

# Treatment of hepatitis B and C

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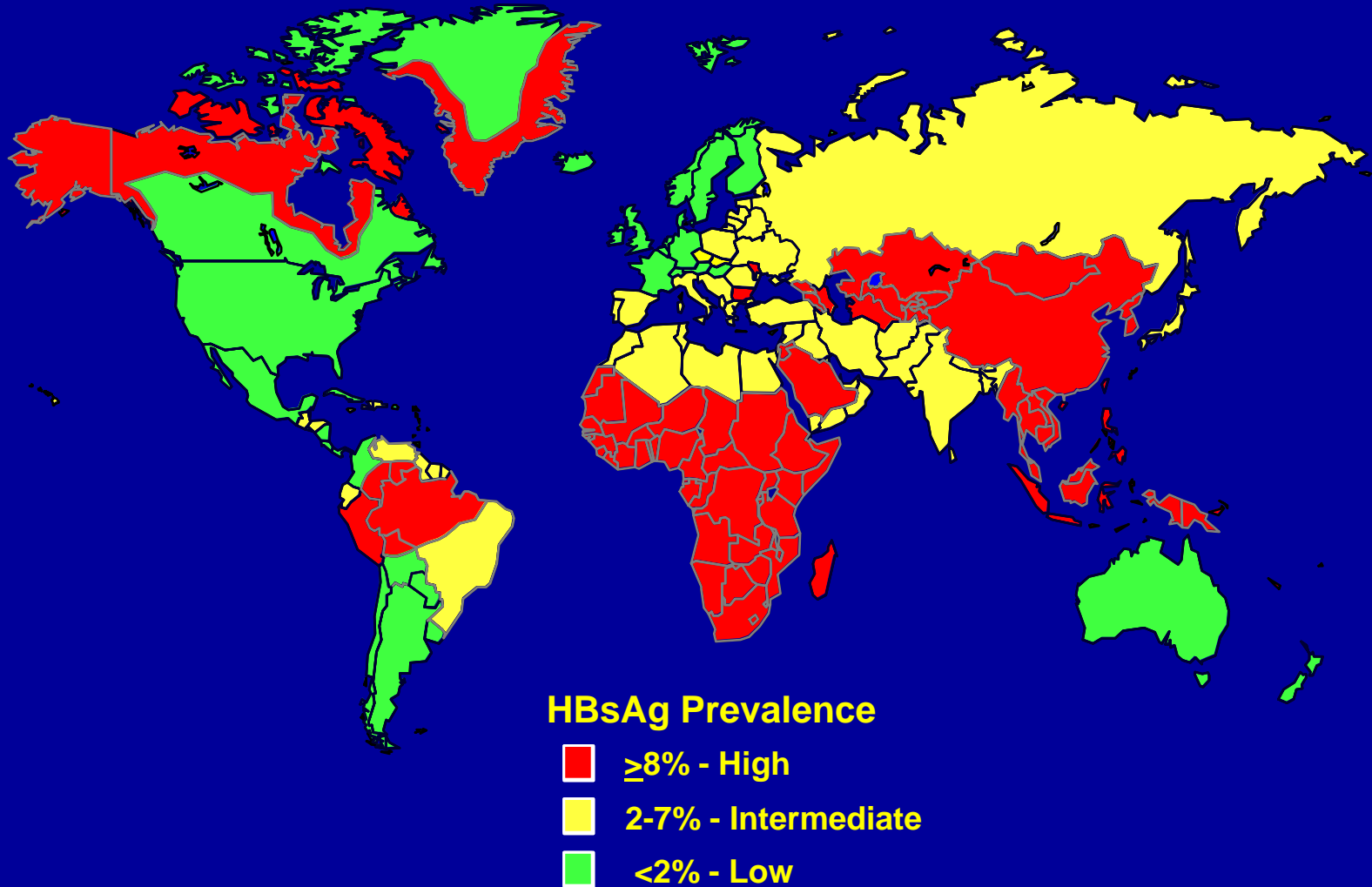
# Global Disease Burden from Bloodborne Viral Infections

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## Estimated no. chronic infections

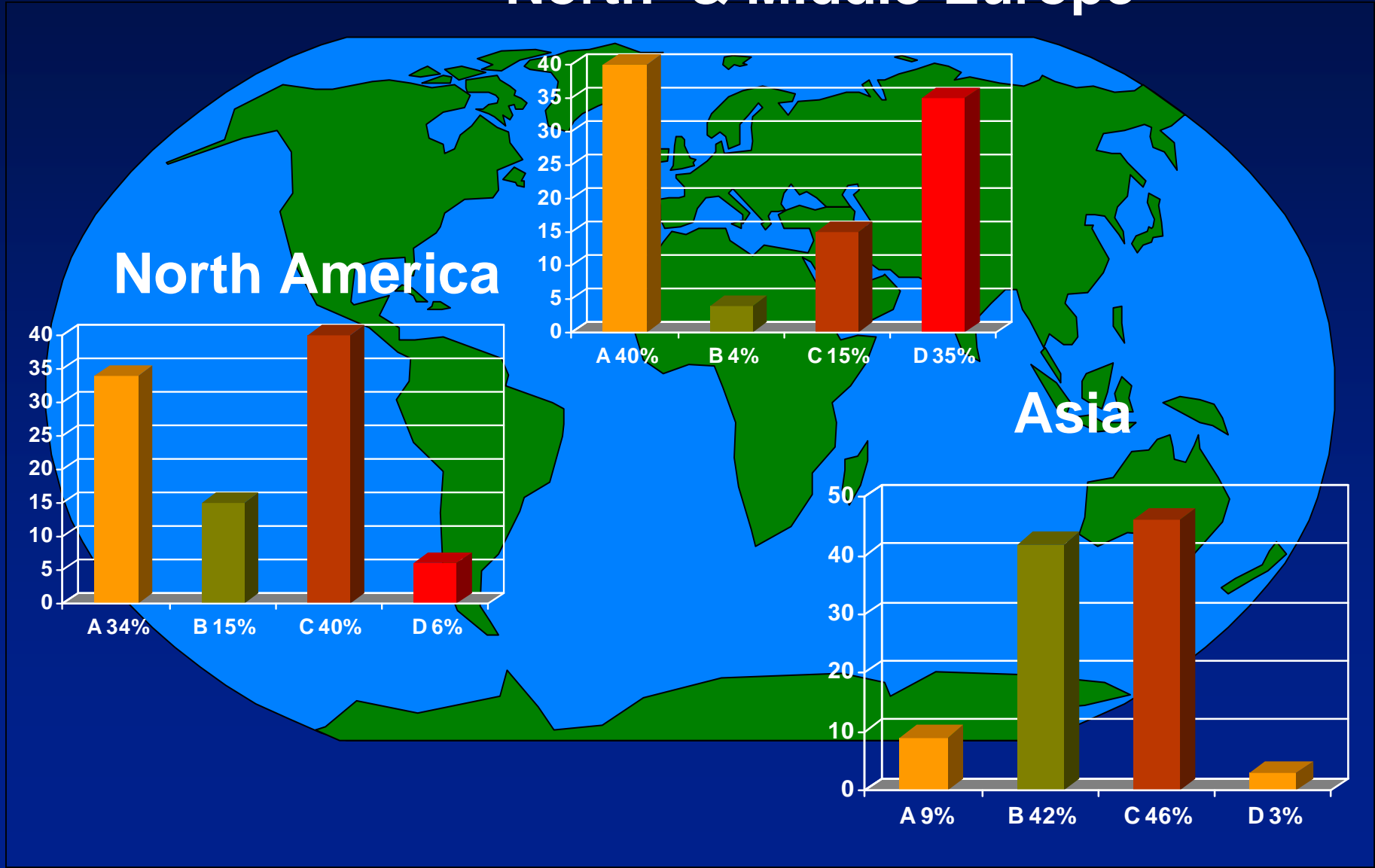
HBV	370 million
HCV	130 million
HIV	33 million
HIV/HBV	(2-4 million)
HIV/HCV	(4-5 million)

