

What Treatment for Nonresponders to SOC ?

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What Treatment for Non Responders to SOC

- **Prevention of the nonresponse to SOC**
- **Management of the nonresponse to SOC**
- **Future SOC and retreatment of non-responders**

I

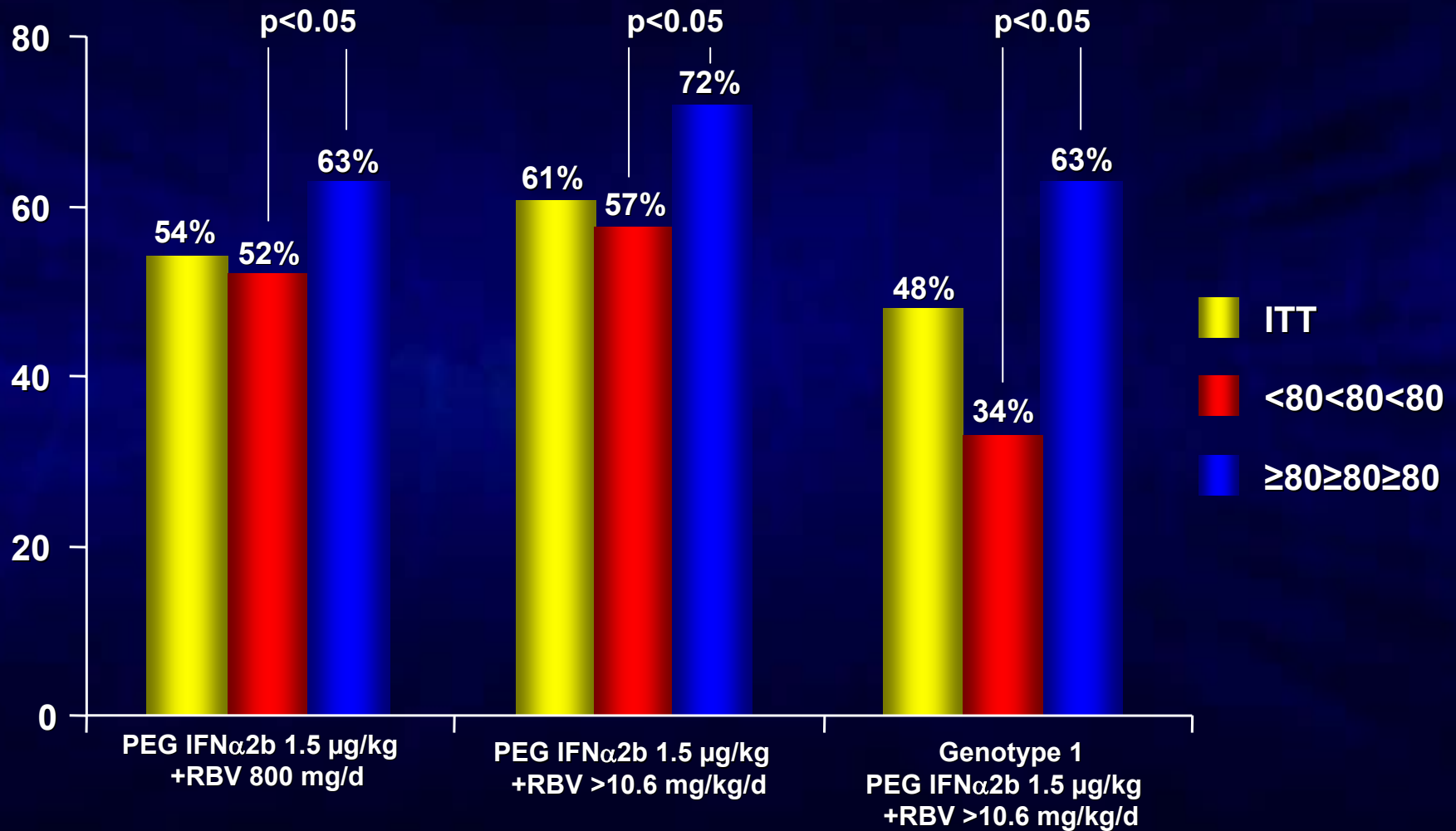
Preventing Nonresponse to Standard-of-Care

Improving Peg-IFN α -Ribavirin Treatment Outcomes

- Improve compliance
- Reduce weight and control insulin resistance
- Manage side-effects
- Tailor Peg-IFN α /ribavirin treatment duration
- Increase drug exposure

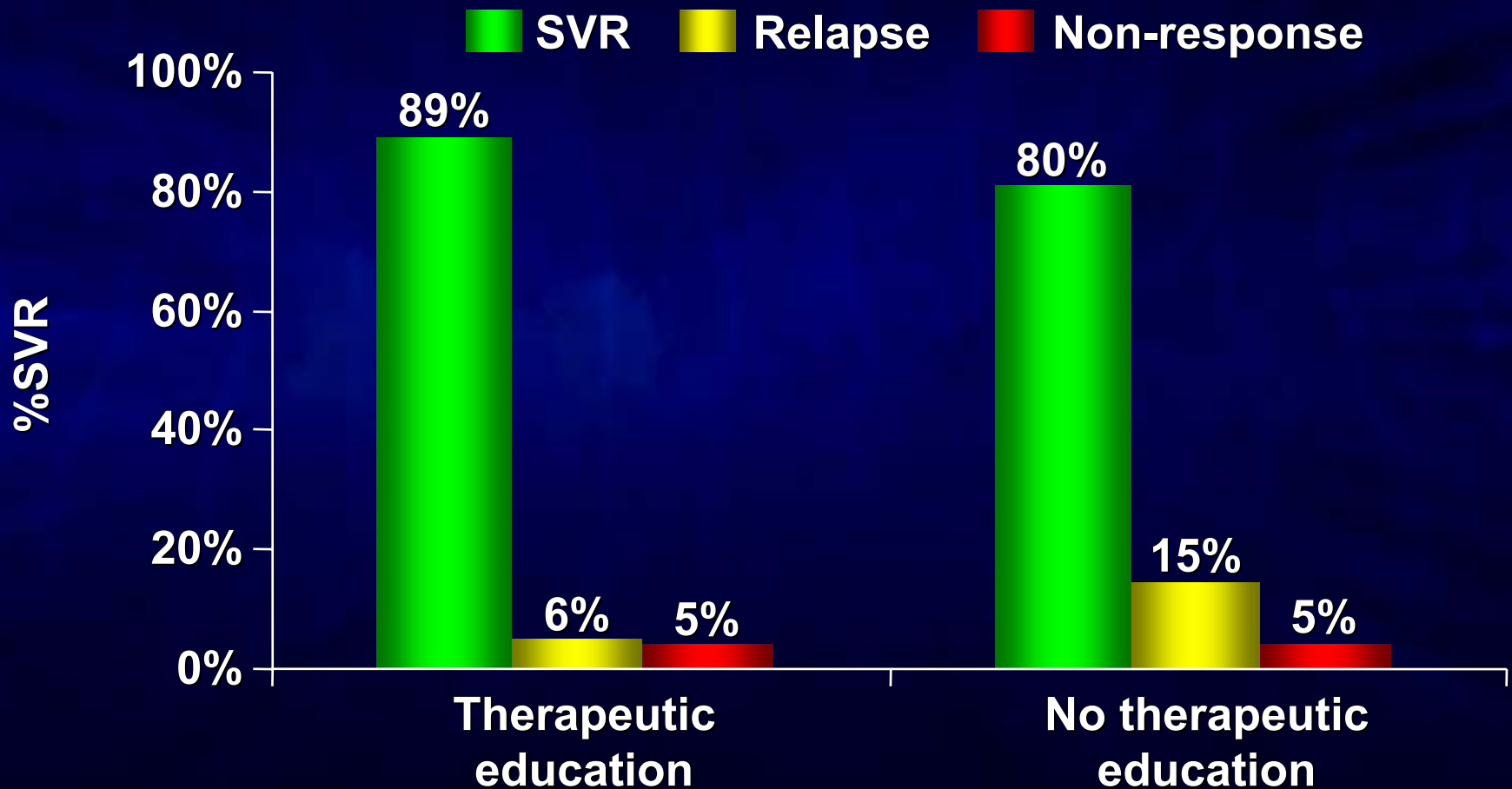
Improve Compliance

Influence of Compliance on SVR

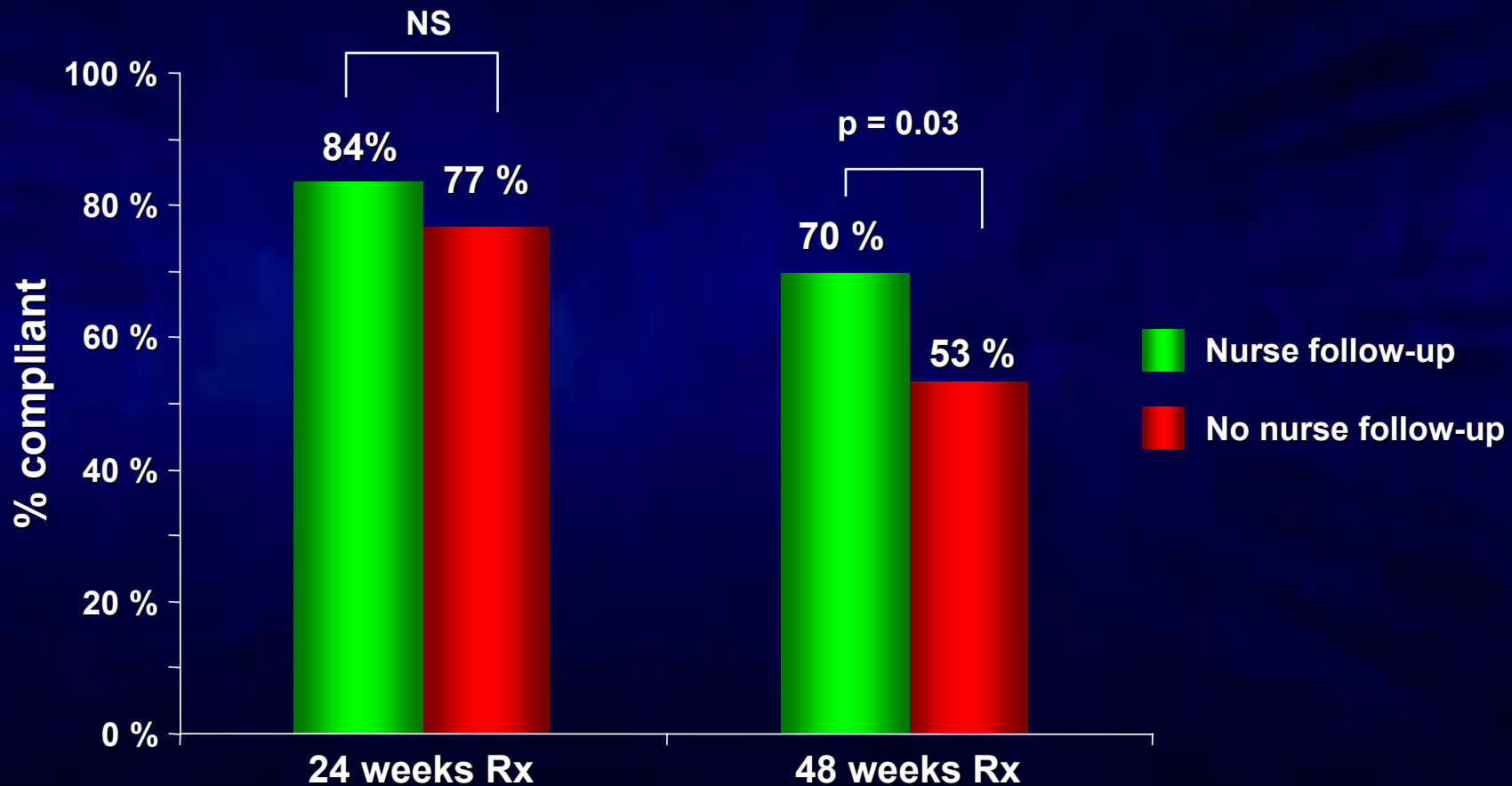


Role of Therapeutic Education

CHEOBS Observatory (Genotypes 2/3)

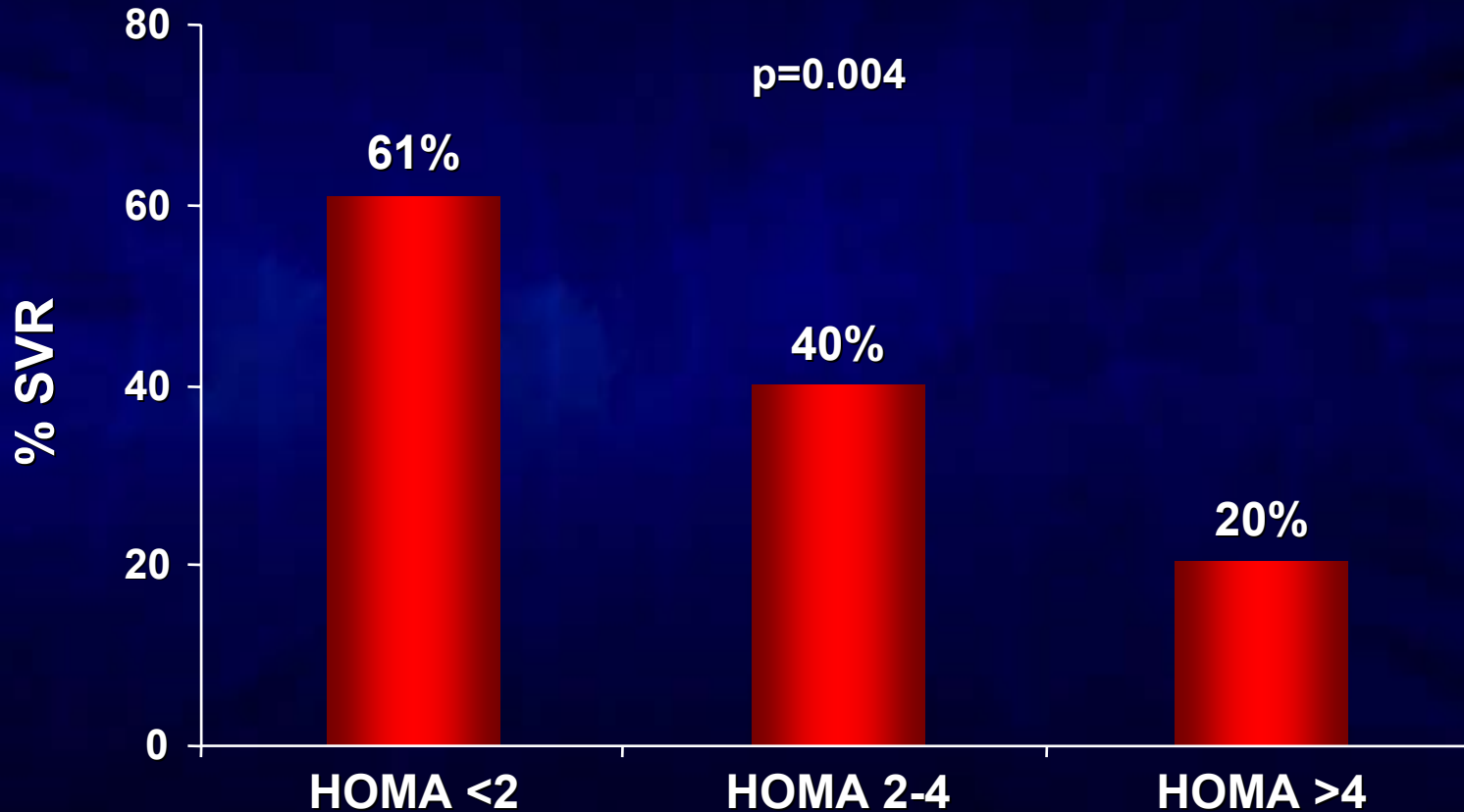


Impact of Nurse Follow-up on Compliance



***Reduce Weight and Control
Insulin Resistance***

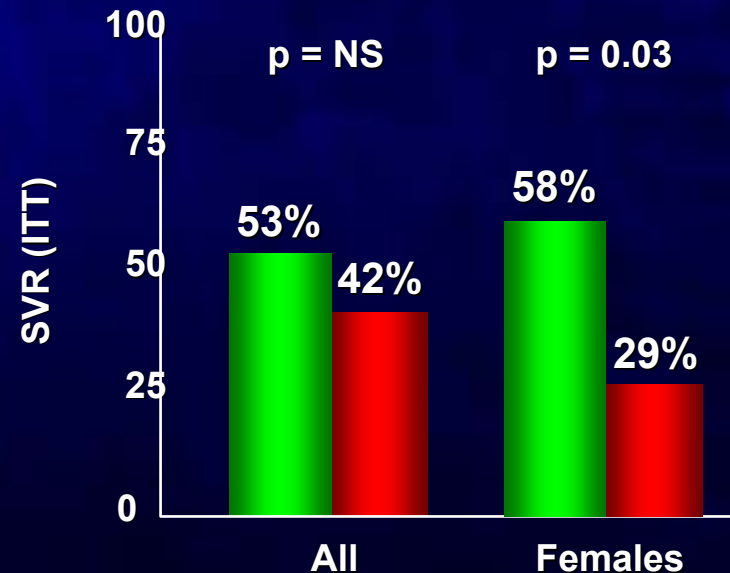
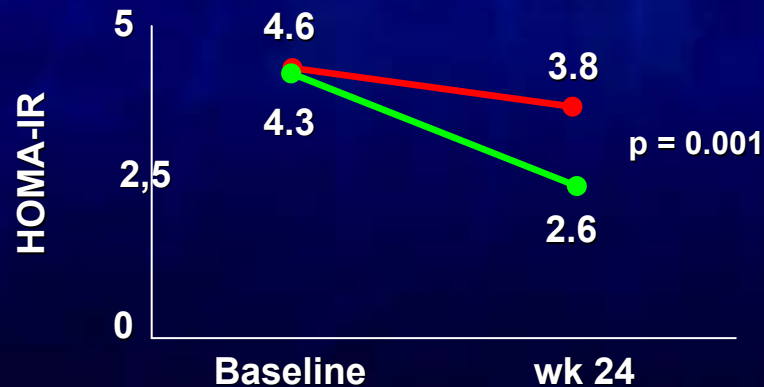
Influence of Insulin Resistance *HCV genotype 1*



