Aktuelle Therapie chronischer Virushepatitiden

Fortbildungsveranstaltung
Arbeitskreis AIDS
Berlin, 2. Dezember 2009

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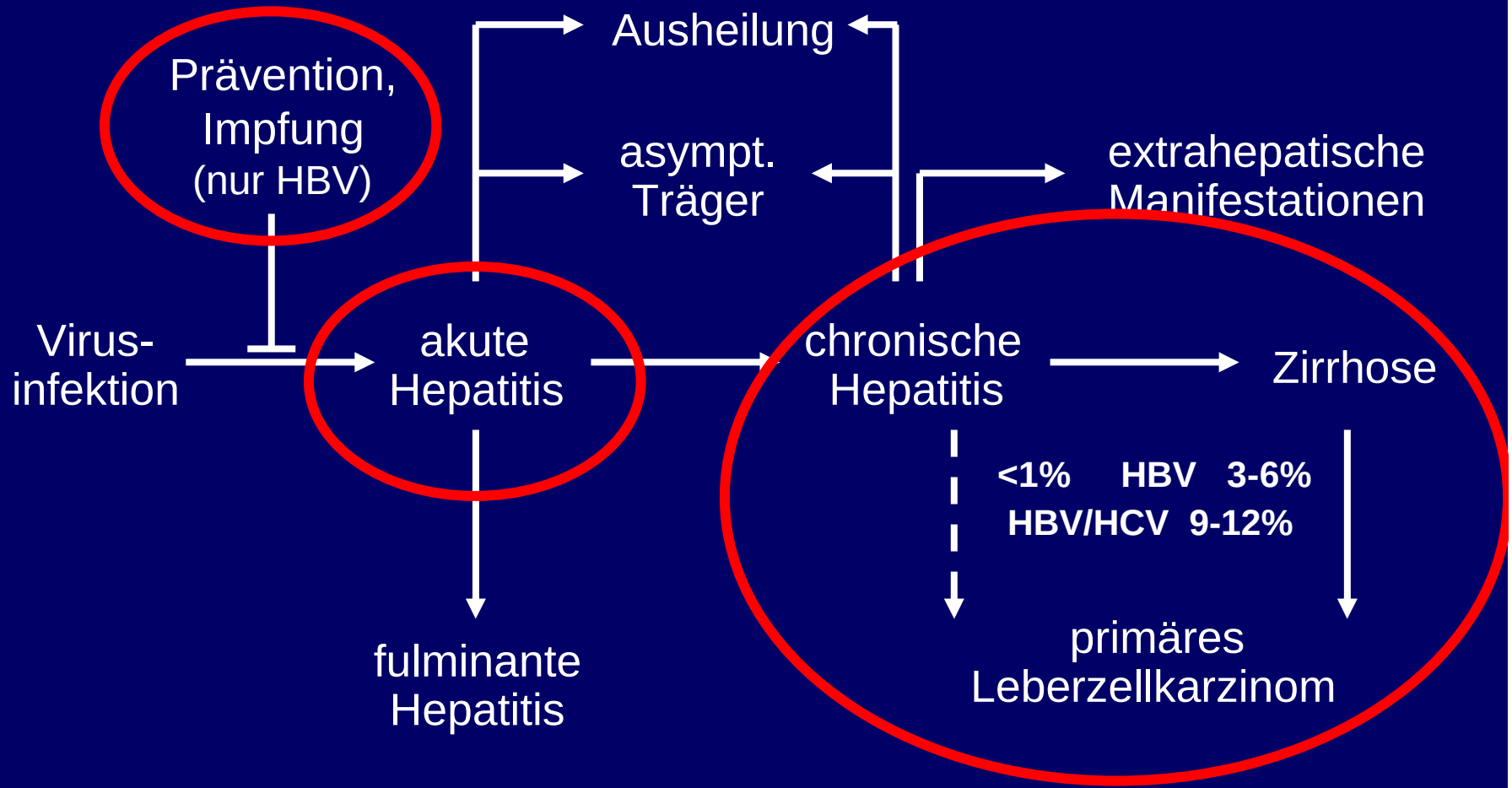
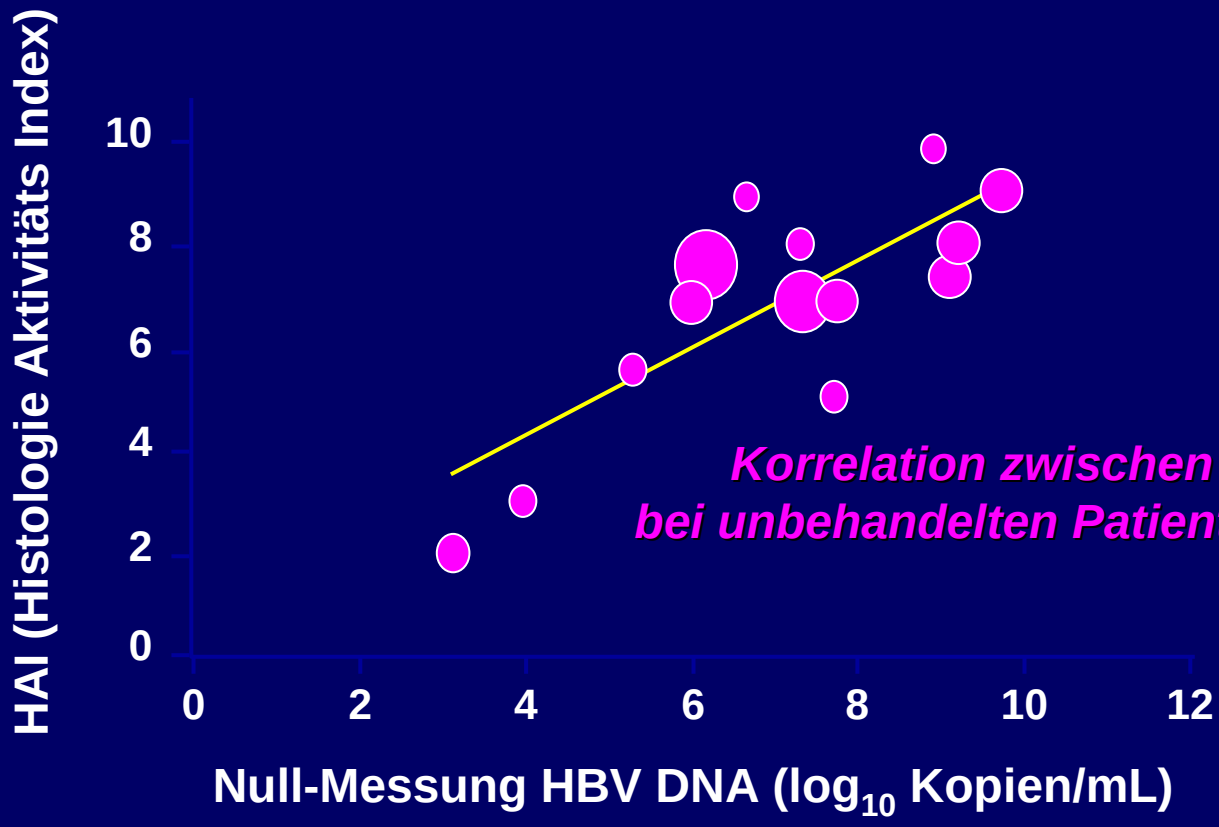
MEDIZINISCHE KLINIK 1

Klinischer Verlauf chronischer Virushepatitiden



Baseline Serum HBV DNA Spiegel und histologische “Nekrotische Entzündung”

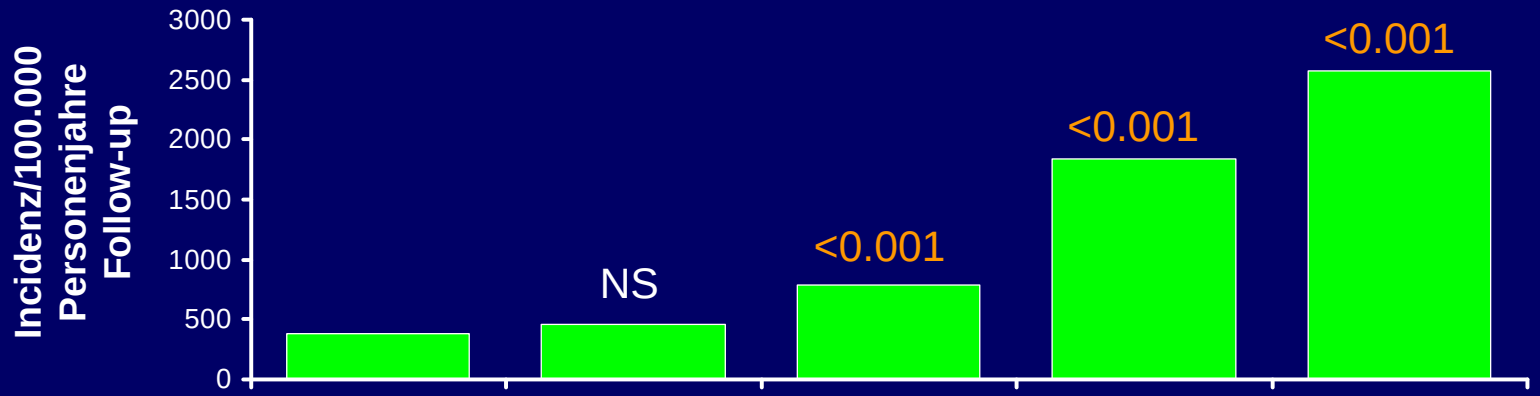
- 3246 Patienten in 26 Studien zu CHB
  - HBV DNA und Biopsien “gematcht”



Korrelation zwischen HAI and HBV DNA bei unbehandelten Patienten (r=0.78; P=0.0001)

Mommeja-Marin H, et al. *Hepatology.* 2003;101:2537-2545.

Höhere Ausgangswerte von HBV DNA sind mit einer Progression zur Zirrhose verknüpft



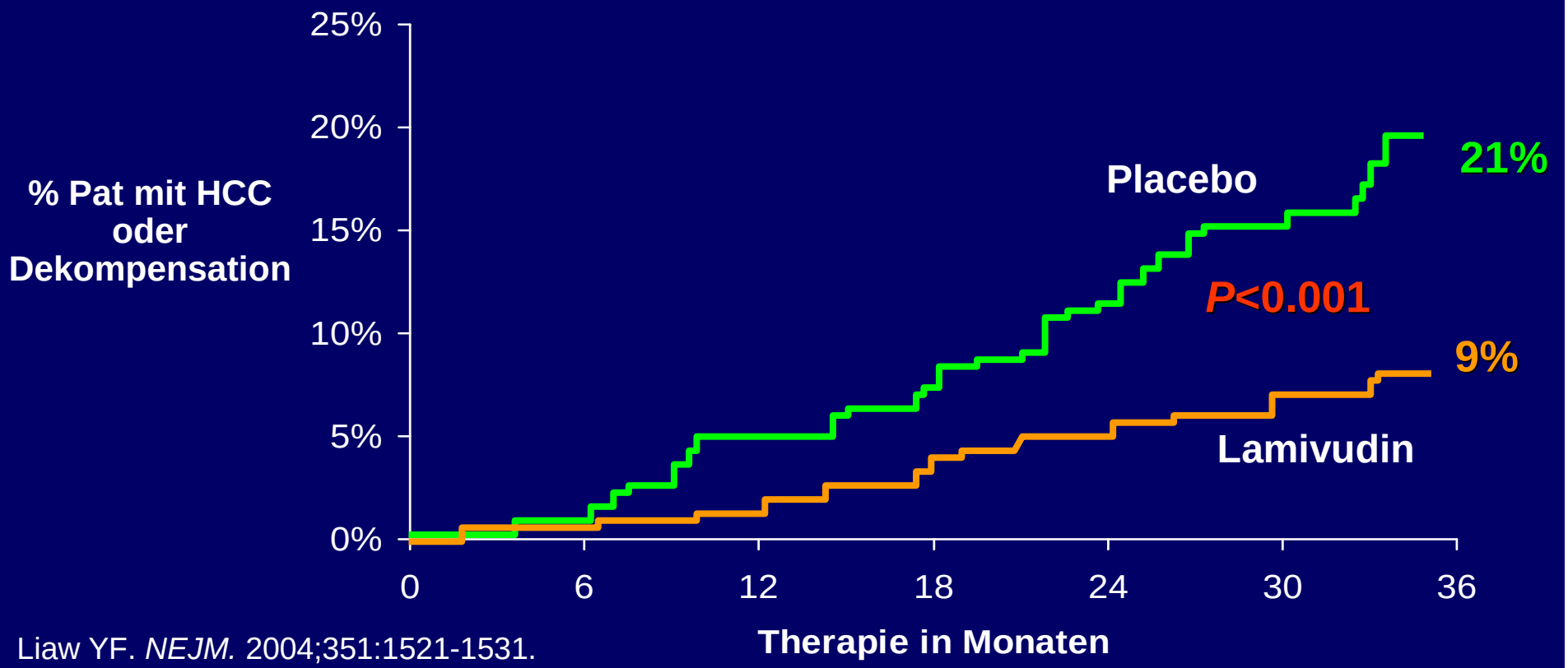
HBV DNA (Kopien/mL)	<300	300–<10^4	10^4–<10^5	10^5–<10^6	≥10^6
Adjust. RR **(95% Konfidenz -Intervall)**	1,0 (ref)	1,3 (0,9–2,0)	2,2 (1,5–3,3)	5,0 (3,4–7,4)	8,6 (6,2–12,3)
P Wert	–	NS	<0.001	<0.001	<0.001

*****Adjustiert für Geschlecht, Alter, anti-HCV Status, Rauchen, und Alkoholkonsum; NS=nicht signifikant

Iloeje UH, et al. *Gastroenterology.* 2006;130:678–686.

Virus-Suppression vermindert Komplikationen bei chron. Hepatitis B

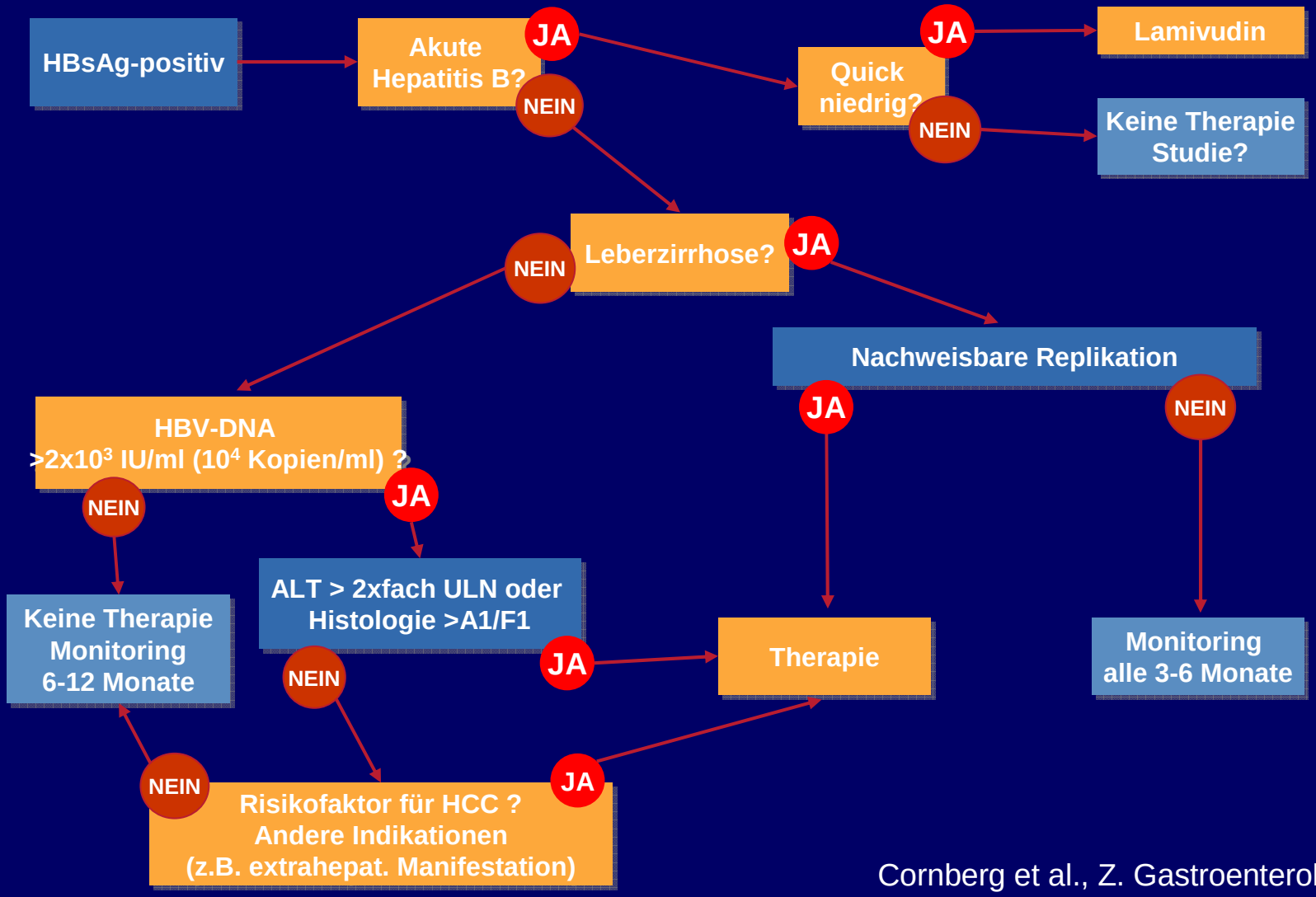
- 651 Patienten erhielten Lamivudin vs. Placebo (2:1)
- Mediane f/u = > 36 Monate



Liaw YF. *NEJM.* 2004;351:1521-1531.