# Geographic Distribution of Chronic HBV Infection

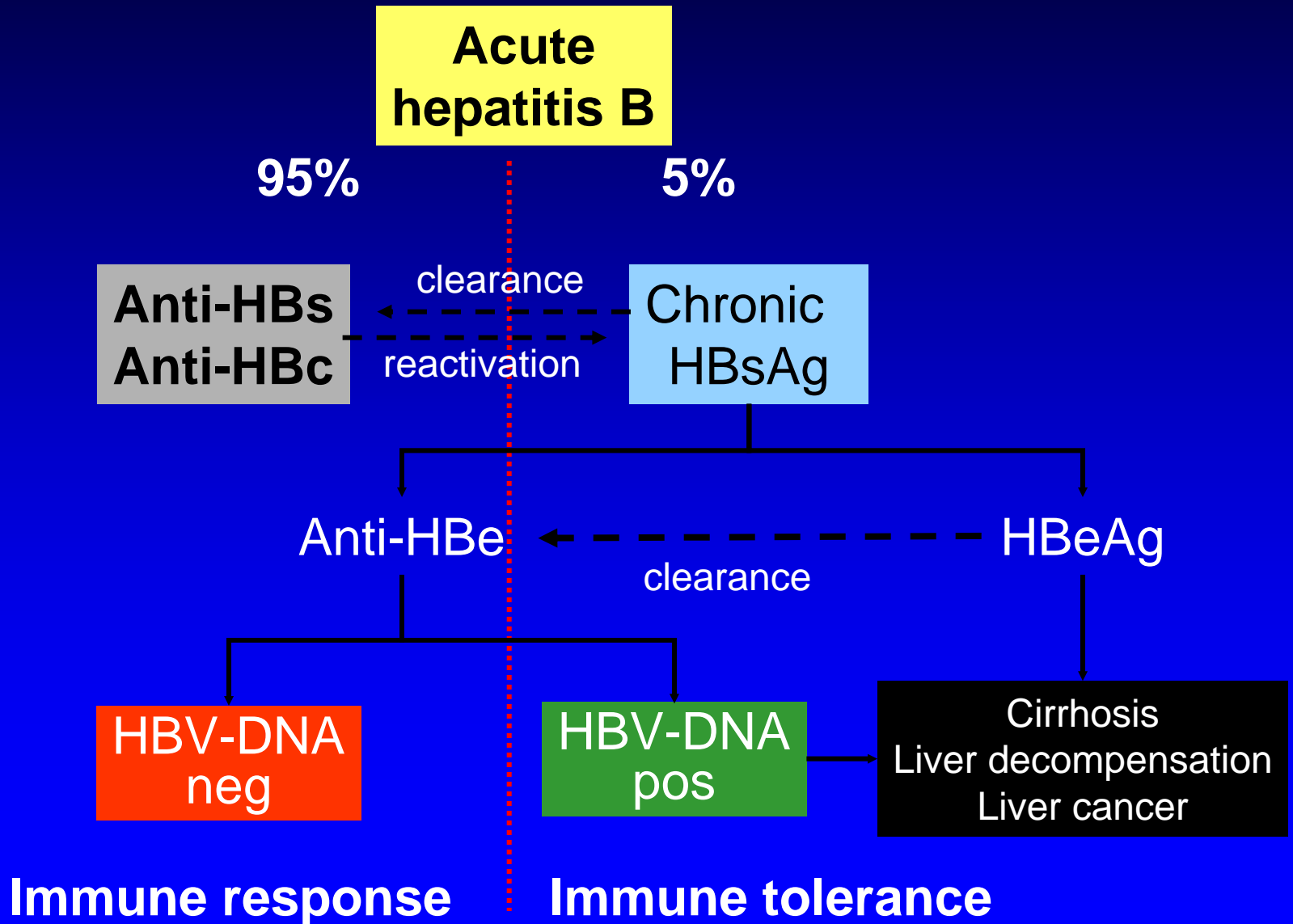


# Hepatitis B: Genotypes

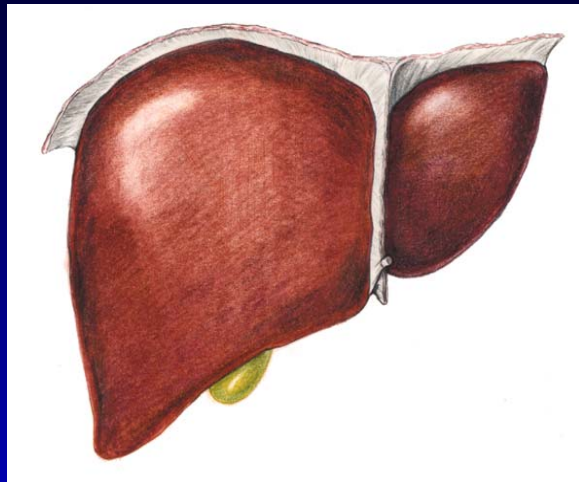
## North- & Middle-Europe



# Natural history of HBV infection



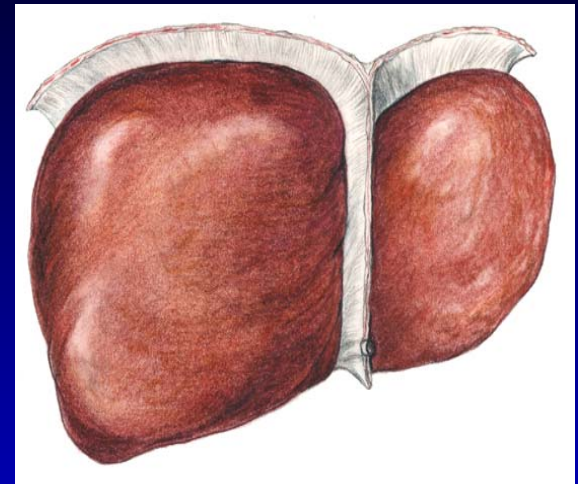
# HBV infection



5-10% of all infected adults

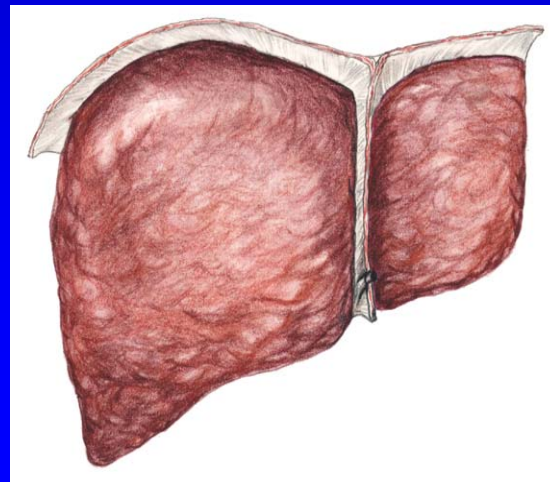


# chronic hepatitis



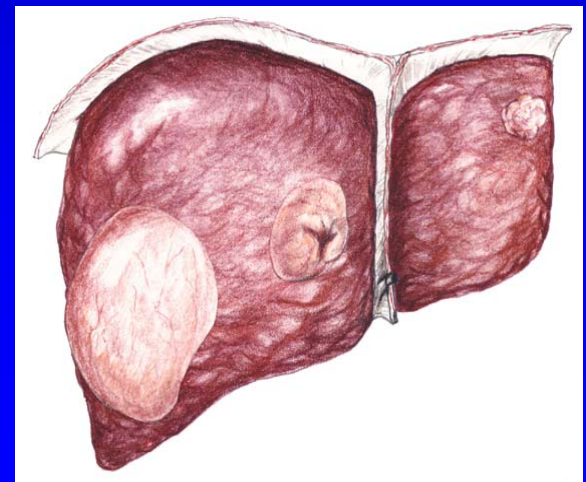
30%

# cirrhosis



470.000 deaths yearly

# HCC



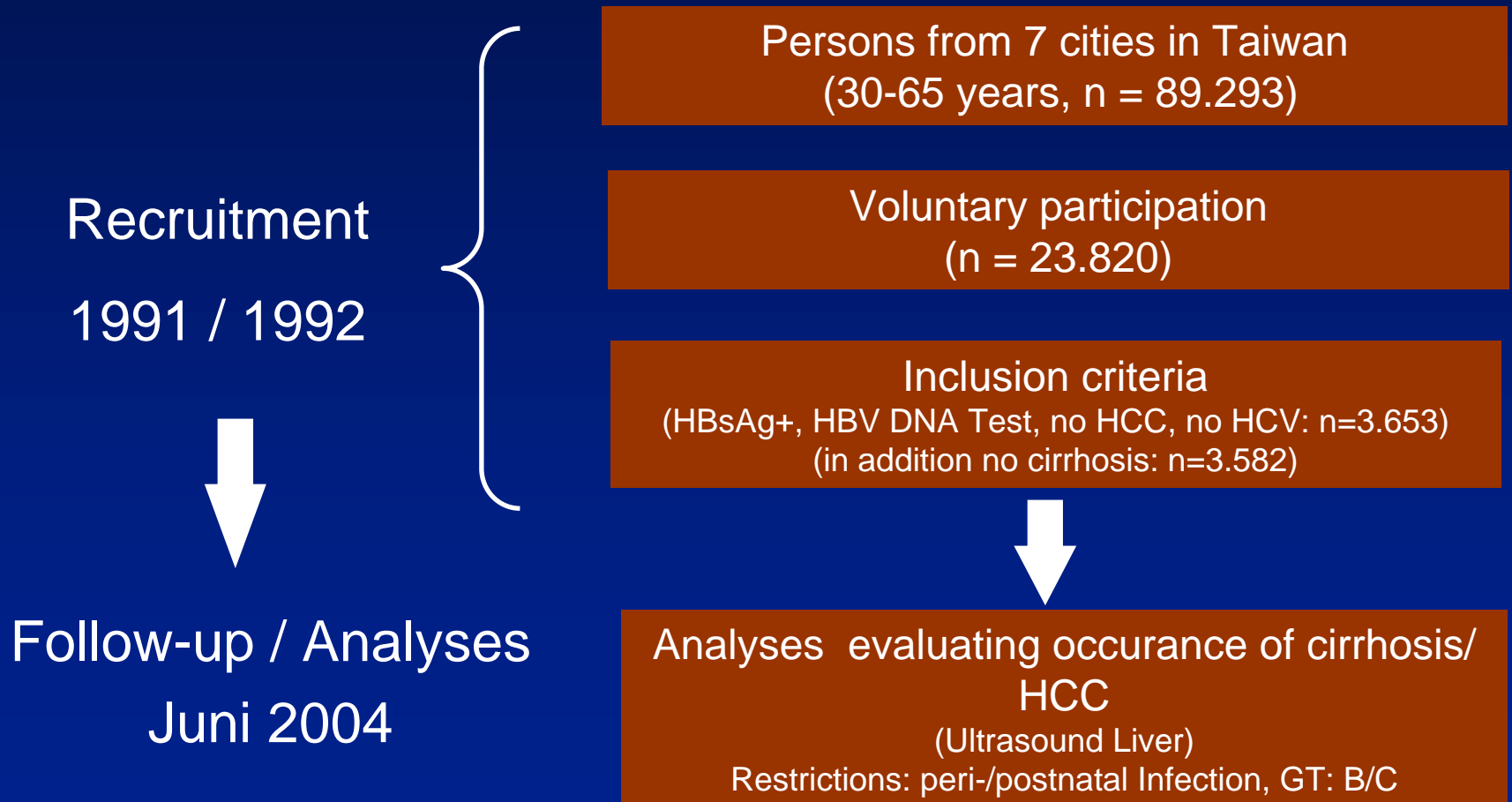
# Treatment Objectives

- Improve disease free survival
  - ▶ Prevent liver decompensation and HCC
  - ▶ Prevent progression to cirrhosis
  - ▶ Obtain durable suppression of HBV replication
- Treatment endpoints in practice
  - Decrease serum HBV DNA
  - Normalize serum ALT
  - Induce HBeAg/HBsAg loss or seroconversion

# Chronic Hepatitis B

## *cut-off HBV DNA Viral load*

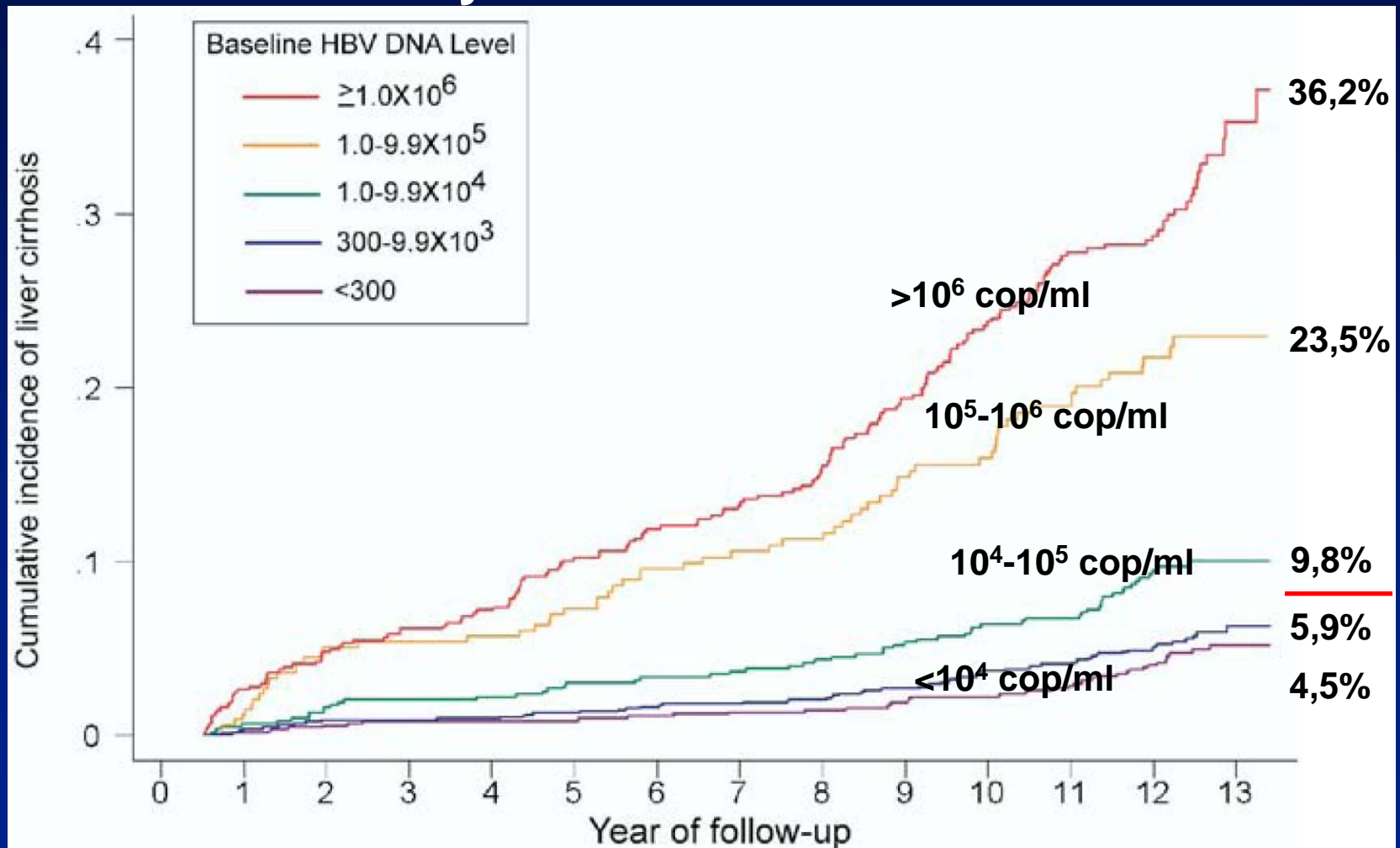
### REVEAL Study (prospective cohort study, Taiwan)



# Chronic Hepatitis B

## cut-off HBV DNA Viral Load

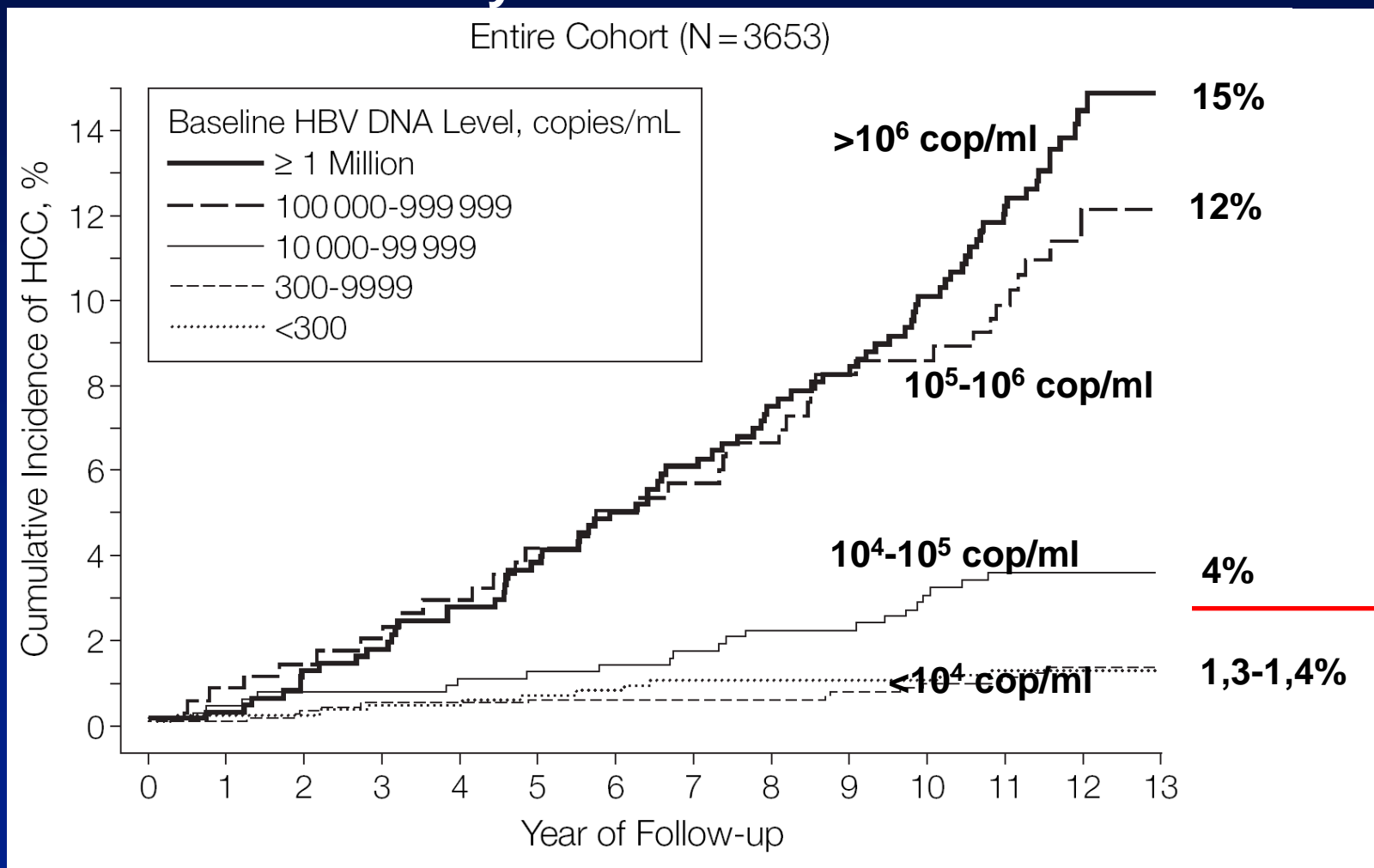
### REVEAL Study: cumulative incidence cirrhosis



# Chronic Hepatitis B

## cut-off HBV DNA Viral Load

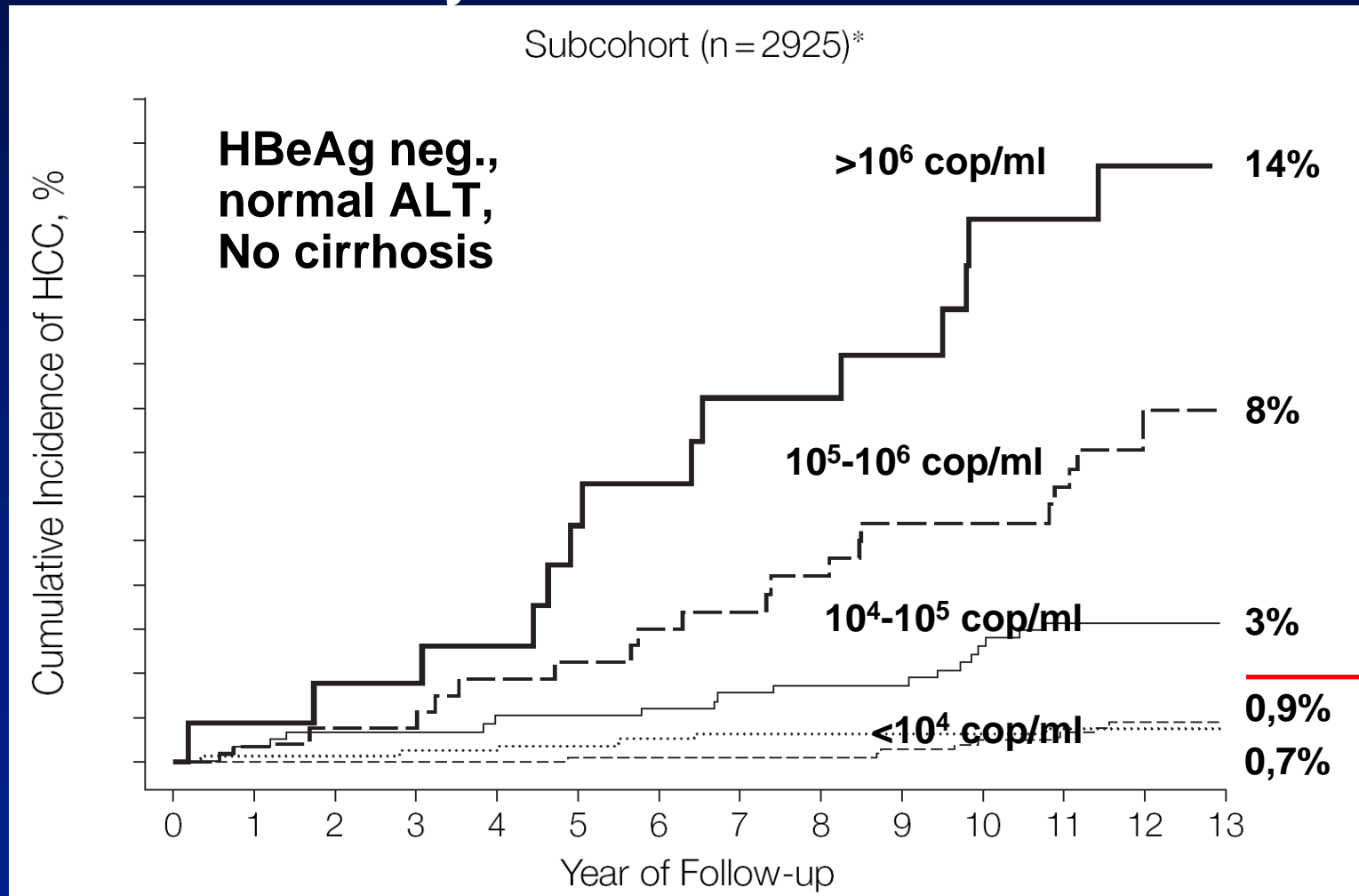
### REVEAL Study: cumulative incidence HCC