Impact of Metformine

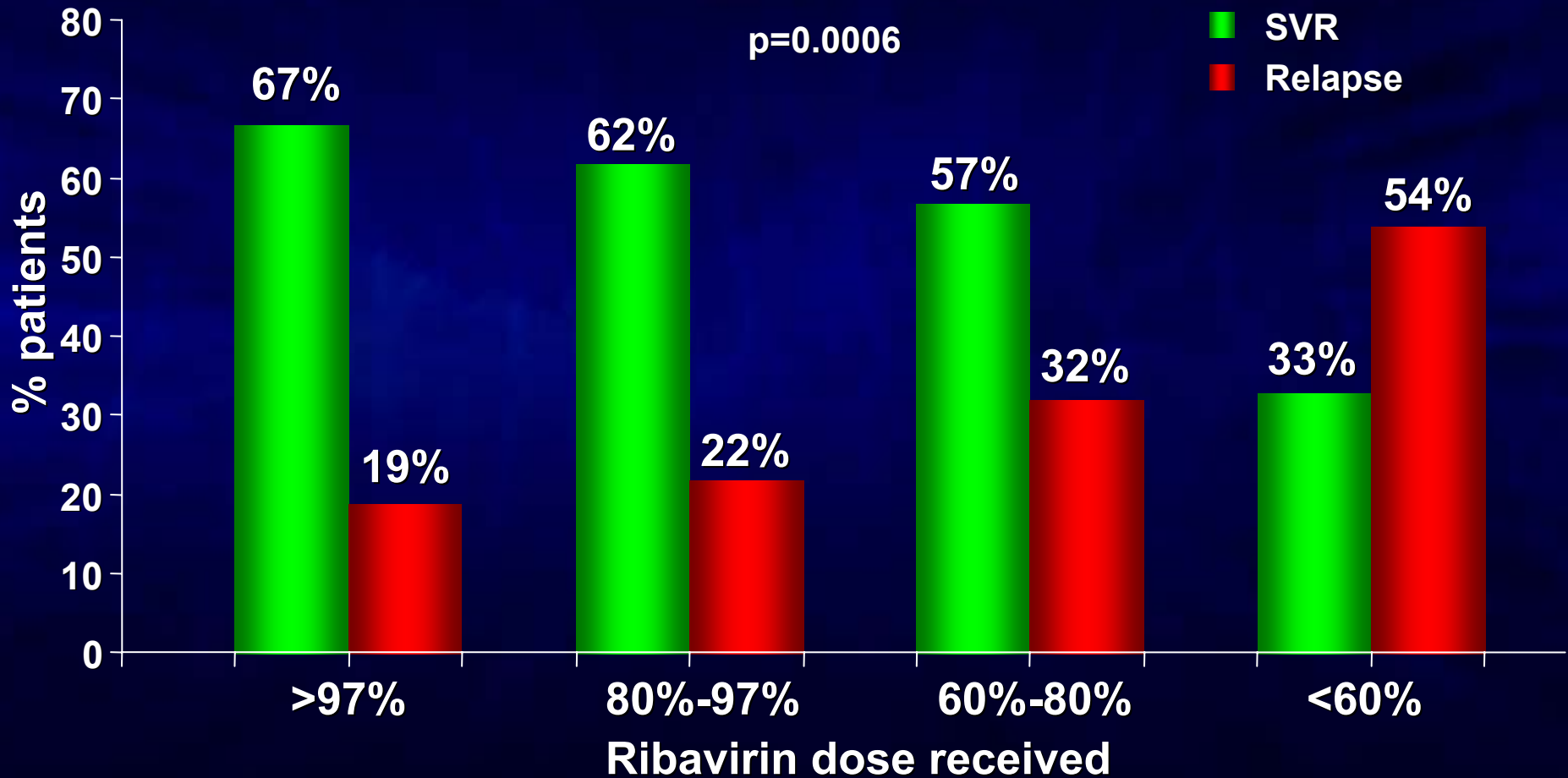
HOMA >2, Genotype 1 (n=123)

- PegIFN- α 2a + ribavirin + 850 mg/d metformine (n = 59)
- PegIFN- α 2a + ribavirin + placebo (n = 64)



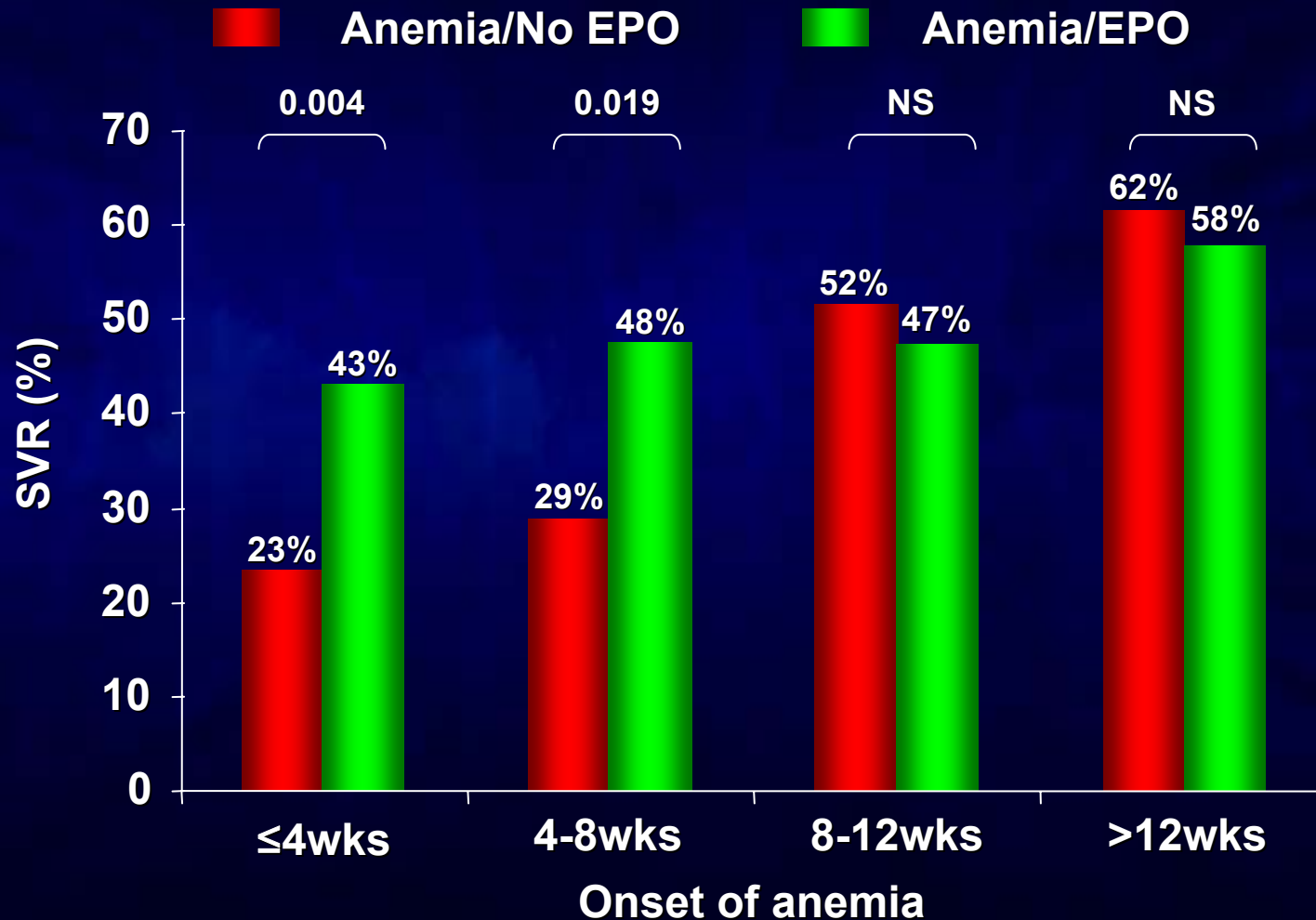
Manage Side-Effects

Impact of Ribavirin Dose Reduction on SVR



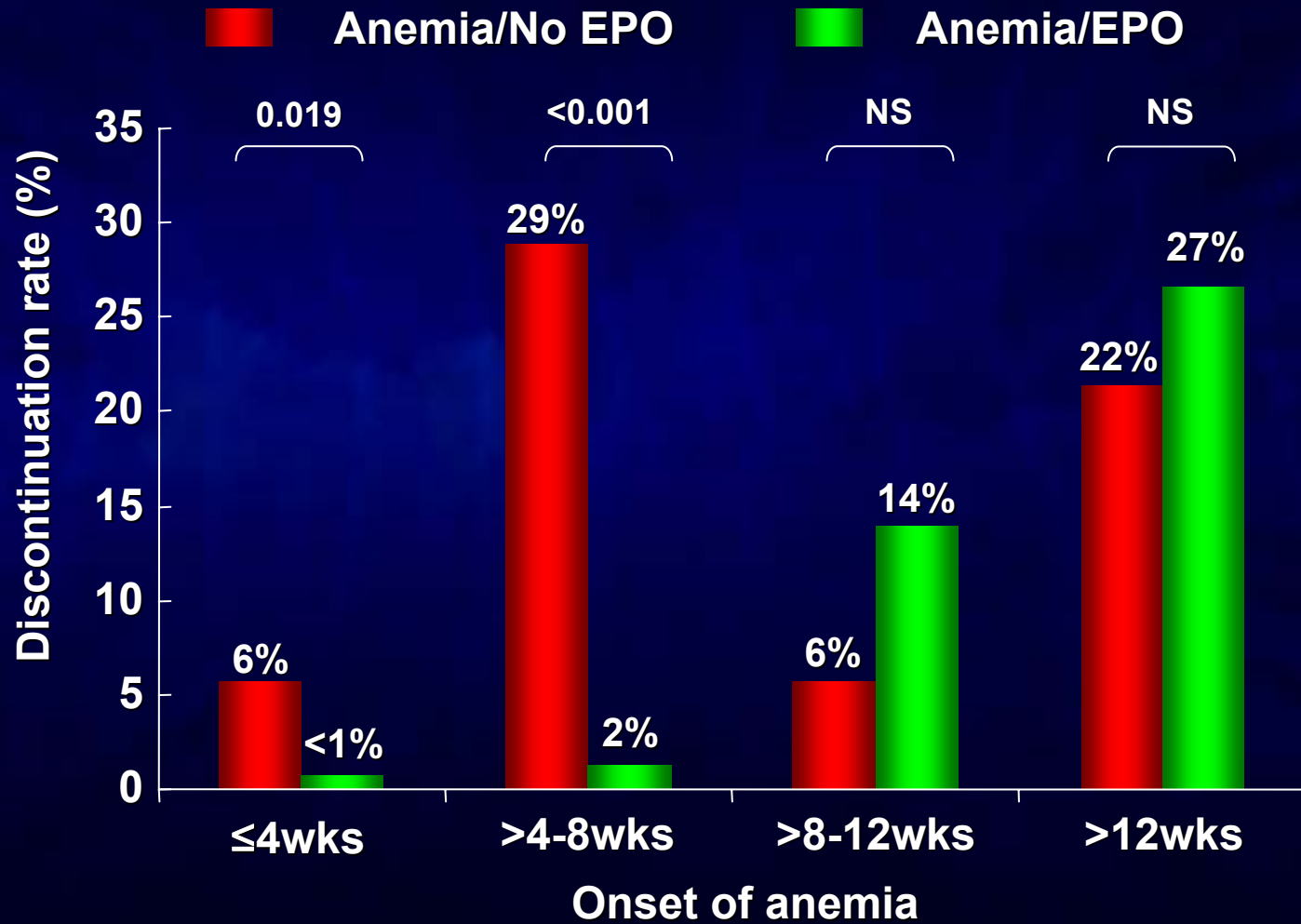
Effect of EPO on SVR

IDEAL Trial



Effect of EPO on Discontinuations

IDEAL Trial



(Sulkowski et al., EASL 2009)