Hepatitis B –
Wer soll behandelt werden ?

S3-Leitlinie – Hepatitis B
Diagnose und Therapie



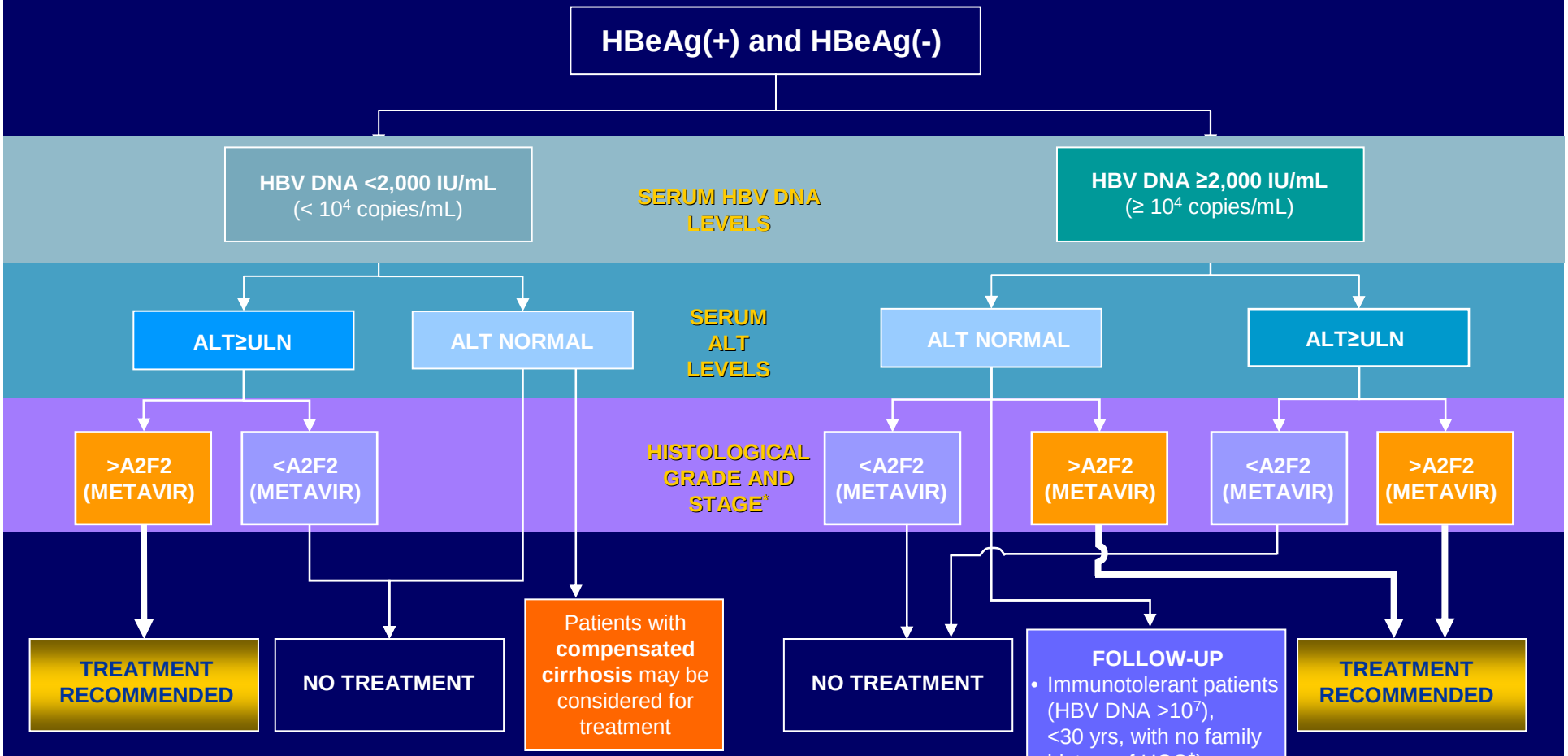
Cornberg et al., Z. Gastroenterol. 2007

EASL clinical practice guidelines: Indication for treatment

- The indication for treatment is mainly based on the combination of three criteria:
  - Serum HBV DNA levels
  - Serum ALT levels
  - Histological grade and stage
- Patients should be considered for treatment when:
  - HBV DNA levels are above 2,000 IU/mL
  - And/or the serum ALT levels are above the ULN
  - And/or liver biopsy shows moderate to severe active necroinflammation and/or fibrosis

Adapted from: EASL Clinical Practice Guidelines Panel. *J Hepatol*. 2009;50:227-42.

Liver biopsy and treatment decisions in the management of HBV infection



* Histological assessment with liver biopsy or non-invasive markers (when validated).
† Immunotolerant patients >30 or/and family history of HCC and/or suspicion of liver disease require immediate liver biopsy.

Adapted from: EASL Clinical Practice Guidelines Panel. *J Hepatol*. 2009;50:227-42.

Hepatitis B –
Wie soll behandelt werden ?

Therapie der chronischen Hepatitis B

Vor- und Nachteile der Medikamente

(PEG) Interferon-alfa

Vorteile

- langjährige Erfahrung
- keine Resistenzentwicklung (Mutanten)
- definierte Therapiedauer

Nachteile

- Nebenwirkungsprofil
- keine Option für Patienten mit Leberzirrhose

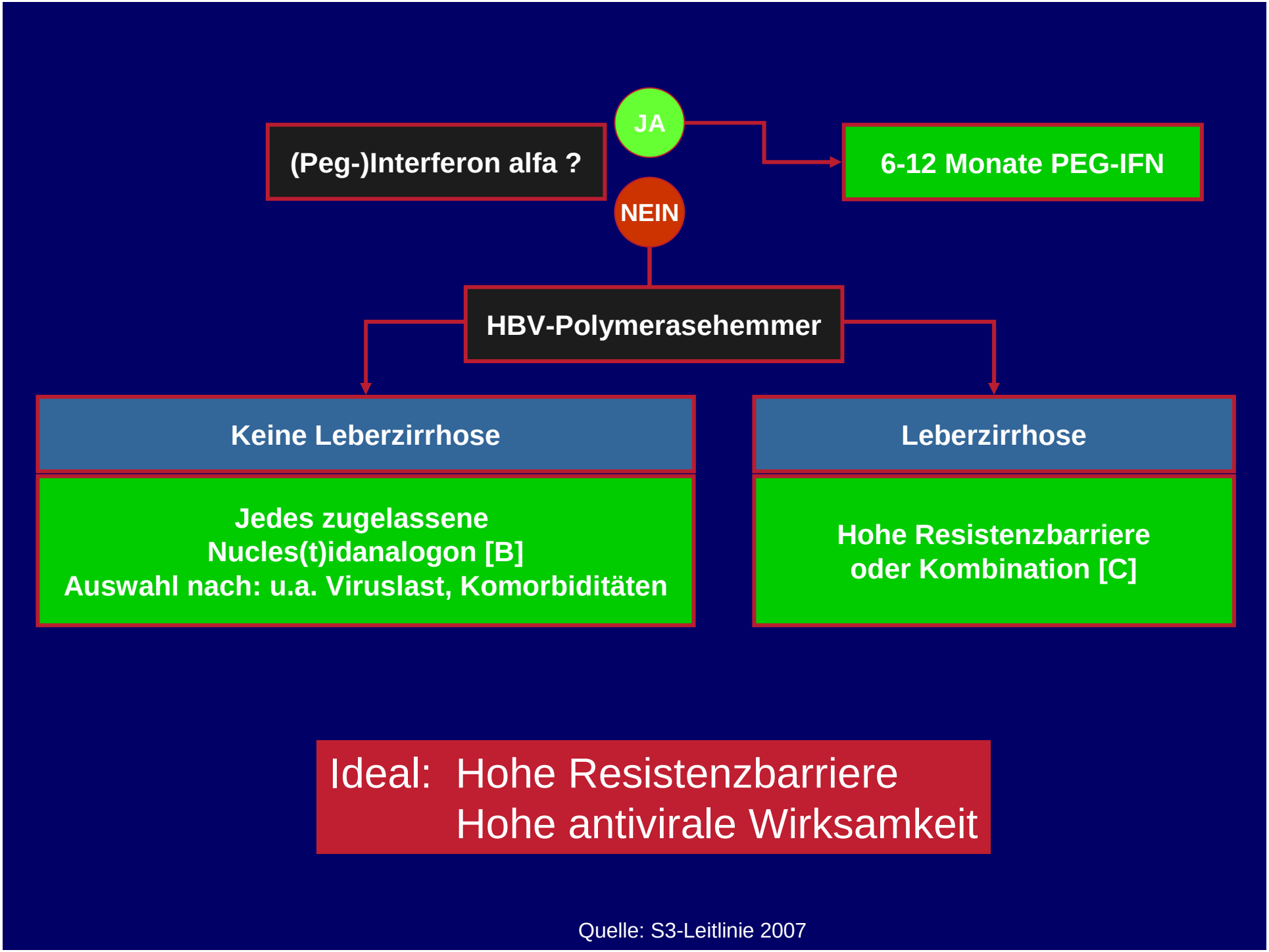
Lamivudin/Telbivudin
Entecavir
Adefovir/Tenofovir

Vorteile

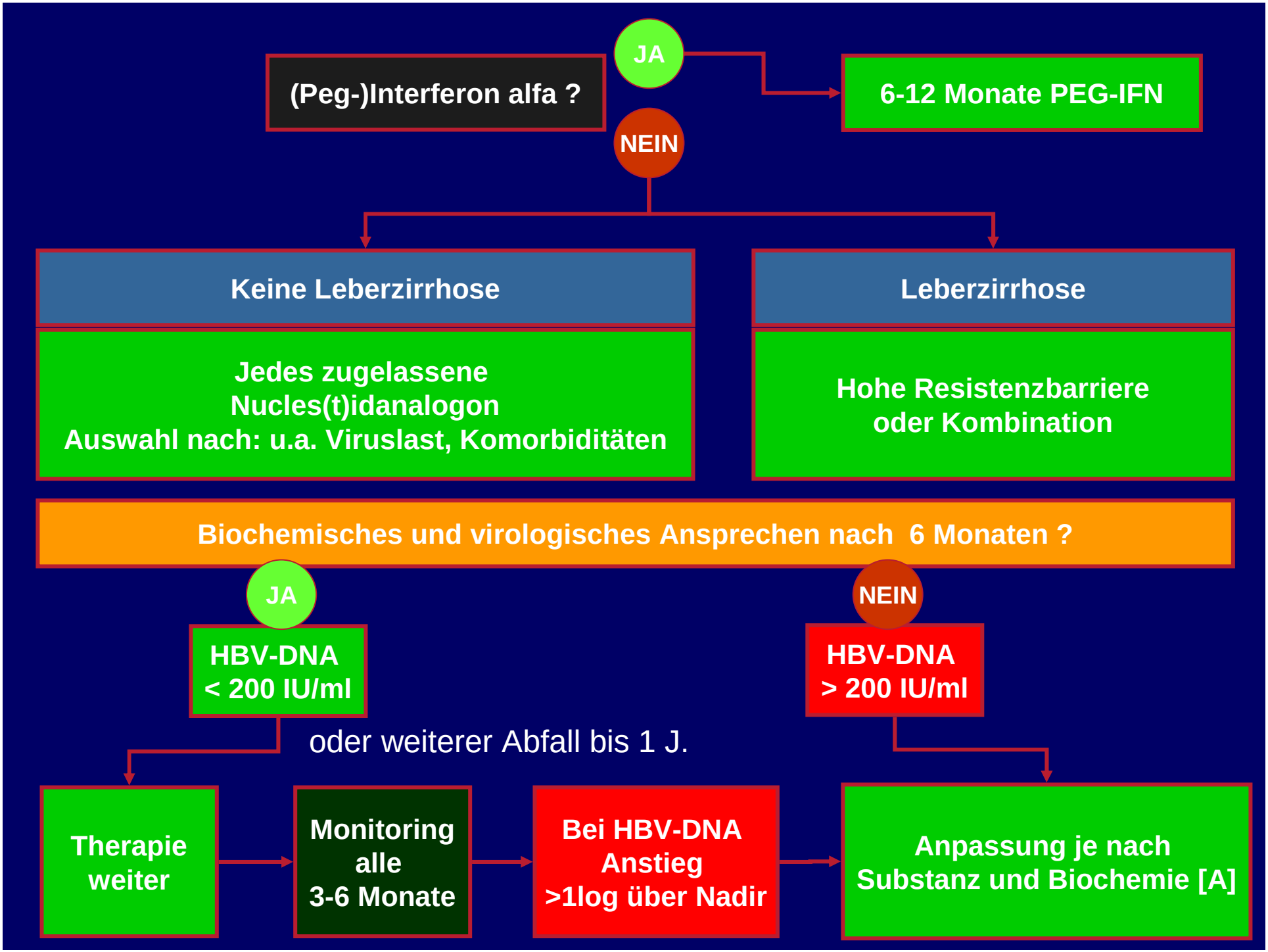
- orale Verfügbarkeit
- Nebenwirkungsprofil
- Option für Patienten mit Leberzirrhose