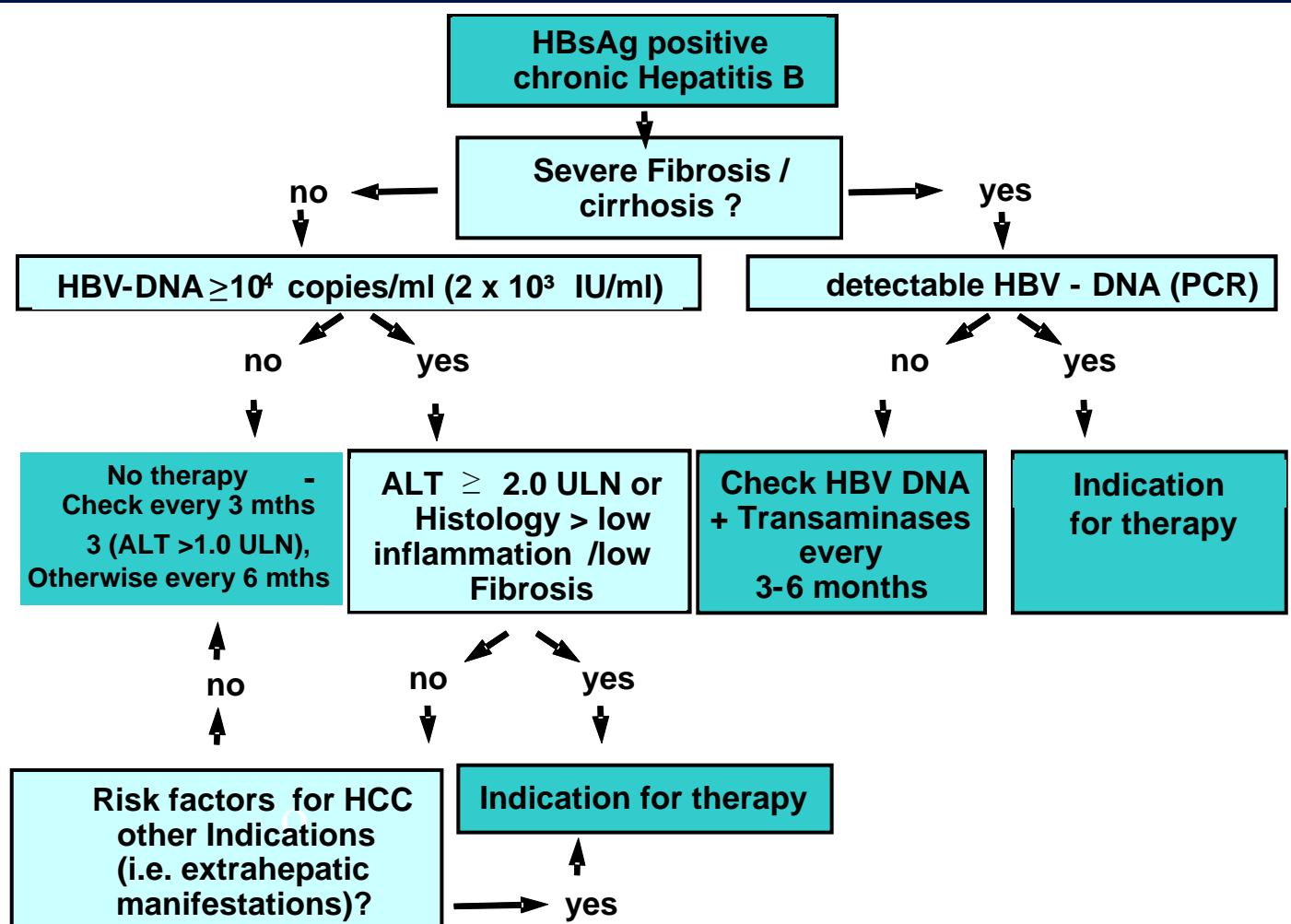
# Chronic Hepatitis B

## *cut-off HBV DNA Viral Load*

### REVEAL Study: cumulative incidence HCC



# Indication for chronic Hepatitis B Therapy



# Before Therapy / Therapy control

## Recommendation:

In case an indication for HBV therapy exists the following investigations are recommended to be carried out prior to therapy as well as monitoring of therapy outcome [B]:

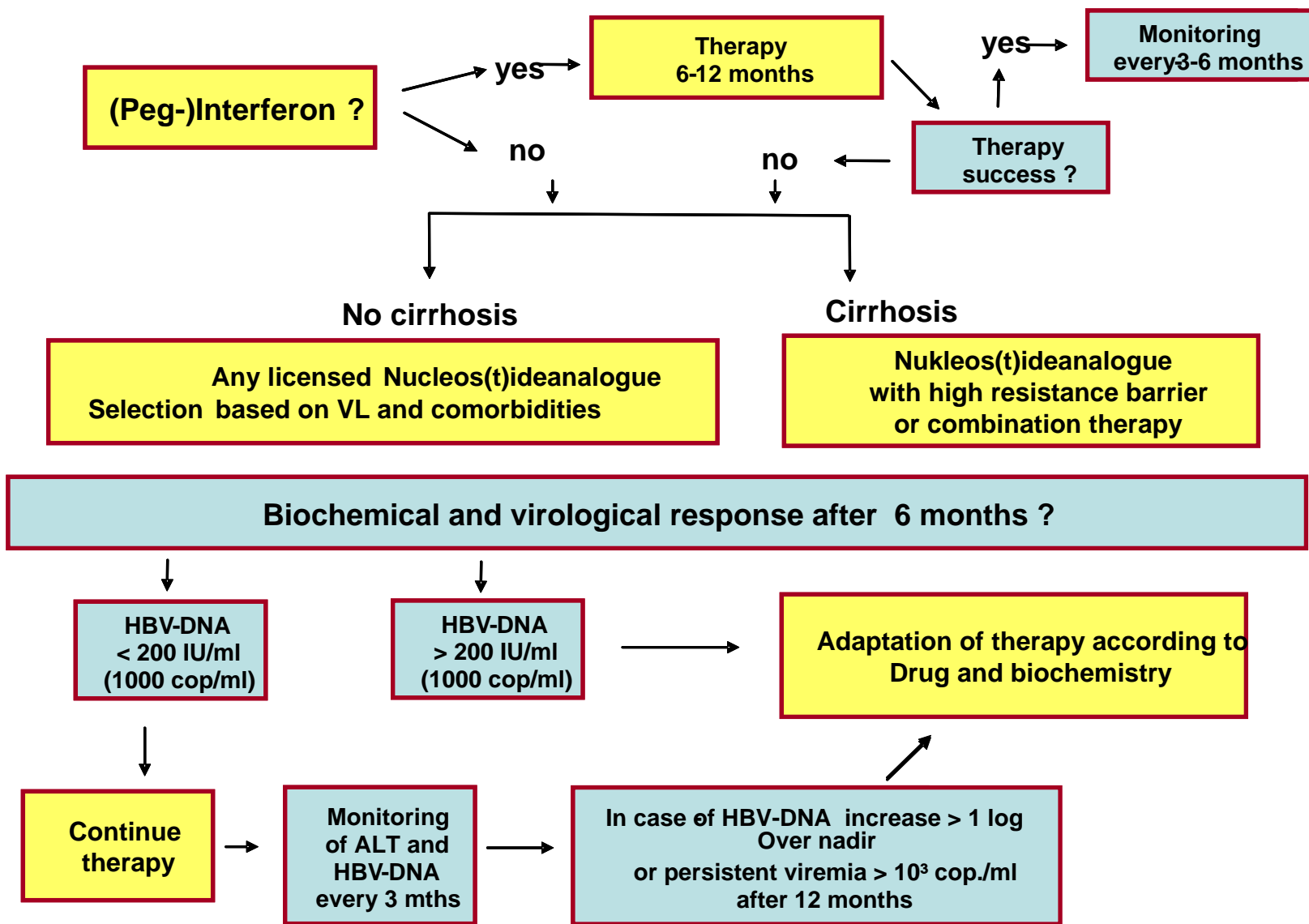
### **Prior to Therapy:**

- **HBV-DNA quantitative**
- **HBV-Genotyping** (in case of therapeutic relevance)
- clinical-chemical Lab tests

### **During Therapy:**

- HBeAg every 3 Monate, in case of loss of HBeAg control for Anti-HBe
- **HBV-DNA quantitative (Viremia) after 4-6 weeks and after 12 weeks, thereafter every 3-6 Months**
- Under therapy with Nukleos(t)ideanalogues: increase in HBV viremia despite drug intake (adherence) or in case no initial response is observed  
**Determination of resistance conferring mutations in the HBV Polymerase-Gene**
- clinical chemistry every 3 months
- HBsAg / Anti-HBs after loss of HBeAg and / or persistent decrease in HBV-DNA ( $<10^3$  copies / ml)

# Treatment algorithm

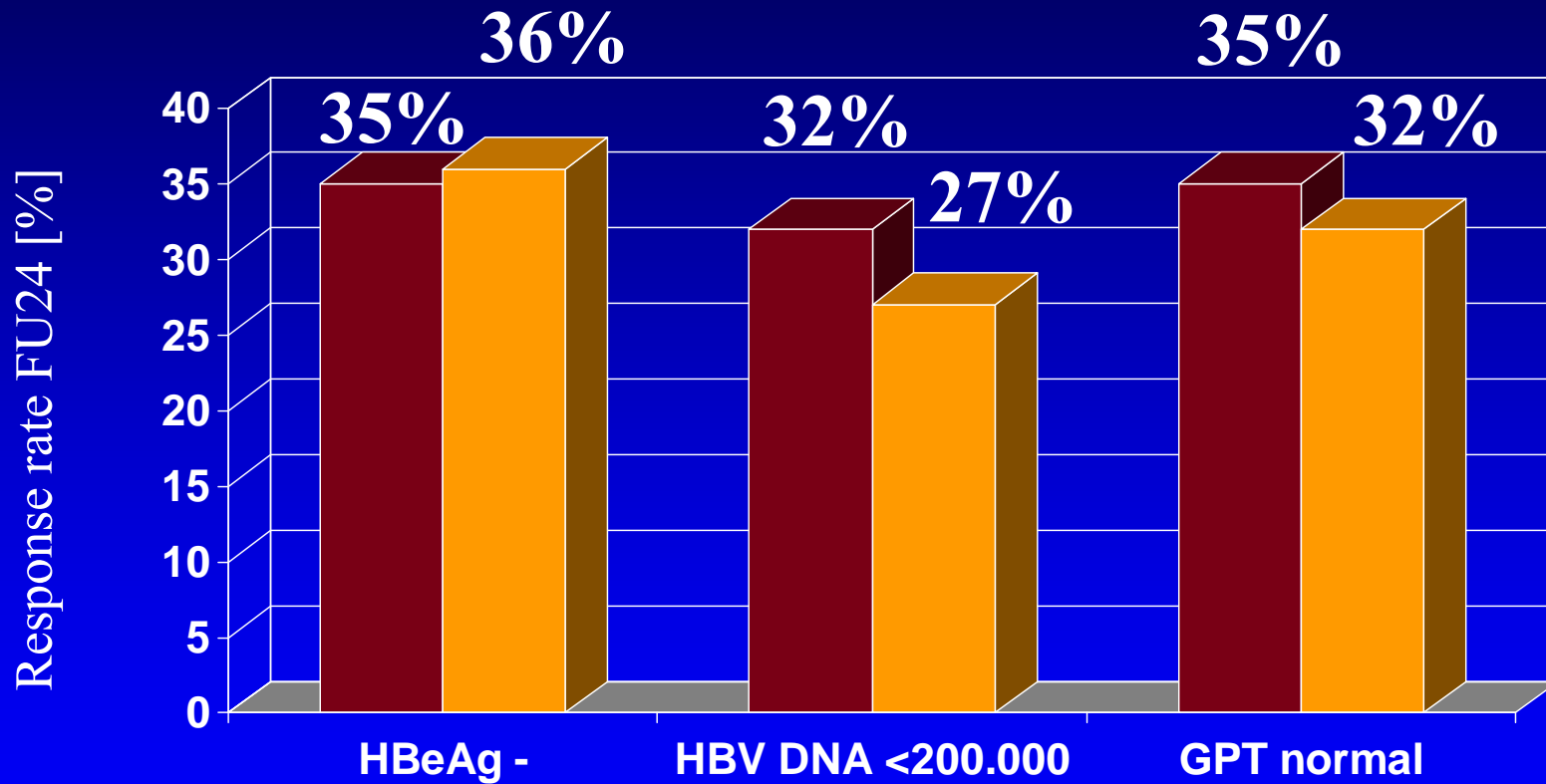


# Treatment of HBV

- *Interferon*
- *Lamivudine*
- *Emtricitabine*
- *Adefovir dipivoxil*
- *Tenofovir fumarate disoproxil*
- *Entecavir*
- *Telbivudine*

# Therapy of chronic Hepatitis B with PEG-IFN- $\alpha$ 2b

## *HBeAg pos.*



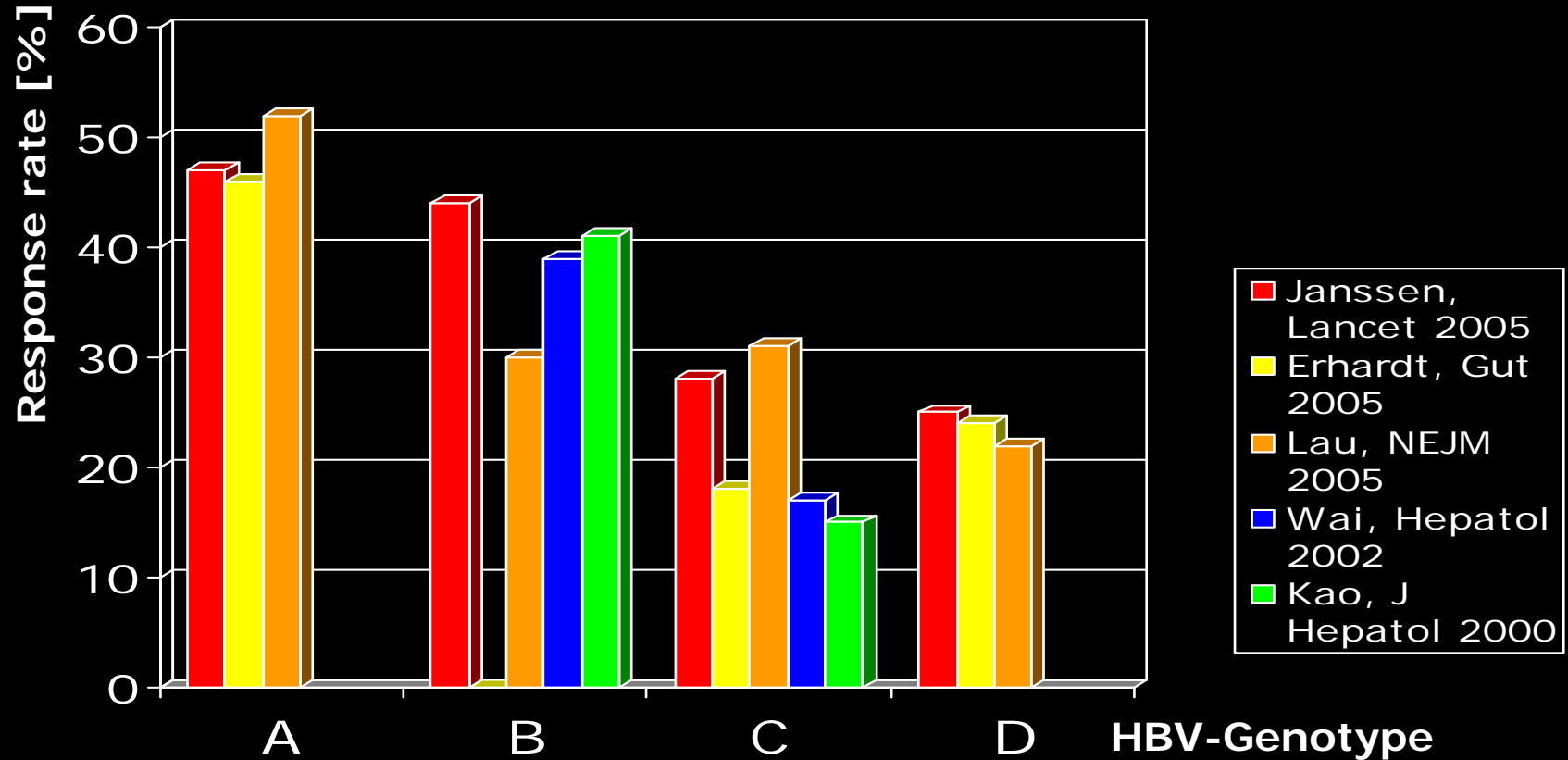
*HBeAg pos.*  
*n=266, 52 Weeks*

PEG2b  
+ Plac

PEG2b  
+ Lami

# IFN Therapy in HBeAg+ Hepatitis B

## Relevance of different HBV Genotypes



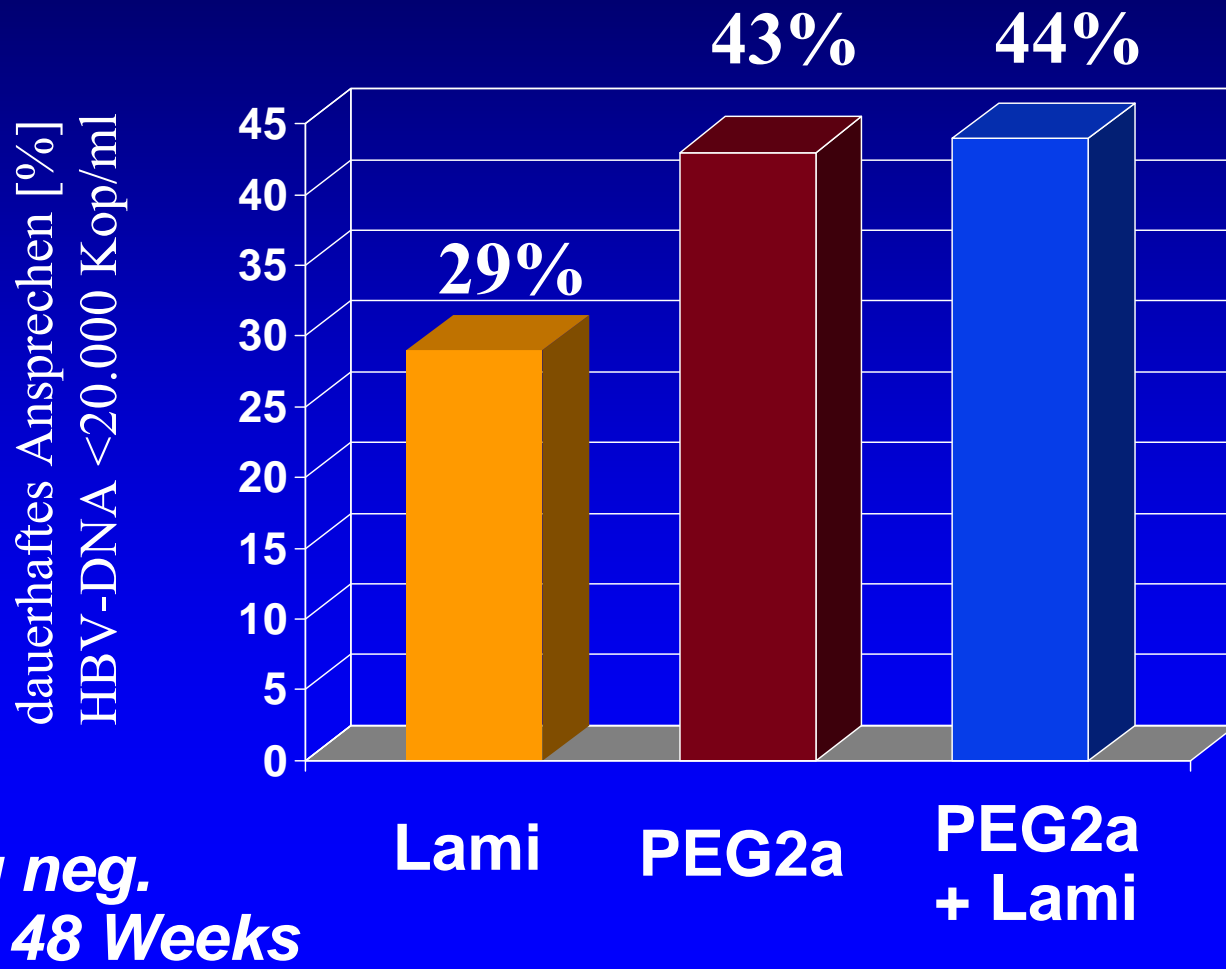
# Favorable Factors for Interferon Therapy