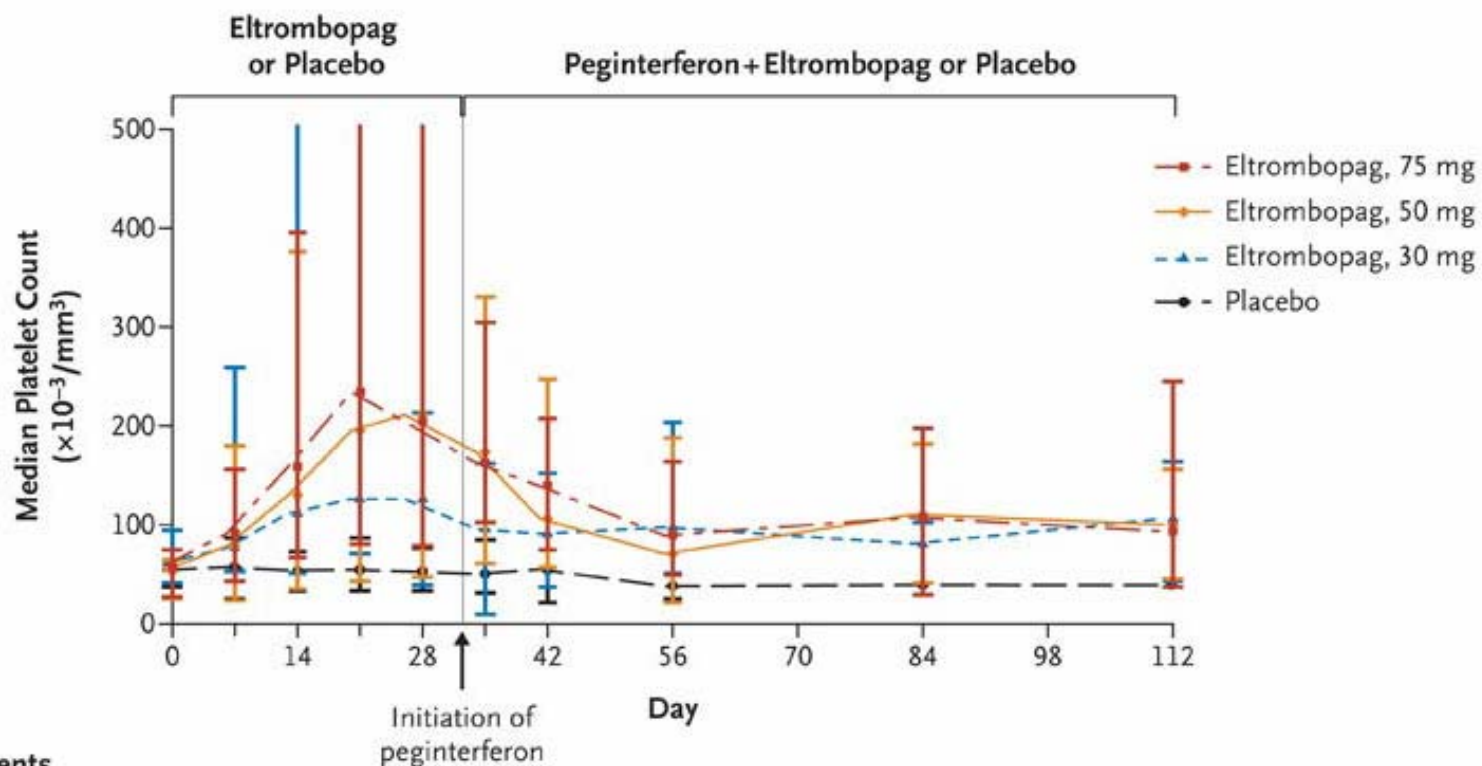
Management of Neutropenia

- Infections during treatment are not related to neutropenia
- Occasional use of G-CSF if neutrophil count $<500/\text{mm}^3$

Thrombocytopenia in Cirrhotics

Eltrombopag trial

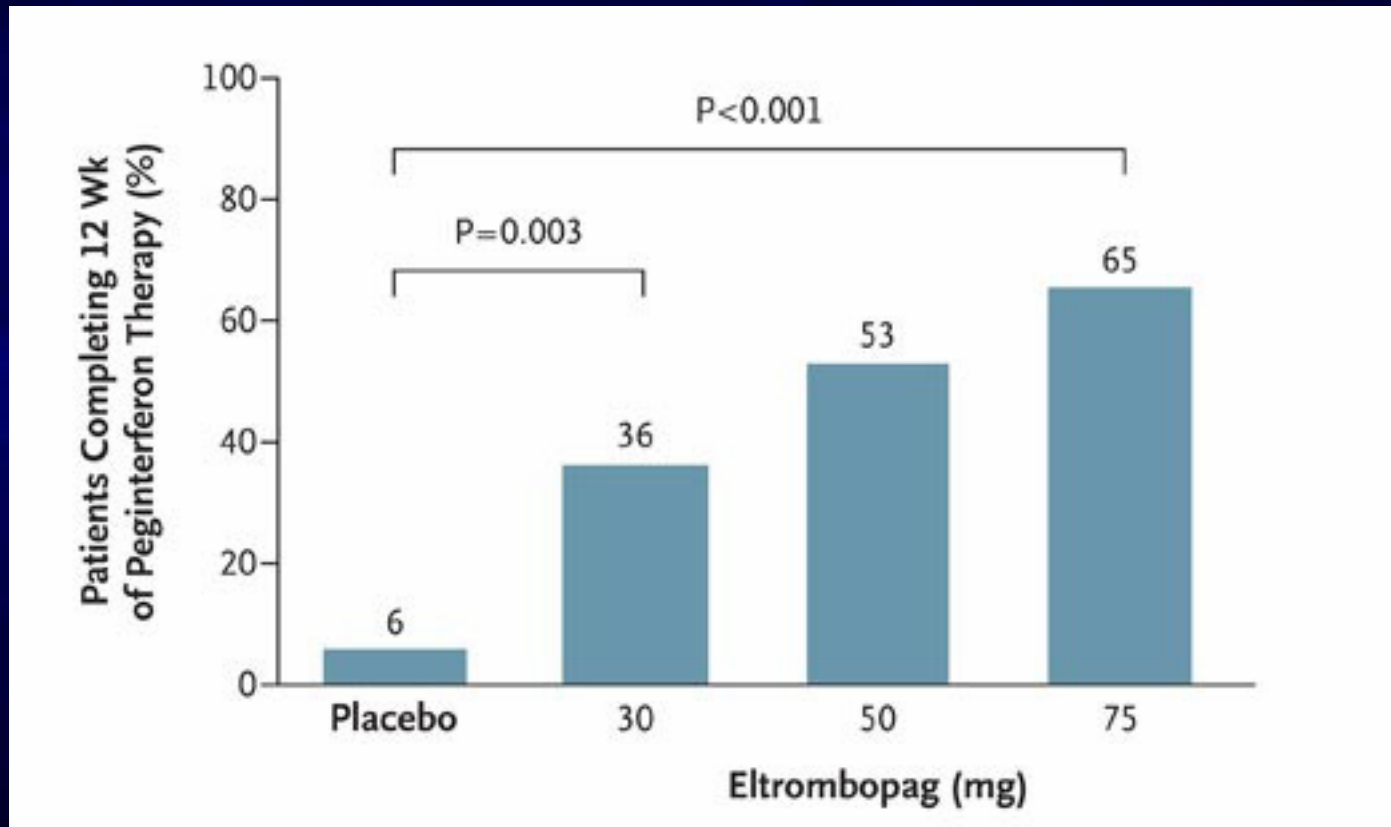
A



No. of Patients

Thrombocytopenia in Cirrhotics

Eltrombopag trial

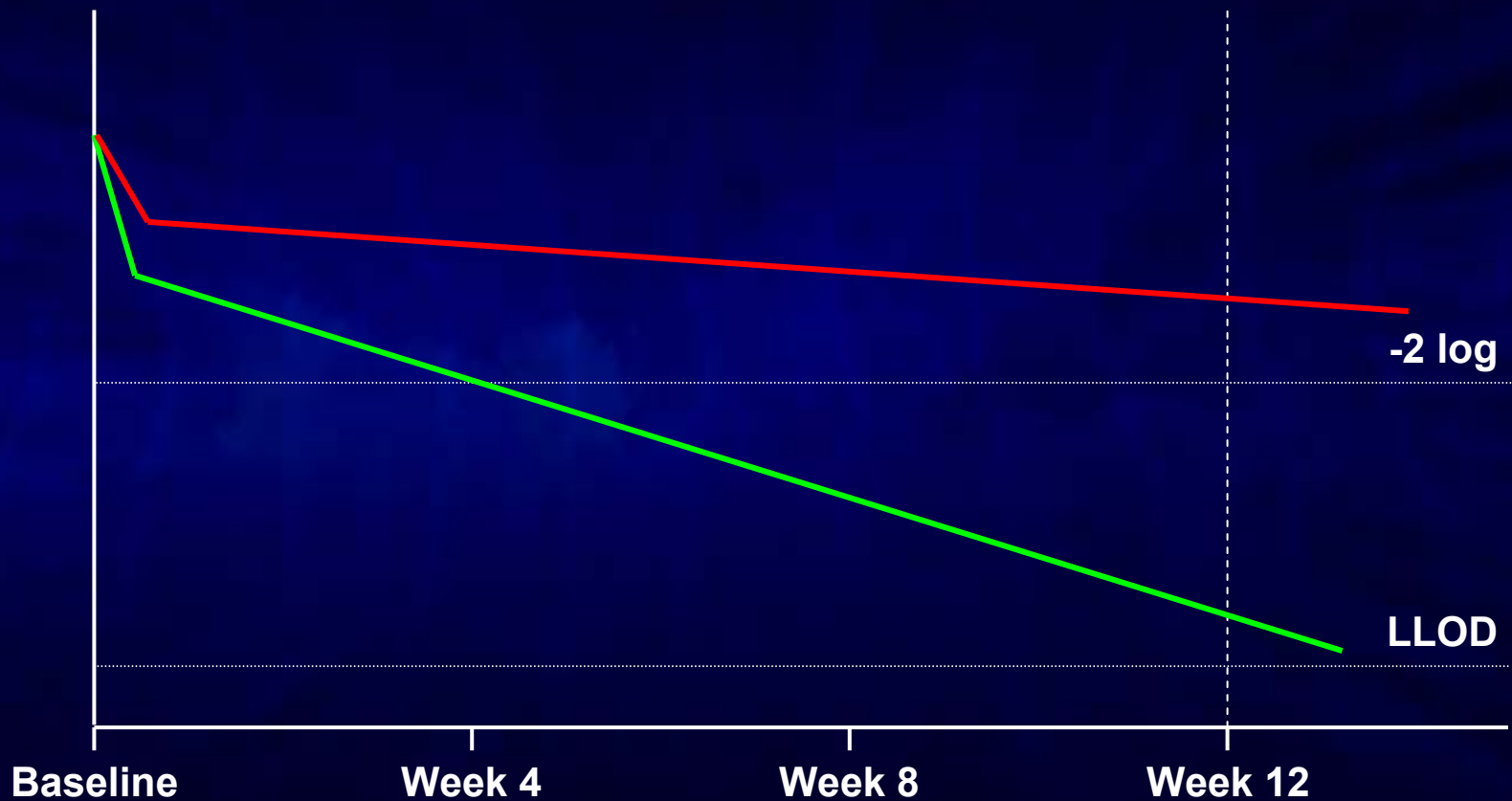


Psychiatric Disorders

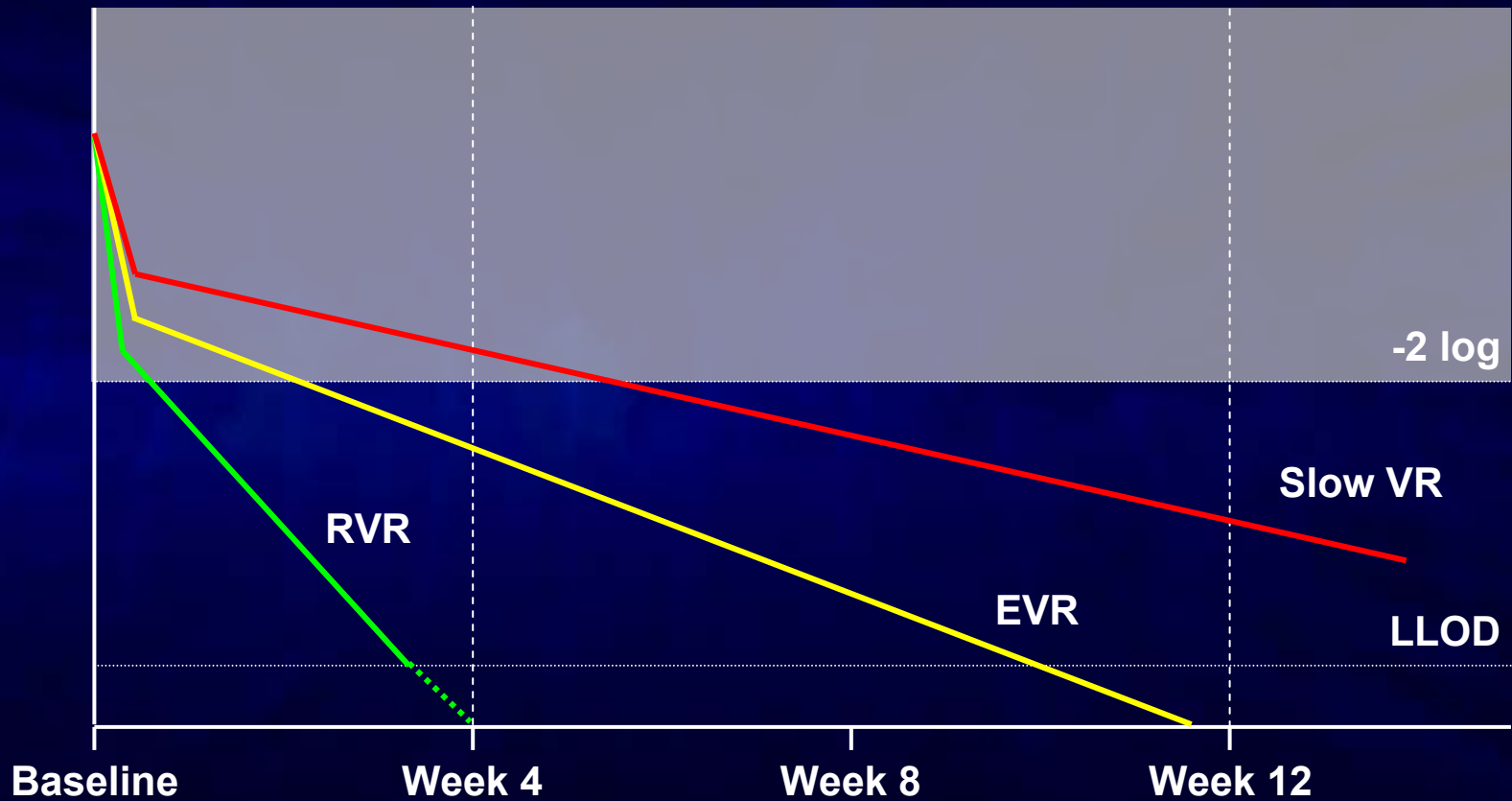
- **Depression:**
 - No prevention
 - Contact psychiatrist if needed
- **Hypersensitivity with irritability and anxiety**
 - Secondary to IFN-induced sleeping deprivation
 - Address sleeping issues with anxiolytics rather than sleeping pills