Nachteile

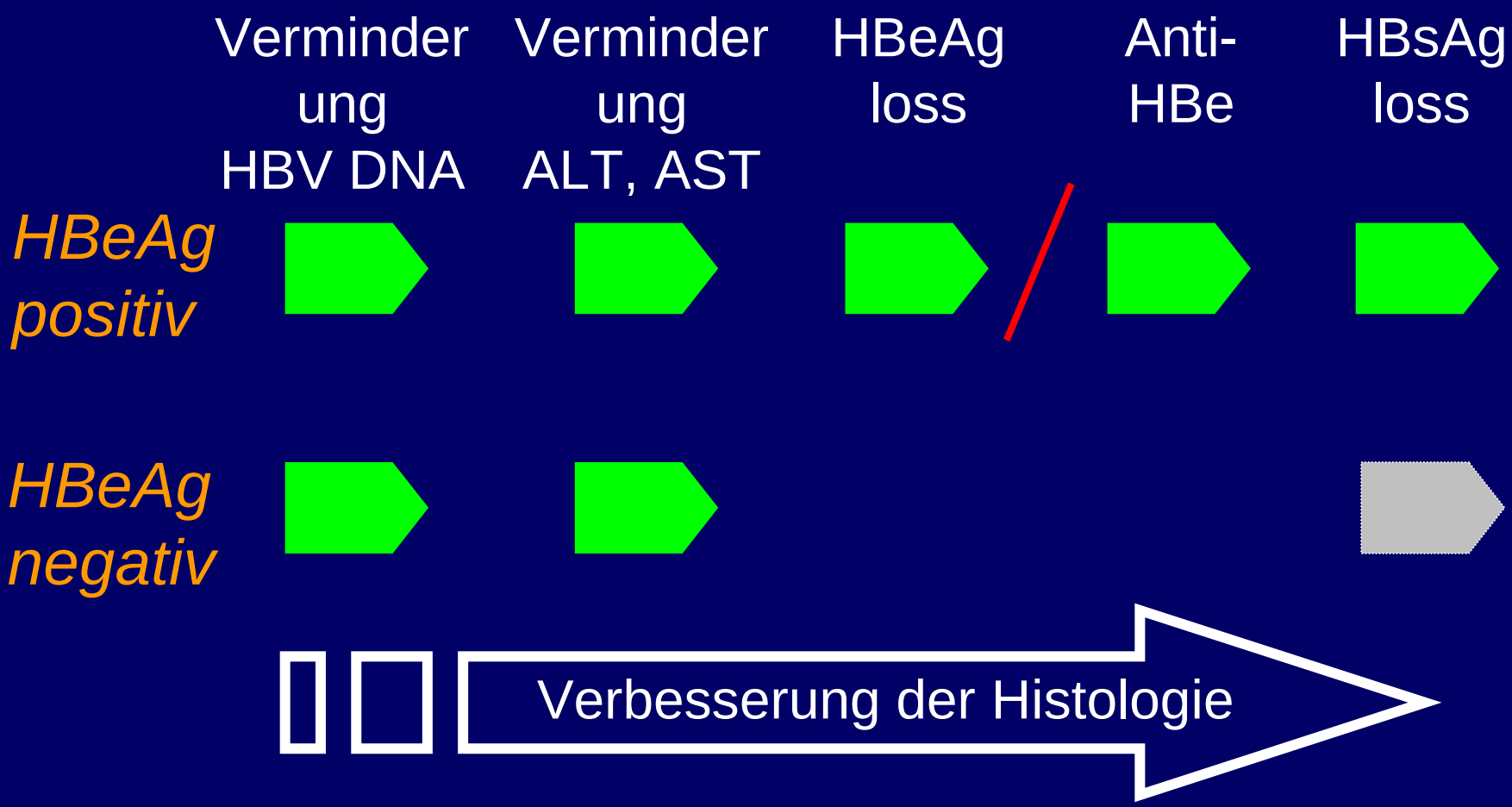
- Therapiedauer
- Resistenzentwicklung



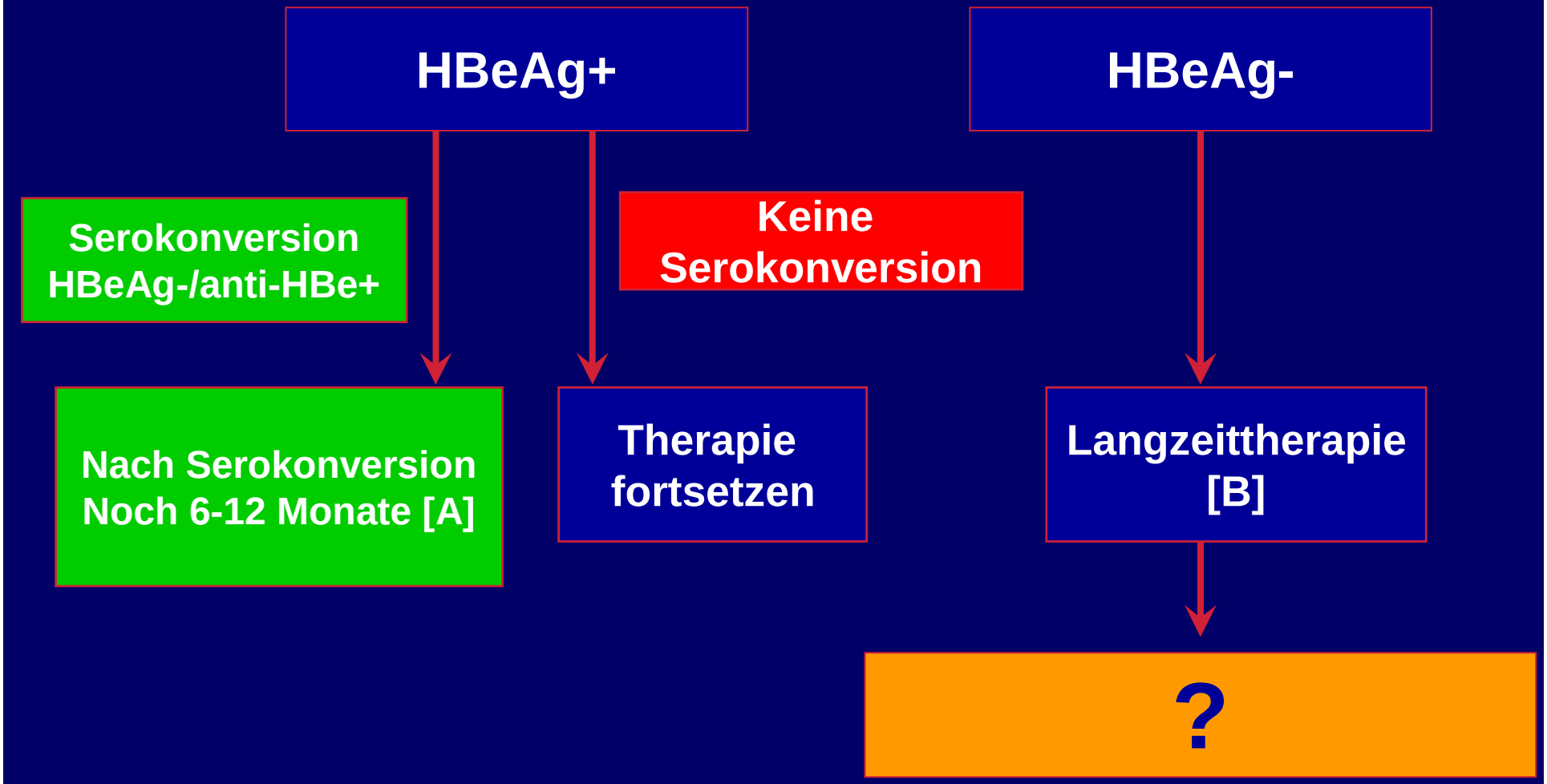
Quelle: S3-Leitlinie 2007


(Peg-)Interferon alfa ?
JA
6-12 Monate PEG-IFN
NEIN
Keine Leberzirrhose
Leberzirrhose
Jedes zugelassene
Nucles(t)idanalogon
Auswahl nach: u.a. Viruslast, Komorbiditäten
Hohe Resistenzbarriere
oder Kombination
Biochemisches und virologisches Ansprechen nach 6 Monaten ?
JA
NEIN
HBV-DNA
< 200 IU/ml
HBV-DNA
> 200 IU/ml
oder weiterer Abfall bis 1 J.
Therapie
weiter
Monitoring
alle
3-6 Monate
Bei HBV-DNA
Anstieg
>1log über Nadir
Anpassung je nach
Substanz und Biochemie [A]

Endpunkt der Therapie der chronischen Hepatitis B



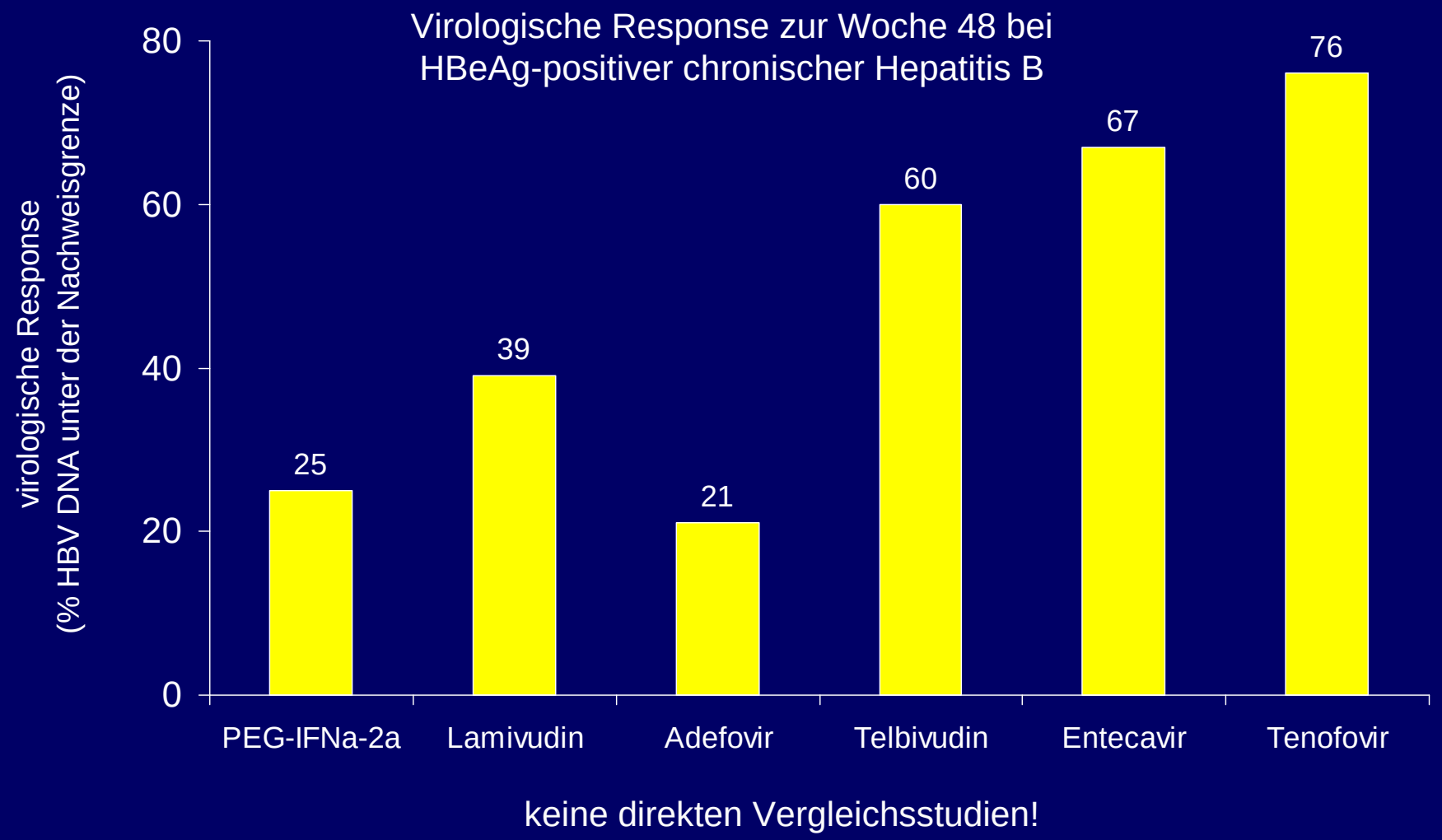
Wann kann eine Therapie beendet werden?



Quelle: S3-Leitlinie 2007

Effektivität der Therapie

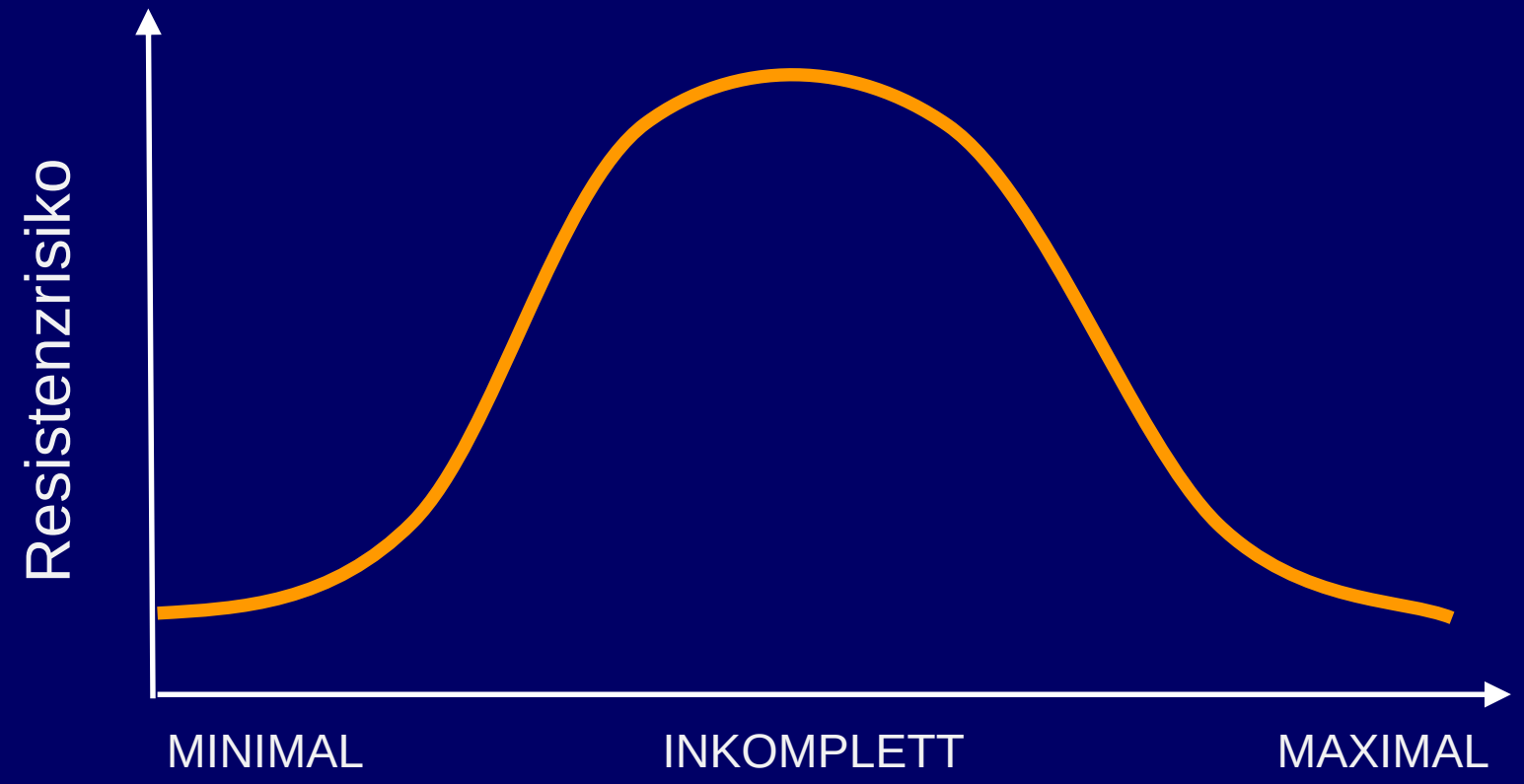
Effektivität der antiviralen Therapie



nach Hoofnagle JH et al. Hepatology 2007; 45: 1056

Effektivität ist nicht alles: Resistenzen

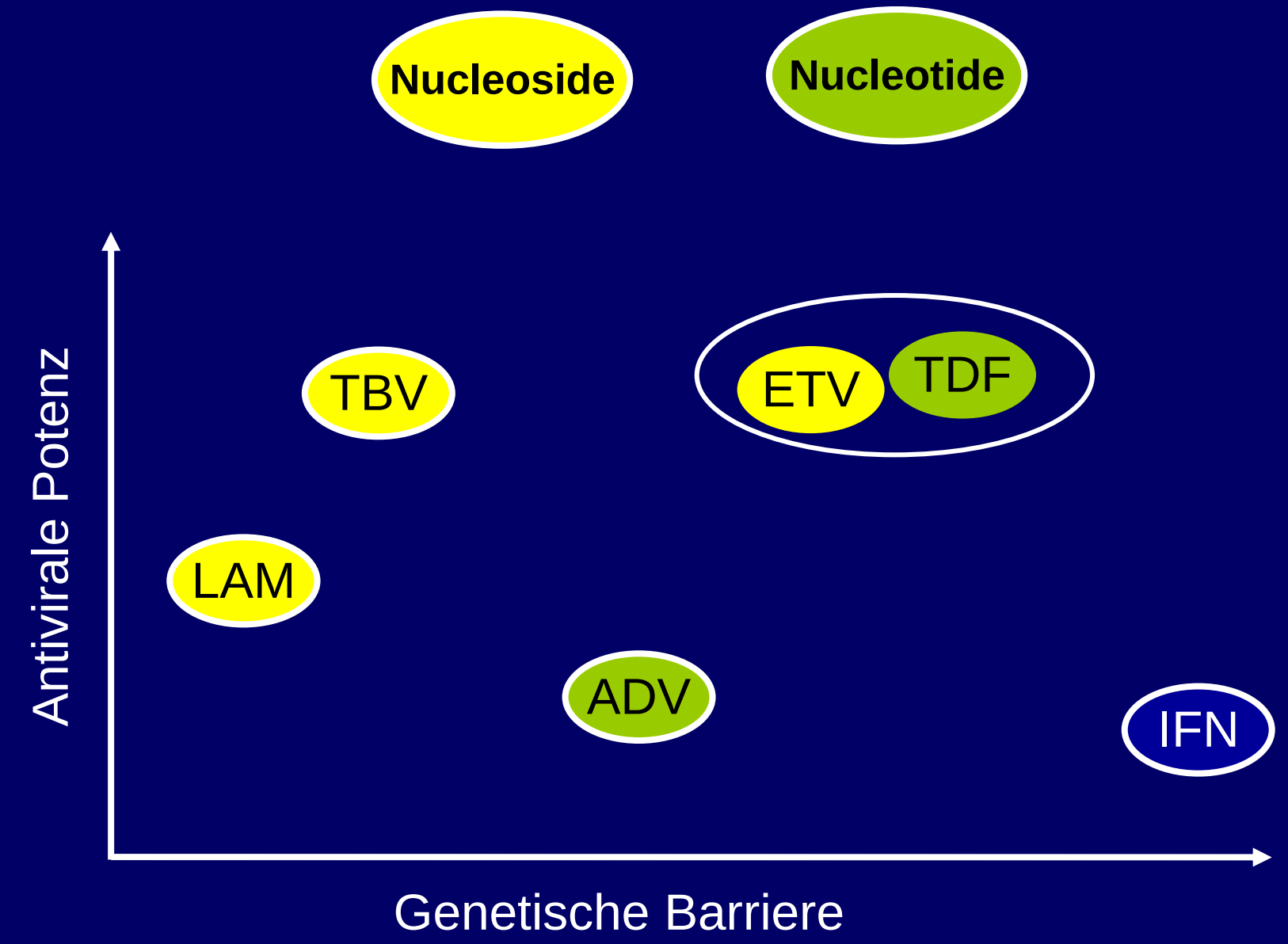
Risiko der Selektion resistenter Virusvarianten



