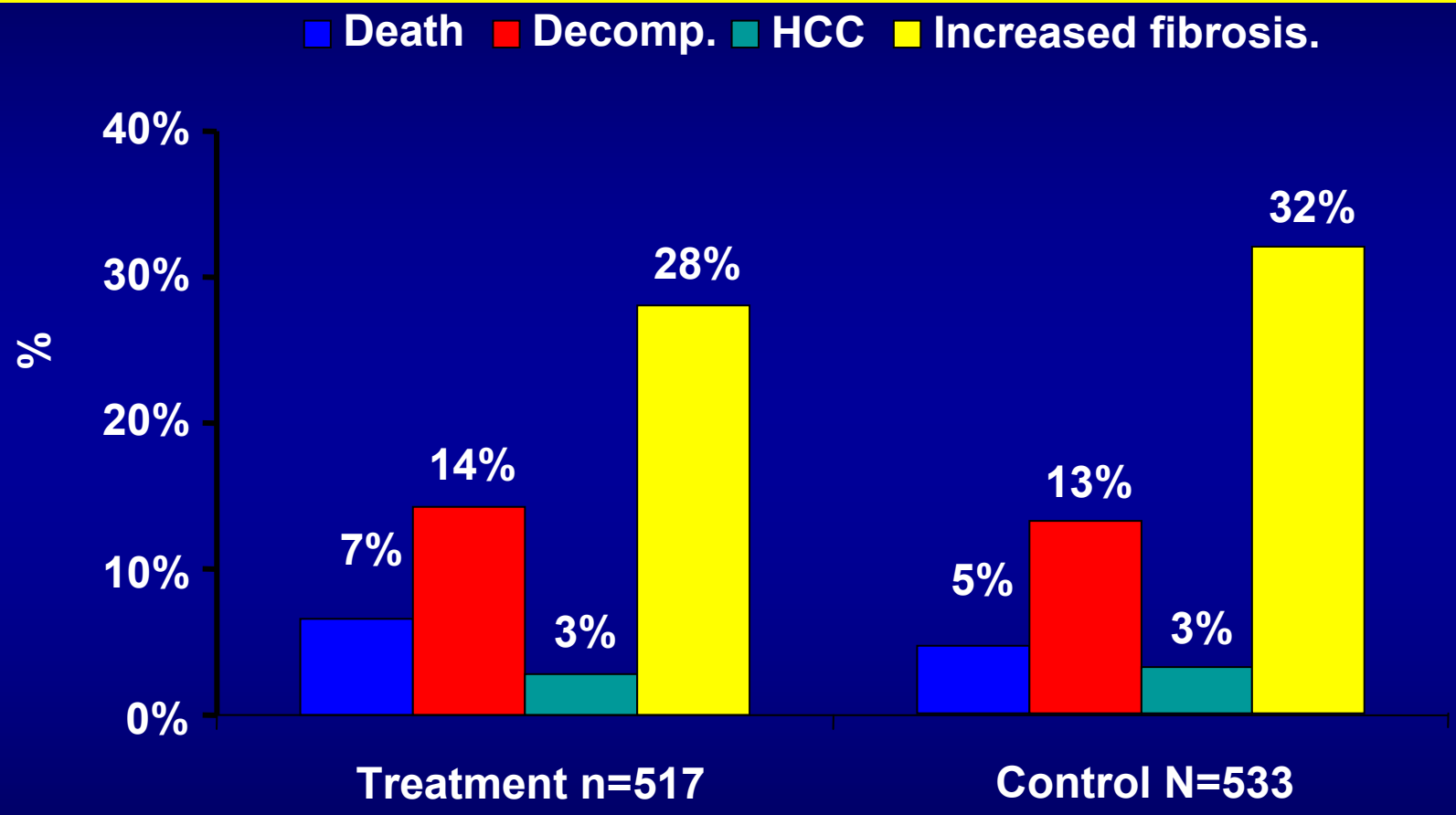
HCV RNA - at week 12: NO 83%



Moucari et al. J Hepatol 2007

Jensen and Marcellin et al. Annals Intern Med 2009

Maintenance Therapy ?
"HALT-C" Study (PEG IFN a2a, 90)



Significant decrease of ALT, HCV RNA and liver necro-inflammation (p<0.0001)

Shiffman et al. NEJM 2009

PERSPECTIVES

PERSPECTIVES:

- Better predict the response and adjust therapy

- The new molecules

Prediction of SVR with Liver Gene Expression: Transcriptome

Table 3. List of the genes that differ between NR and SVR in Group A

Gene	NR / normal	SVR / normal	NR / SVR	*P*-value[a]	FDR
IFI6	126.5 ± 84.3	35.6 ± 48.1	3.5	0.002	0.039
IFI27	141.1 ± 107.3	33.6 ± 40.7	4.2	0.002	0.039
ISG15	88.5 ± 80.3	24.1 ± 33.0	3.7	0.002	0.039
MIX1	40.1 ± 33.9	14.9 ± 19.2	2.7	0.006	0.059
HERC5	11.6 ± 9.1	5.4 ± 5.3	2.2	0.006	0.059
TGFB2	6.2 ± 7.6	2.3 ± 1.7	2.7	0.006	0.059
OAS2	27.0 ± 15.4	14.9 ± 16.0	1.8	0.016	0.118
VEGFD	5.5 ± 5.0	2.3 ± 2.9	2.4	0.020	0.118
IL8	49.2 ± 63.9	15.4 ± 15.5	3.2	0.020	0.118
IFIT1	387.8 ± 1399.3	7.0 ± 8.2	55.3	0.020	0.118

Best signature : *IFI27 et CXCL9*

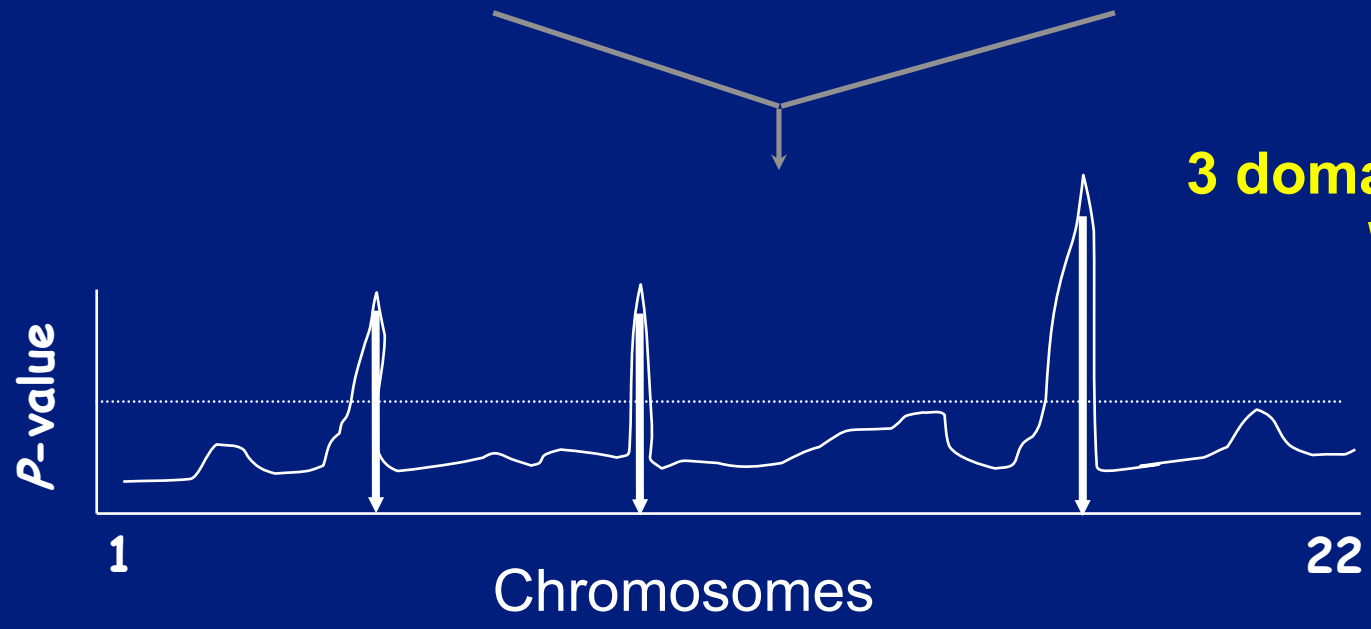
Accuracy: 78 %

Asselah et al. GUT 2008

Prediction of SVR by Genomic

Responders
N=500

Non responders
N=500



3 domains associated With SVR

Ge et al. Nature 2009

SVR According to T/C Polymorphism And Ethnicity

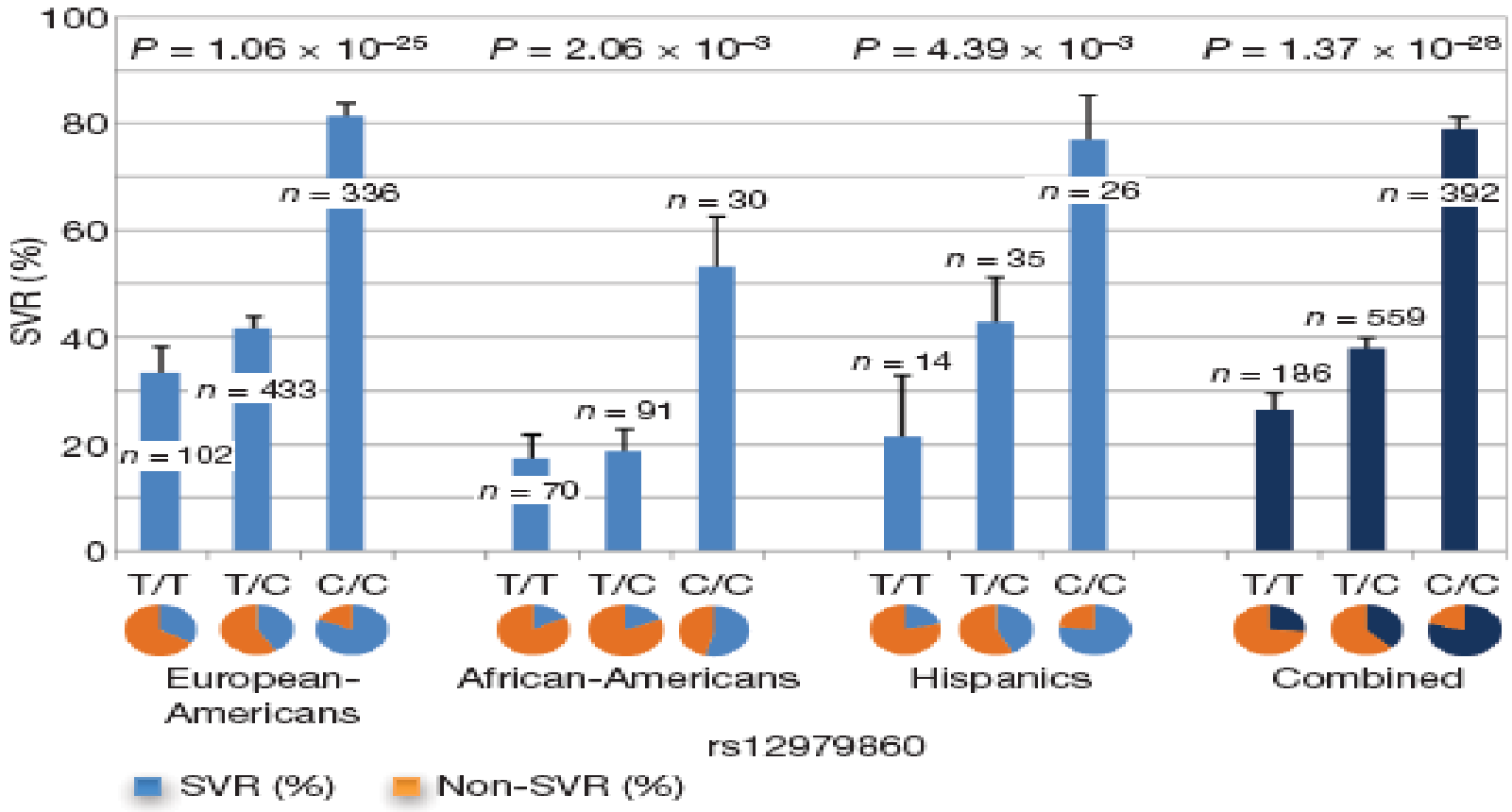


Figure 1 | Percentage of SVR by genotypes of rs12979860. Data are percentages + s.e.m.