***Tailor Peg-IFN α -Ribavirin
Treatment Duration***

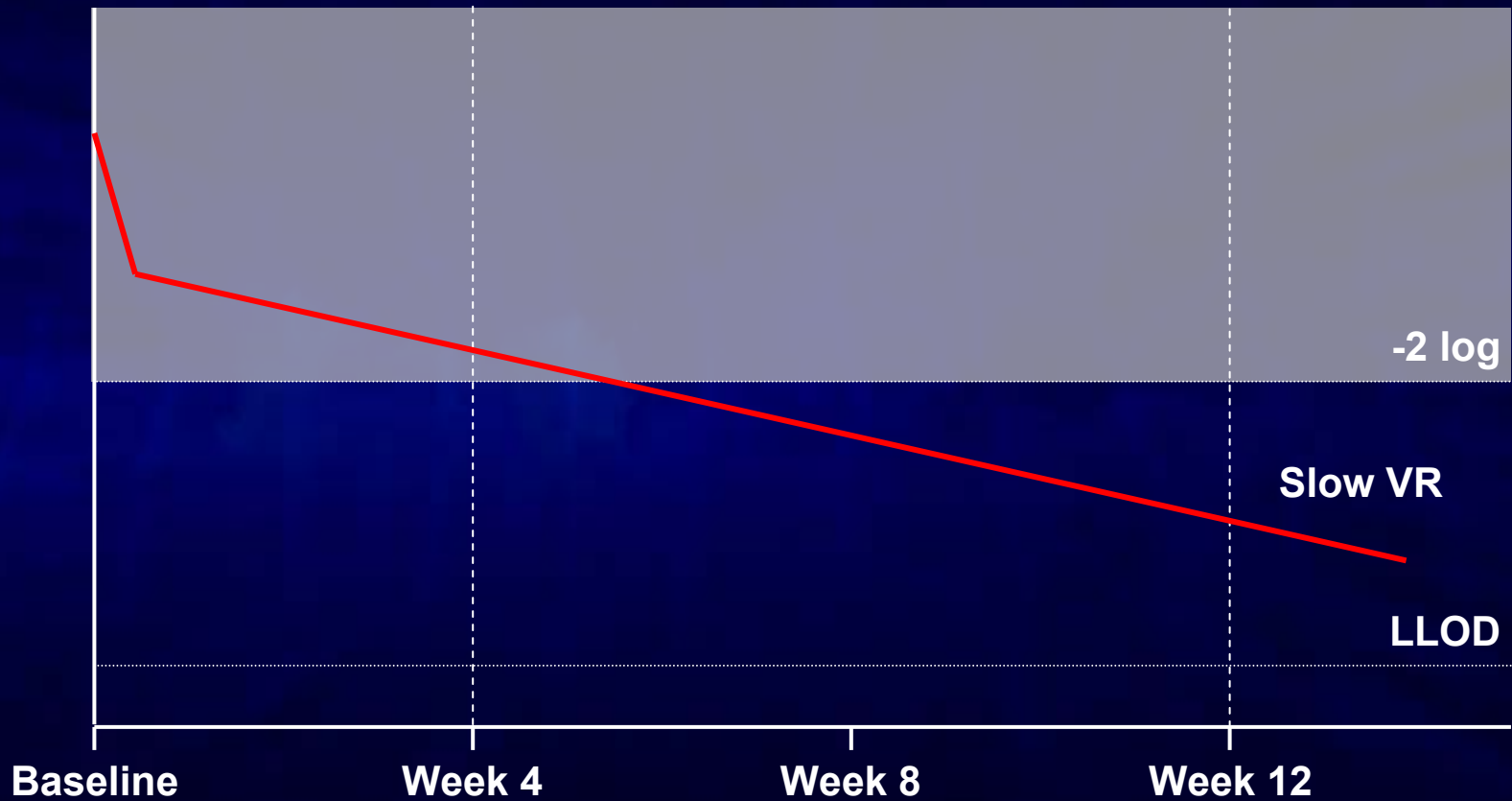
On-Treatment Responses



On-Treatment Responses

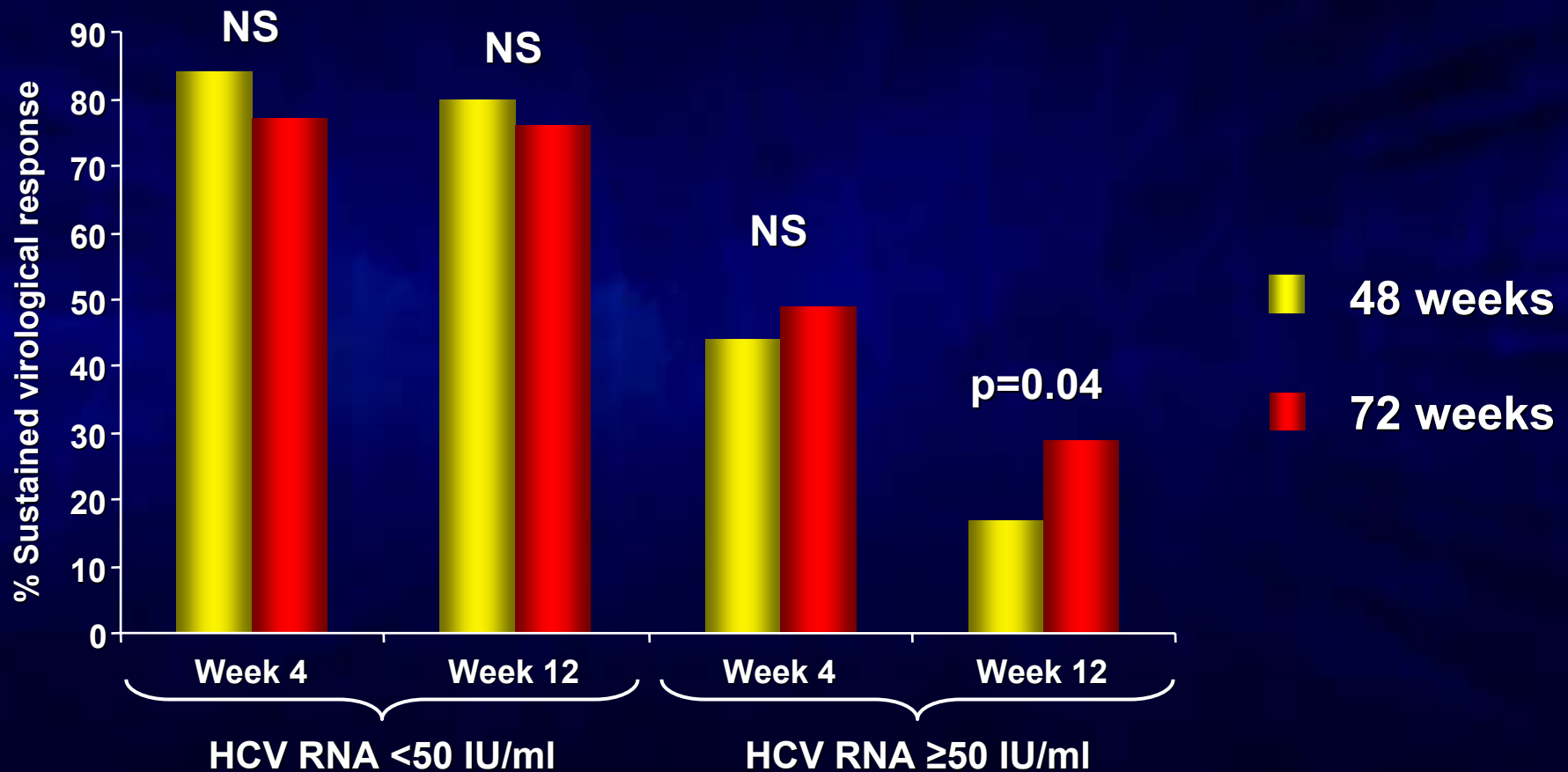


On-Treatment Responses



Longer Treatment Duration

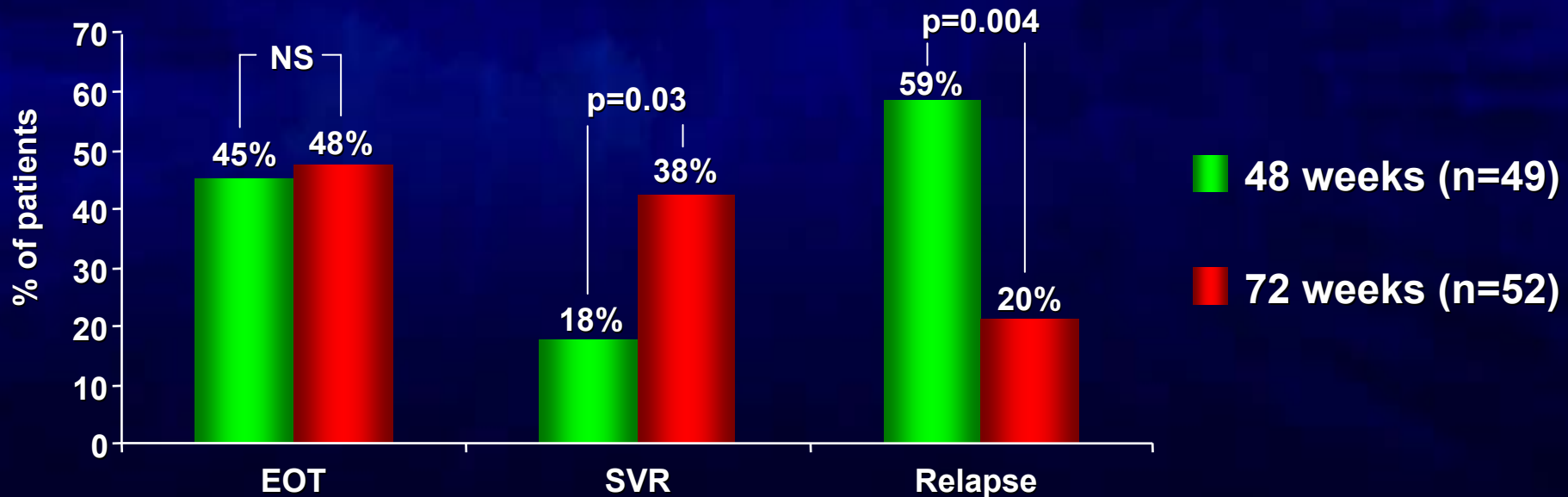
Genotype 1, PegIFN- α 2a



Longer Treatment Duration

Genotype 1, PegIFN- α 2b

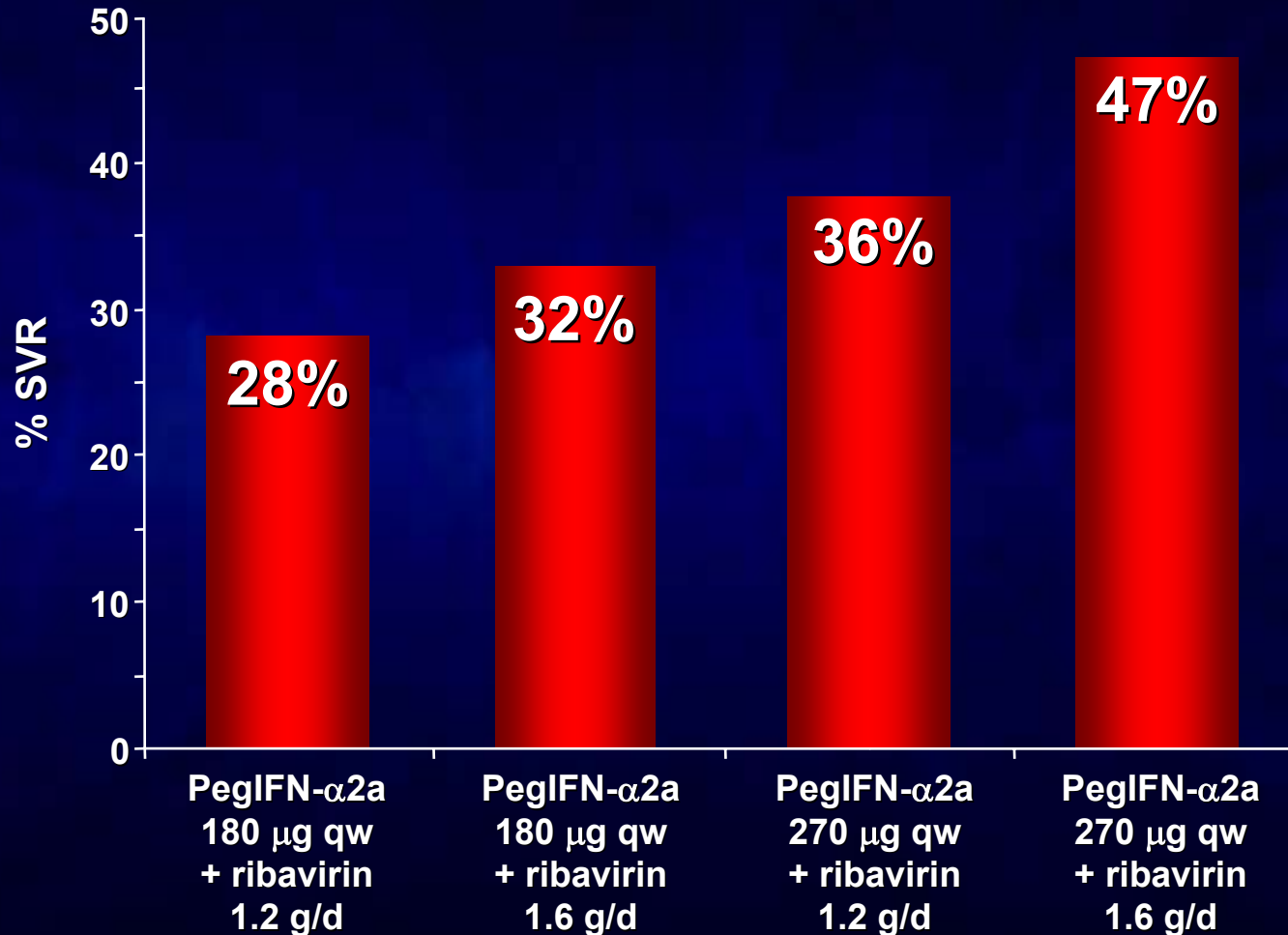
Slow virological responders: 2-log drop at week 12
HCV RNA \geq 10 IU/ml at week 12, HCV RNA < 10 IU/ml at week 24



Increase Drug Exposure

Increase Drug Exposure

“Difficult-to-treat” patients



Summary

- **Failure of peg-IFN α /ribavirin therapy to eradicate HCV can be prevented by simple, non-mutually exclusive measures, including:**
 - **Ensuring optimal compliance**
 - **Reducing weight and controlling insulin resistance**
 - **Avoiding dose-reductions and treatment interruptions by appropriately managing side effects**
 - **Increasing treatment duration in slow virological responders**
 - **Increasing drug exposure in difficult-to-treat patients**

II

Managing Nonresponders to Standard-of-Care

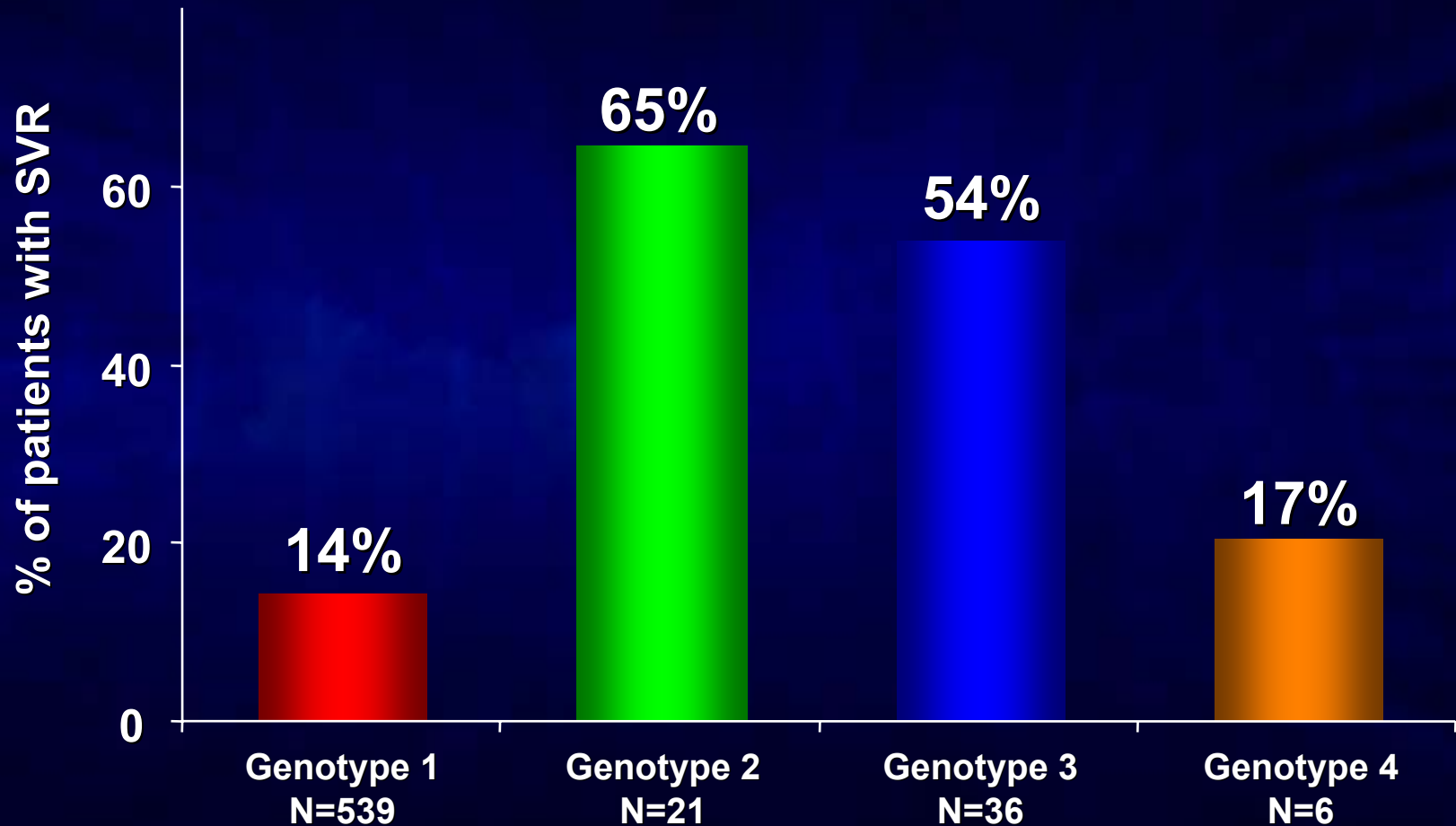
Management of Peg-IFN α - Ribavirin Treatment Failure