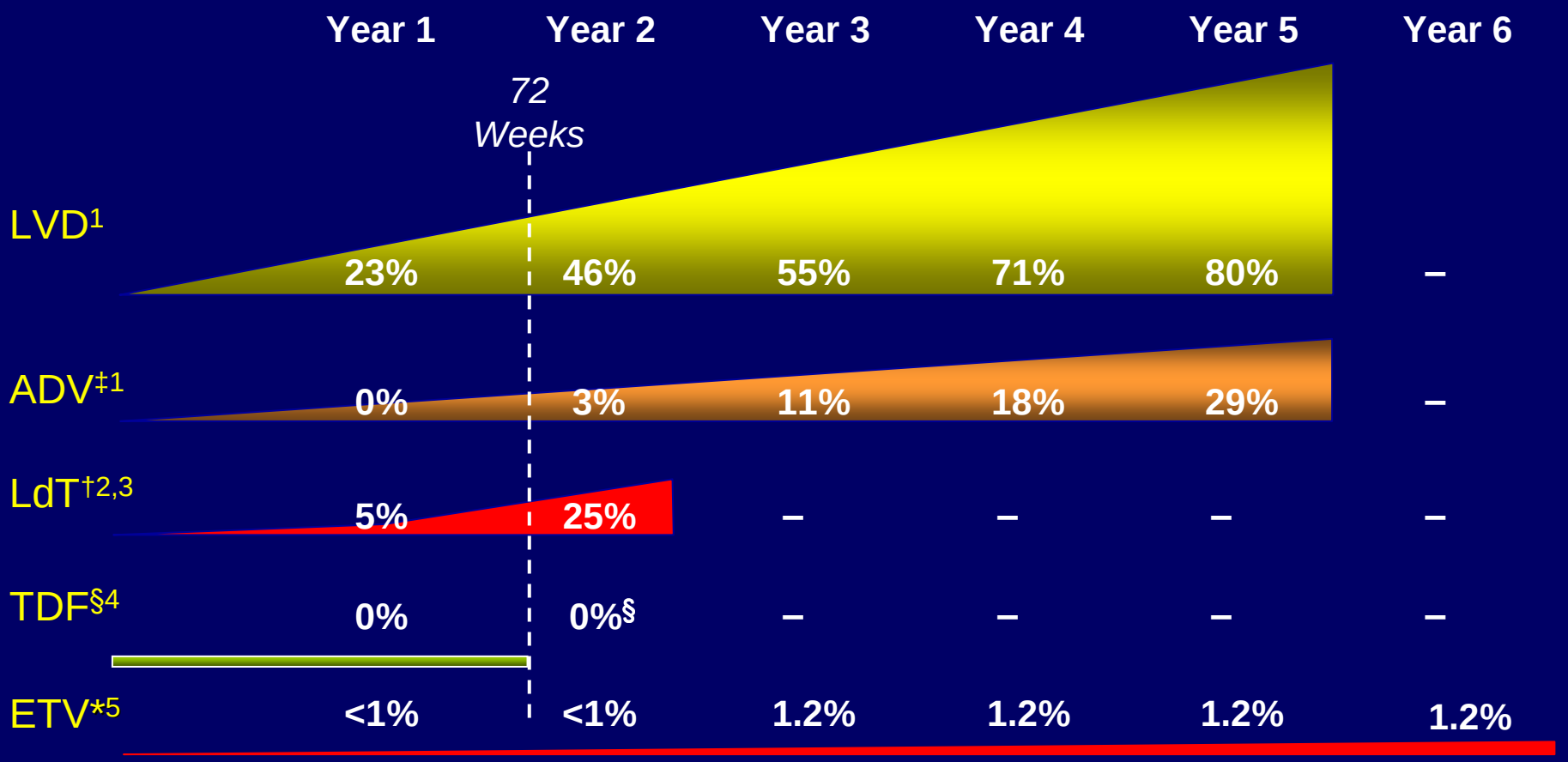
Suppression der viralen Replikation

nach: Richman, Antiviral Research 1996;29:31-33

Antivirale Potenz und Resistenzbarriere



Resistance rates through 6 years among nucleos(t)ide-naïve patients

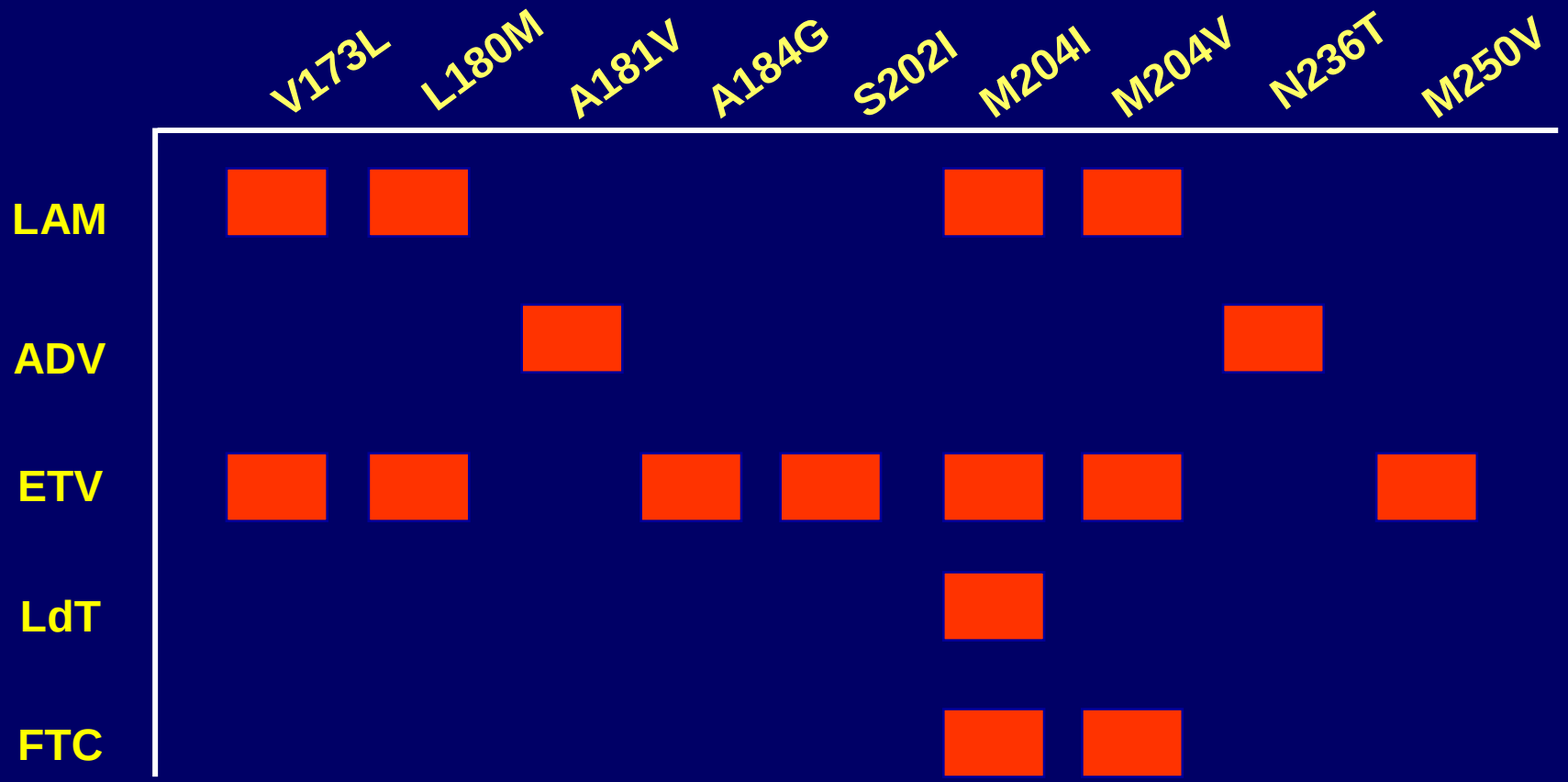


§ Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF; therefore resistance to TDF monotherapy after 72 weeks cannot be fully ascertained[5,6] * Cumulative probabilities of resistance taken; † Naïve HBeAg (+) ; ‡ Naïve HBeAg(-); N/A not available

1. Locarnini S. *Hepatol Int*. 2008;2:147-51. 2. Lai CL, et al. *N Engl J Med,* 2007;357:2576-8; 3. Liaw YF, et al. *Gastroenterology* 2009;136:486-95. 4. Snow-Lampart A, et al. AASLD Oct 31–Nov 4, 2008, San Francisco, USA. Oral Presentation 977 *Hepatology* 2008;48:745A. 5. Baraclude EU SmPC, February 2009. 6. Tenney et al. EASL April 22–26, 2009, Copenhagen, Denmark, Oral Presentation 1761.

HBV Polymerase Mutationen unterschieden nach Behandlung

Resistenz Mutationen assoziiert mit Virus-Wiederanstieg bei Patienten unter Behandlung



Therapie der chron. Hepatitis B

- HBs-Antigen u.a. bei jedem Patienten mit erhöhten Leberwerten, Migranten, vor immunsuppressiver Chemotherapie bestimmen
- Bei HBsAg positiven Patienten anti-HDV bestimmen
- Therapieindikation bei chronischer Hepatitis B (>2.000 IU/mL), Leberzirrhose wenn HBV-DNA nachweisbar
- PEG-IFN alfa bedenken
- Bei der Therapie mit Nukleos(t)idanaloga rechtzeitig die Therapie anpassen → Resistenzen verhindern
- HBV-DNA alle 3 Monate kontrollieren, um rechtzeitig Resistenzen zu erkennen

Praktische Therapieempfehlungen

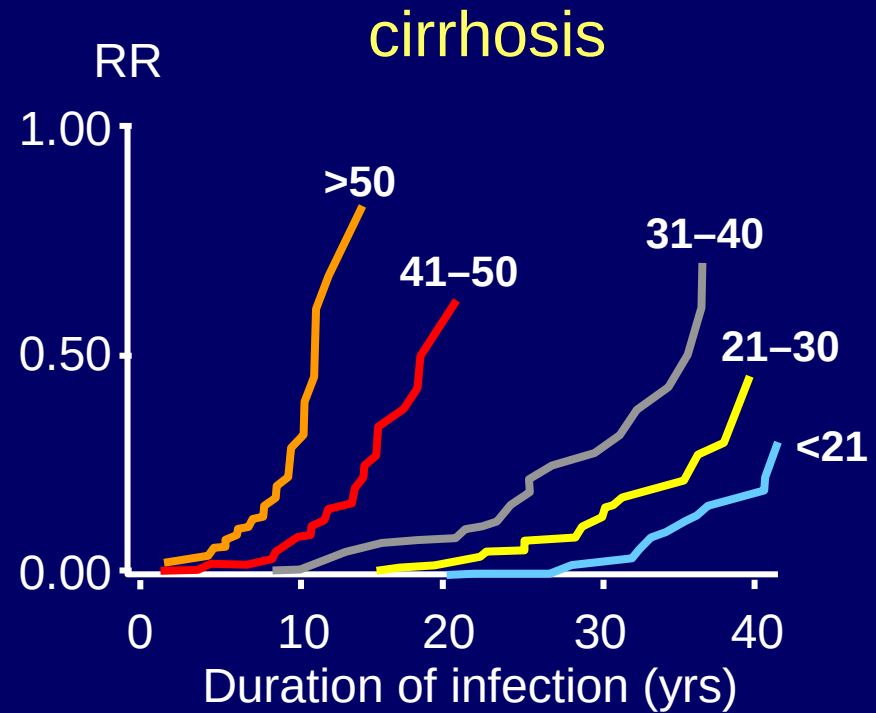
Chronische Hepatitis B

- HBeAg +: PEG-IFN (bei Genotyp A)
  LAM, ADV, ETV, TBV, TDF
- HBeAg -: PEG-IFN
  LAM, ADV, ETV, TBV, TDF
- Zirrhose & post-Ltx: LAM, ADV, ETV, TBV, TDF
- Carrier: keine antivirale Therapie
  präventiv vor Immunsuppr. oder Chemotherapie

HCV

Clinical Course of Hepatitis C Virus Infection

acute hepatitis → 50-80% → chronic hepatitis → cirrhosis



acute hepatitis → <1% → fulminant hepatitis

chronic hepatitis → 5-10% → extrahepatic manifestations

cirrhosis → decompensation
variceal bleeding, etc.
HCC (2-5% per year)

Aims of anti-HCV treatment

Viral eradication (SVR) as treatment aim for patients with hepatitis C

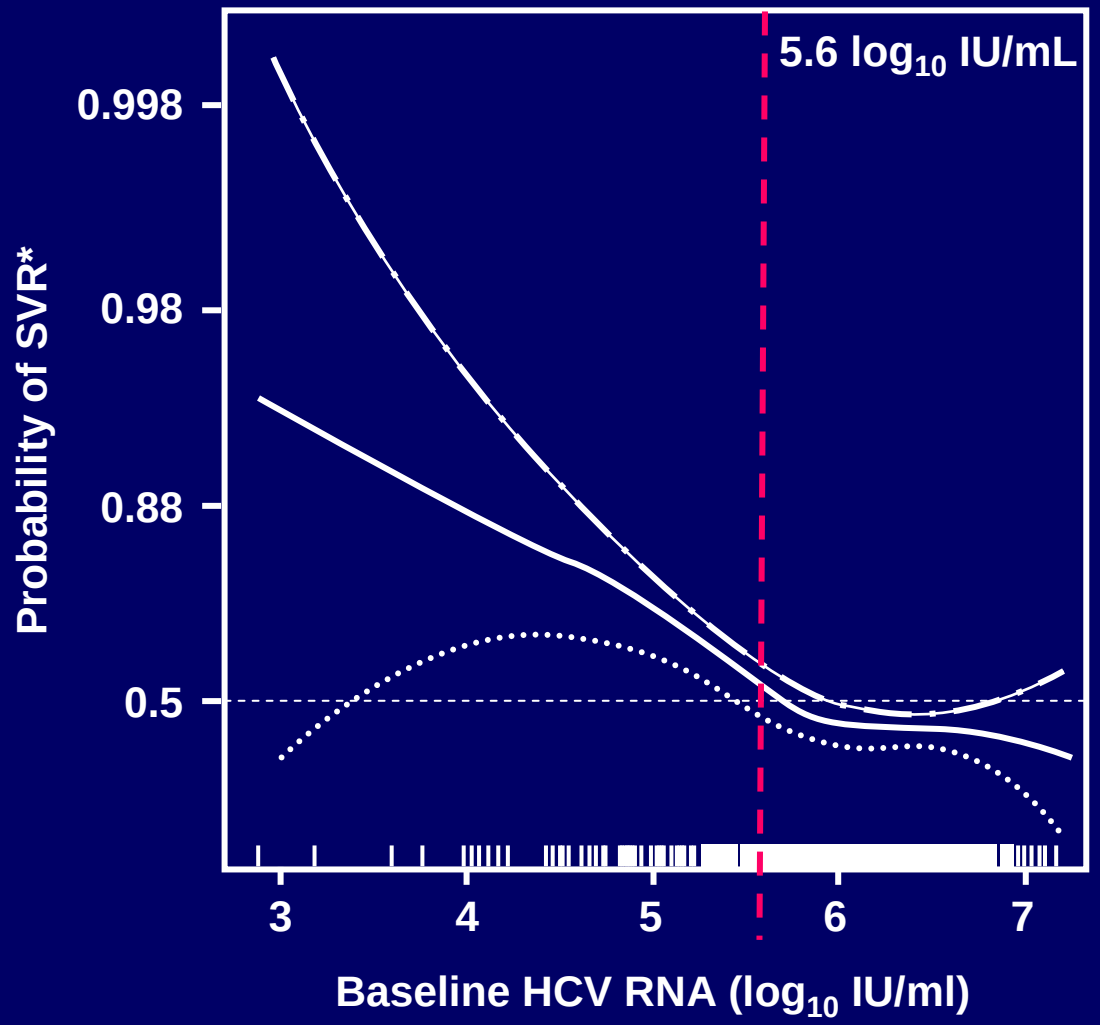
- Acute hepatitis C
  - Prevent chronification
- Chronic hepatitis C
  - Improves HRQoL
  - Prevents progression of disease (cirrhosis, HCC)
  - Is durable (95-100% for > 10 years)
  - Reduces mortality

Baseline parameters as predictors for sustained virologic response

Pretreatment Factors Associated with Sustained Virologic Response

- HCV genotype
- Baseline viremia
- γ-GT
- Histology
- Insulin resistance
- ALT quotient
- Race
- Age
- Gender
- …..

Effect of pre-treatment HCV RNA on sustained virologic response rates



*Logit scale

5.6 $\log_{10}$ IU/mL ~400 x10^3 IU/mL

Zeuzem et al., AASLD 2007

Pretreatment Factors Associated with Sustained Virologic Response

- HCV genotype
- Baseline viremia
- γ-GT
- Histology
- Insulin resistance
- ALT quotient
- Race
- Age
- Gender
- …..

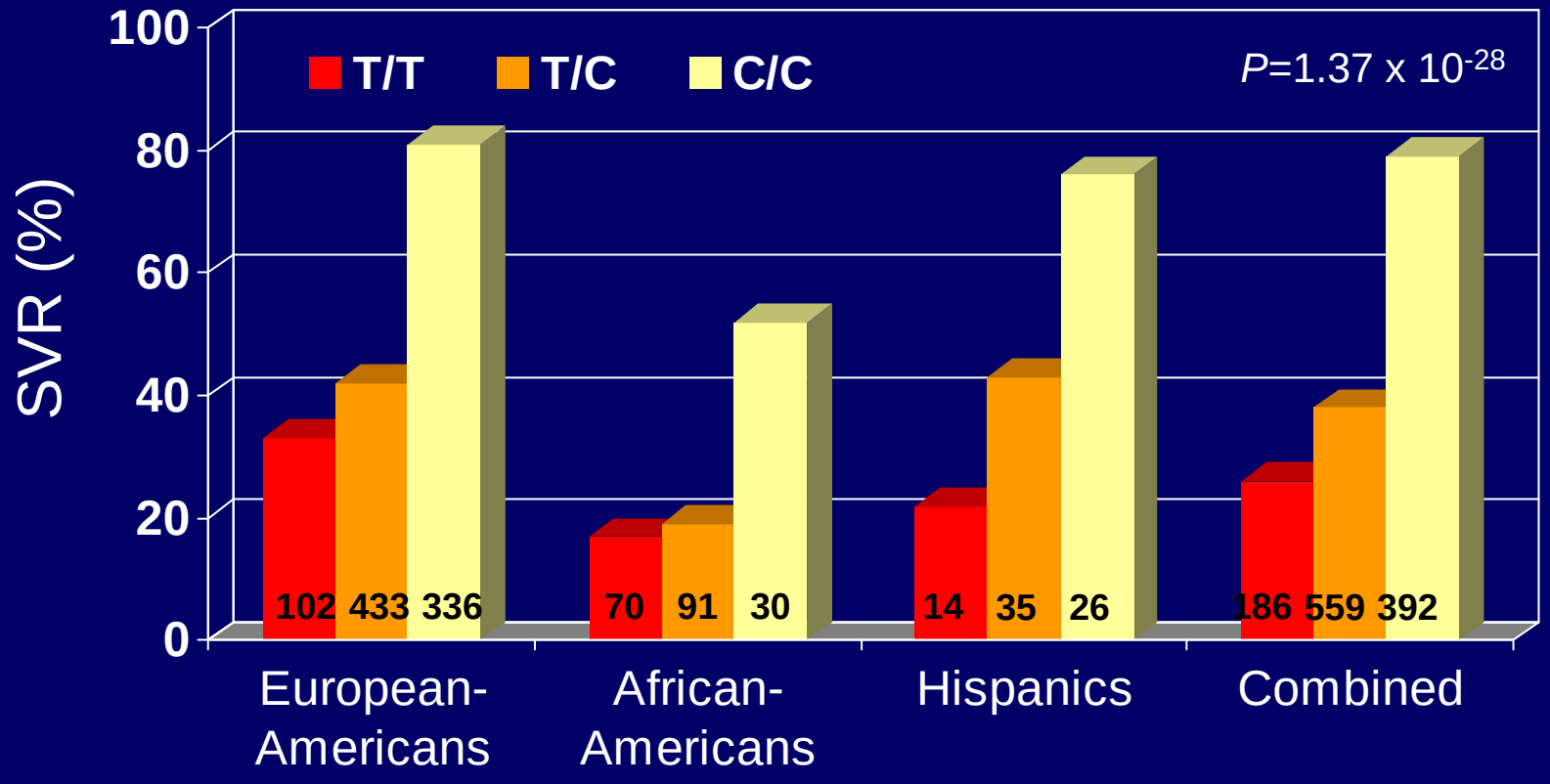
Viral genetics

- NS5A (ISDR)
- Resistant mutants (STAT-C)