Ge et al. Nature 2009

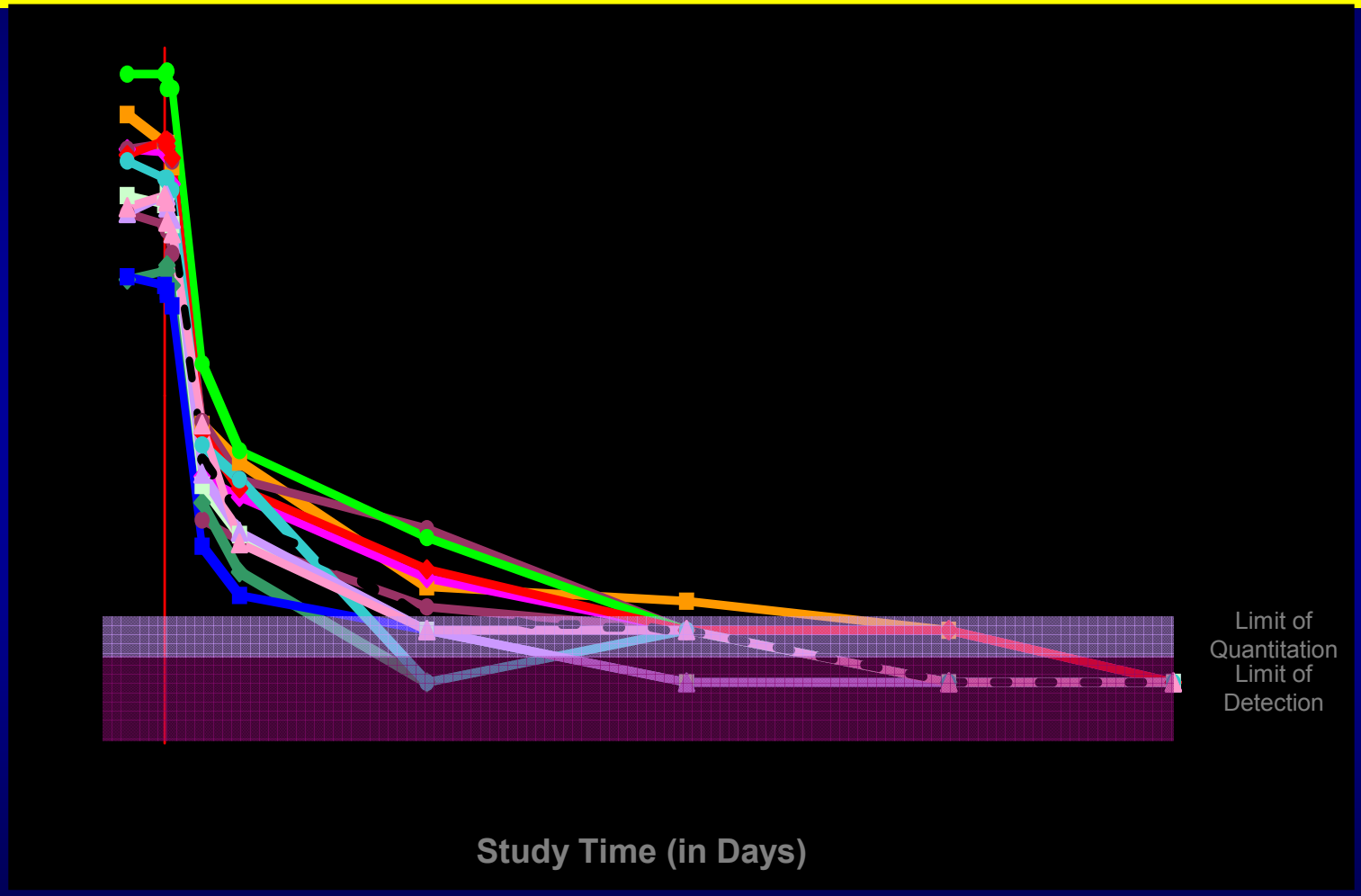
PREDICTION OF SVR WITH GENETIC POLYMORPHISM

- C/T polymorphism (chromosome19) associated with SVR
  C/C : 80%
  T/T : 25%
- Higher frequency of T/T in Africans might explain poor response
- Mécanisms implicated?
  Domain close to IL28 gene coding for lambda 3 IFN