- **HBV Genotype A**
- **Low viral load (< 10<sup>6</sup> copies/ml)**
- **Higher liver enzyme elevations**
- **Previously untreated patients**

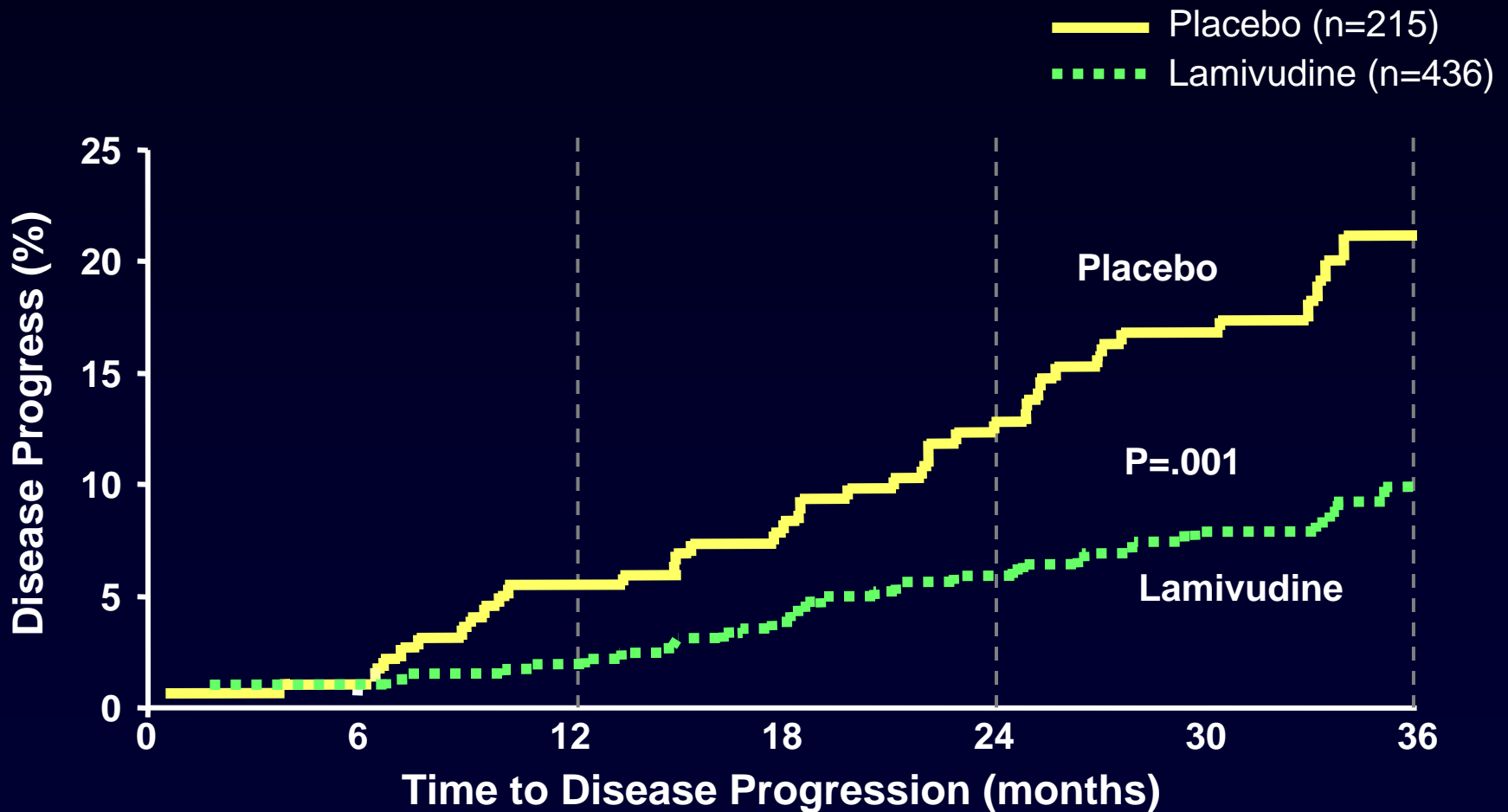
**Pegylated Interferon is the preferred interferon**

# Therapy of chronic Hepatitis B with PEG-IFN- $\alpha$ 2a

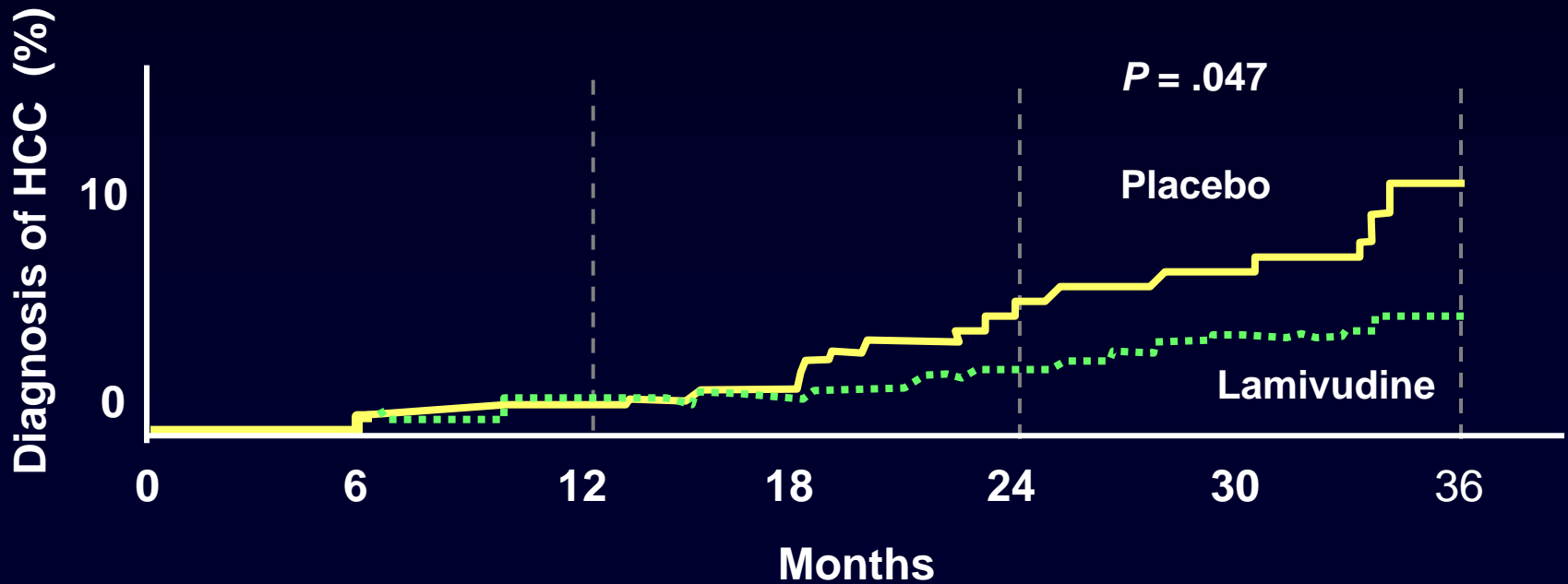
## *HBeAg neg*



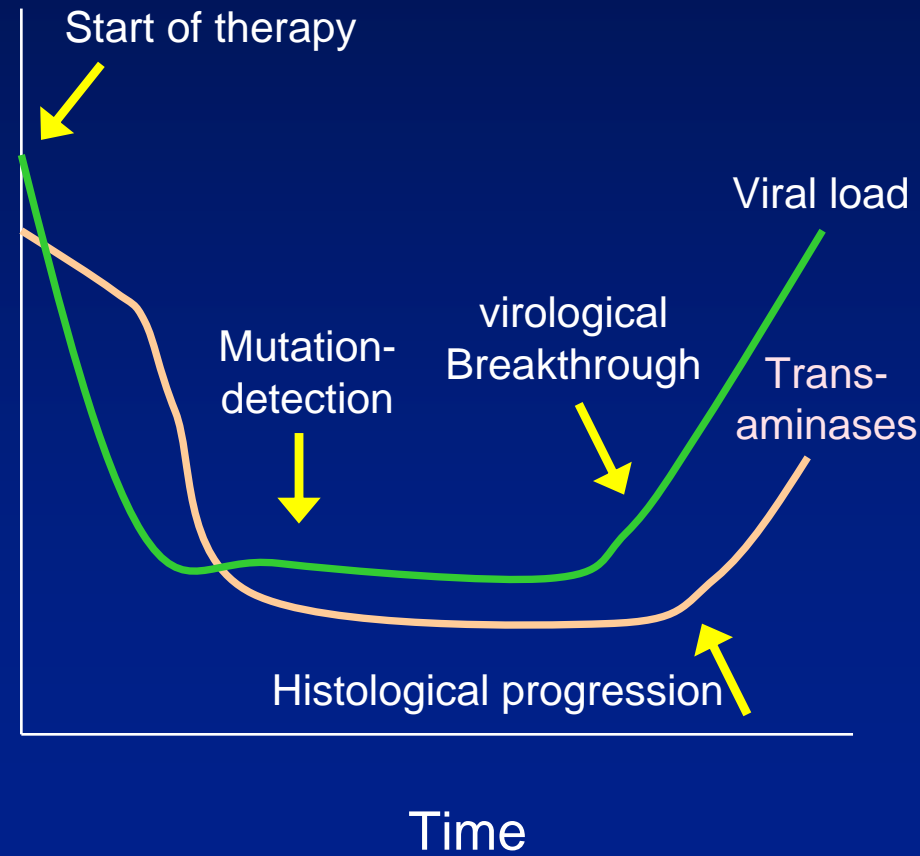
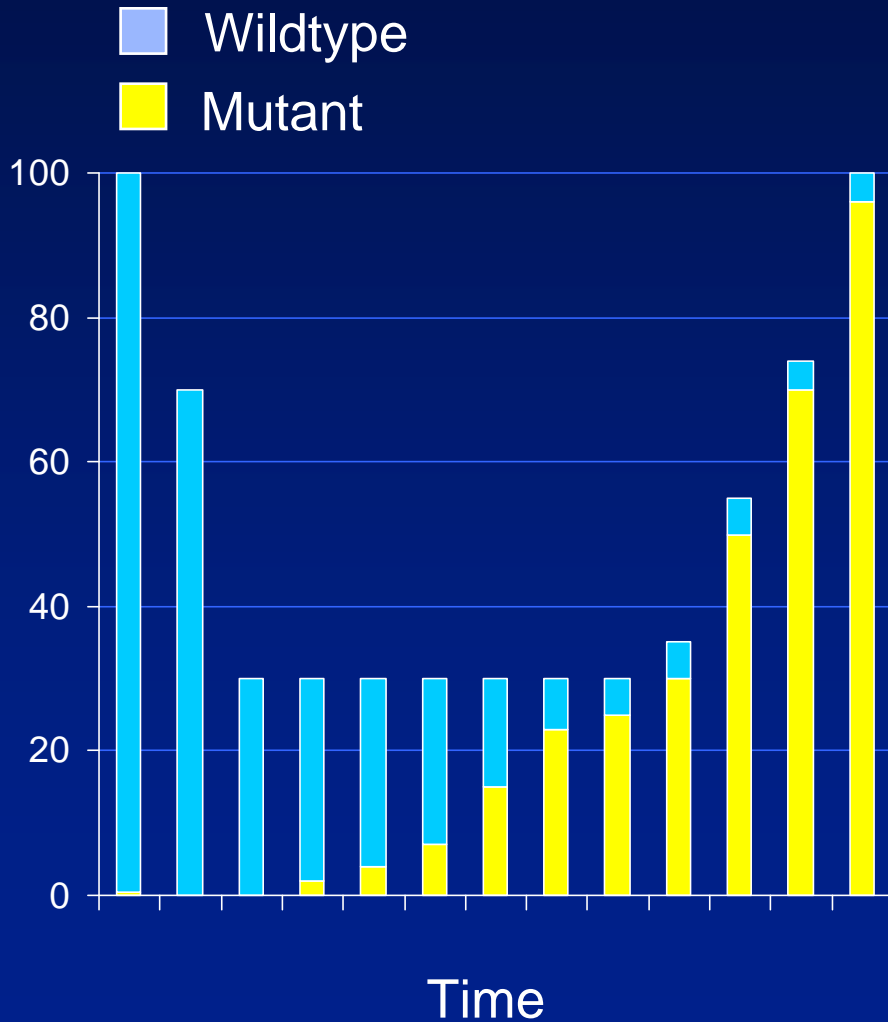
# Effect of Rx (lam) on Disease Progression in Patients with Advanced Fibrosis