Host genetics

- *IL28B* genetic polymorphism

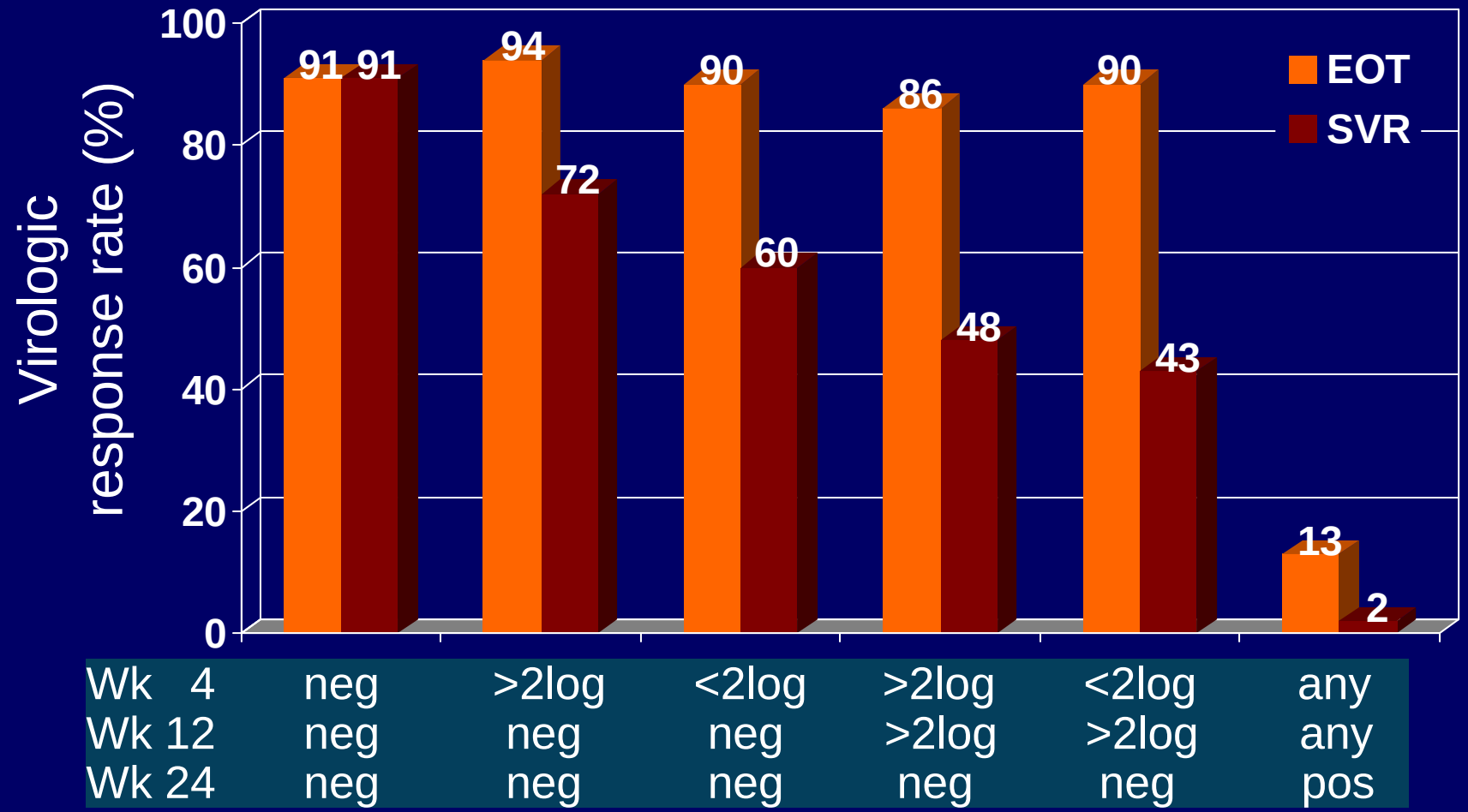
Genetic variation in *IL28B* (rs12979860) predicts SVR in HCV-1



Ge et al., Nature 2009 epub ahead

Initial viral decline as predictor for sustained virologic response

Predicting virologic response in patients (HCV-1) treated with PEG-IFN alfa-2a + RBV



Ferenci et al., *J Hepatol* 2005;43:425-433

Predictive Value of Initial Kinetics is Independent of Baseline Parameters

	Single Variable Analysis		Multi Variable Analysis	
	Odds Ratio	P-value	Odds Ratio	P-value
Gender (Female)	--	NS	--	NS
Age (< 42 years)	2.1	0.001	--	NS
Weight (< 75 kg)	2.1	<0.0001	--	NS
HCV Genotype (2-3)	4.2	<0.0001	--	NS
Baseline VL (< $2x10^6$)	2.8	<0.0001	2.8	0.003
Early response (RVR)	59.7	<0.0001	38.7	<0.0001

Logistic Regression Predicting Sustained Viral Response

Neumann, Zeuzem et al., AASLD 2000

RVR is an important predictor of SVR

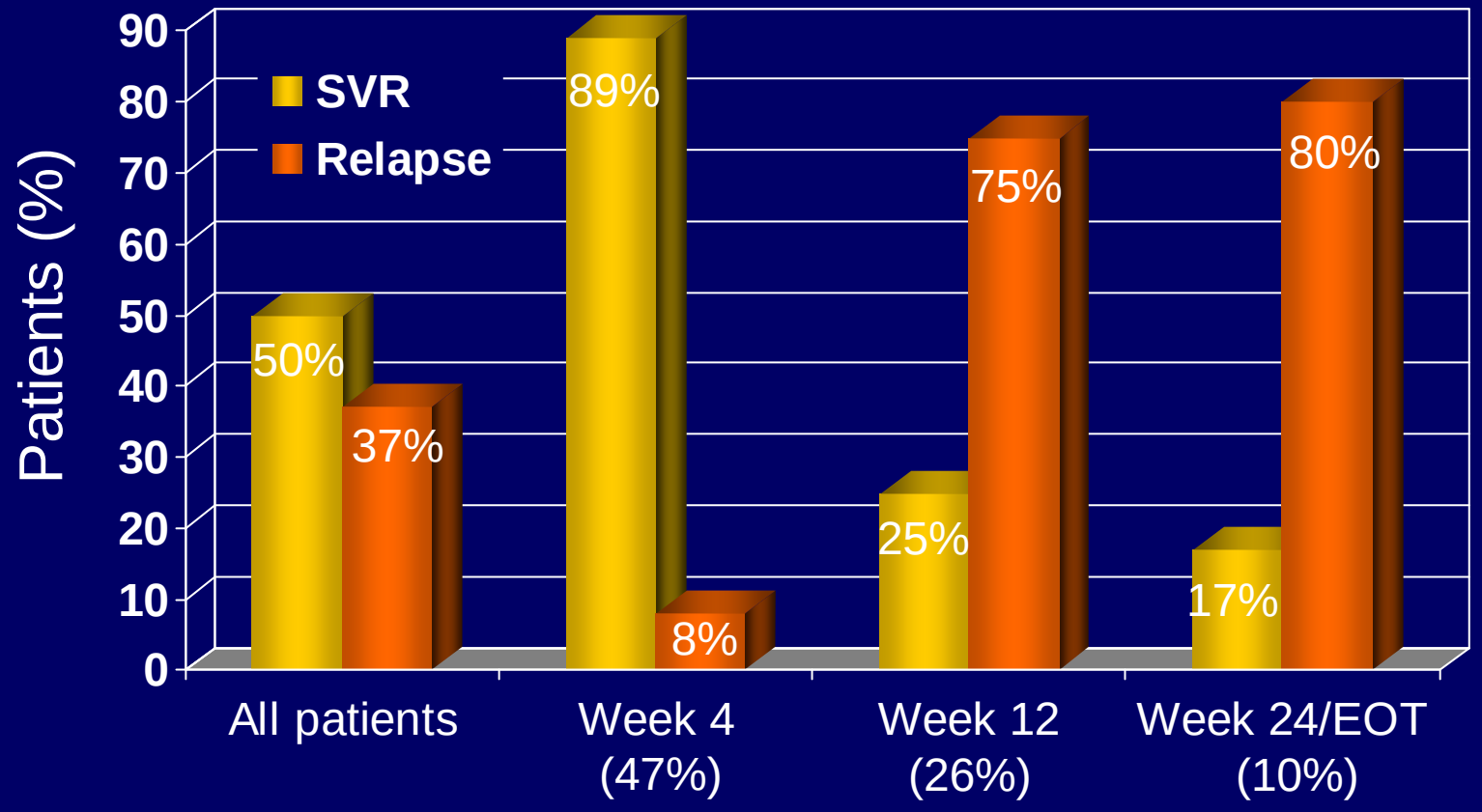
Subanalysis of 3 phase III trials	HCV-1 (N=569)	HCV-2 (N=395)	HCV-3 (N=426)	HCV-4 (N=24)
RVR	16%	71%	60%	36%
cEVR	42%	24%	29%	46%
pEVR	20%	1%	3%	8%
SVR	49%	77%	68%	79%
SVR in patients with RVR	**88%**	**86%**	**86%**	**100%**
SVR in patients with cEVR*	68%	61%	54%	91%
SVR in patients with pEVR**	29%	-	-	-