- **Retreatment with Peg-IFN α and Ribavirin**
- **Maintenance therapy**

***Retreatment with Peg-IFN α
and Ribavirin***

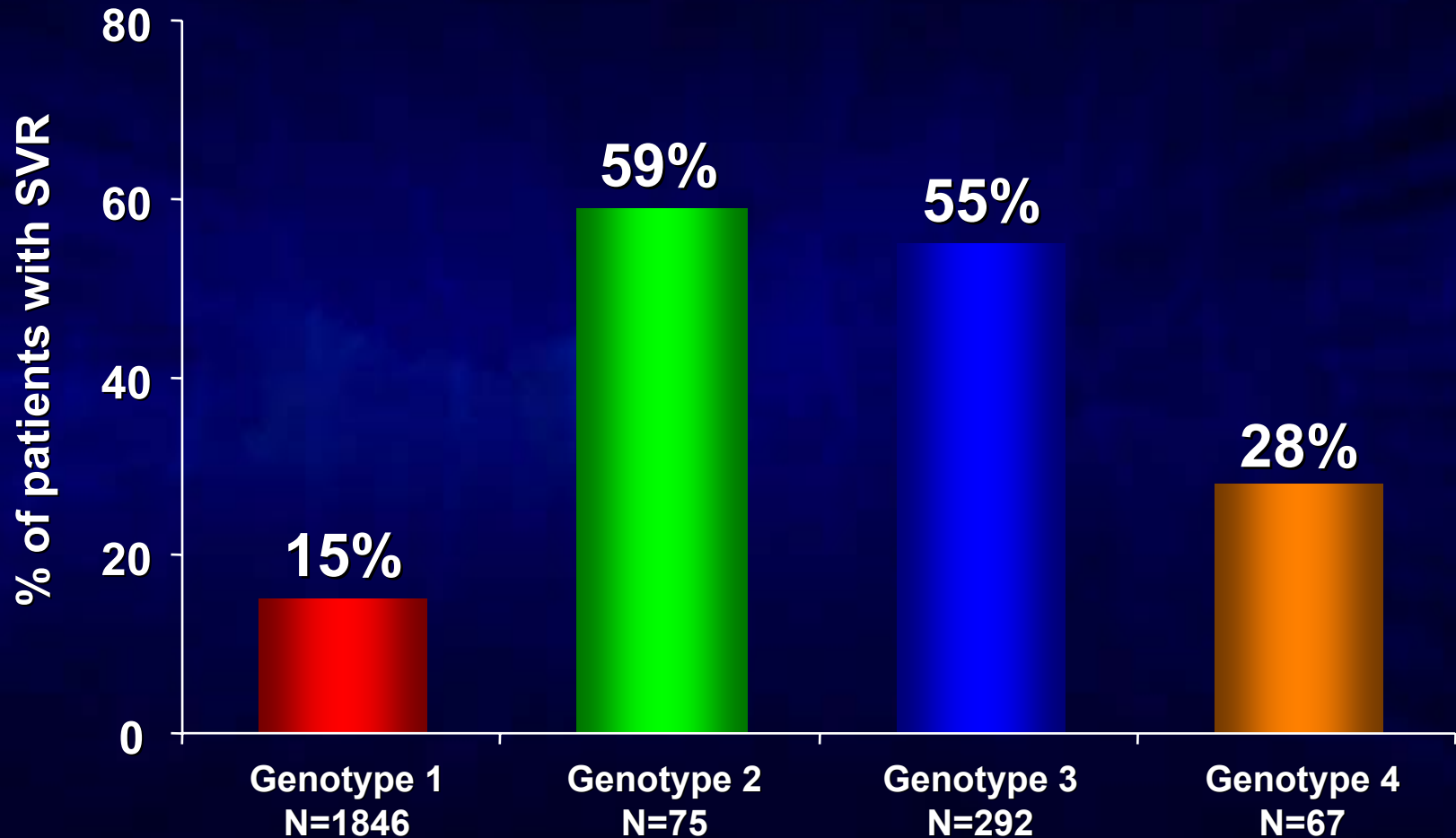
HALT-C Trial

Nonresponders, Advanced Fibrosis, Peg-IFN α 2a + RBV



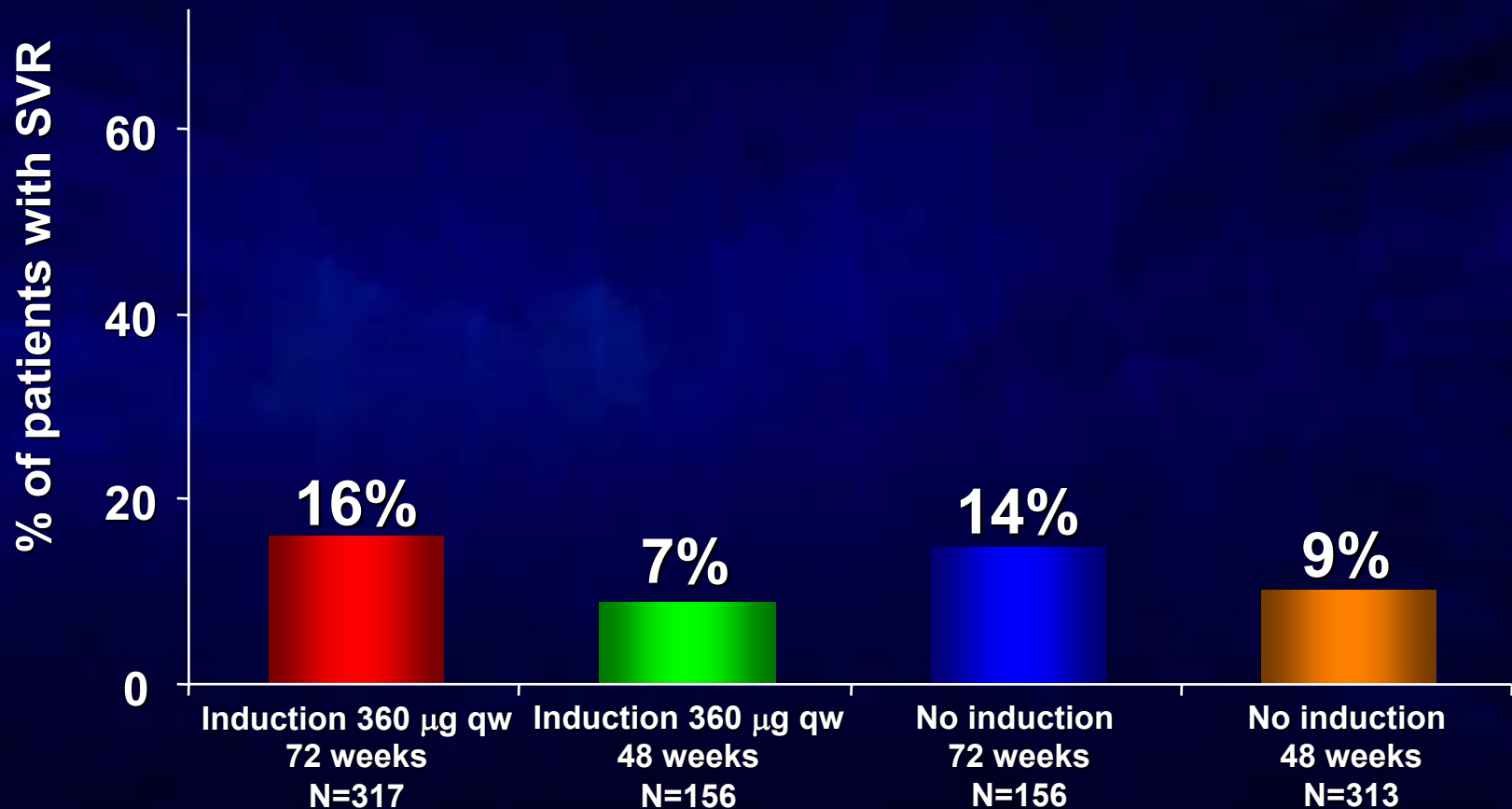
EPIC-3 Trial

Nonresponders, Advanced Fibrosis, Peg-IFN α 2b + RBV

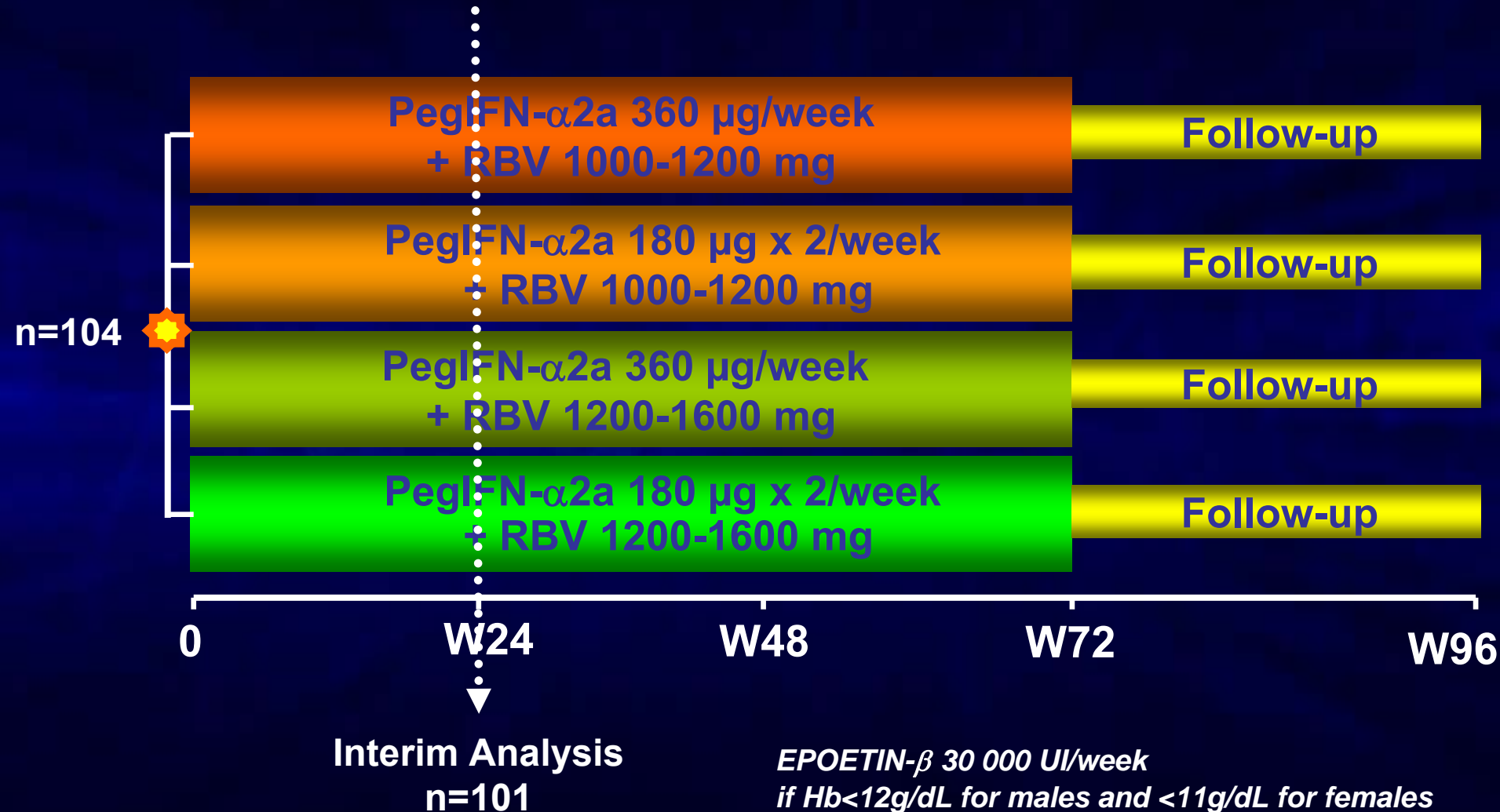


REPEAT Trial

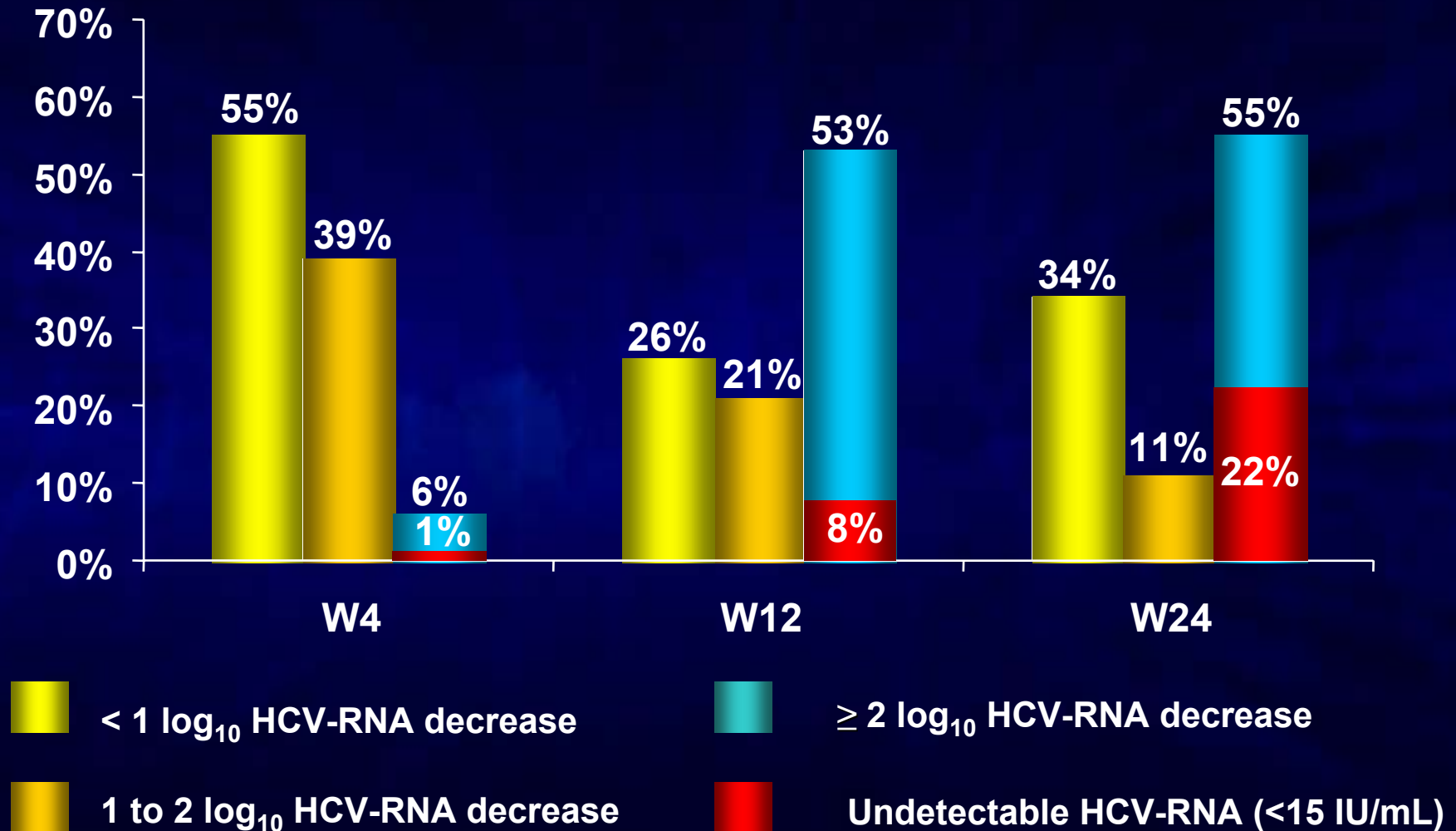
Nonresponders Peg-IFN α 2b + RBV, Peg-IFN α 2a \pm Induction + RBV