# Effect of Rx (lam) on Incidence of HCC in Patients with Advanced Fibrosis

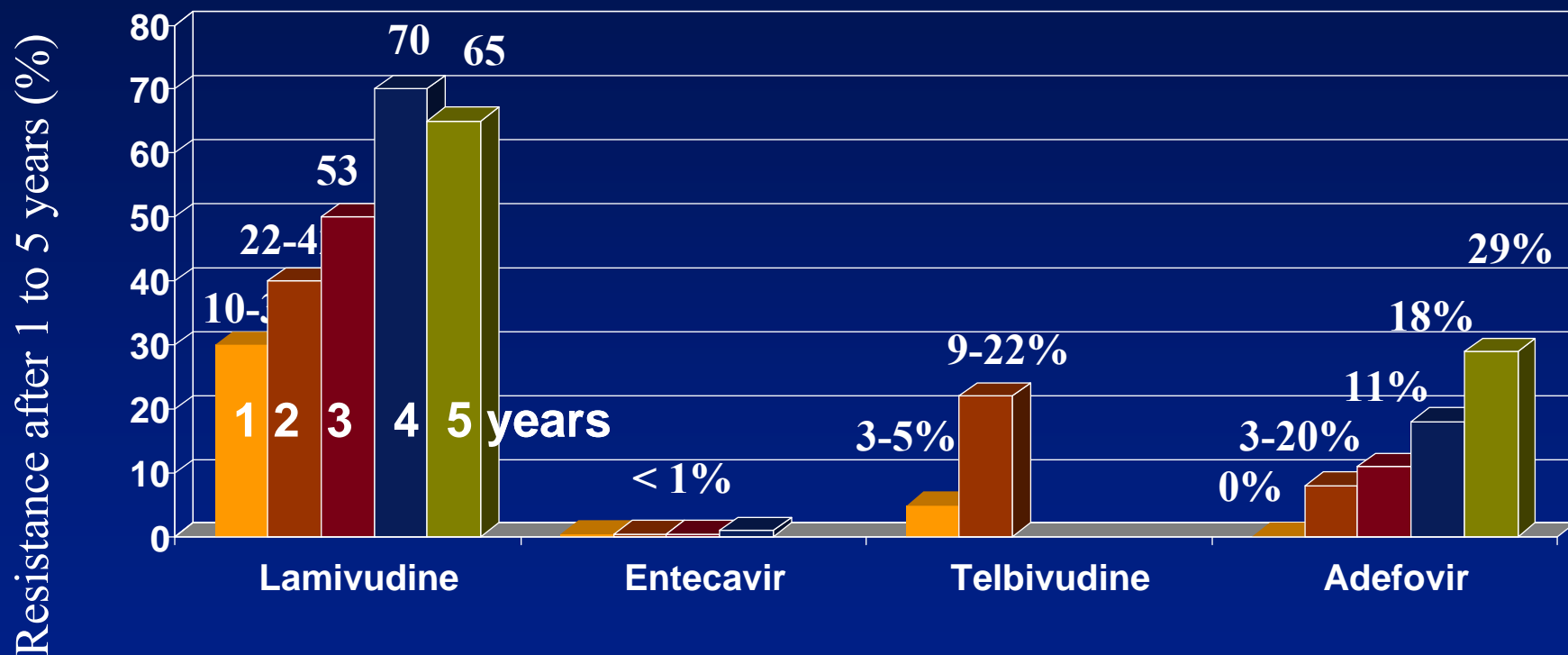


# Development of antiviral resistance



# Therapy of chronic HBV with Polymerase Inhibitors

## *HBeAg neg.: genetic Barrier*



*Lai et al., AASLD 2005*

*Marcellin et al., NEJM 2003*

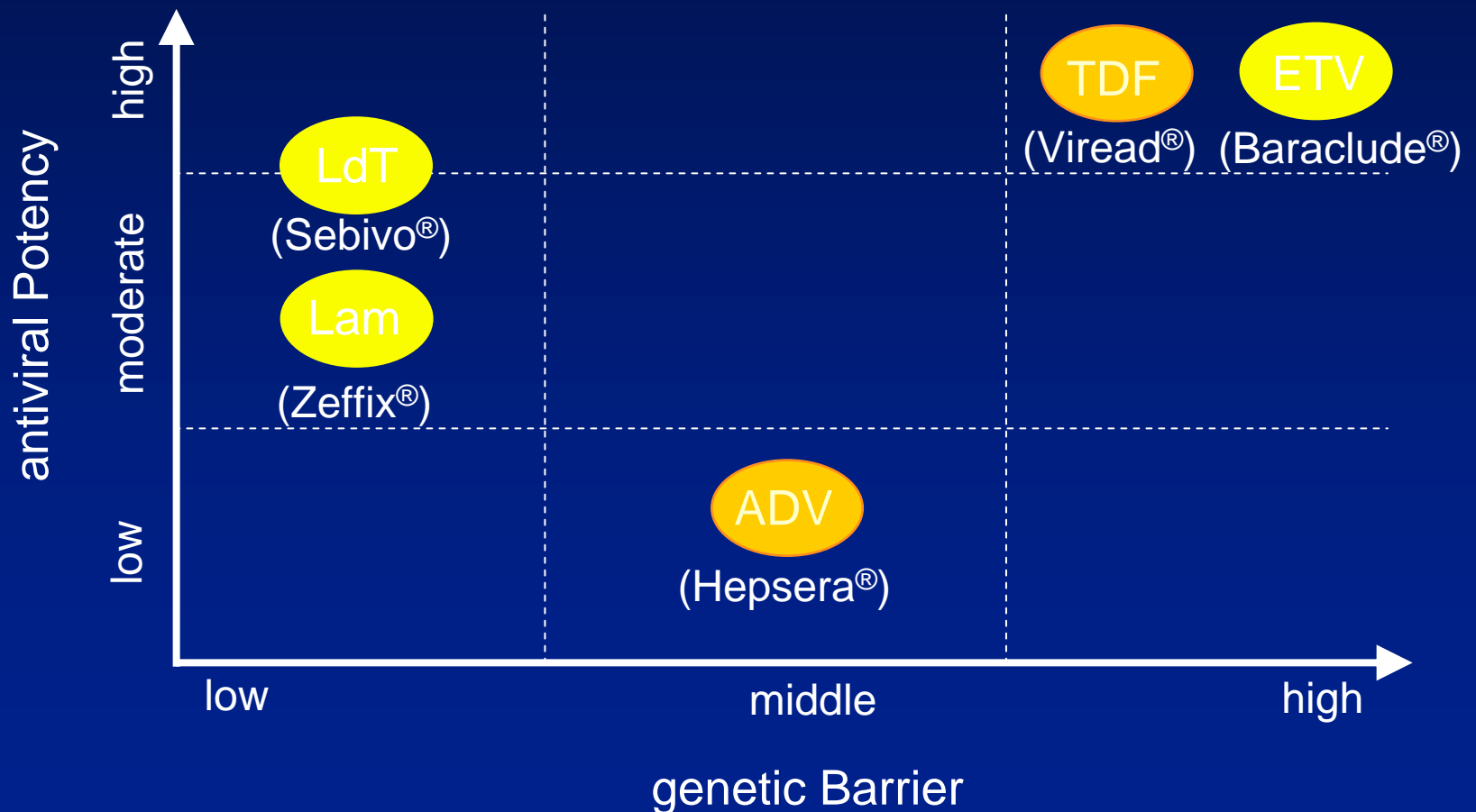
*van Bömmel et al., Hepatology 2004*

*Lai CL et al., NEJM 2006*

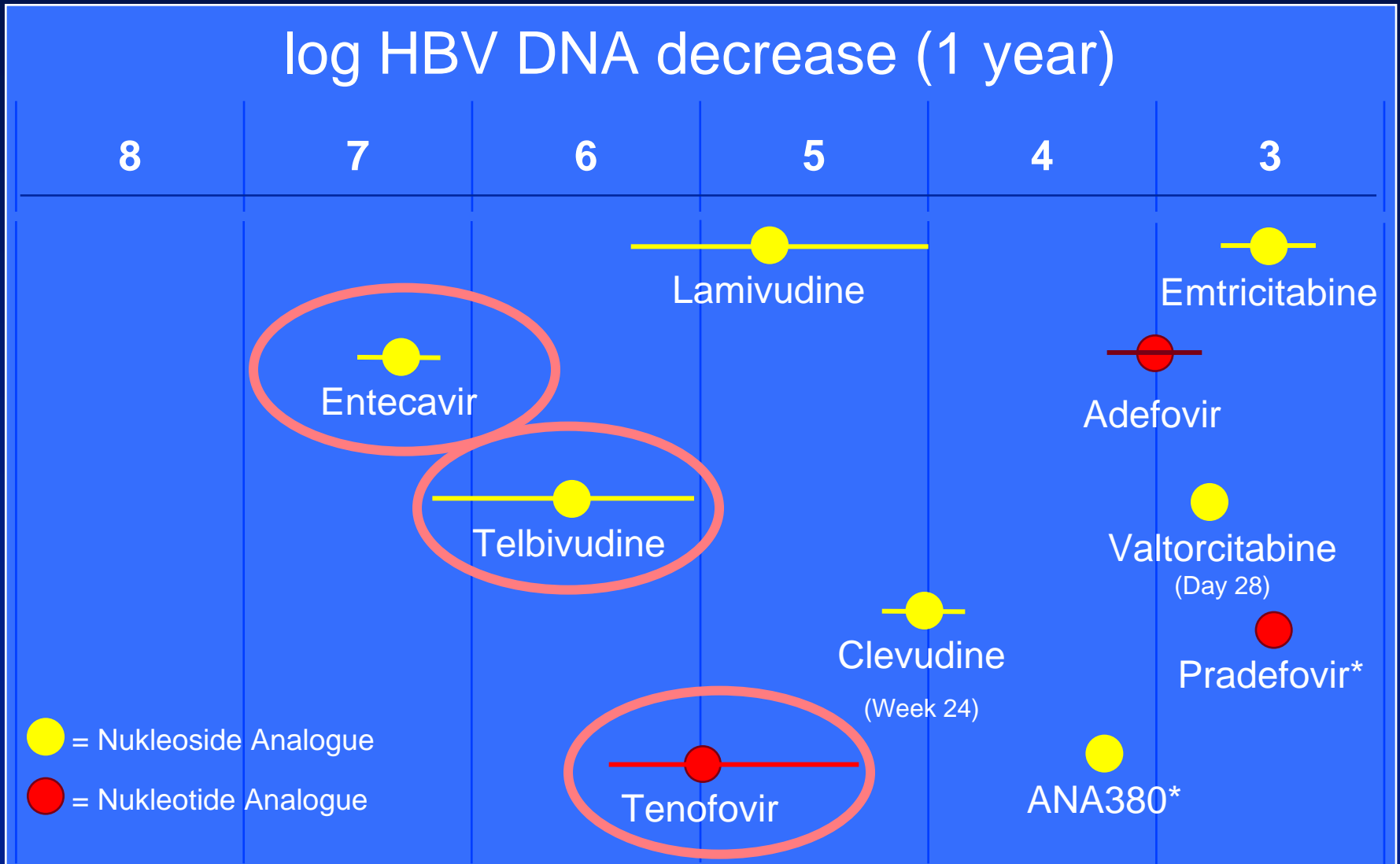
*Colonno et al. EASL 2007*

# Characteristics of different Nukleos(t)ide-Analogues

● Nukleoside-Analogue    ● Nukleotide-Analogue

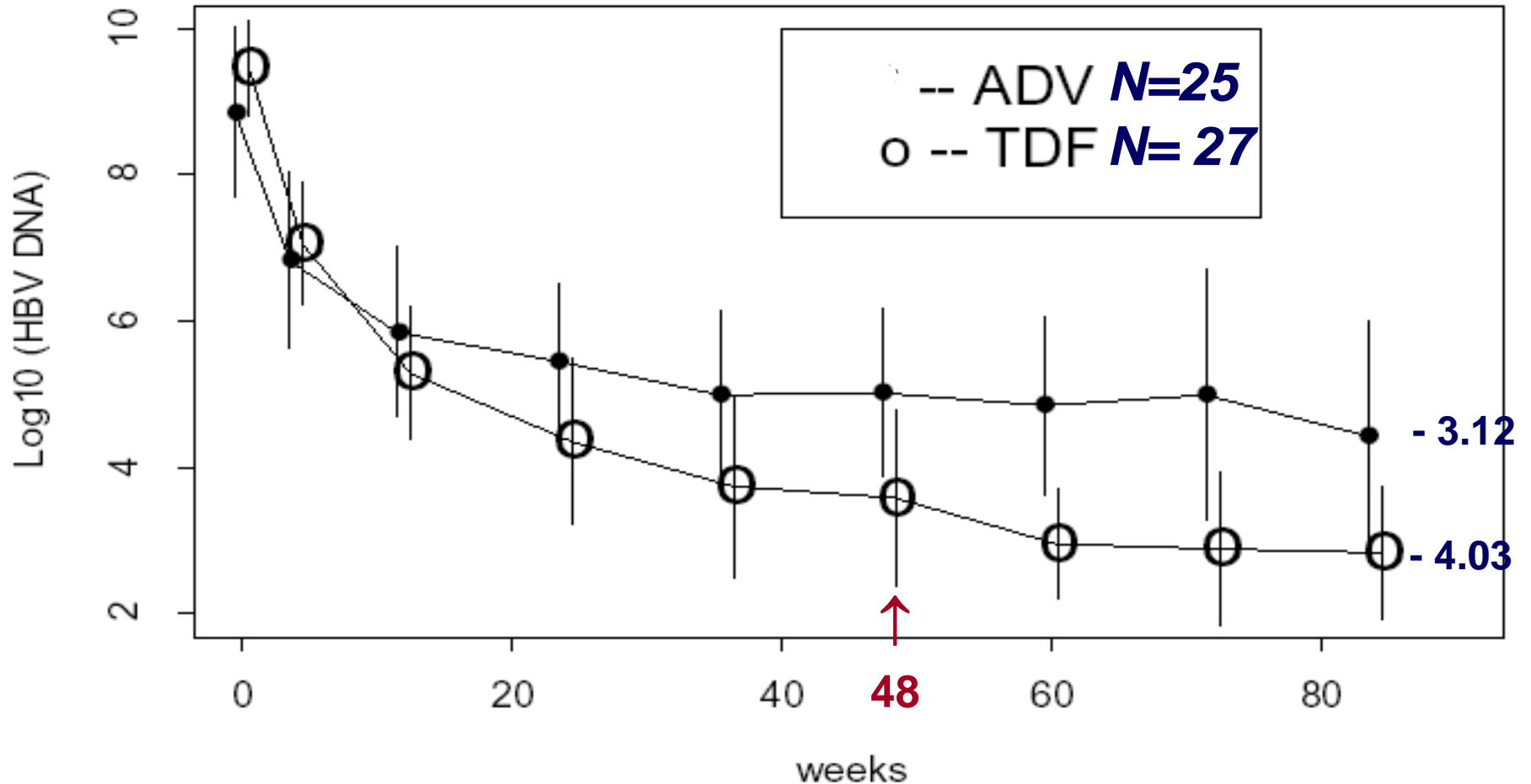


# Antiviral potency of different Nucleos(t)ide-Analogues in HBV



# ADV vs TDF in HIV/HBV co-infected patients

## Mean serum HBV DNA

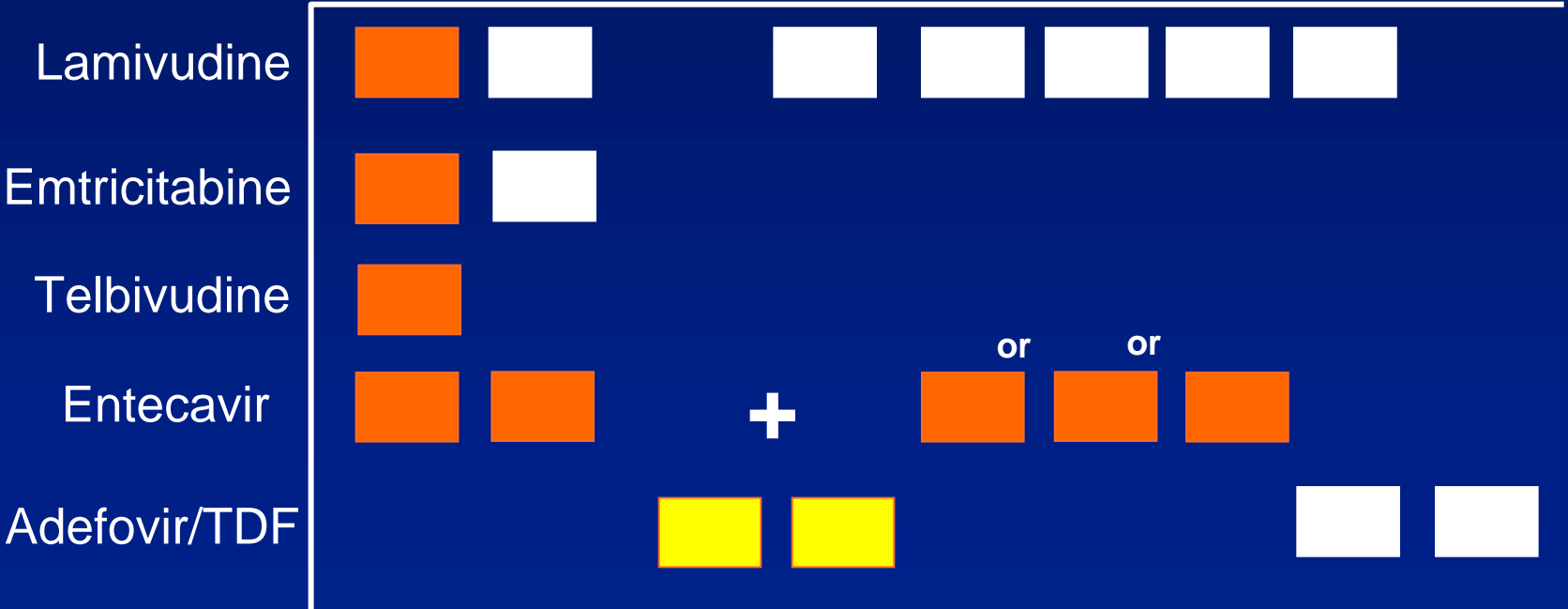


# Nukleos(t)id-Analogue Resistance-associated Mutations



Mutations associated with virological breakthrough  
 additional (compensatory) Mutations