* not including RVR; ** not including RVR or cEVR

Fried et al., EASL 2008

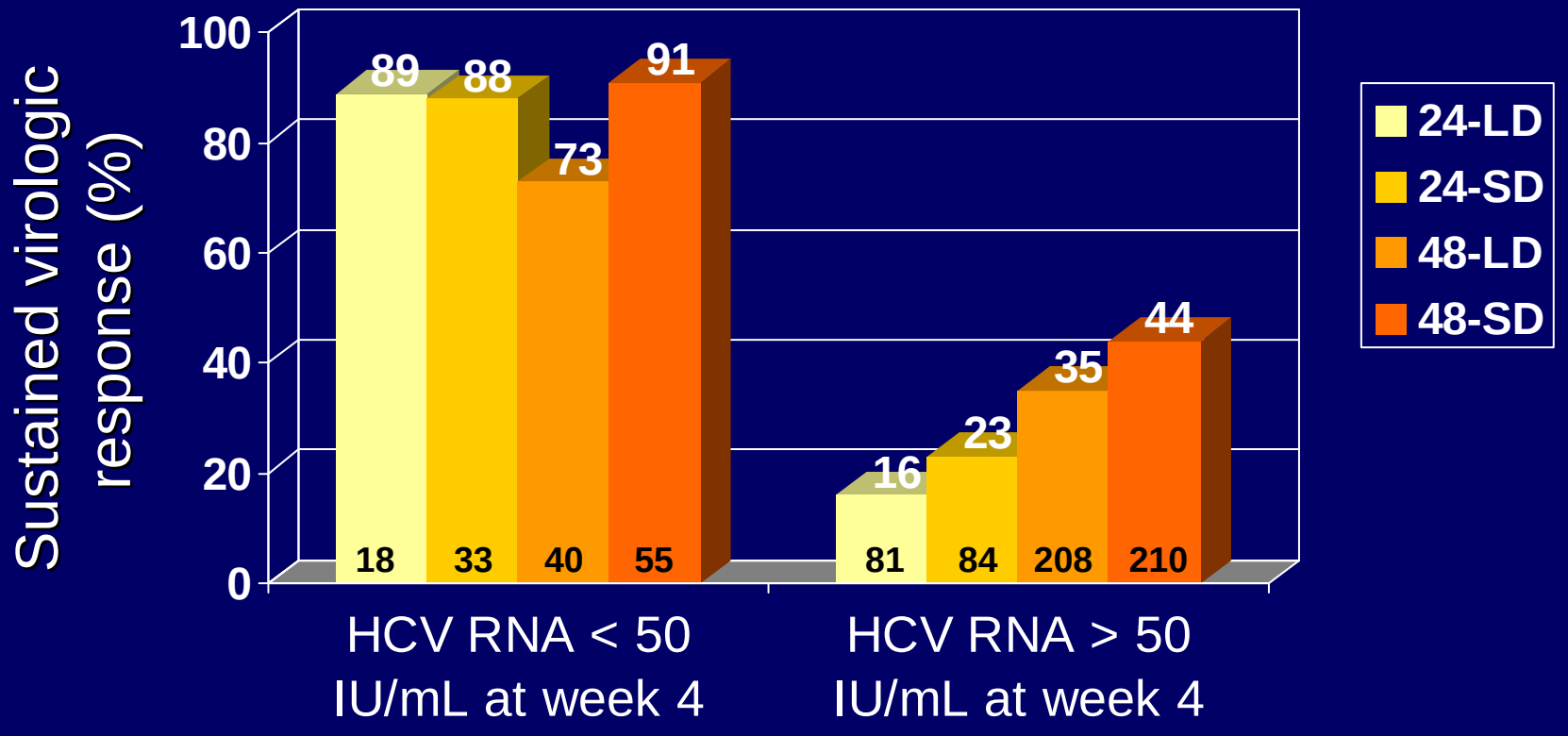
Individualization of Treatment

Virologic response in patients with HCV-1 and HCV RNA < 600,000 IU/mL



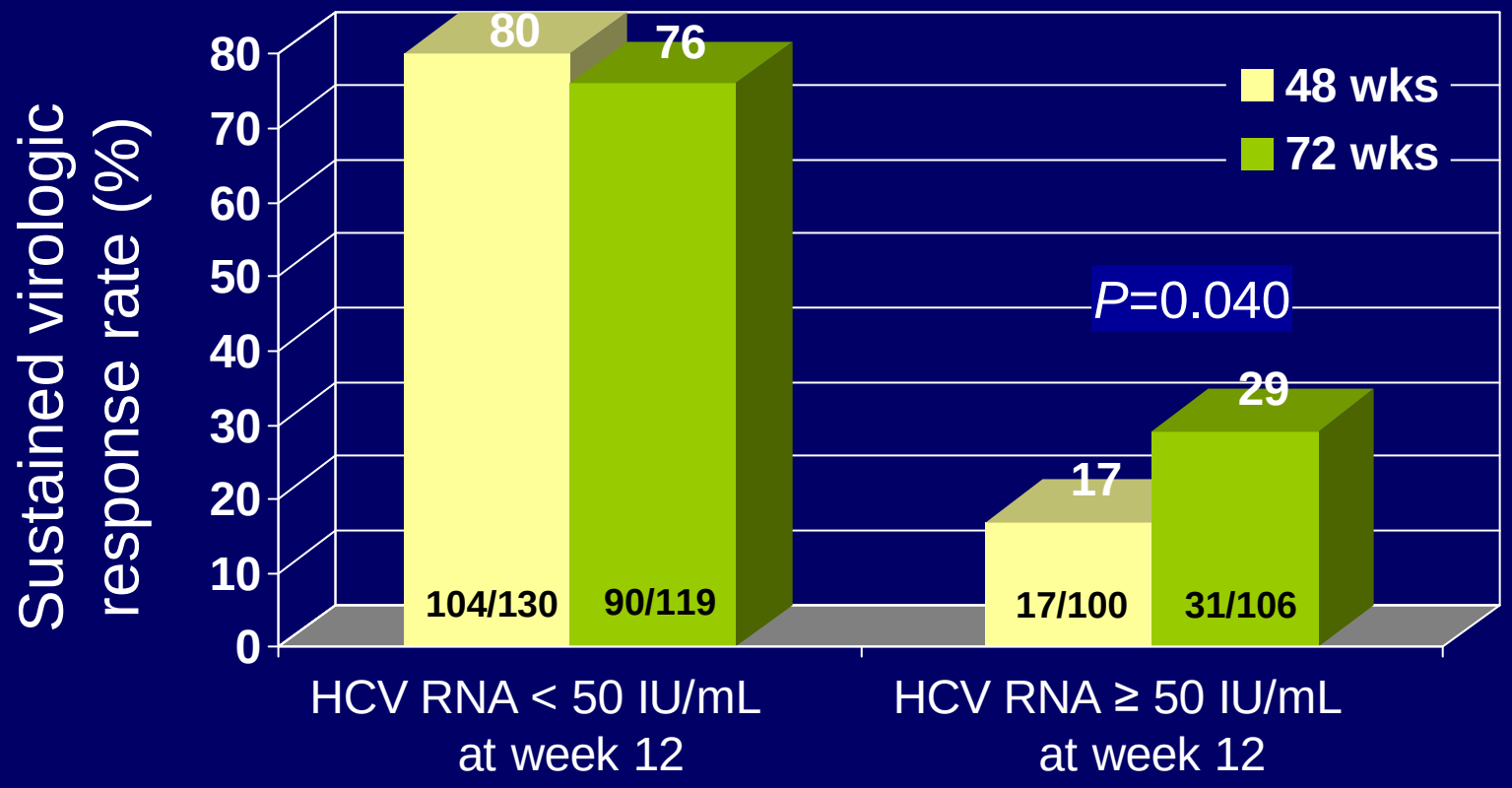
Zeuzem et al., *J Hepatol 2006*

Early identification of HCV 1 patients responding to 24 wks PEG-IFN alfa-2a/RBV



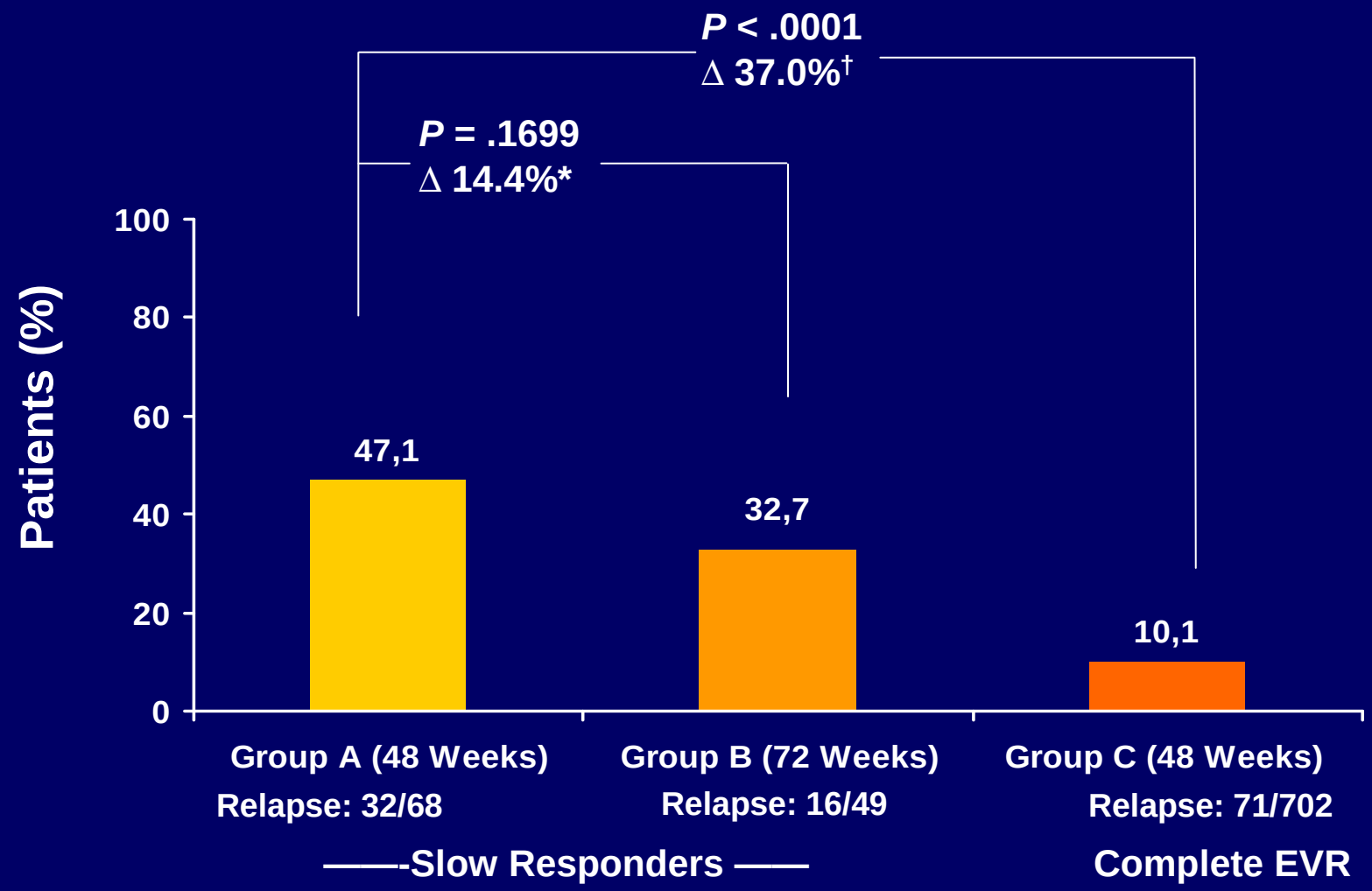
Jensen et al., *Hepatology* 2006;43:954-60

Extended treatment duration for HCV 1: 48 vs 72 weeks of PEG-IFN alfa-2a + RBV



Berg, et al. *Gastroenterology* 2006;130:1086-1097

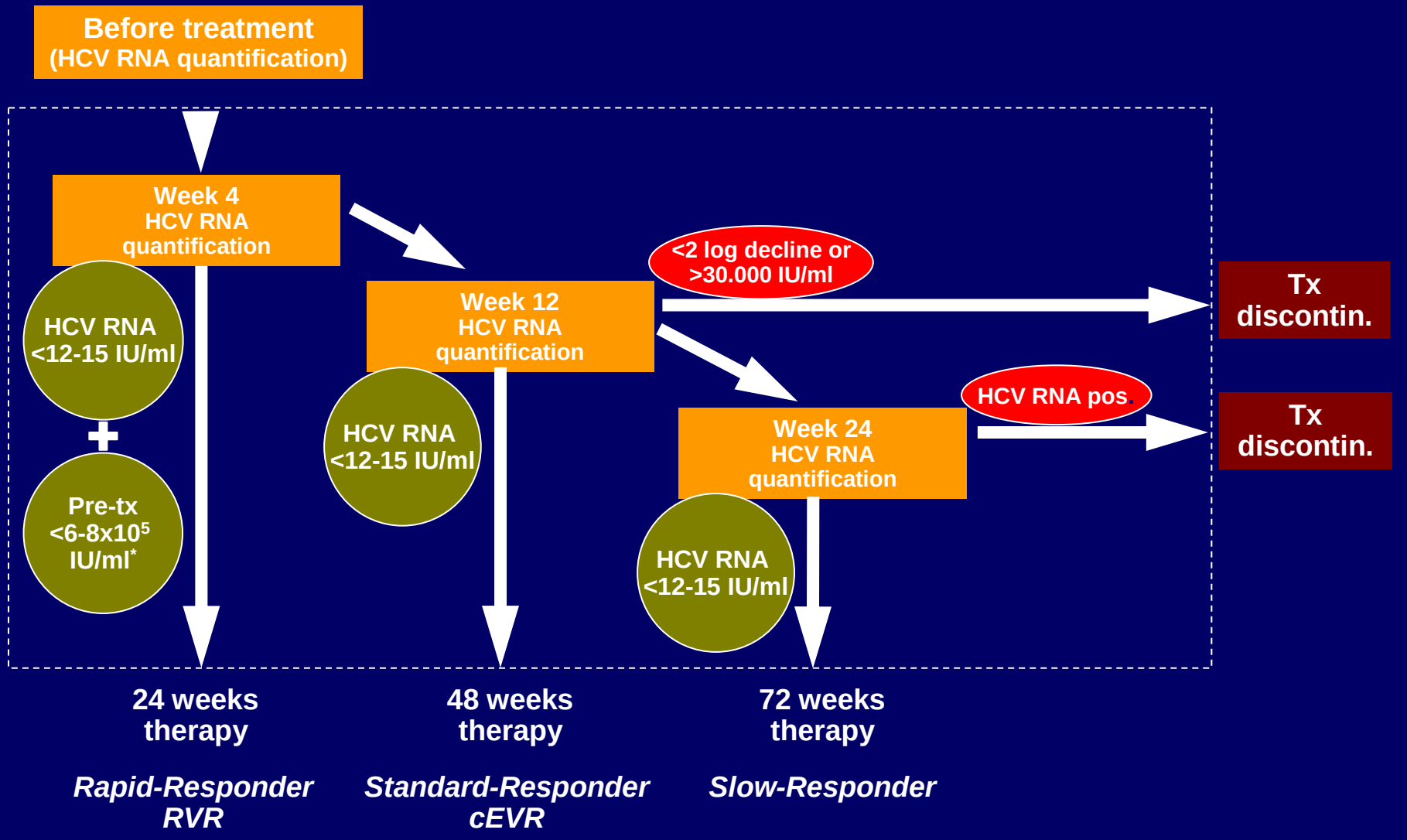
Relapse rates for 48- and 72-week treatment groups in slow responders (SUCCESS Study)



*95% CI: –3.3%, 32.1%.
†95% CI: 24.9%, 49.0%.

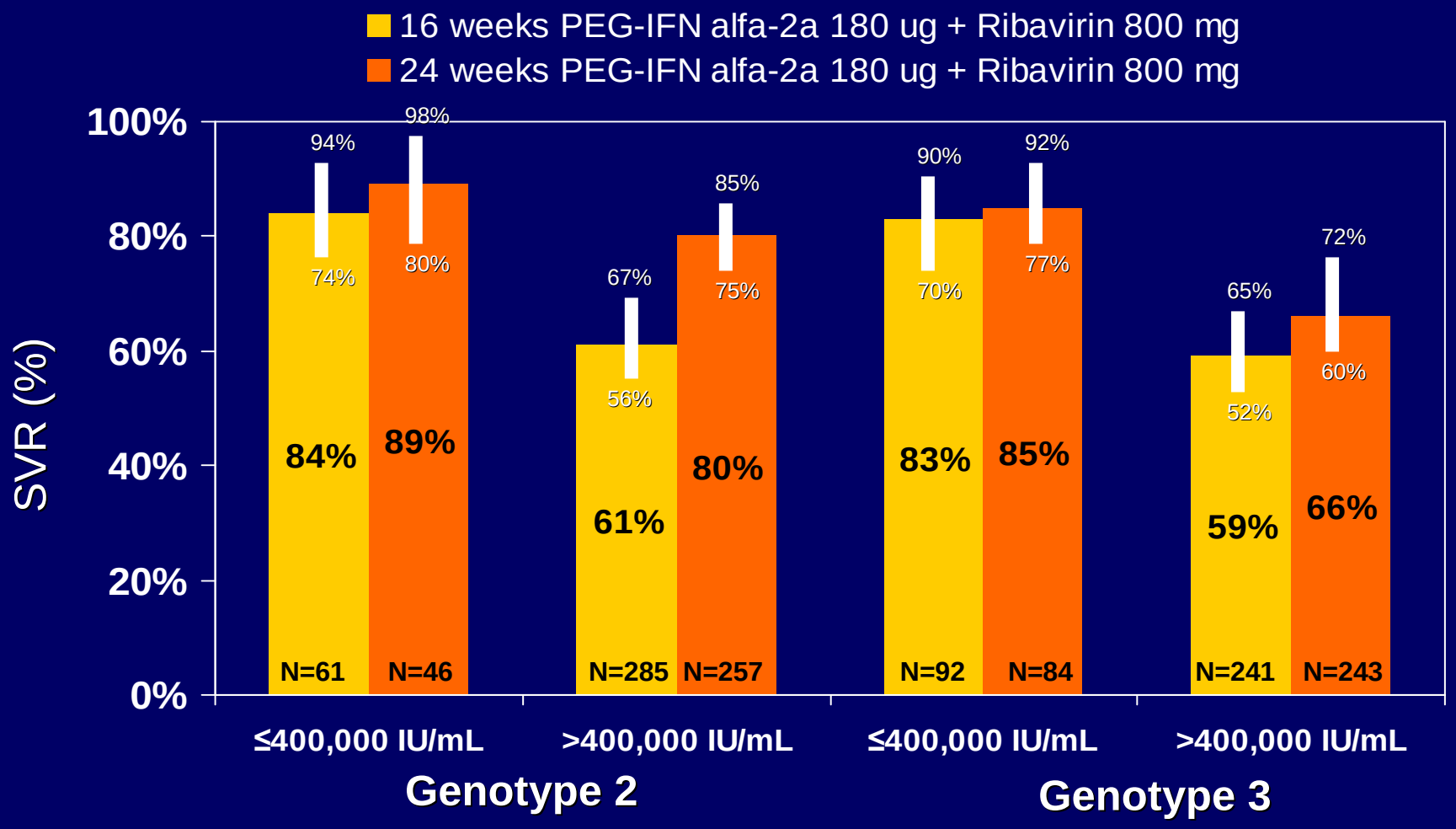
Buti et al., EASL 2009

Standard treatment for HCV genotype 1/4



* No treatment shortening in patients with advanced fibrosis, cirrhosis, metabolic syndrome, insulin resistance, HIV/HCV coinfection, etc. No data for patients with persistently normal ALT levels.

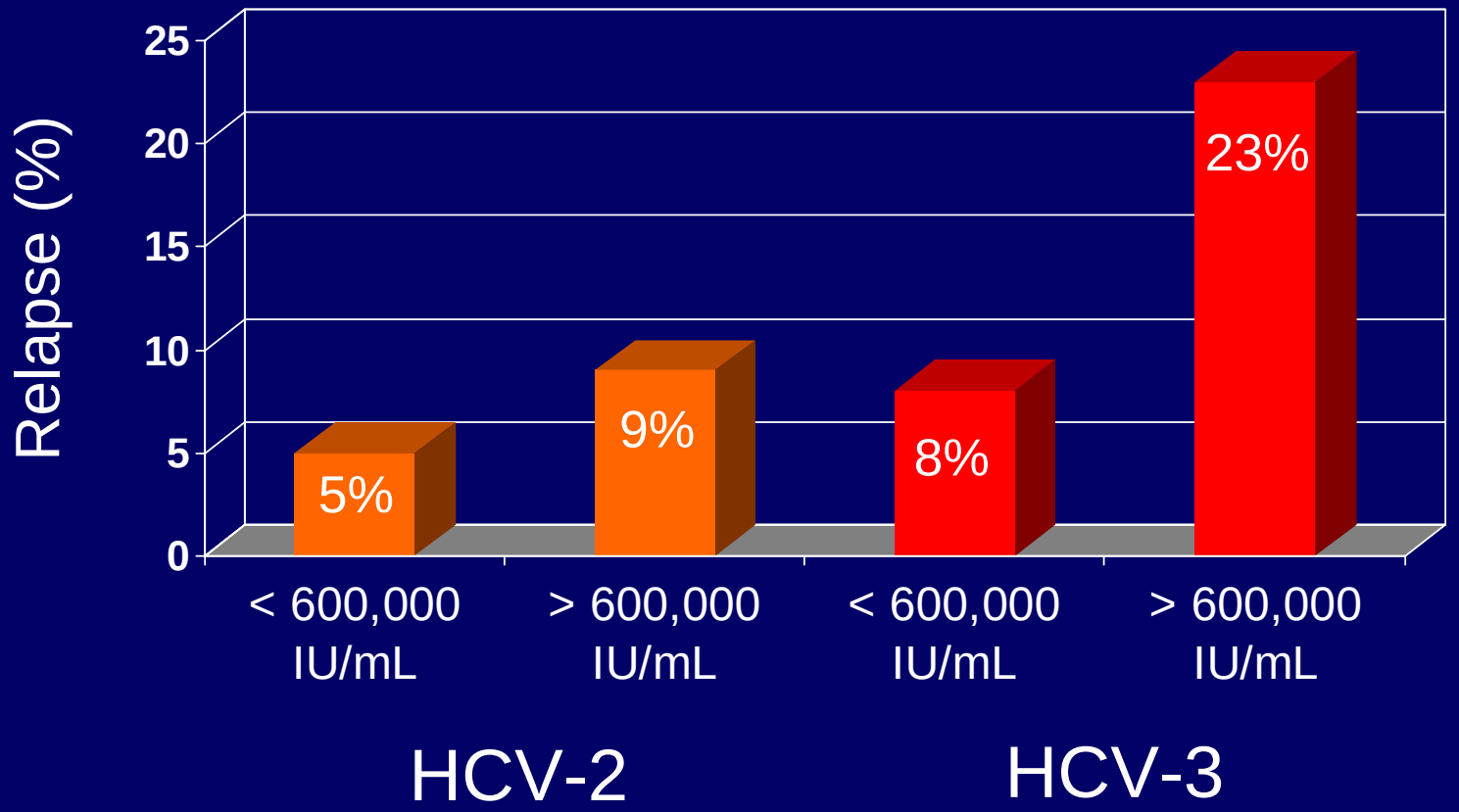
PEG-IFN alfa-2a + RBV for 16 or 24 weeks in HCV-2 and -3 (ACCELERATE Study)