SYREN Trial



SYREN Trial

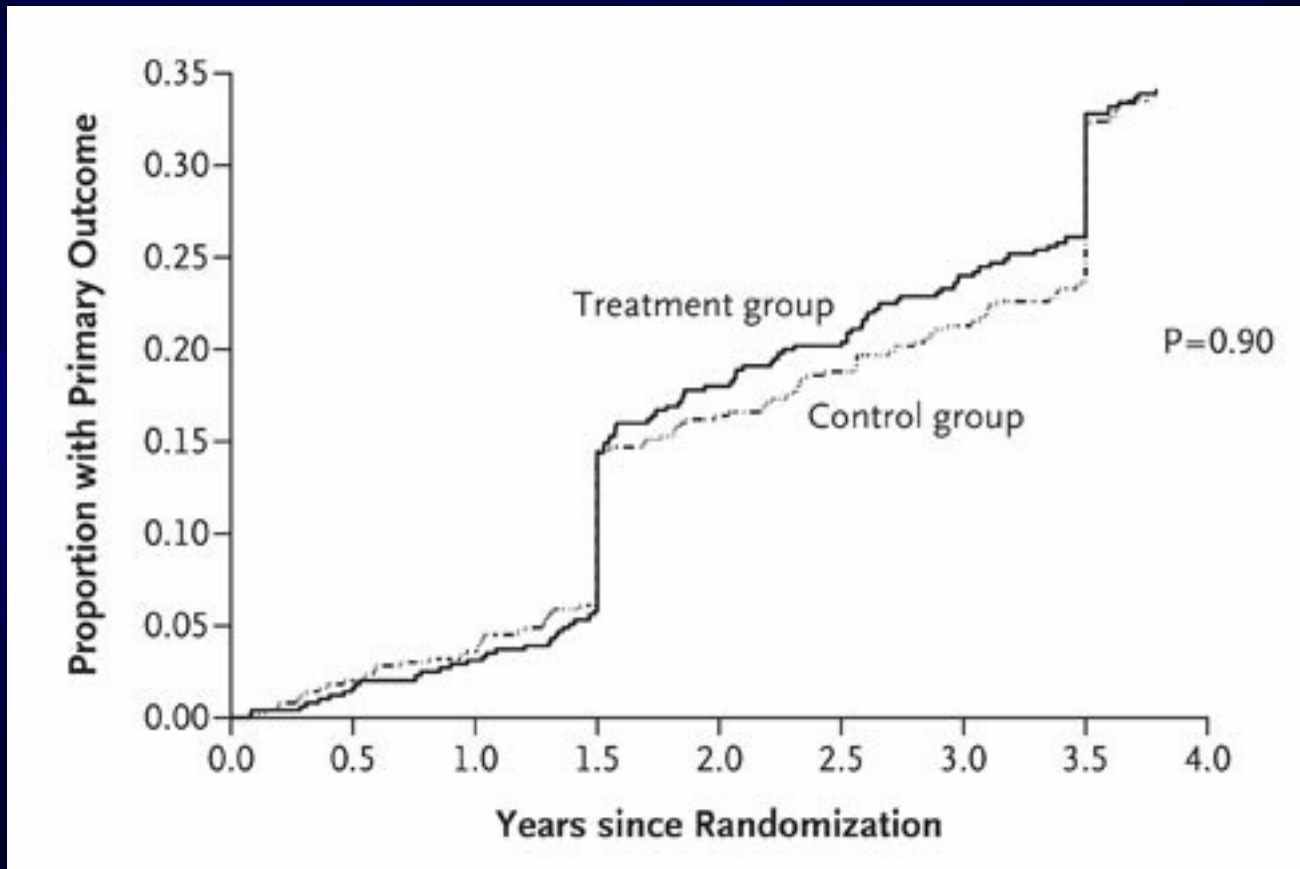


Maintenance Therapy

HALT-C Trial

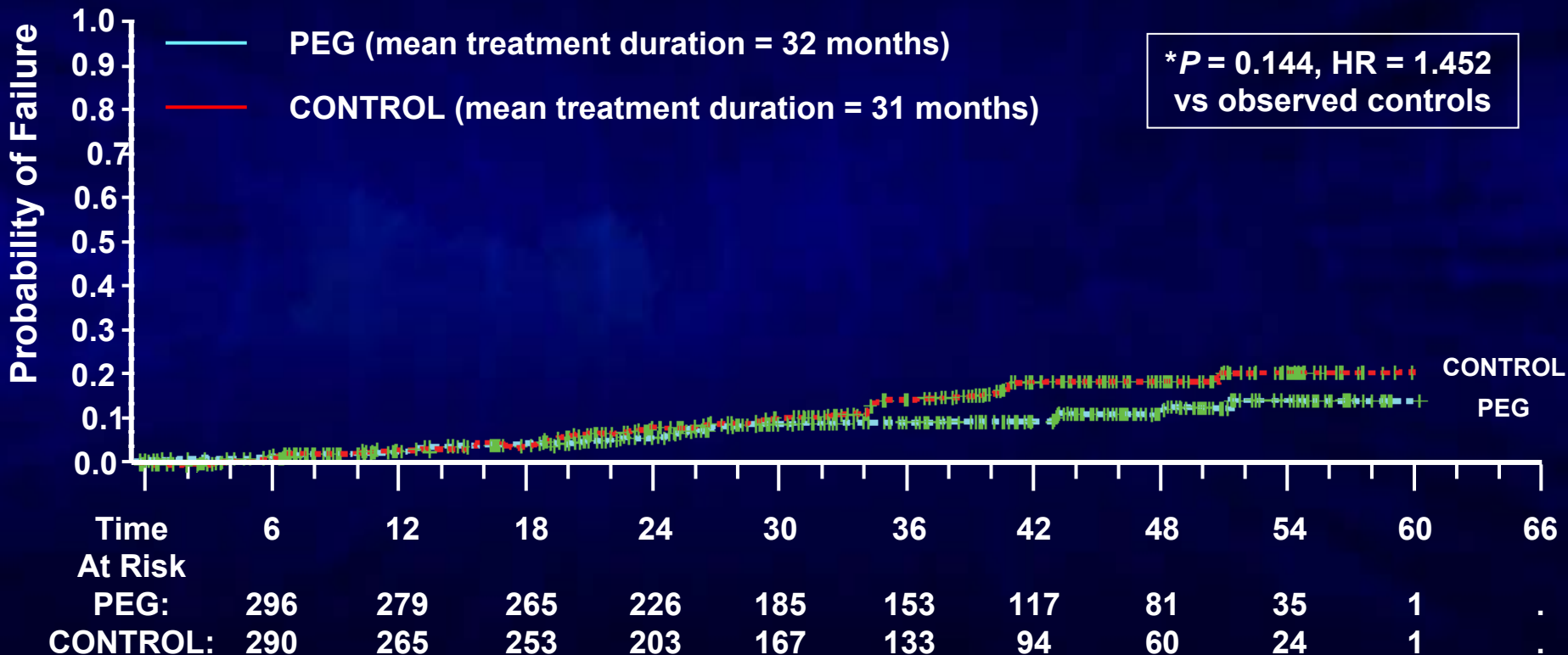
Nonresponders, Advanced Fibrosis

90 $\mu\text{g}/\text{wk}$ PegIFN- α 2a + RBV Maintenance (3.5 years)



EPIC-3 Time to 1st Clinical Event

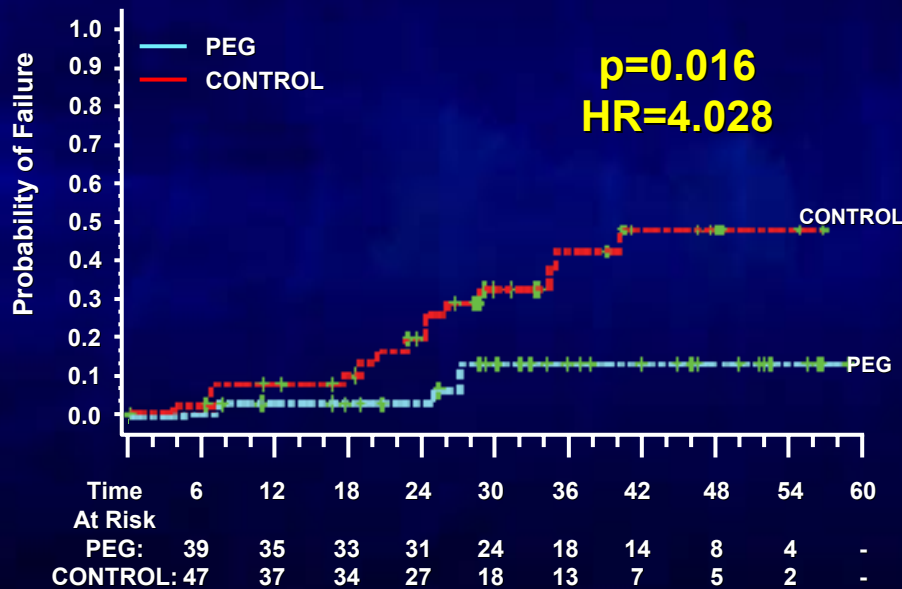
Liver Decompensation, HCC, Death, Liver transplantation



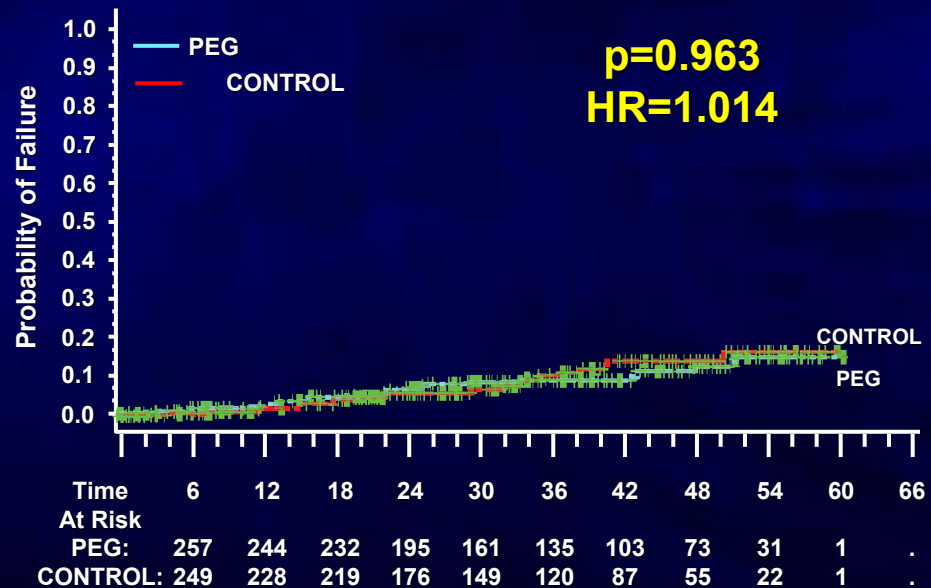
EPIC-3 Time to 1st Clinical Event

According to the Presence of Varices at Baseline

Varices at Baseline



No Varices at Baseline



Summary

- **In patients who failed to respond to peg-IFN α -Ribavirin therapy,**
 - **Retreatment yields very low SVR rates in patients infected with genotypes 1 and 4**
 - **Retreatment with higher doses of peg-IFN α and/or ribavirin may restore a significant antiviral response**
 - **Maintenance therapy does not appear to bring any substantial benefit in the majority of non-responders**