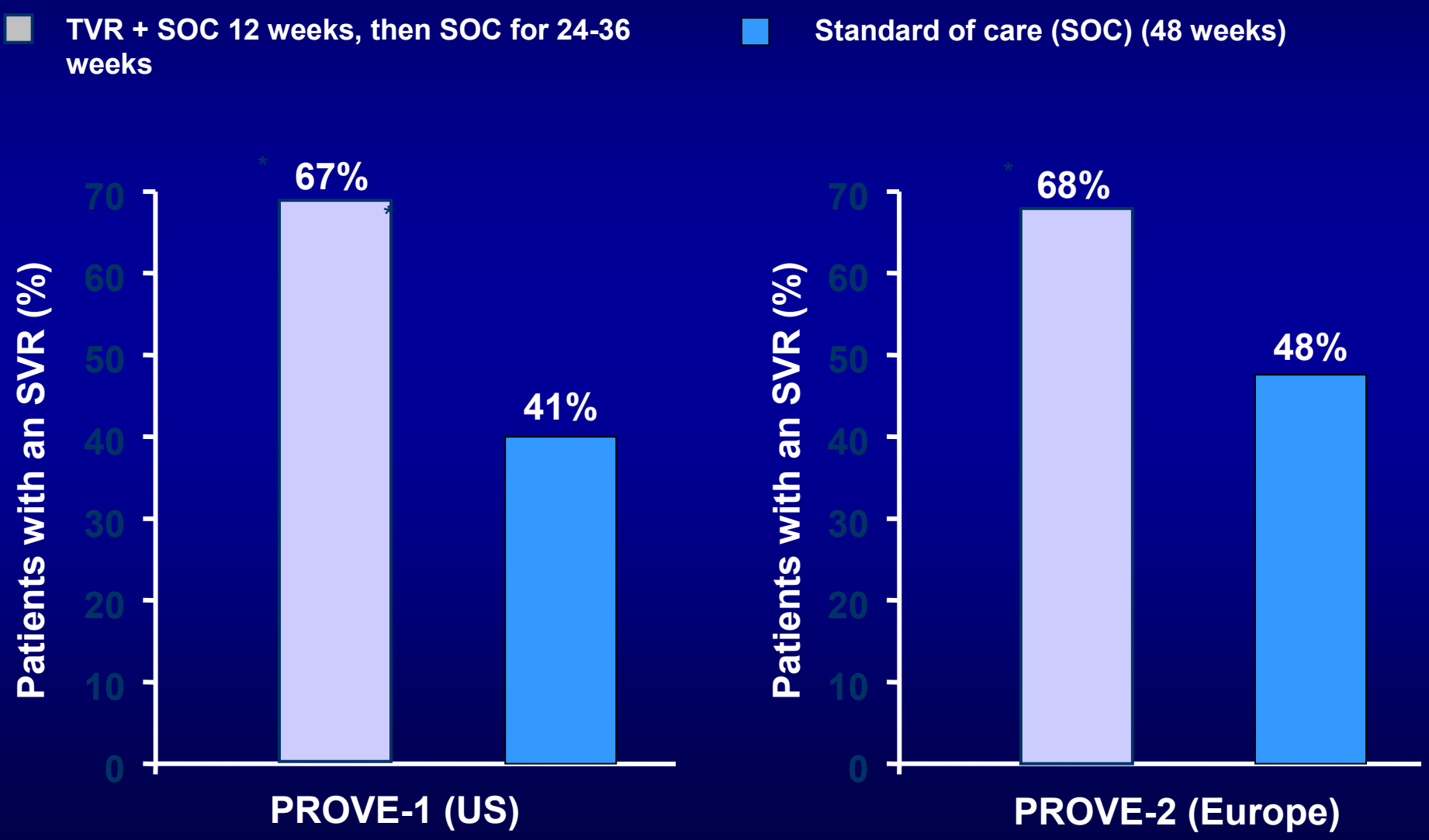
PROTEASE AND POLYMERASE INHIBITORS

Cible	Molécule	Phase
Protease	Telaprevir/VX-950 (Vertex/J&J)	Phase III
	Boceprevir/SCH 503034 (SP)	Phase III
Protease	R7227/ITMN-191 (Roche/InterMune)	Phase II
	TMC435350 (Tibotec/Medivir)	Phase II
Polymerase (Nucleoside)	R1626 (Roche)	Phase II
	R7128/PSI-6130 (Roche/Pharmasset)	Phase II
Polymerase (non-nuc)	A-837093 (Abbott)	Phase II
	BILB 1941 (Böhringer-Ingelheim)	Phase II
	GS 9190 (Gilead)	Phase II
	VCH 759 (VircoChem)	Phase I

