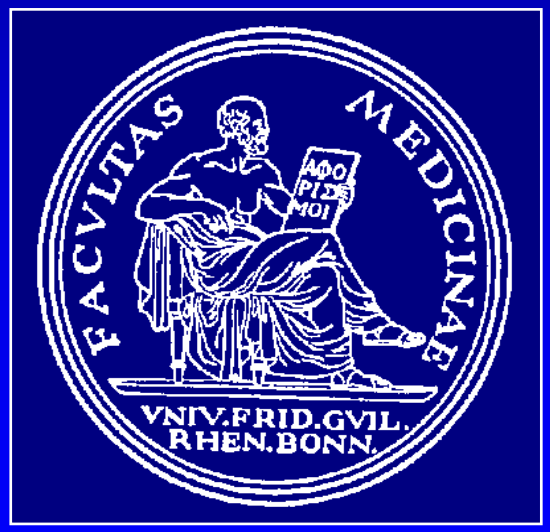
Treatment of hepatitis B and C



7th ESCMID Summer School, Regensburg, Germany, 19-25 July 2008

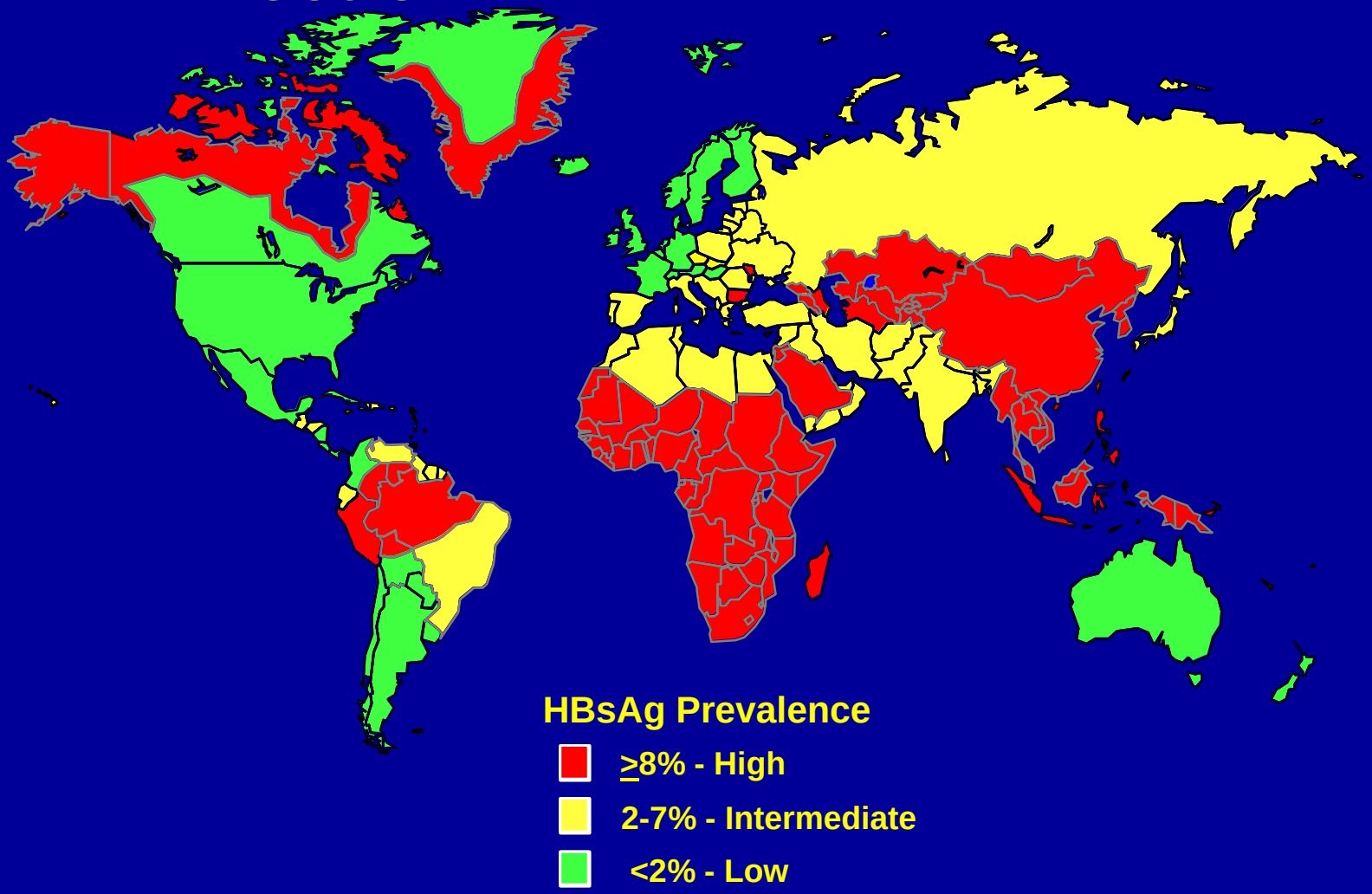
Jürgen Rockstroh

Department of Medicine I, University of Bonn