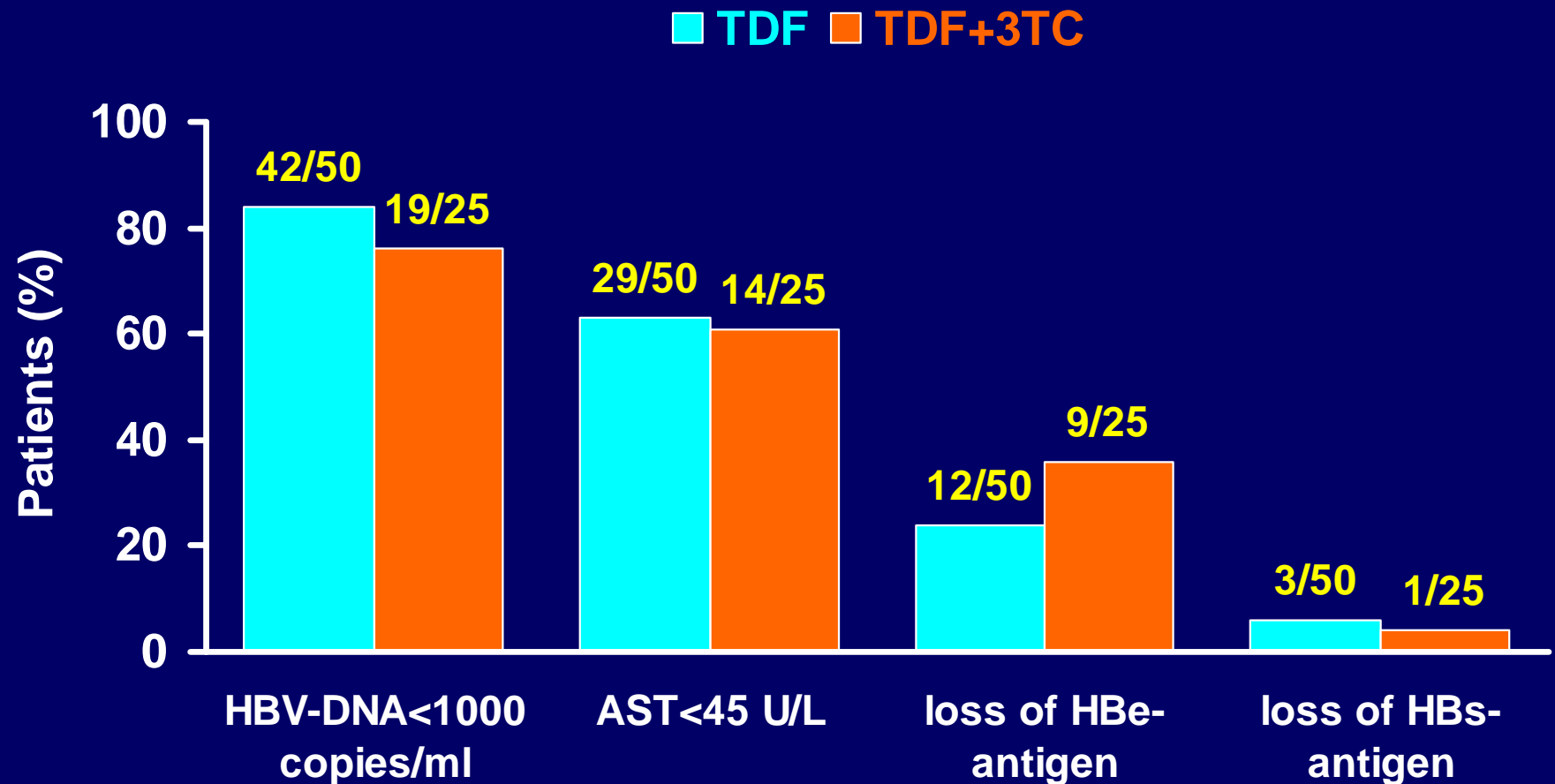
M204V/I L180M N236T A181V/T T184G/S S202I M250V V214A/Q215S V84M/S85A



Adapted from: Locarnini S. Monothematic Conference, Istanbul, Turkey, 6-8 October 2005. Yuen M-F & Lai C-L. Expert Rev Anti Infect Ther. 2005;3:489-94. Adapted from: Locarnini S, et al. Antivir Ther. 2004;9:679-93

# Tenofovir vs. Tenofovir + Lamivudine

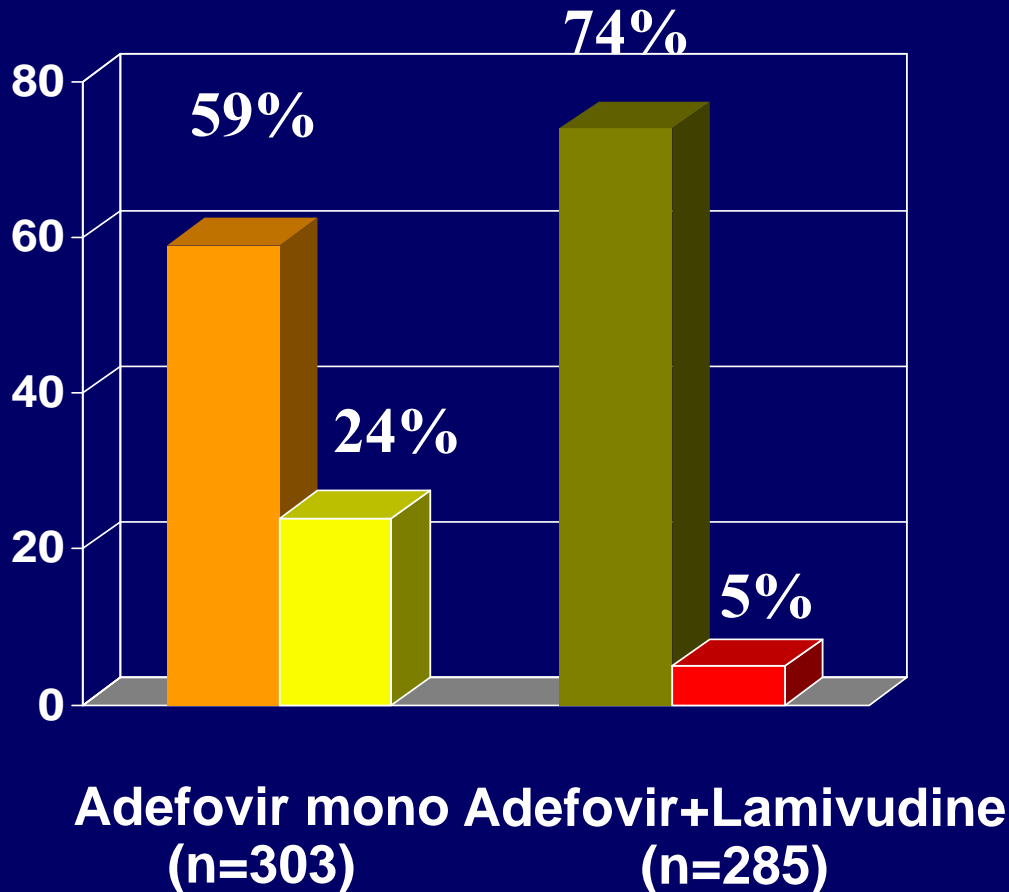
(HBV/HIV-coinfection)



# Lamivudin-Resistance

## Switch to Adefovir versus Add-on

HBV DNA 33 Mo. <400 cop/ml [%]  
and Breakthrough [%]



- HBe-Ag neg.
- n=588
- Lam.-Resistance
- switch vs. add-on
- Mean follow-up 33 Months
- Kreatinine increase in 8% of cases

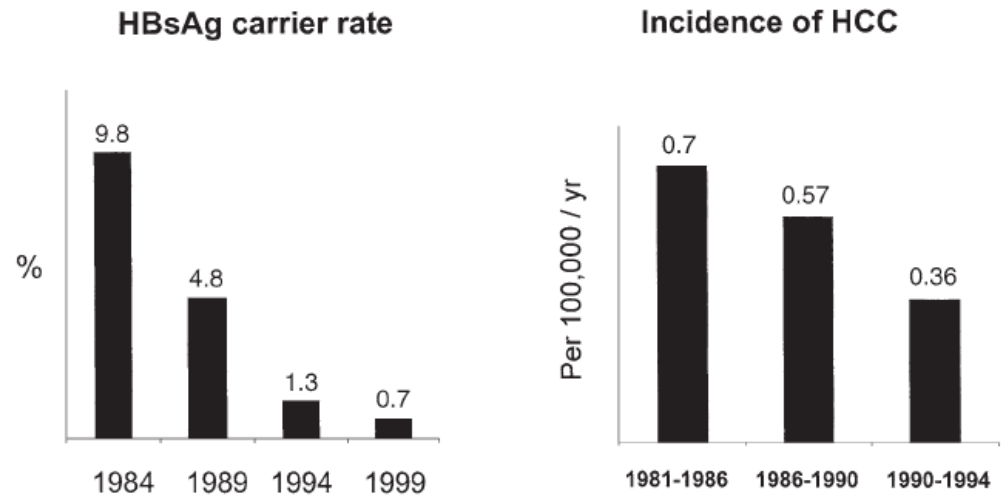
# Treatment goal and duration

- IFN: treatment length 48 weeks for PEG INF; goal HBe and HBs-Ag seroconversion
- for the nucleoside analogues: HBsAg seroconversion + 6-12 mths.
- anti-HBV therapy may be stopped cautiously in HBeAg+ patients who have achieved HBe-seroconversion or HBs-seroconversion for at least six months
- The treatment duration in HBe-Ag negative patients is still not well defined and in most cases is an ongoing therapy
- Any oral antiviral HBV therapy can be stopped once HBs-Ag seroconversion and anti-HBs Titer > 100 IU/L have been achieved

# The most successful intervention against HBV is the HBV vaccination

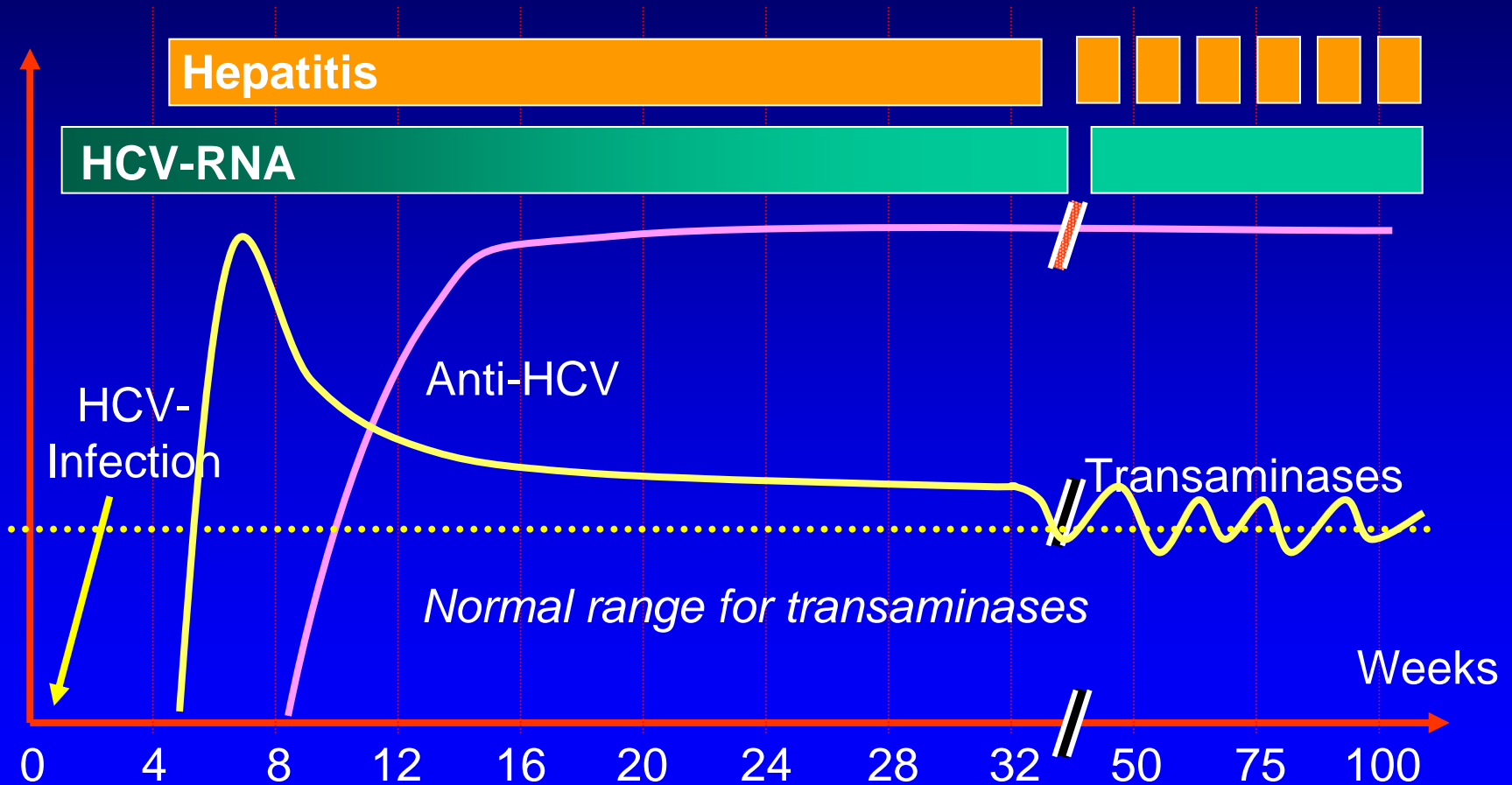


## Impact of Universal HBV Vaccination on HBV Infection and HCC in Taiwanese Children



Nach Lok et al. Gastroenterology 2004

# Natural Course of Hepatitis C Infection



# Symptoms of Hepatitis C



AST / ALT

- **Fatigue**
- **Inefficiency**
- **Abdominal pain or discomfort**
- **Arthritis**

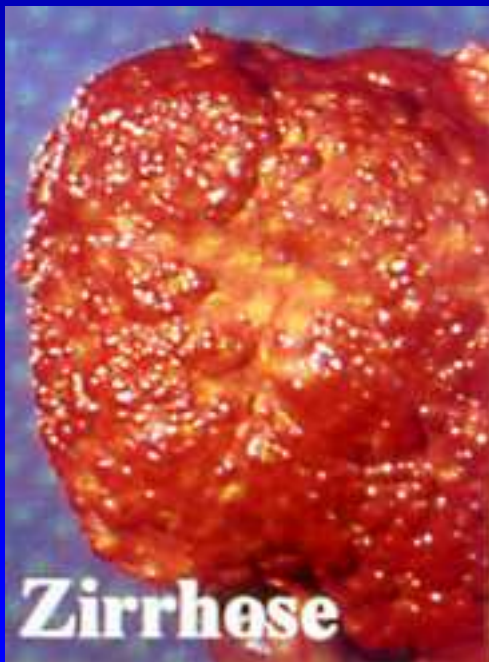
**Mostly mild and unspecific**



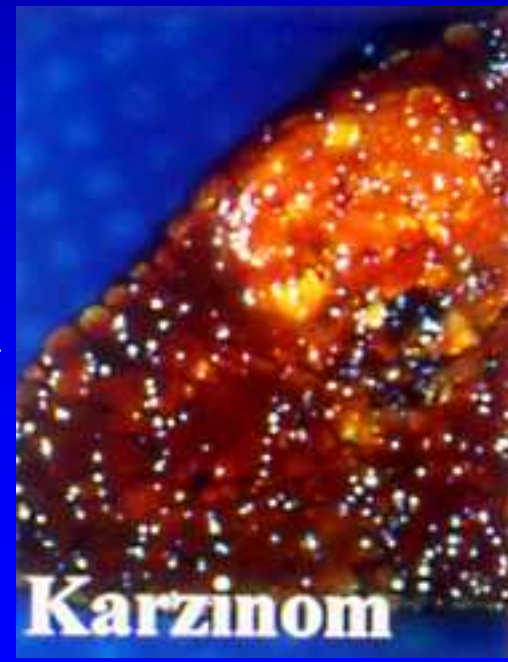
Chronic  
Hepatitis with  
Fibrosis  
50%