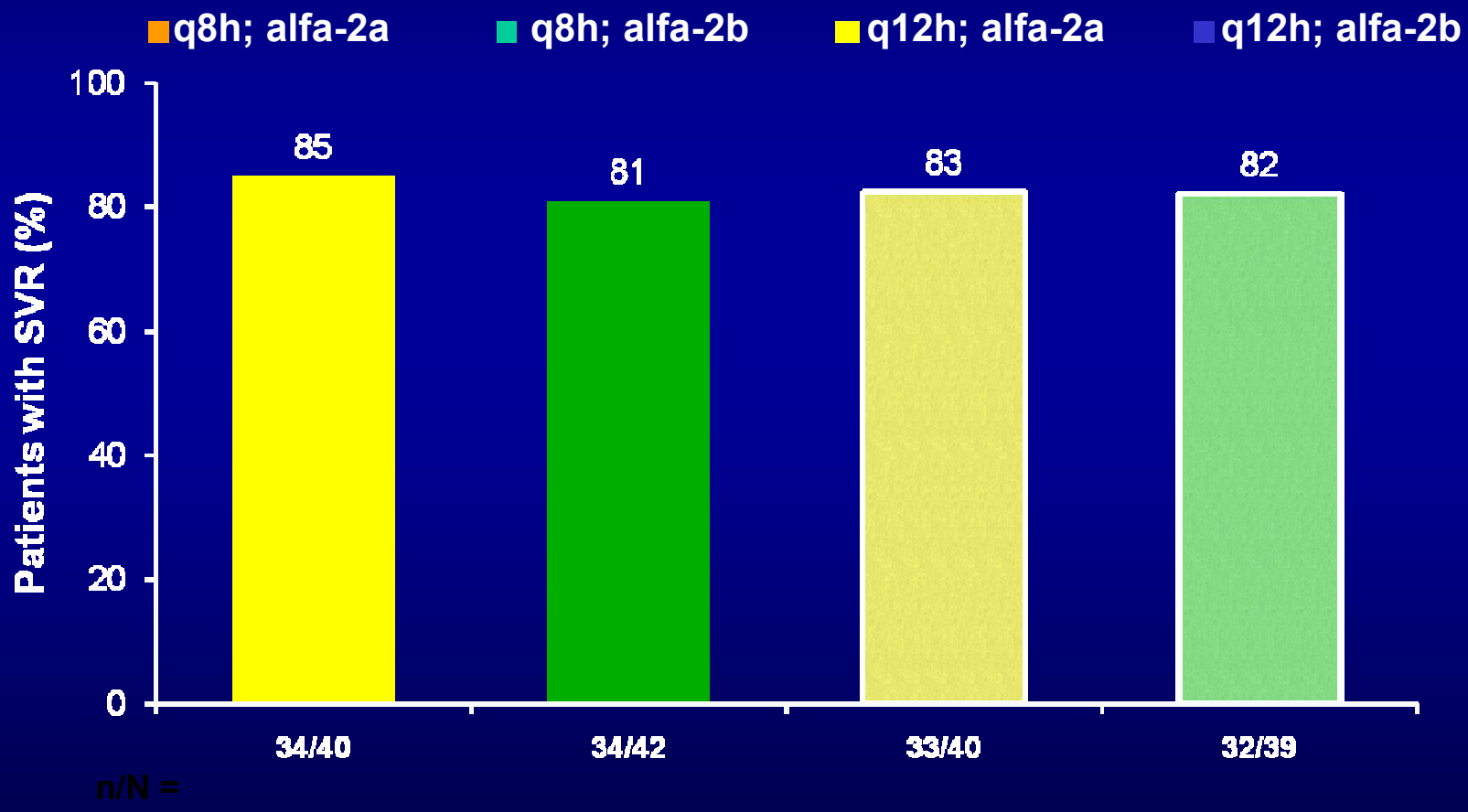
Telaprevir + PEG IFN + Ribavirine



Telaprevir + PEG IFN a2a + ribavirin in genotype 1, naive patients



TELAPREVIR + PEG IFN + RBV
according to posology and type of PEG IFN



Marcellin et al. AASLD 2009

Perspectives

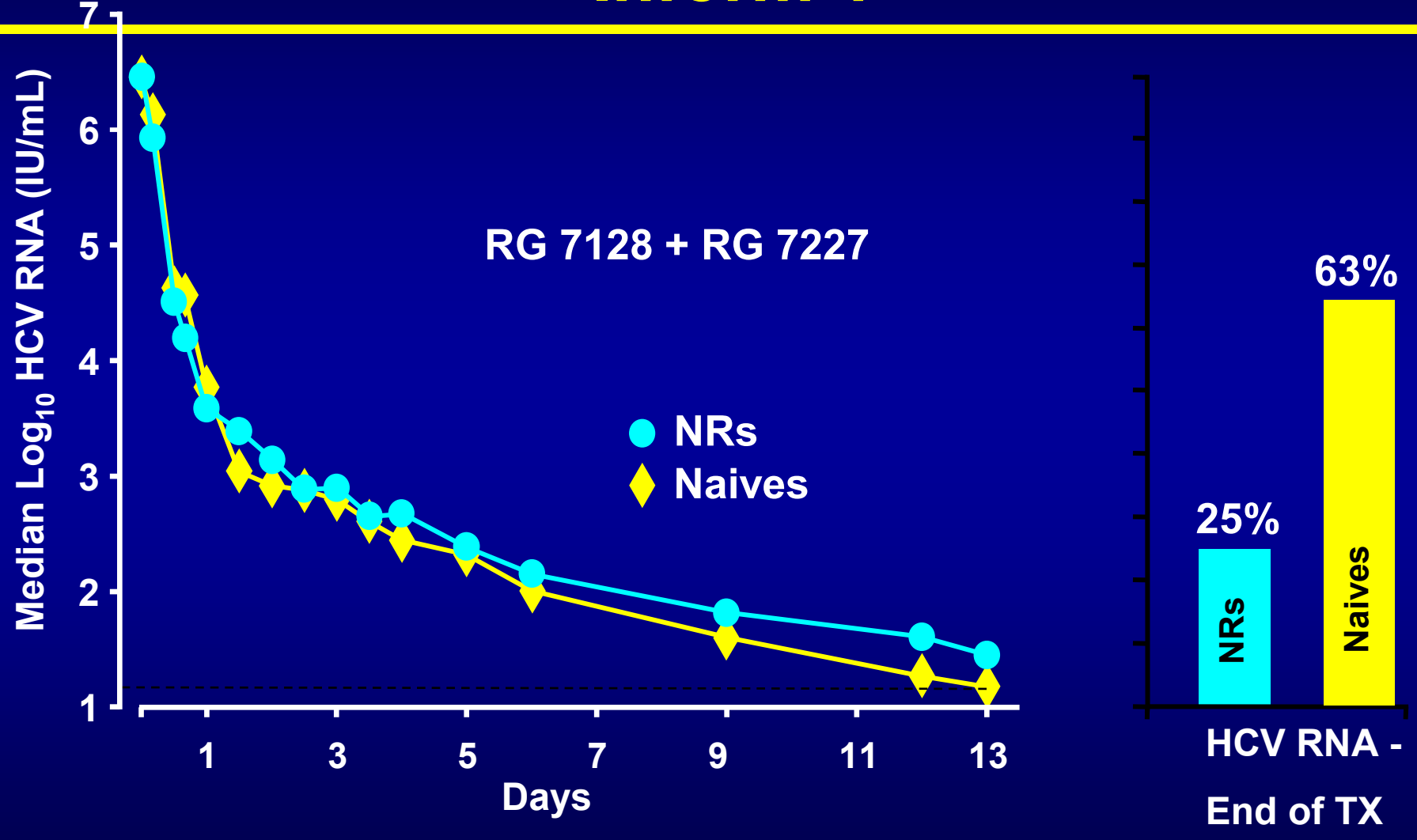
-Triple therapy with Telaprevir or Boceprevir in 2011-2012:

70-80% SVR rate

24 weeks in the majority (RVR)

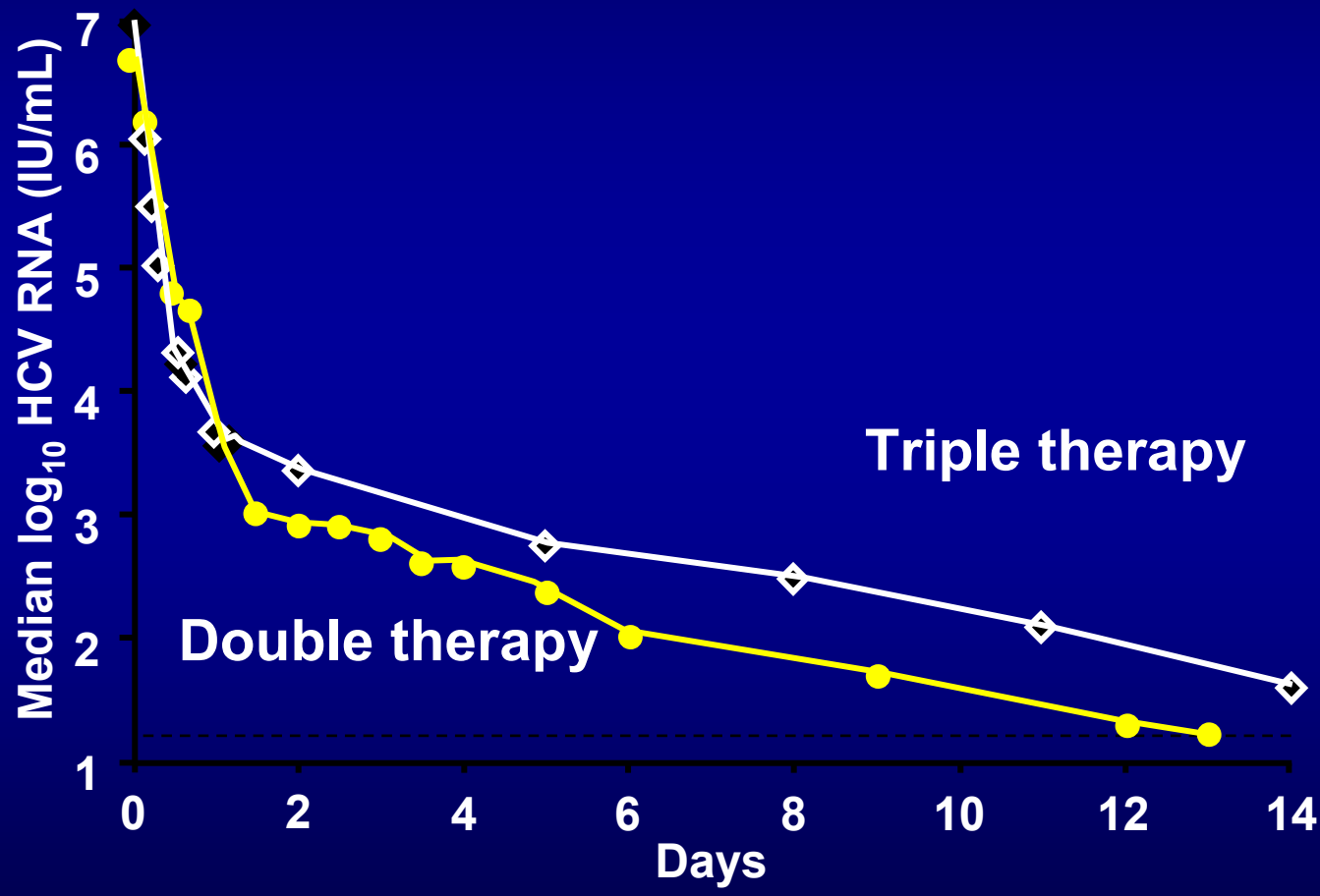
- Prot inhibitor + pol inhibitor without PEG IFN and RBV ?