Standard population; VR = HCV RNA < 50 IU/mL

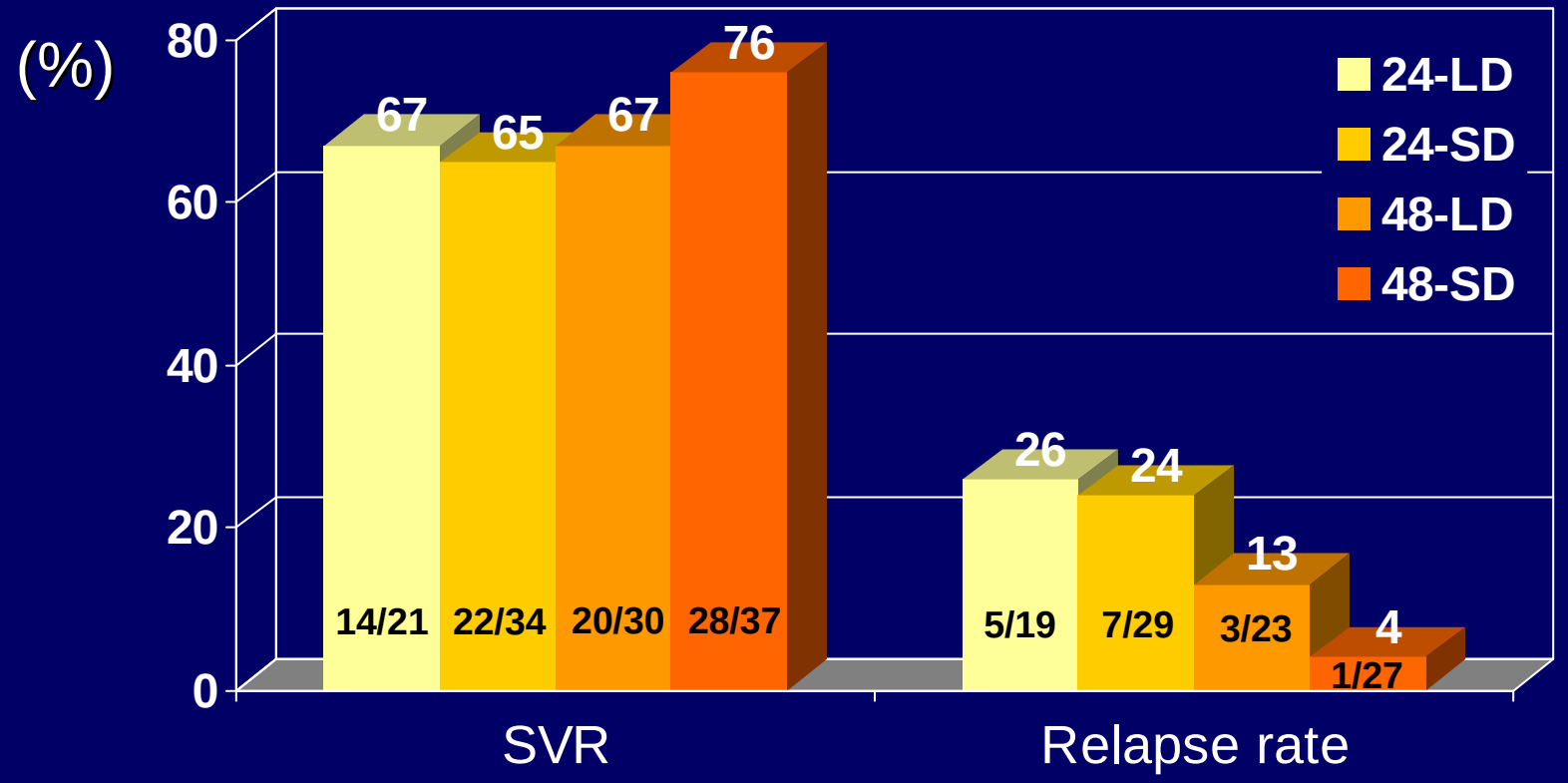
Shiffman et al., NEJM 2007

Relapse rate by HCV genotype and baseline viral load in patients treated for 24 weeks (Peg-IFN alfa-2b + RBV)



Zeuzem et al., *J Hepatol* 2004

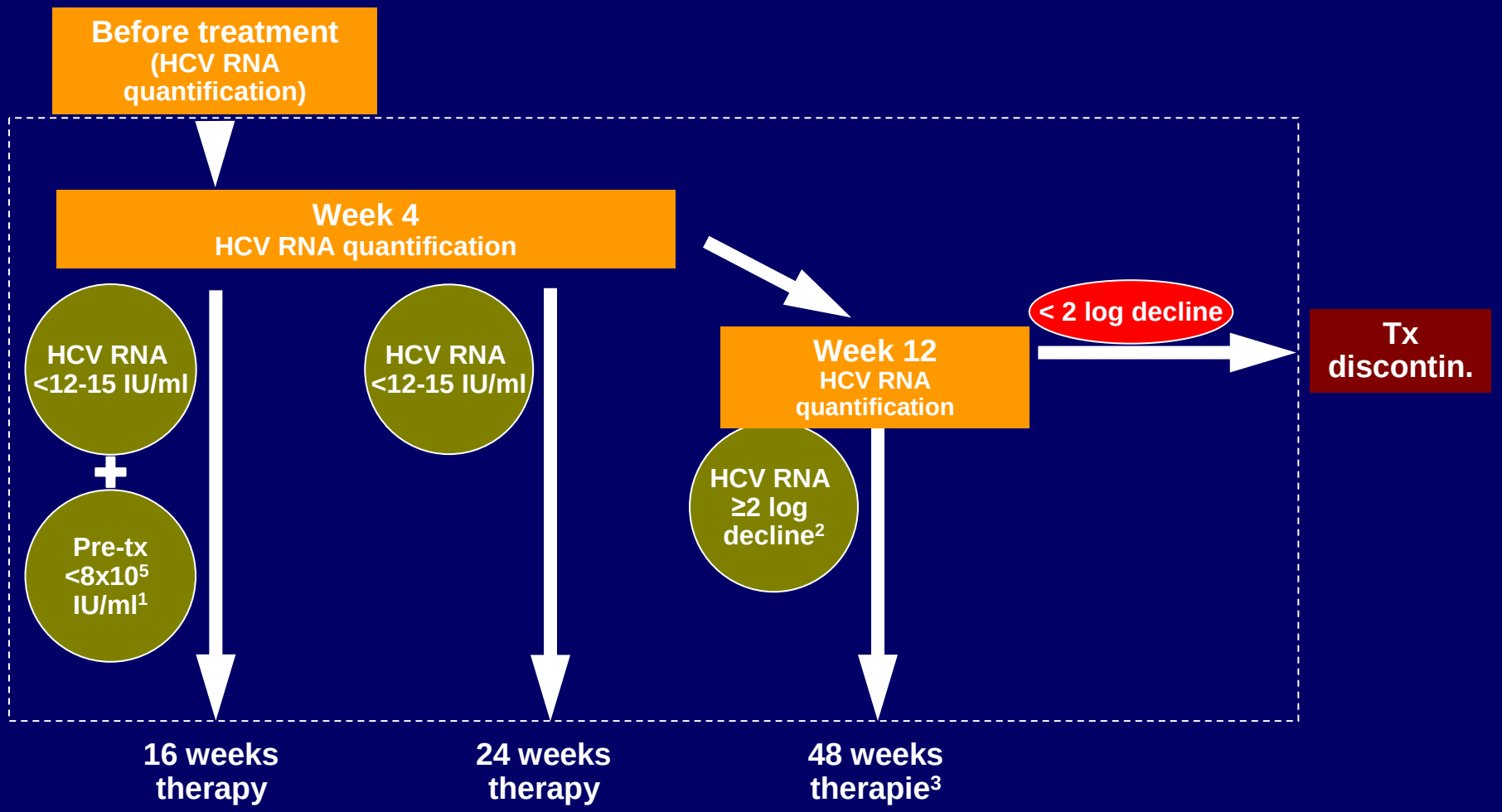
Response rates in HCV-2 and 3 infected patients without RVR (> 50 IU/mL at wk 4)



Peginterferon alfa-2a 180 µg/wk
RBV 800 mg/d vs 1000-1200 mg/d

Hadziyannis et al., *Ann Intern Med* 2004
Fried et al., *N Engl J Med* 2002
Willems et al., *DDW* 2007

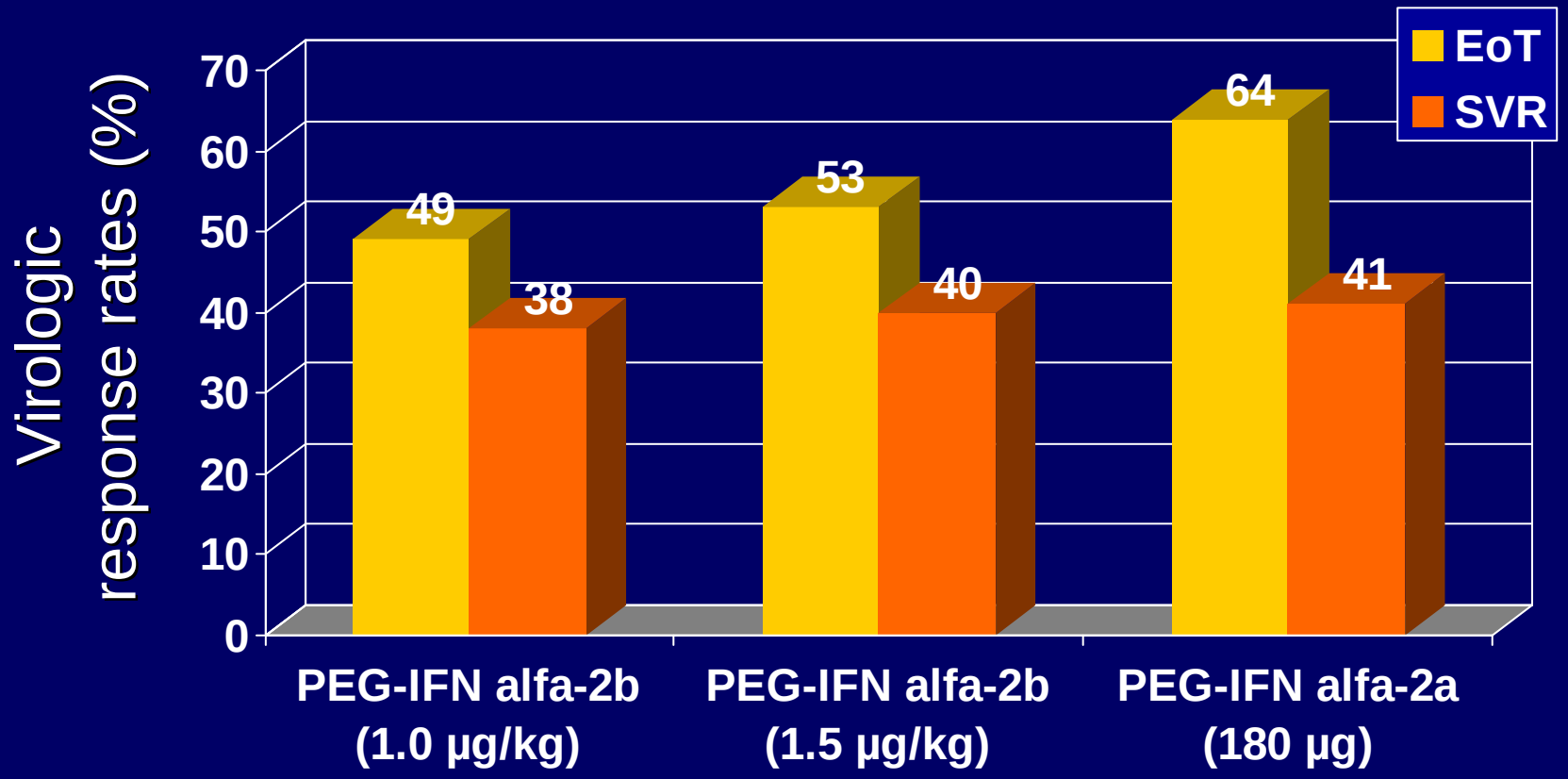
Standard treatment for HCV genotype 2/3



1. No treatment shortening in patients with advanced fibrosis, cirrhosis, metabolic syndrome, insulin resistance, HIV/HCV coinfection, etc. No data for patients with persistently normal ALT levels.
2. Detectable HCV-RNA at week 24: discontinuation of treatment.
3. Treatment duration of 36, 48, 72 weeks in „slow-responders“ is currently investigated in prospective trials.

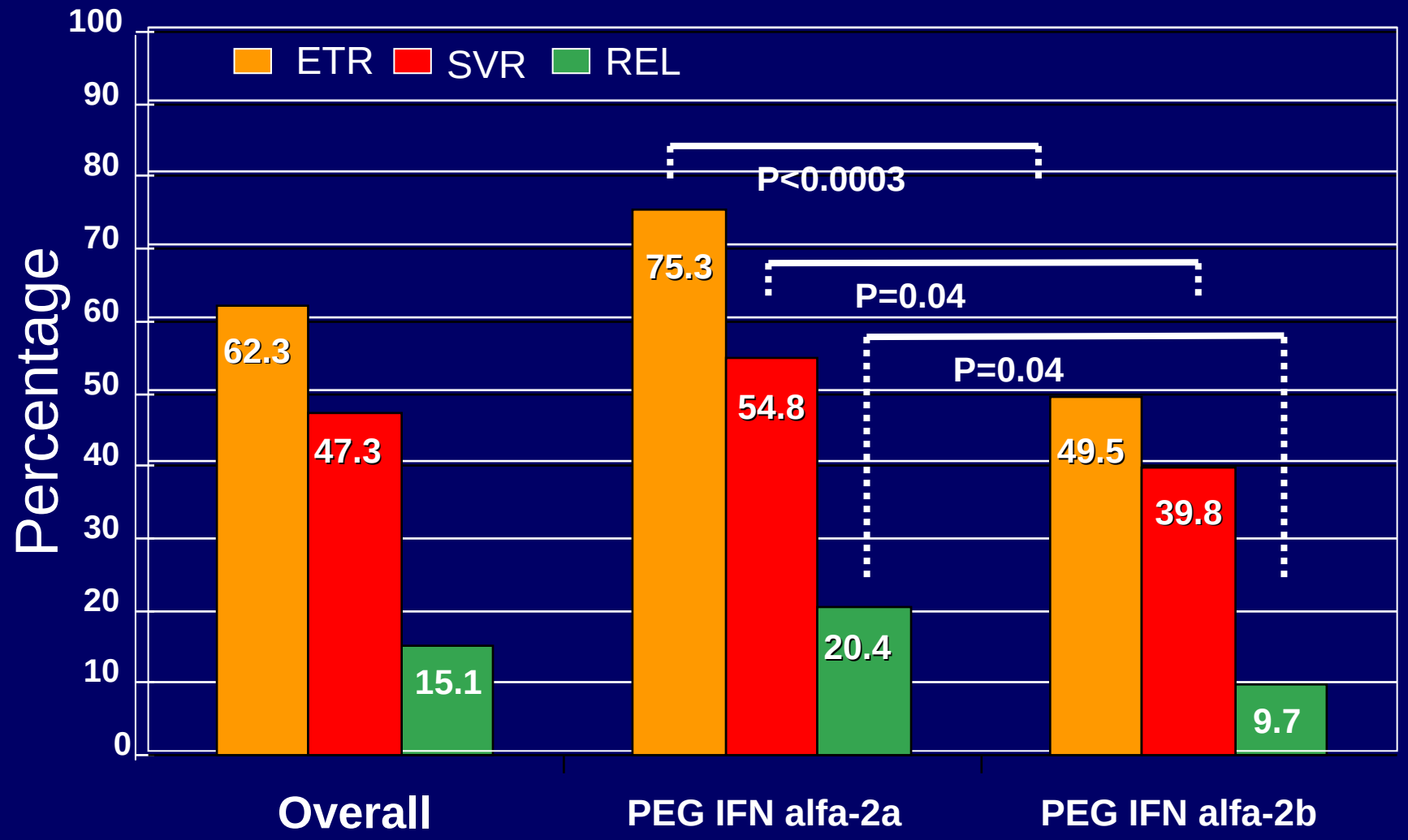
Comparison between Peginterferon alfa-2a and -2b

Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL study)



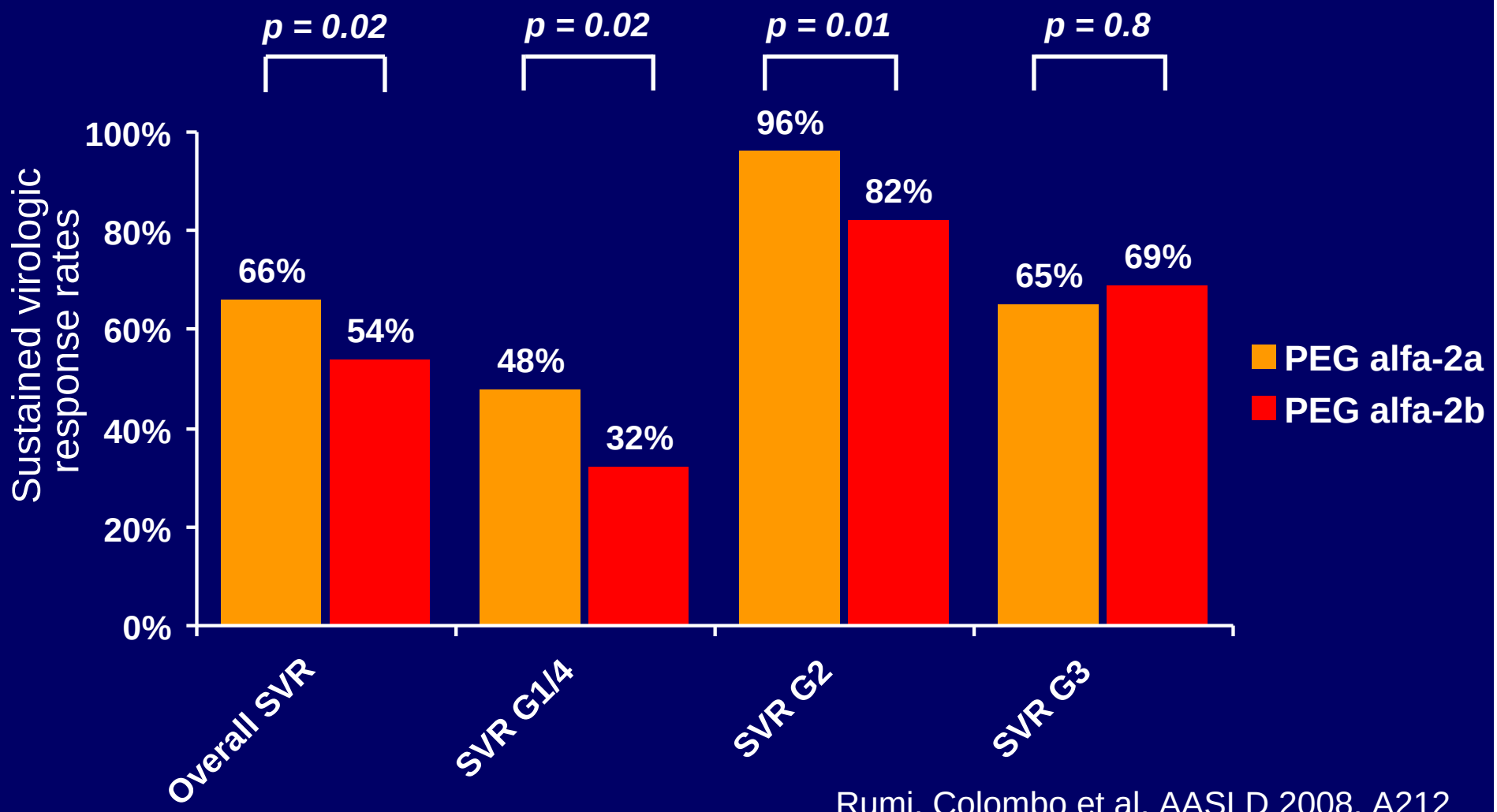
Mc Hutchison et al., *N Engl J Med* 2009