50-80%  
chronic  
Infection

Chronic  
Hepatitis  
without  
Fibrosis 50%



3-5 % / Year



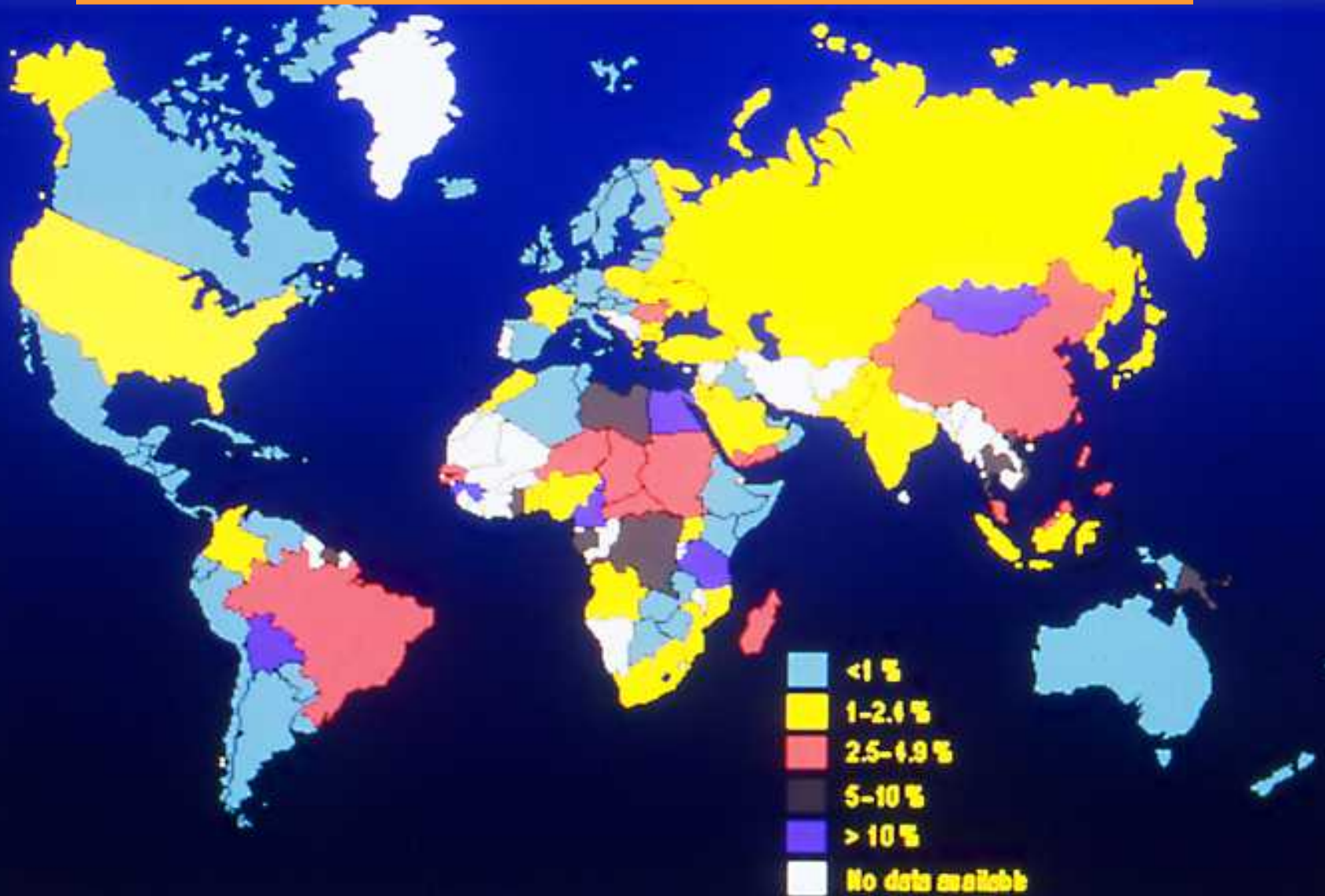
# Extrahepatic Manifestations of Hepatitis C