III

Future SOC and Retreatment of Nonresponders

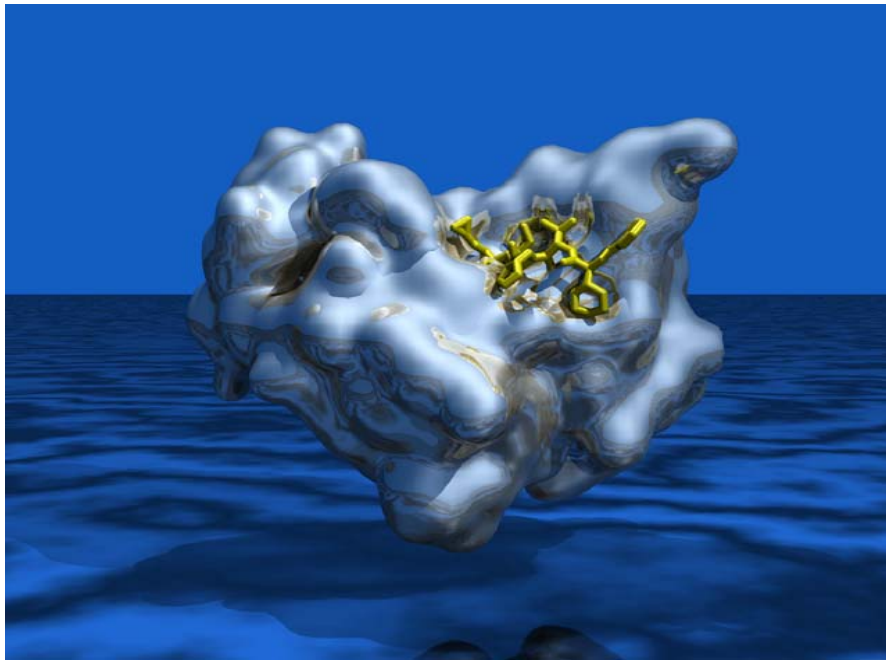
**HCV
inhibitor**

+

**Pegylated
IFN- α**

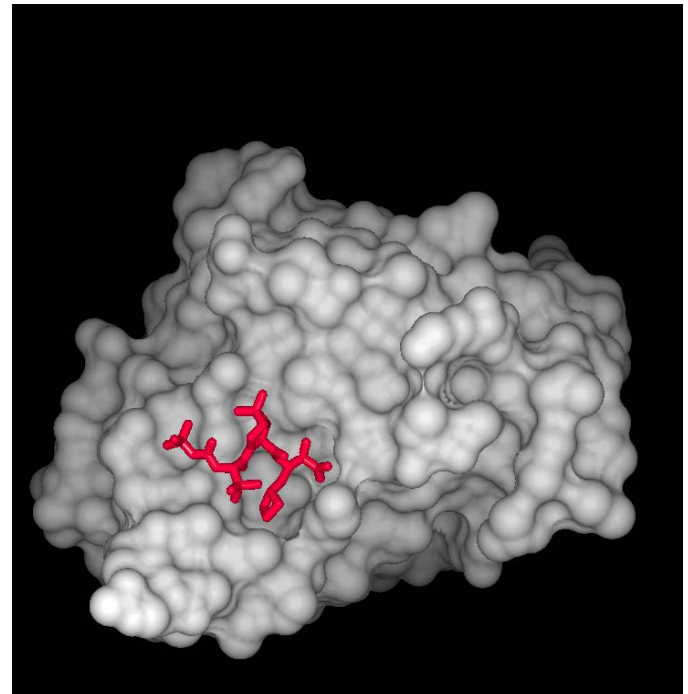
Ribavirin

NS3/4A Protease Inhibitors in Phase III Development



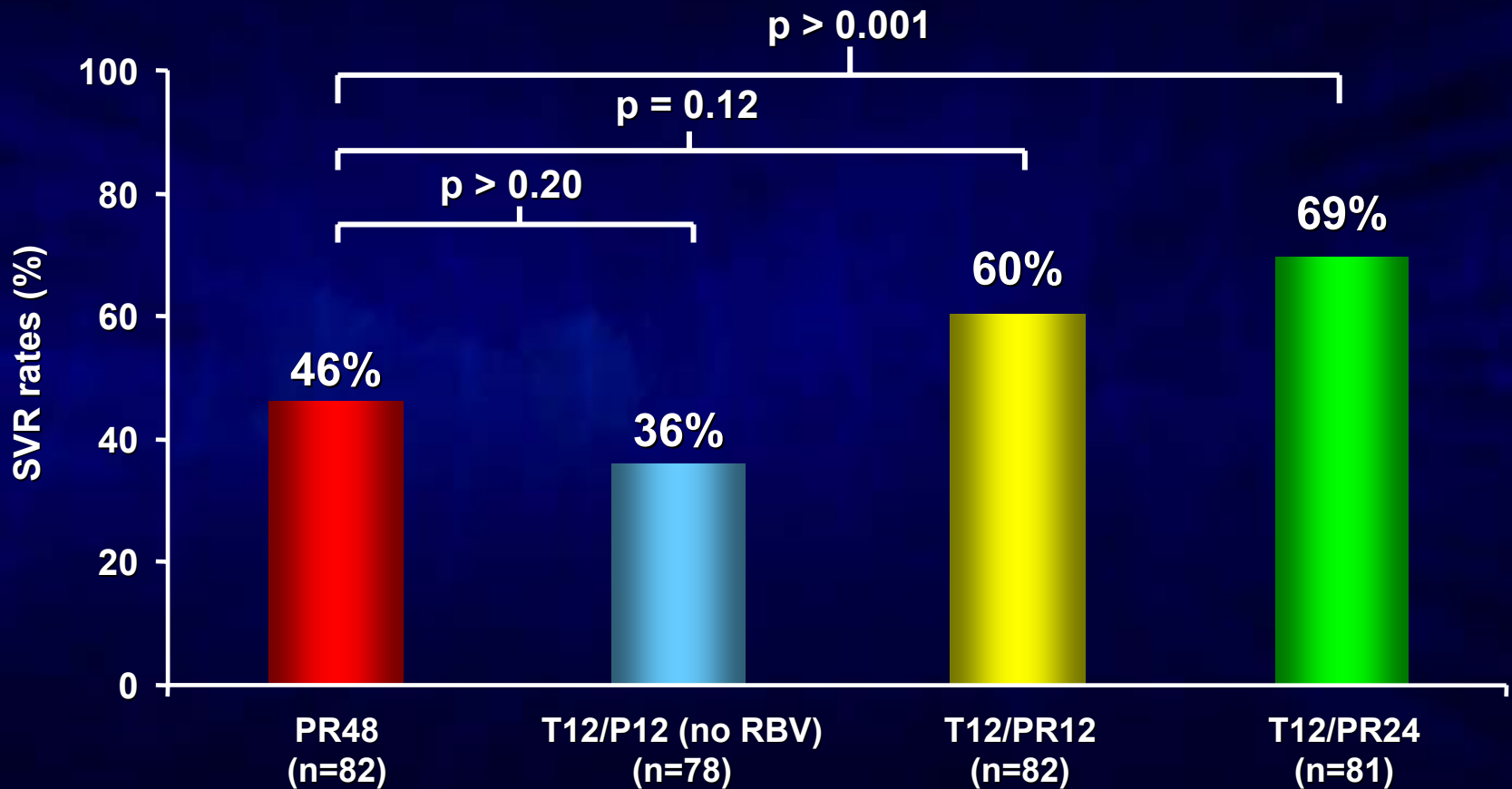
Telaprevir (Vertex)

Boceprevir (Merck)



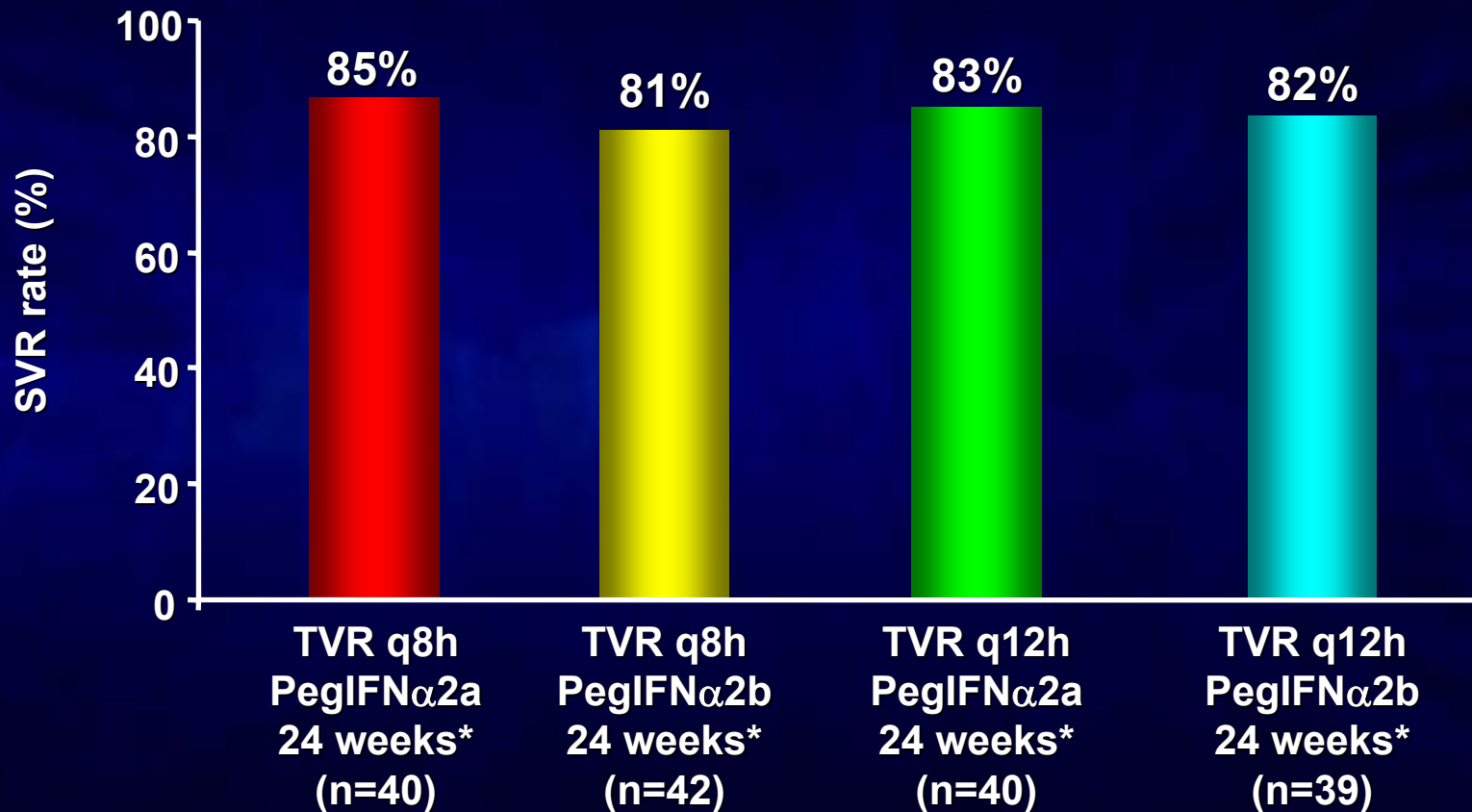
PROVE 2 Trial (Phase II)

Naïve, Genotype 1, Europe



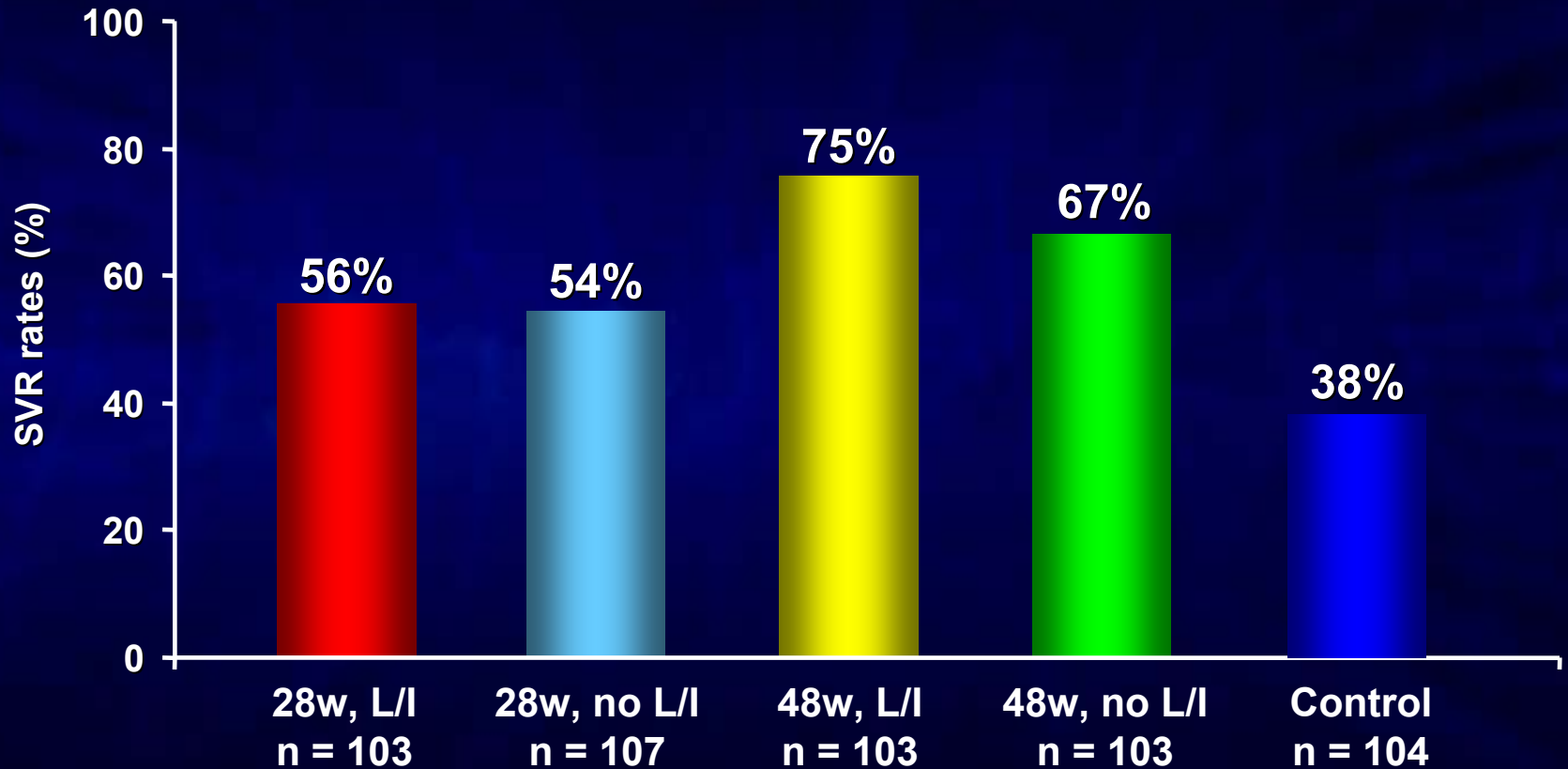
Telaprevir q8h vs q12h

Naïve, Genotype 1, Europe



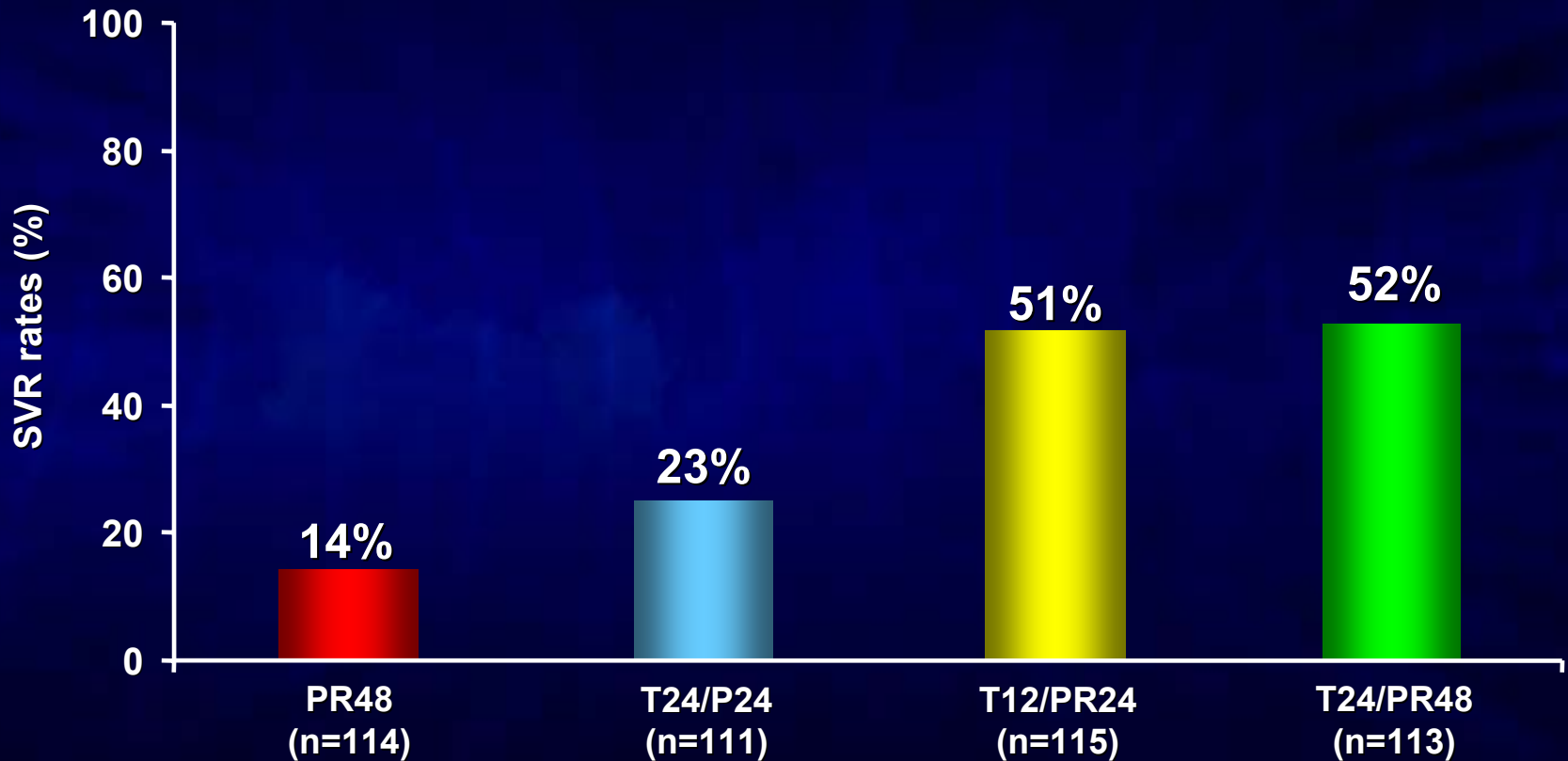
*18% of the patients without an RVR were treated for 48 weeks

SPRINT-1 Trial (Naive, Gen 1)