Virologic response in HCV genotype 1 or 4 infected patients



Ascione et al., EASL 2008

Milan Safety Tolerability (MIST) Study



Rumi, Colombo et al, AASLD 2008, A212

Treatment decisons in real life

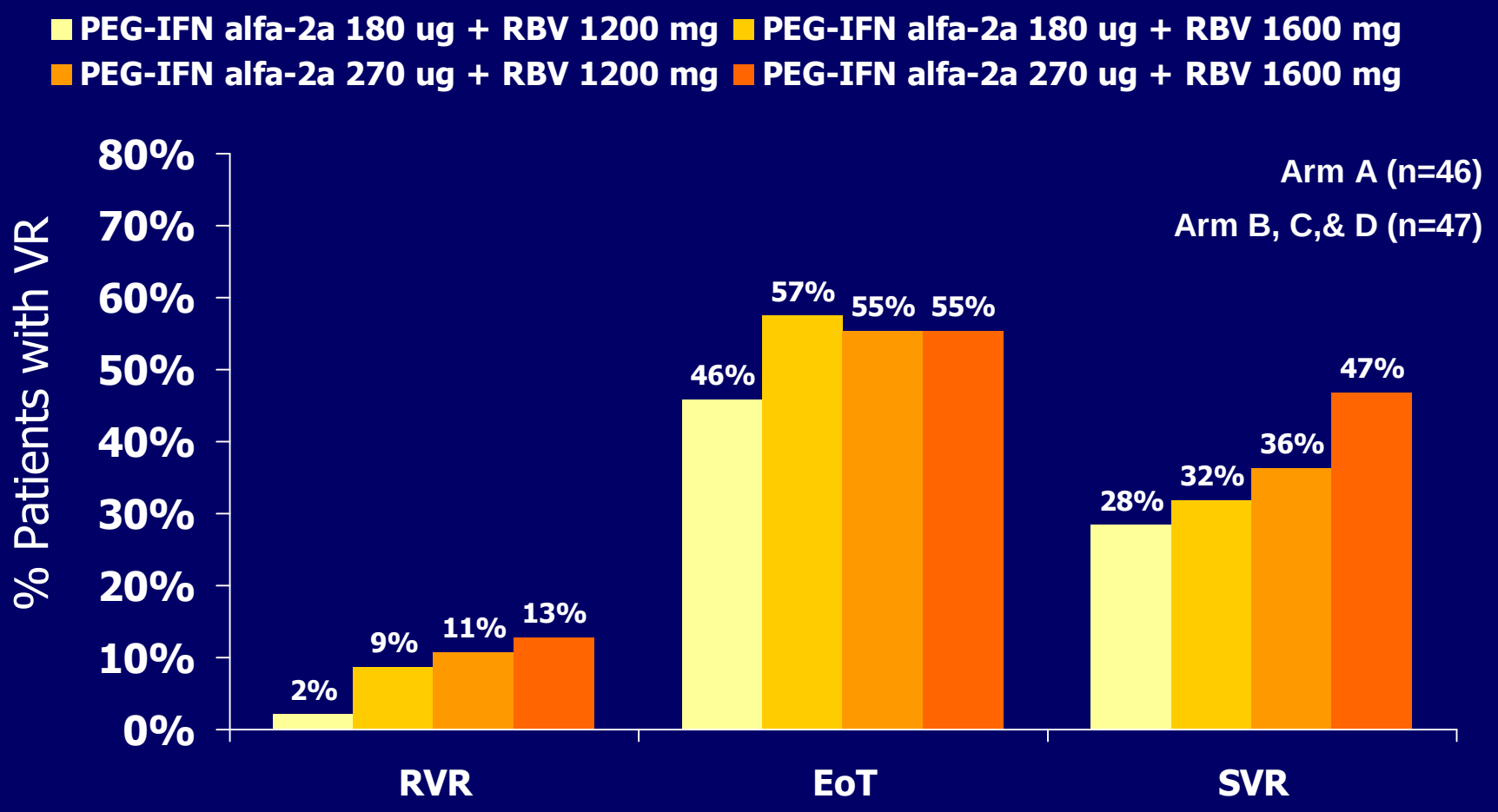
Case # 1

- HCV-1, 1.200.000 IU/mL
- 54 yrs, male, 105 kg
- Impaired glucose tolerance
- Biopsy: A2 F2 S3

Treatment considerations according to German-Austrian-Swiss Guidelines 2009

- HCV 1, HVL
  - Peginterferon alfa
  - Ribavirin 1200 mg
  - Treatment duration
    - cEVR: 48 weeks
    - pEVR: 72 weeks

Virologic Response in patients with HCV1, HVL, and > 85 kg

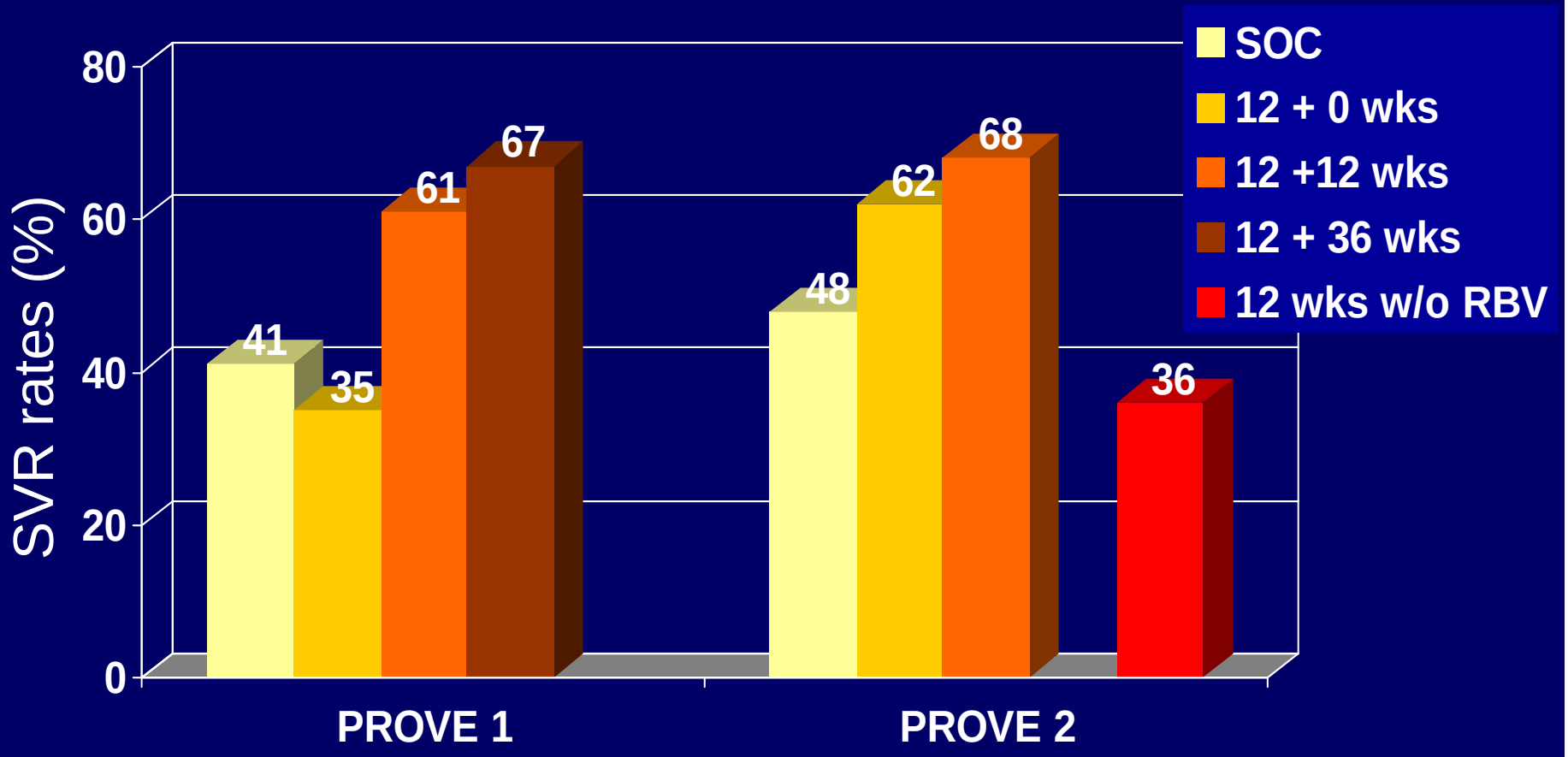


Fried et al., Hepatology 2008;48:1033-1043

Personal considerations

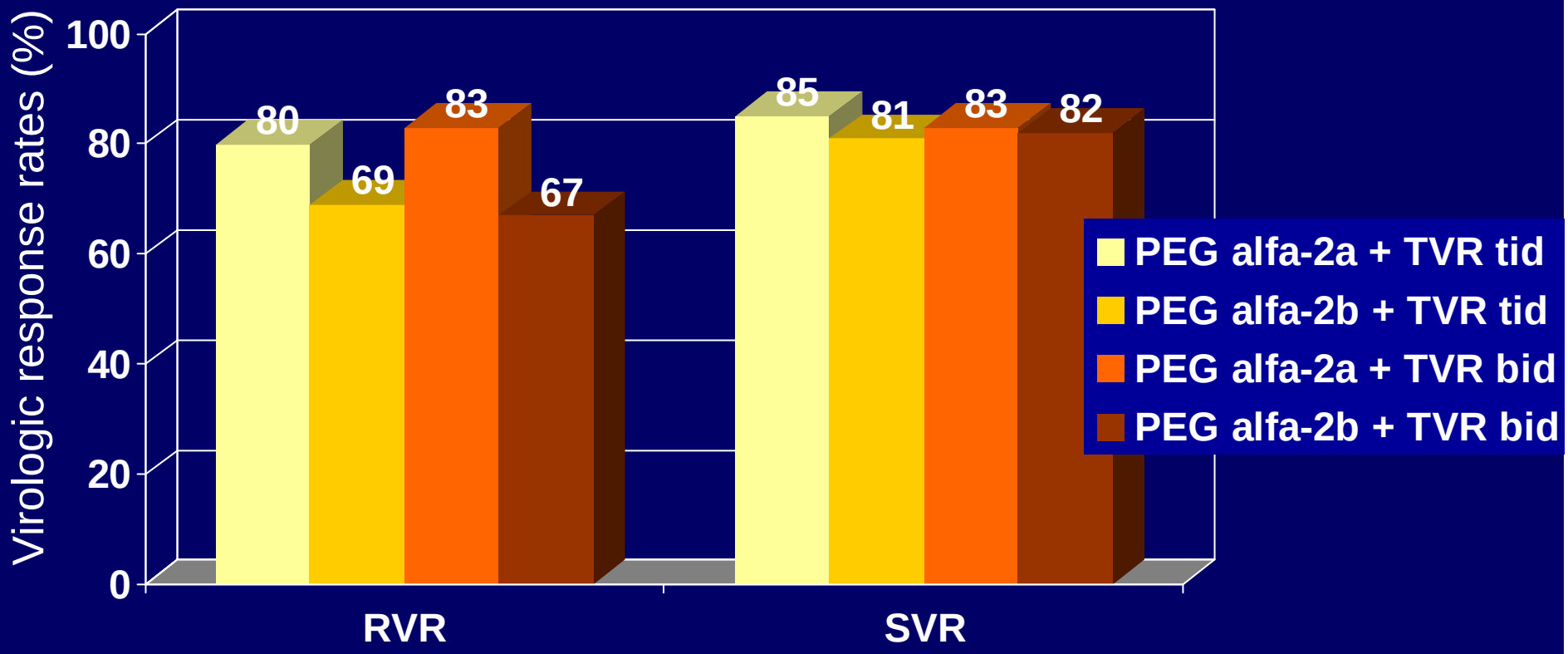
- SVR probability (HCV-1, HVL, > 85 kg) still below 50%
- Comorbidity NASH and HCV
- Reduce weight, improve glycemic control
- Consider treatment with PEG/RBV plus STAT-C (Protease-Inhibitor) 2011/12

SVR rates with PegIFN, RBV and Telaprevir (PROVE 1 and 2 studies)



McHutchison et al., *NEJM* 2009; Hezode, Forestier et al., *NEJM* 2009

SVR rates in C208



Marcellin et al., AASLD 2009

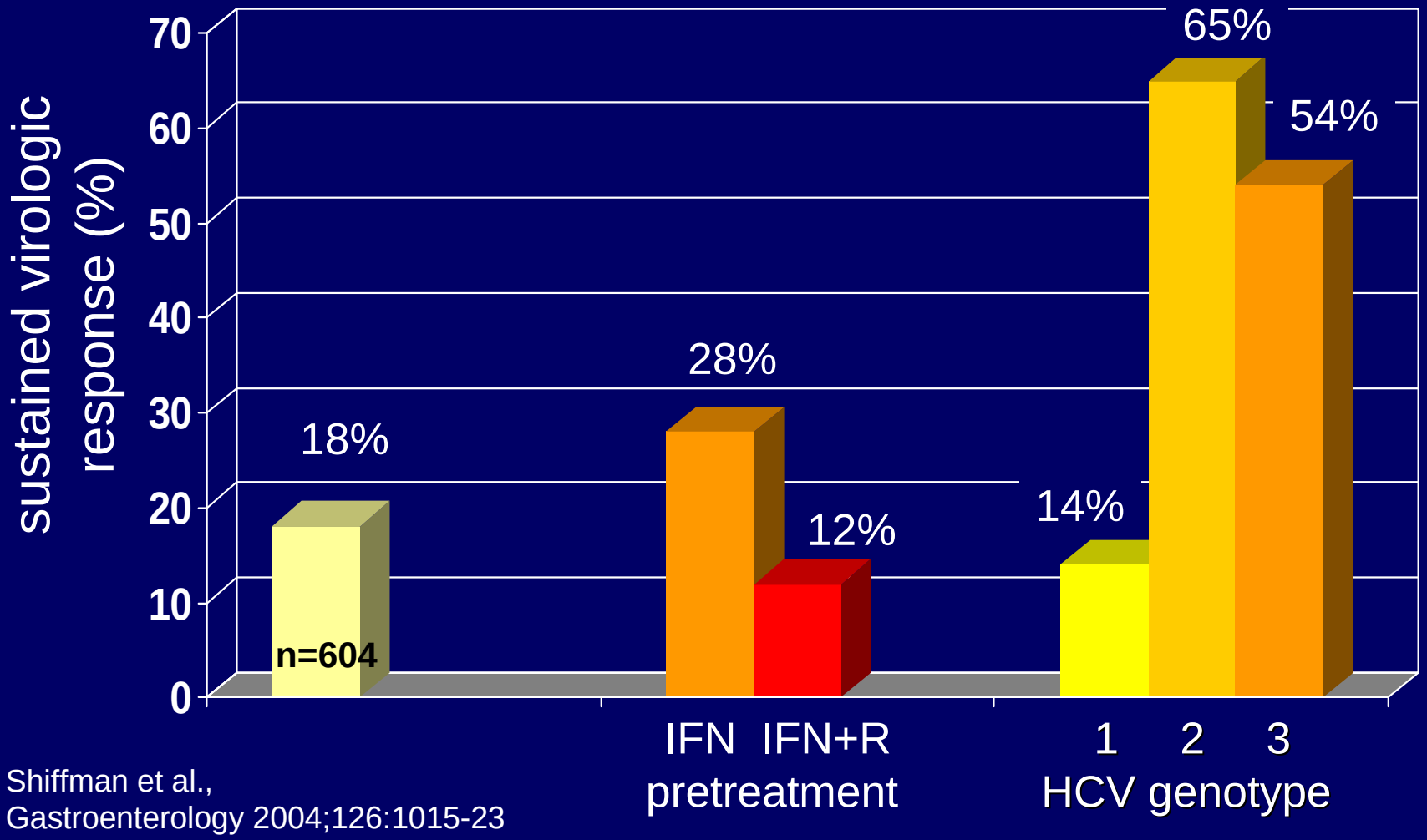
Case # 2

- HCV-3, 850.000 IU/mL
- 43 yrs, female, 68 kg
- Non-Responder to PegIFN + RBV in standard dose for 24 weeks
- Biopsy refused
- Liver Stiffness by Fibroscan: 8.7 kPa

Treatment options

- Wait for new anti-HCV drugs
- Retreat with PegIFN and RBV

PEG-IFN-α2a + ribavirin for treatment of non-responder patients (HALT-C)



Shiffman et al.,
Gastroenterology 2004;126:1015-23

Personal considerations

- Protease inhibitors in phase 3 of clinical development not active in HCV-3
- Nucleosic polymerase inhibitors only in phase 2 trials
- Possibly advanced fibrosis
- Retreatment with PegIFN and RBV
  - Standard dose PegIFN
  - Ribavirin (at least) 1000 mg/day
  - Treatment duration 48 wks

Conclusions

- HCV genotype and baseline viral load are important pretreatment predictors for SVR
- Best cut-off for BL viral load: 400,000 IU/mL
- Further evaluation of the IL28B genetic polymorphism in HCV-1 and other genotypes
- Initial viral decline (RVR) is the best on-treatment predictor of SVR
- BL viral load and VK help to define duration of therapy and to individualize antiviral strategies
- Potent new drugs in development