## Essential mixed cryoglobulinemia

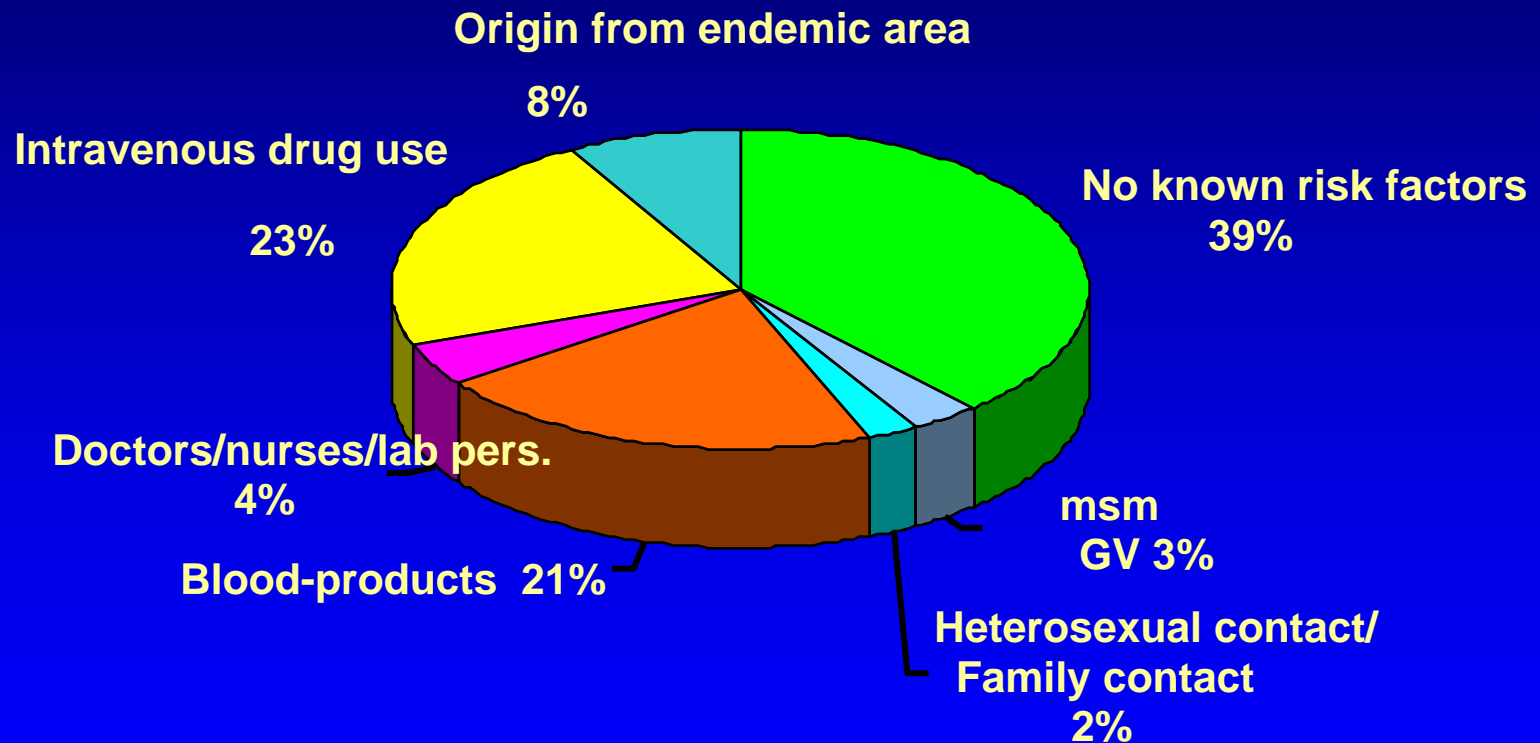


- Palpable Purpura
- Arthralgia
- weakness
  
- Involvement of nerves and kidney possible

# Distribution of HCV

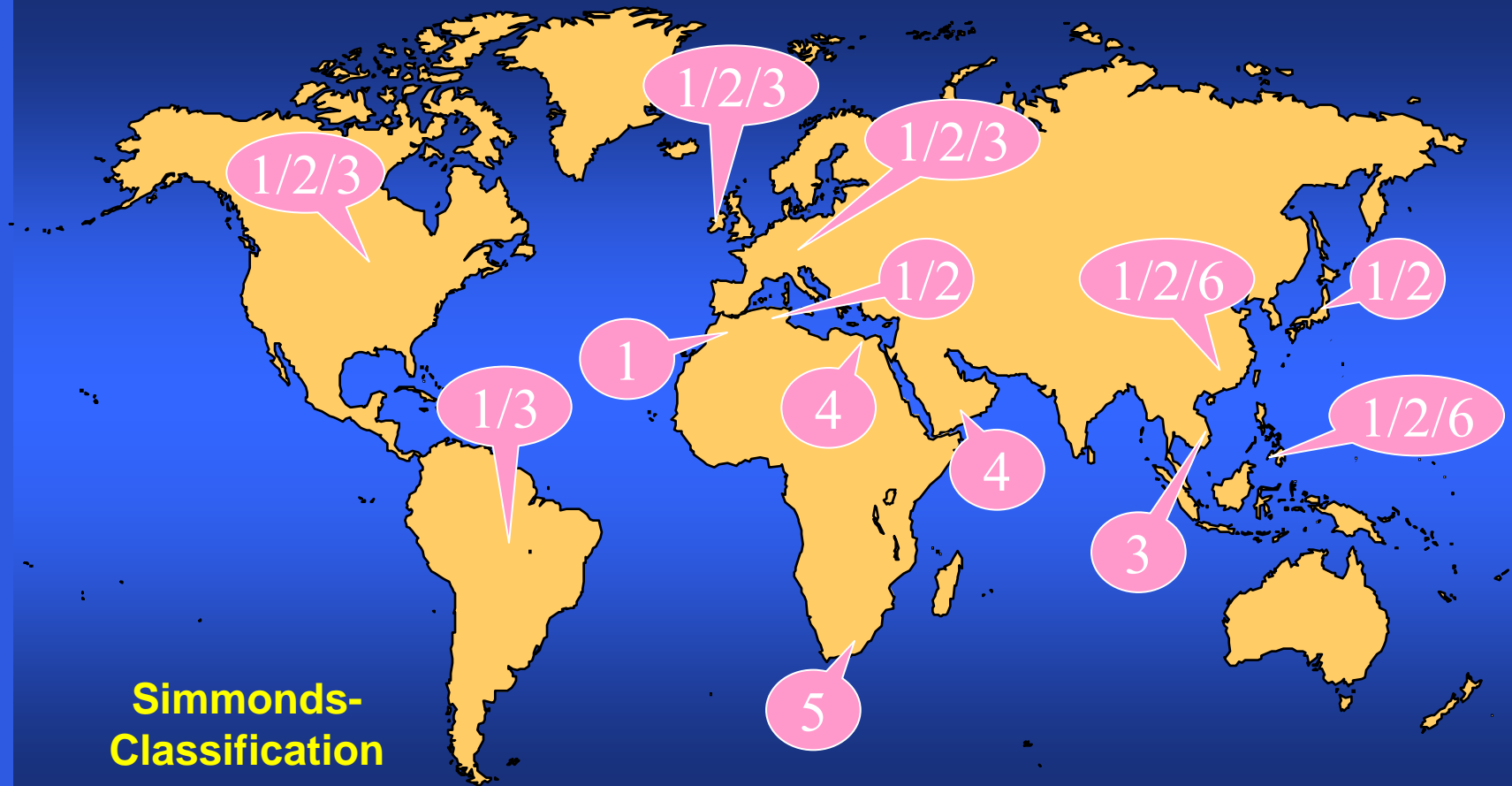


# Hepatitis C - Possible transmission risk factors



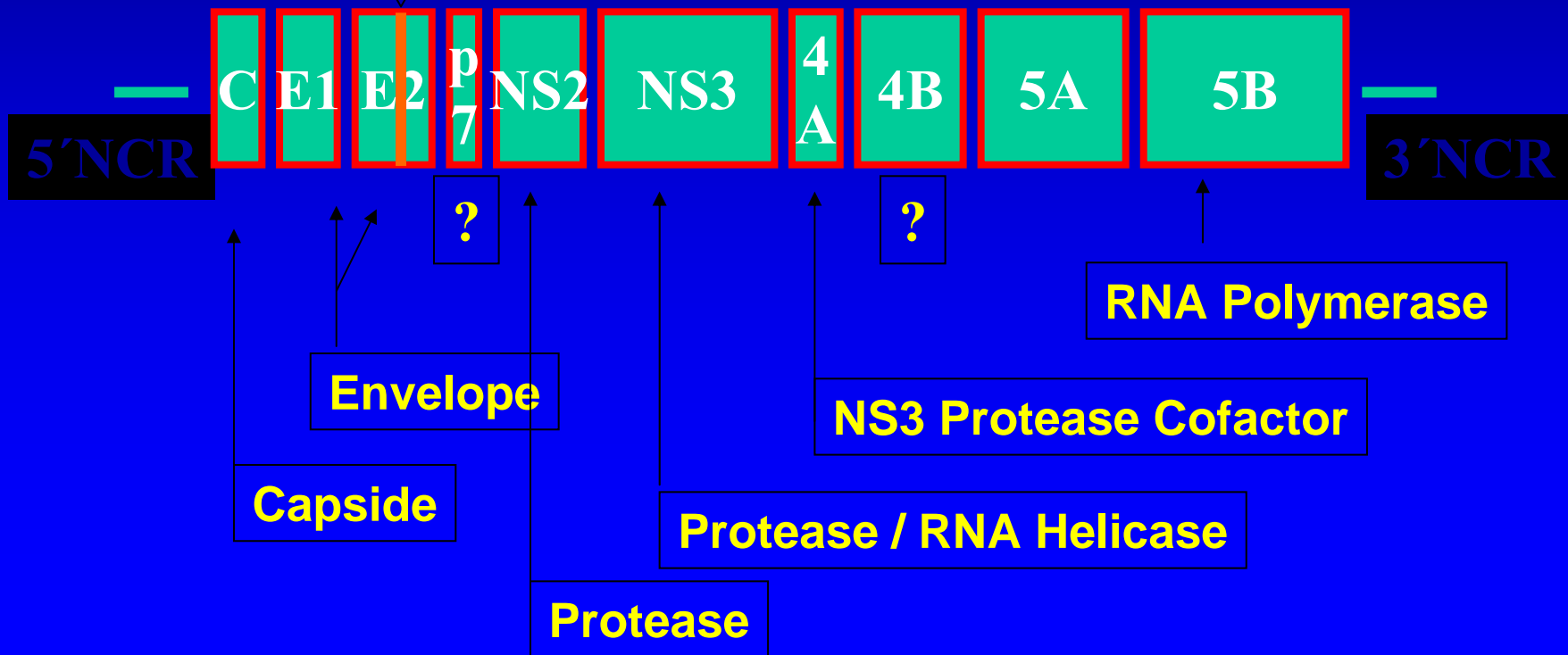
# Hepatitis C

## Distribution of HCV-Genotypes



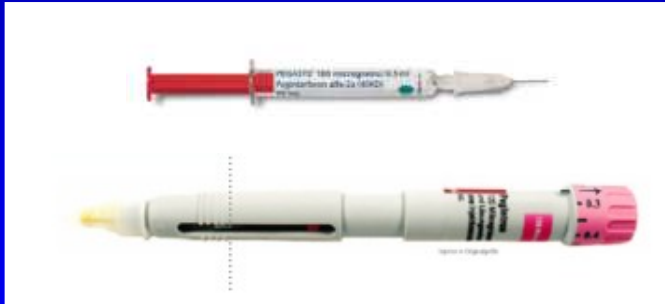
Simmonds-  
Classification

# Structure of the Hepatitis C Virus



# Drugs for treatment of Hepatitis C

**Pegylated  
Interferon alfa**



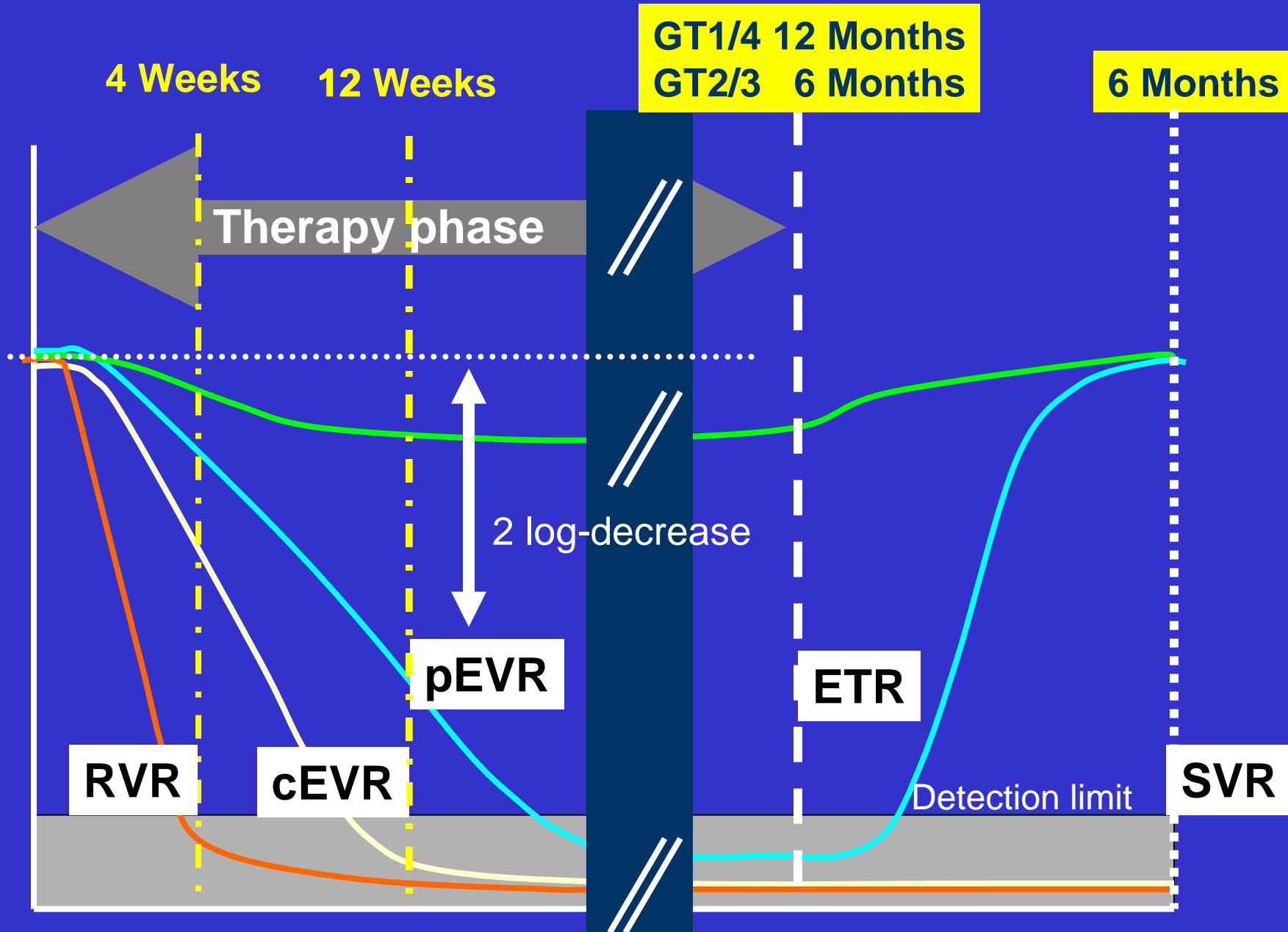
**1 x weekly**

**Ribavirin**

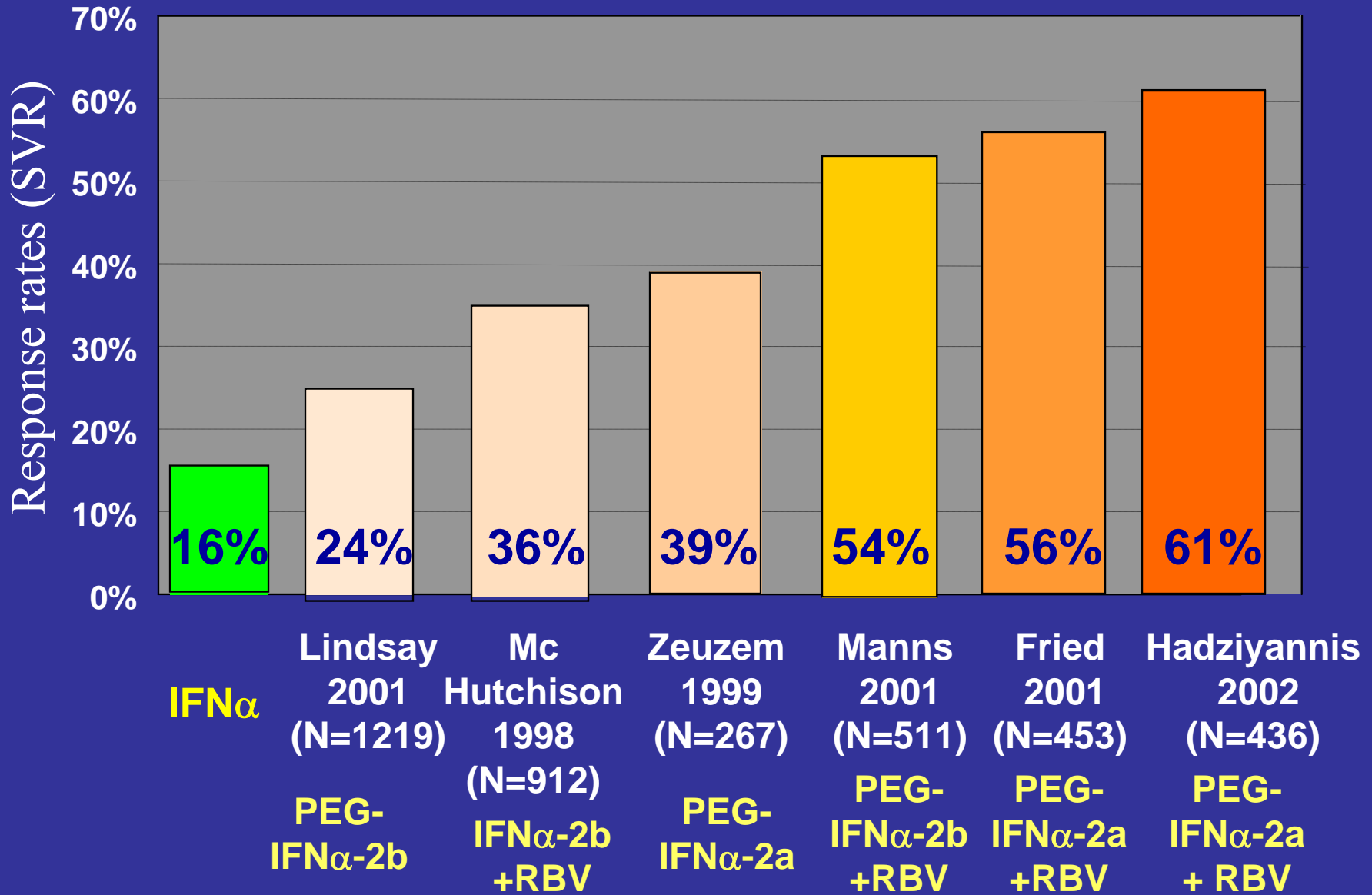


**2 x daily**

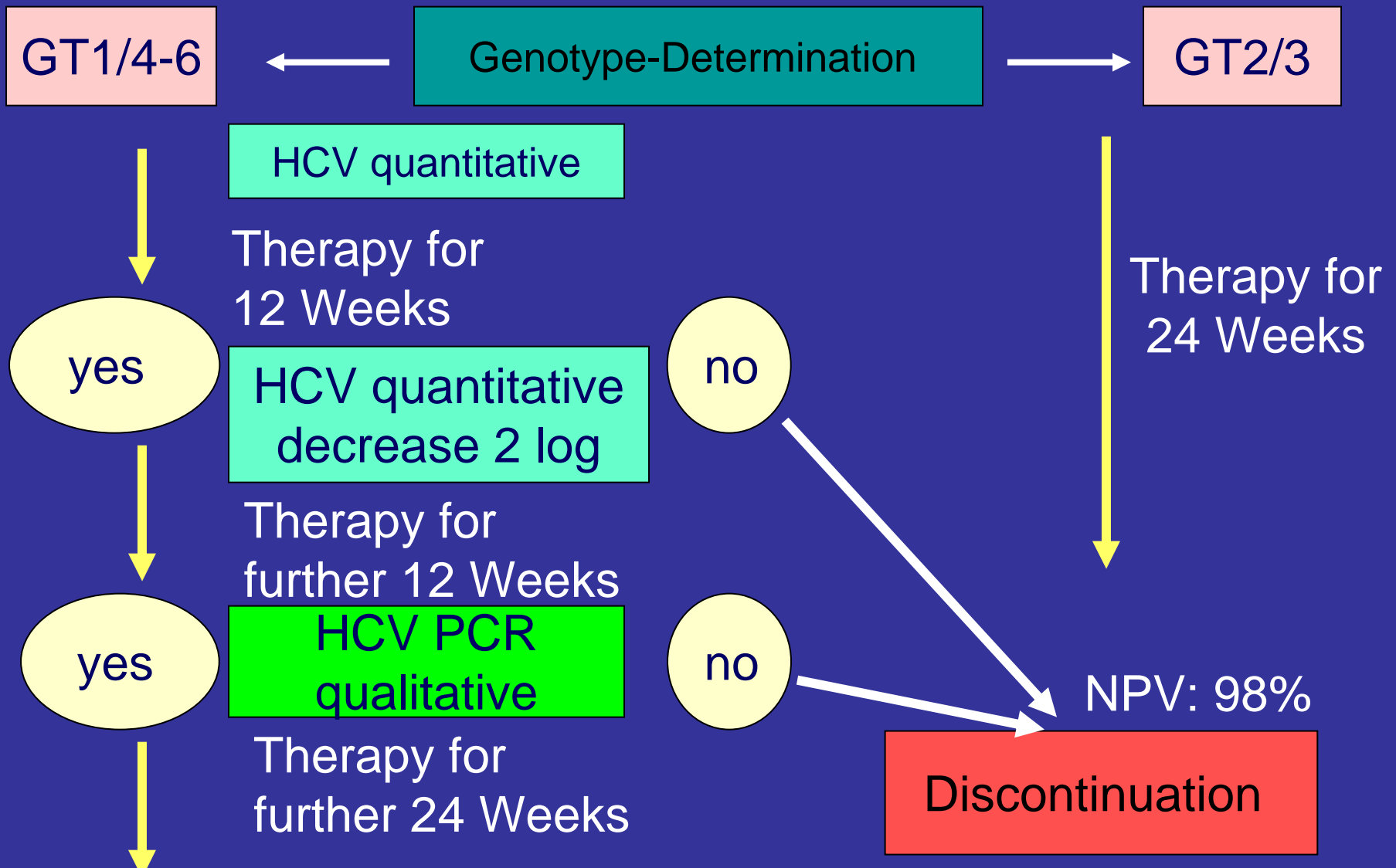
# HCV Therapy



# Interferon and Ribavirin for treatment of Hepatitis C



# Chronic Hepatitis C



# Individualised HCV-Therapy

Shortened treatment duration in the presence of RVR  
and/or low baseline viral load

## Genotype 1:

Zeuzem et al.	J Hepatol 2006	24 vs. 48 W	89%
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## Genotypes 2/3:

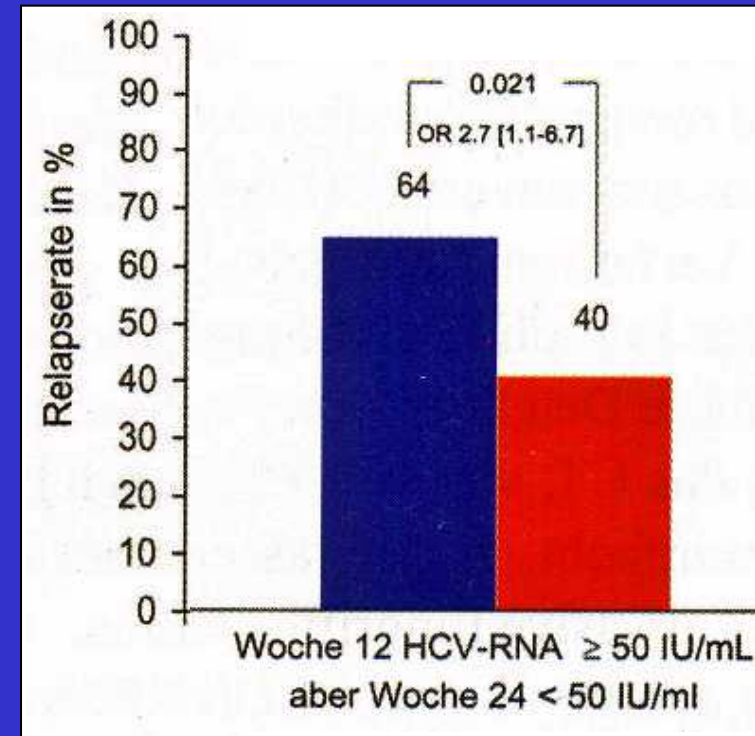
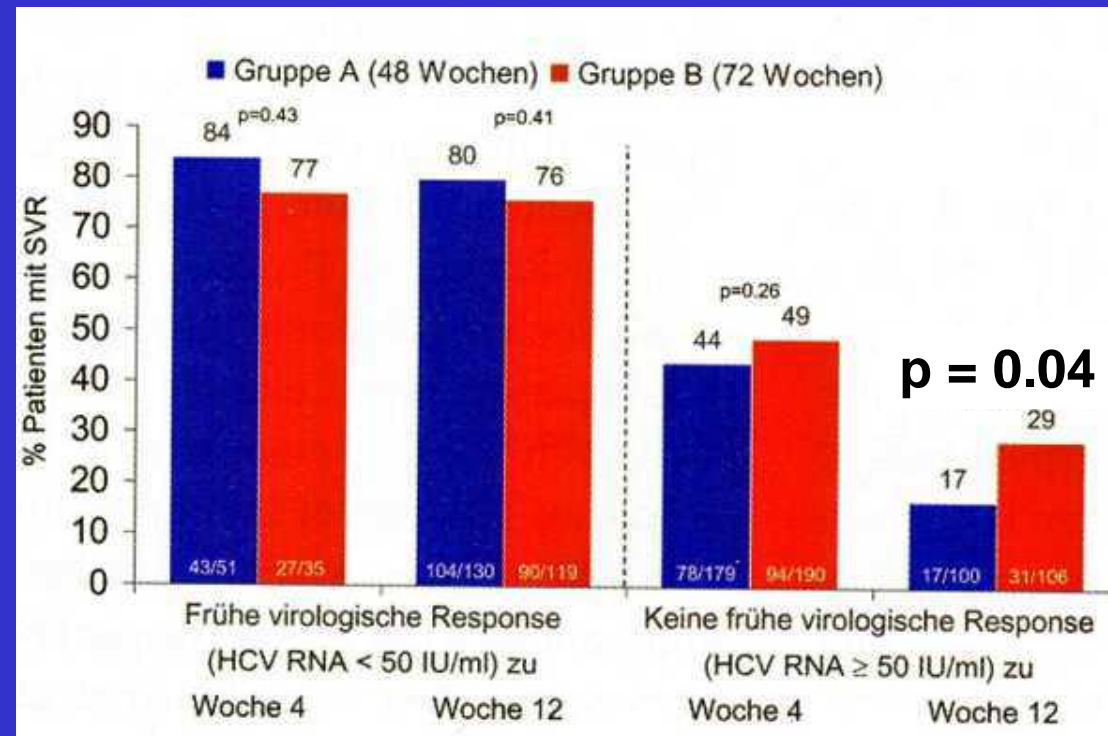
Dalgard et al.	Hepatology 2004	14 vs. 24 W	90%
v. Wagner et al.	Gastroenterology 2005	16 vs. 24 W	92% (GT2)
	hohe VL (>600KU/ml)		59% (GT3)
	niedrige VL (<600KU/ml)		85% (GT3)
Mangia et al.	N Engl J Med 2005	12 vs. 24 W	87% (GT2)
			77% (GT3)
Yu et al.	Gut 2006	16 vs. 24 W	94% (GT2)

## Genotype 4:

Kamal et al.	Gut 2005	36 vs. 48 W	66%
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# Individualised HCV-Therapy

Prolonged treatment duration  
in the presence of delayed response



Berg et al.

Sanchez-Tapia et al.

Gastroenterology 2006; 130: 1086

Gastroenterology 2006; 131: 451

# New Oral Small Molecule Antivirals in Development for the Treatment of HCV

Drug name	Drug class	Preclinical	Phase I	Phase II	Phase III
MK-0608 (Merck)	Nucleoside polymerase inhibitor	X			
R7128 (Pharmasset & Roche)	Nucleoside polymerase inhibitor		X		
NIM811 (Novartis)	Cyclophilin inhibitor		X		
ITMN-191 (InterMune & Roche)	Protease inhibitor		X		
MK-7009 (Merck)	Protease inhibitor		X		
BI12202 (Boehringer)	Protease inhibitor		X		
BI 1220 (Boehringer)	Nucleoside polymerase inhibitor		X		
R1626 (Roche)	Nucleoside polymerase inhibitor			X	
DEBIO-025 (Debiopharm)	Cyclophilin inhibitor			X	
Telaprevir (Vertex Pharmaceuticals)	Protease inhibitor				X
Boceprevir (Schering-Plough)	Protease inhibitor			X	
TMC435350 (Tibotec & Medivir)	Protease inhibitor			X	

Adapted from Manns MP et al. *Nat Rev Drug Discovery*. 2007;6:991-1000.

# **Conclusion:**

## **Therapy of Hepatitis C**

**Interferon-Ribavirin combination therapy is the current gold standard**

**Presence: Individualized Therapy depending on genotype and kinetics of HCV viral load under combination therapy**

**Future: Intensified Therapy with use of new HCV drugs targeting specific enzymes in the HCV replication life-cycle**

# Chemoprophylaxis and HCC in Hepatitis C



## Meta-Analyses:

Larsson & Wok 2007 (240 000 Persons)

43% Risk reduction if > 2 cups/d

Bravi et al. 2007 (3800 Patienten)

30% Risk reduction if 1 cup /d

55% Risk reduction if >2 cups/ d

Wakai et al. 2007 (111 000 Persons)

		<b>HCV+</b>	<b>HCV-</b>
Risik reduction:	1 cup /d	21%	38%
	>2 cup /d	61%	37%