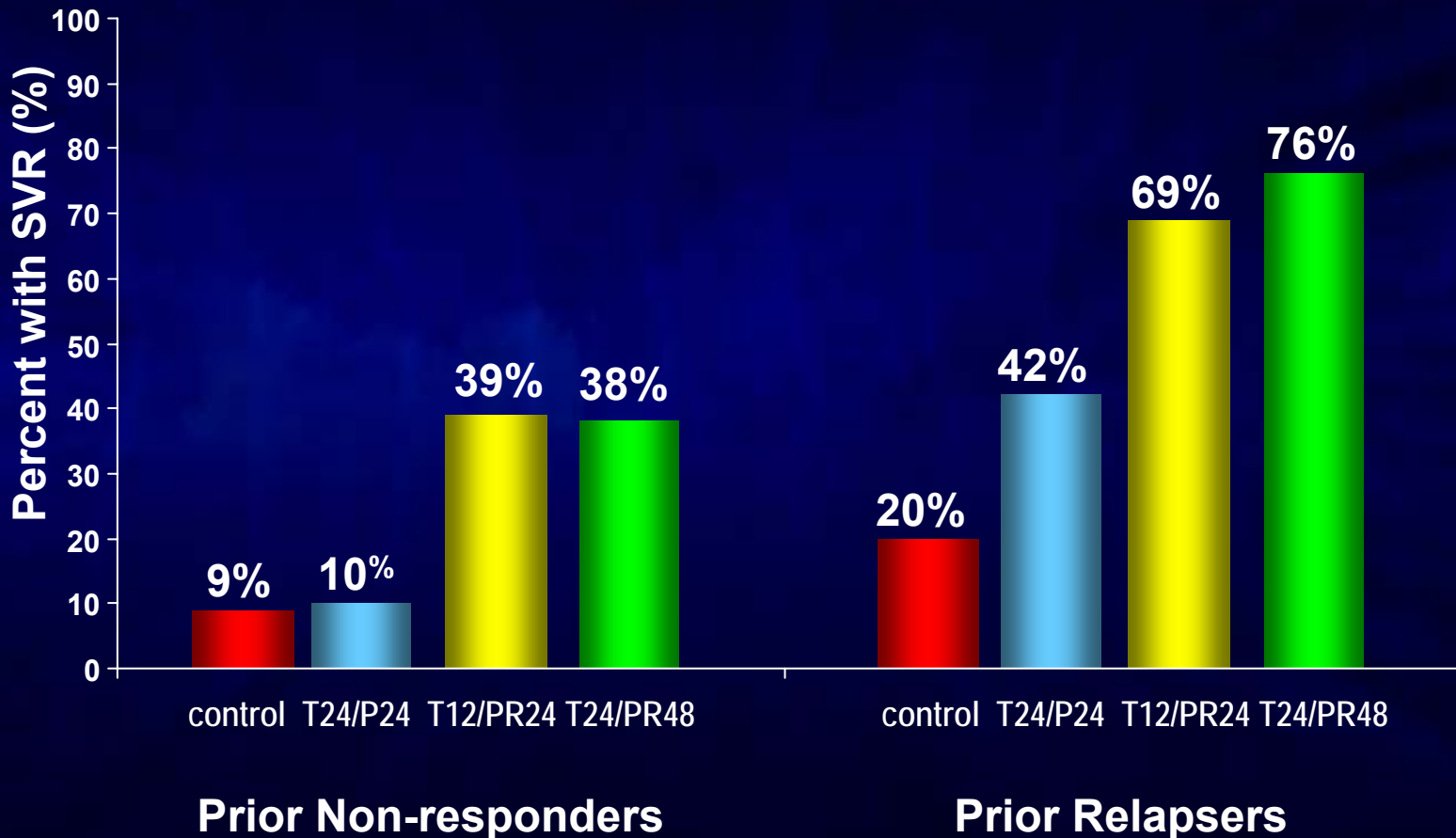
PROVE 3 Trial (Phase II)

Nonresponders, Genotype 1



PROVE 3 Trial (Phase II)

Nonresponders, Genotype 1



Telaprevir Side-Effects

- **More frequent than SOC**
 - **Rash**
 - Severe (grade 3) rash <10%
 - No grade 4 rash
 - **Pruritus**
 - **Anemia**

Boceprevir Side-Effects

- **More frequent than SOC**
 - **Anemia**
 - ~1g/dL incremental hemoglobin decrease
 - Management with EPO is associated with increased completion rates
 - **Dysgueusia**

Telaprevir in HCV Genotypes Other Than 1

	Genotype 1	Genotype 2	Genotype 3	Genotype 4
Day 3	-3.6	-3.0	-0.8	-1.2
Day 15	-4.2	-3.1	-0.1	-0.9

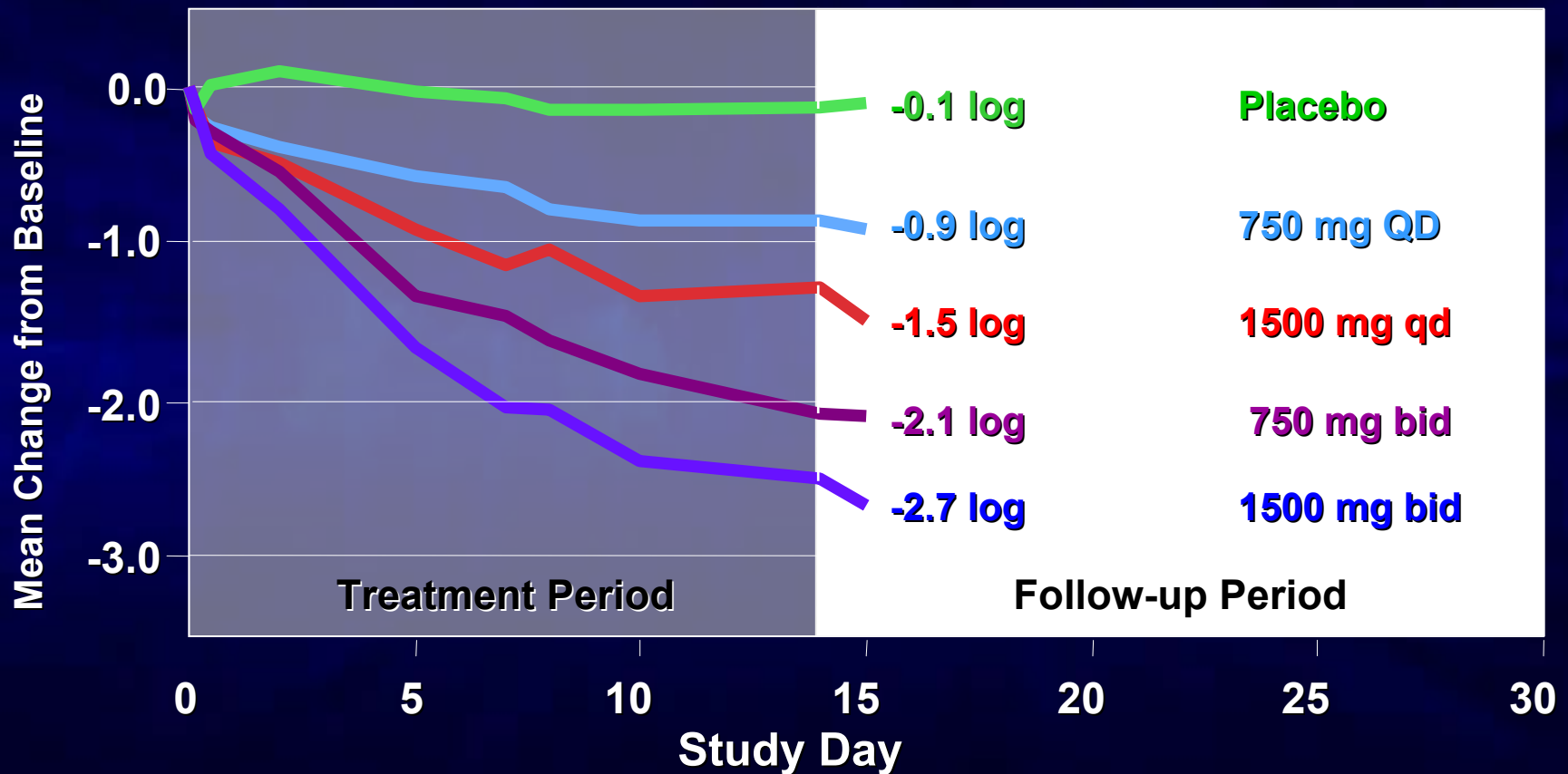
DAAAs in Development

- **NS3/4A protease inhibitors**
- **Inhibitors of HCV replication**
 - **Nucleoside/nucleotide analogues**
 - **Nonnucleoside inhibitors of RdRp**
 - **NS5A inhibitors**
 - **Cyclophilin inhibitors**
 - **Antagonists of miR122**

Antiviral Efficacy of NS3/4A Protease Inhibitors

Drug	Phase	Dose	Duration	Median/mean log HCV RNA reduction
Telaprevir	III	750 mg q8h	14 days	-4.4
Boceprevir	III	400 mg tid	7 days	-1.6
TMC435	II	200 mg qd	7 days	-4.1
ITMN-191/R7227	II	200 mg q8h	14 days	-3.8
MK-7009	II	700 mg bid	8 days	-4.7
BI201335	II	240 mg qd	14 days	-4.0
Narlaprevir	II	400 mg bid	7 days	-4.2
BMS-650032	I	300 mg bid	3 days	-3.3

R7128 (Phase Ib)

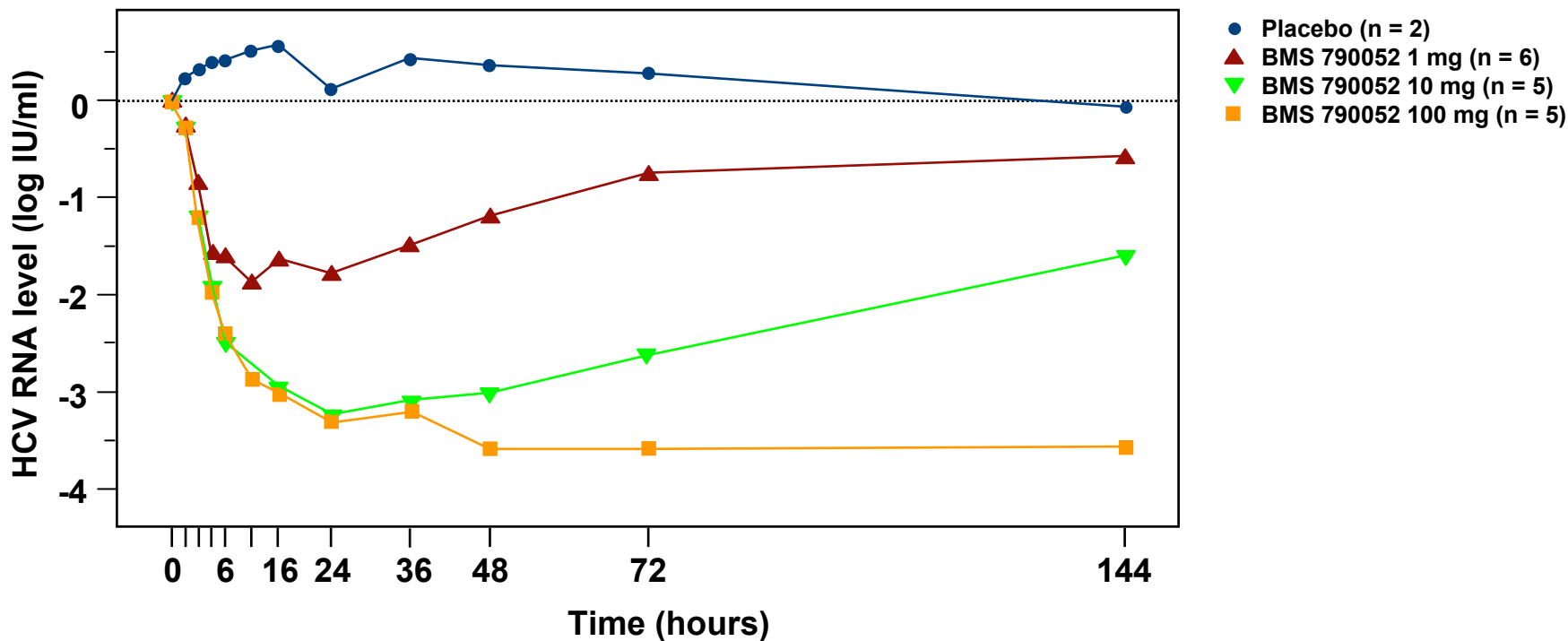


Antiviral Efficacy of NNIs

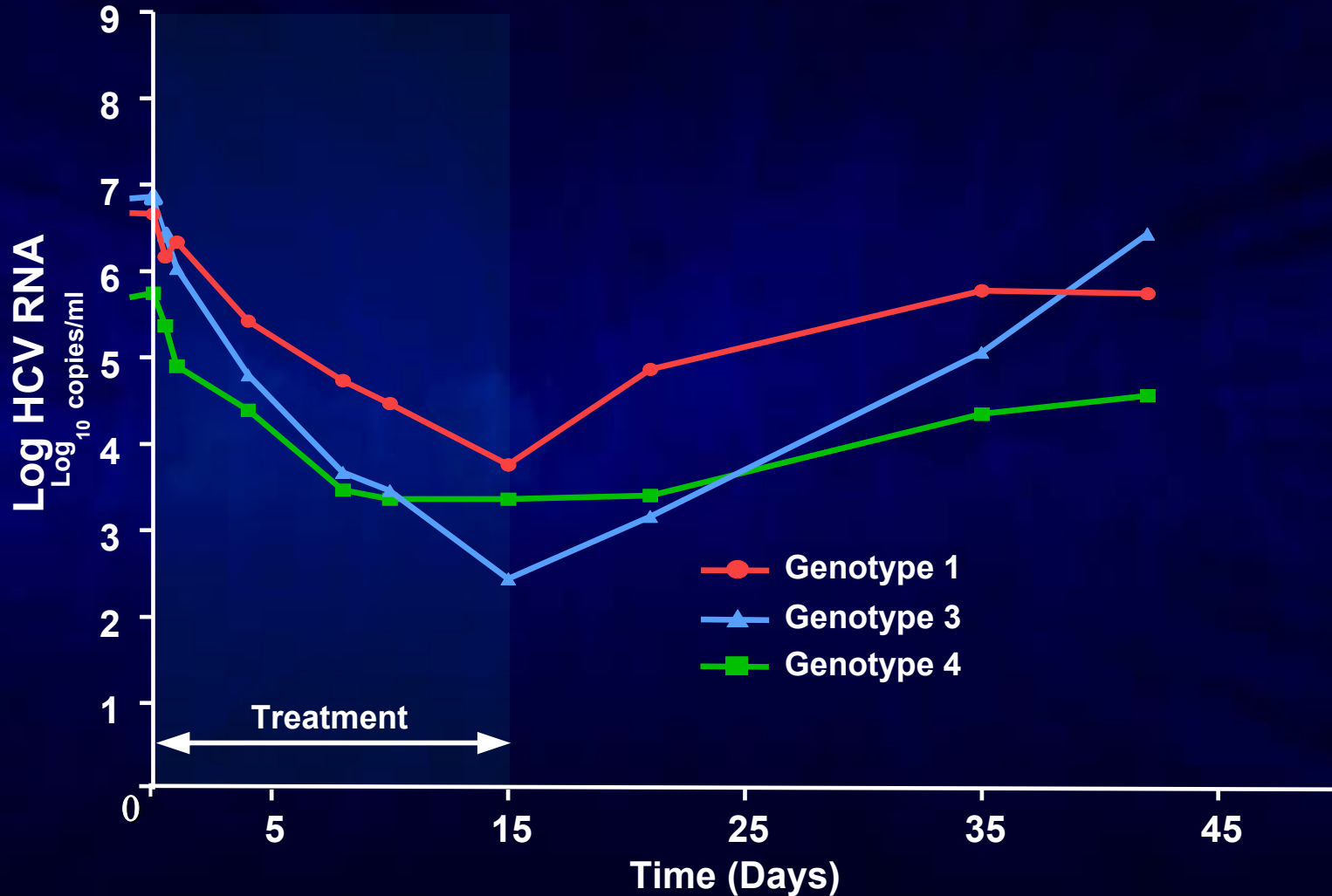
Drug	Phase	Dose	Duration	Median/mean log HCV RNA reduction
GS-9190	II	40 mg bid	8 days	-1.4
Filibuvir	II	300 mg bid	8 days	-2.1
ANA598	II	800 mg bid	3 days	-2.9
BI207127	II	800 mg q8h	3 days	-3.1
VCH-759	II	400 mg tid	10 days	-1.7
ABT-333	II	600 mg bid	2 days	-1.5
VX-222	Ib	750 mg bid	3 days	-3.7
MK-3281	Ib	800 mg bid	7 days	-1.3 (1a), -3.8 (1b)

BMS-790052

NS5A Inhibitor, *in vivo* efficacy



DEBIO-025 (Cyclophilin Inhibitor)



(Flisiak et al., Hepatology 2008;47:817-26)

Summary

- **The next standard-of-care treatment of chronic hepatitis C will be a triple combination of peg-IFN α , ribavirin and a protease inhibitor**
- **This treatment yields SVR rates of the order of 70%-80% in naïve and 50% in nonresponder genotype 1 patients**
- **A number of other direct acting antiviral (DAA) drugs with broader genotype coverage are at the clinical developmental stage**