ANTI-PROTEASE + ANTI-POLYMERASE
Inform 1

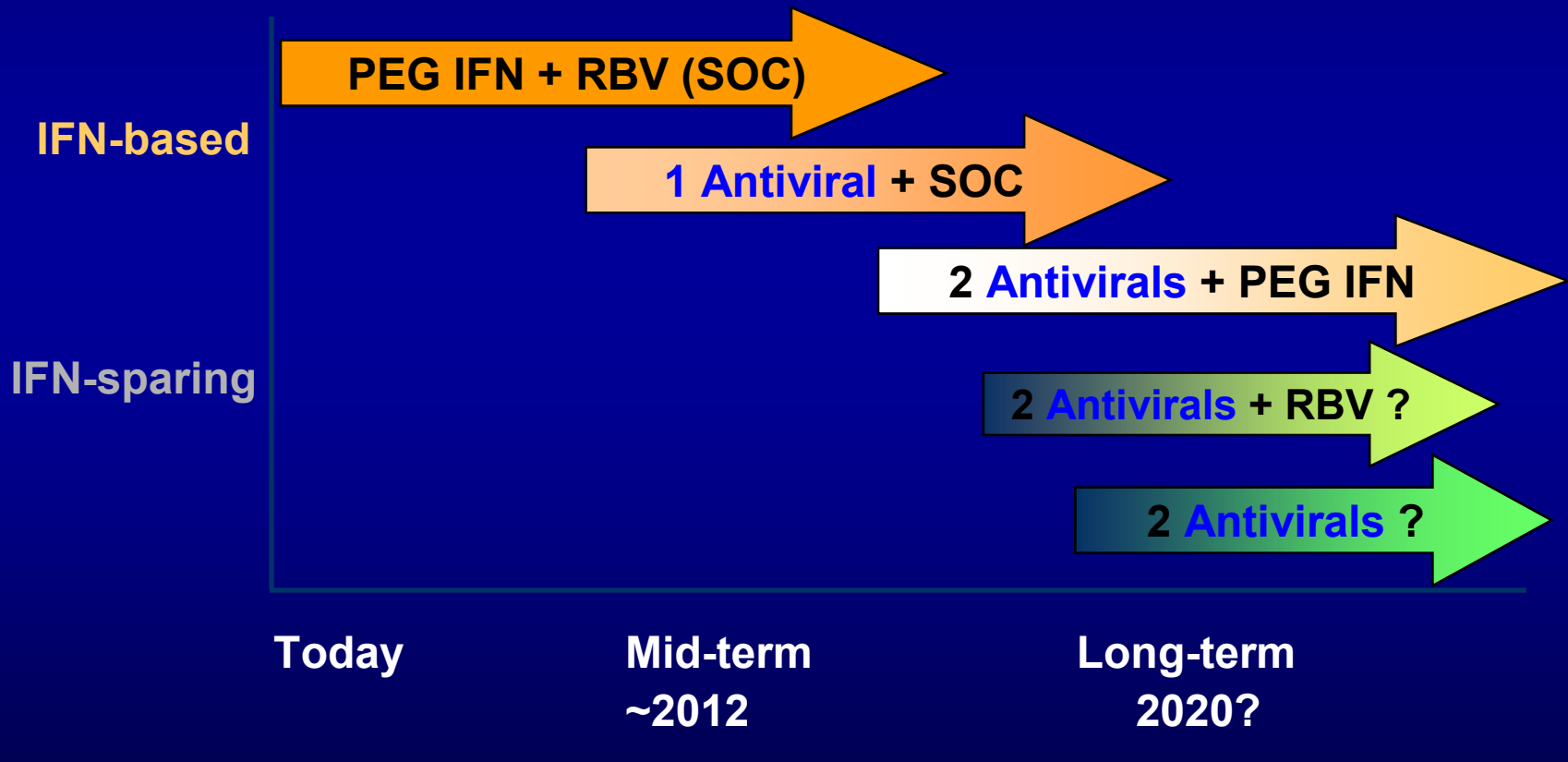


Gane et al. EASL 2009

COMBO ANTI-PROT + ANTI-POL vs TRIPLE THERAPIE TELAPREVIR + IFN + RBV



HCV antivirals as components of new treatment paradigm



CONCLUSION

100% of Cure

Within 10 years

with oral combinations

Short duration and well tolerated?