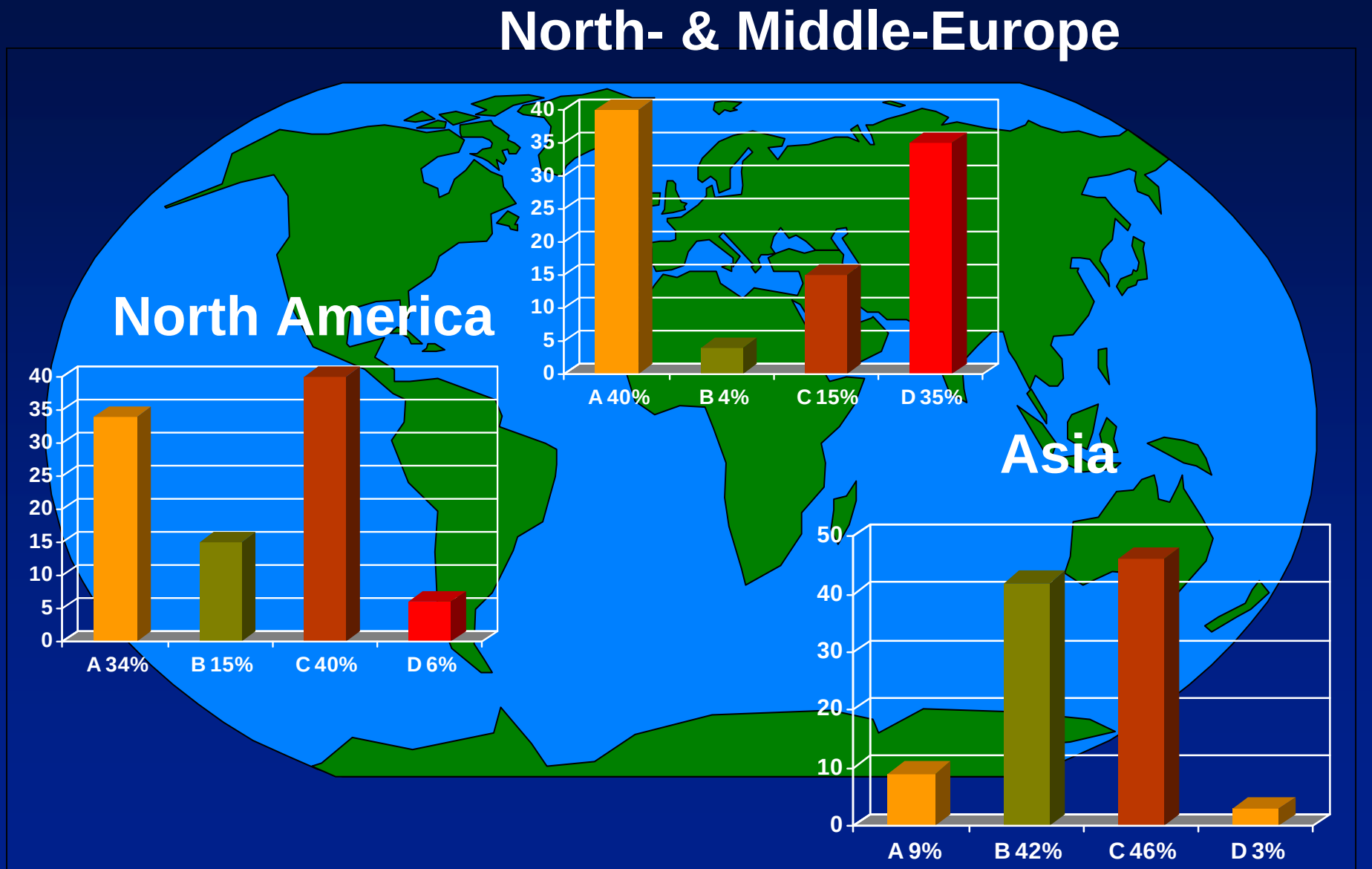
Global Disease Burden from Bloodborne Viral Infections

	Estimated no. chronic infections
HBV	370 million
HCV	130 million
HIV	33 million
HIV/HBV	(2-4 million)
HIV/HCV	(4-5 million)

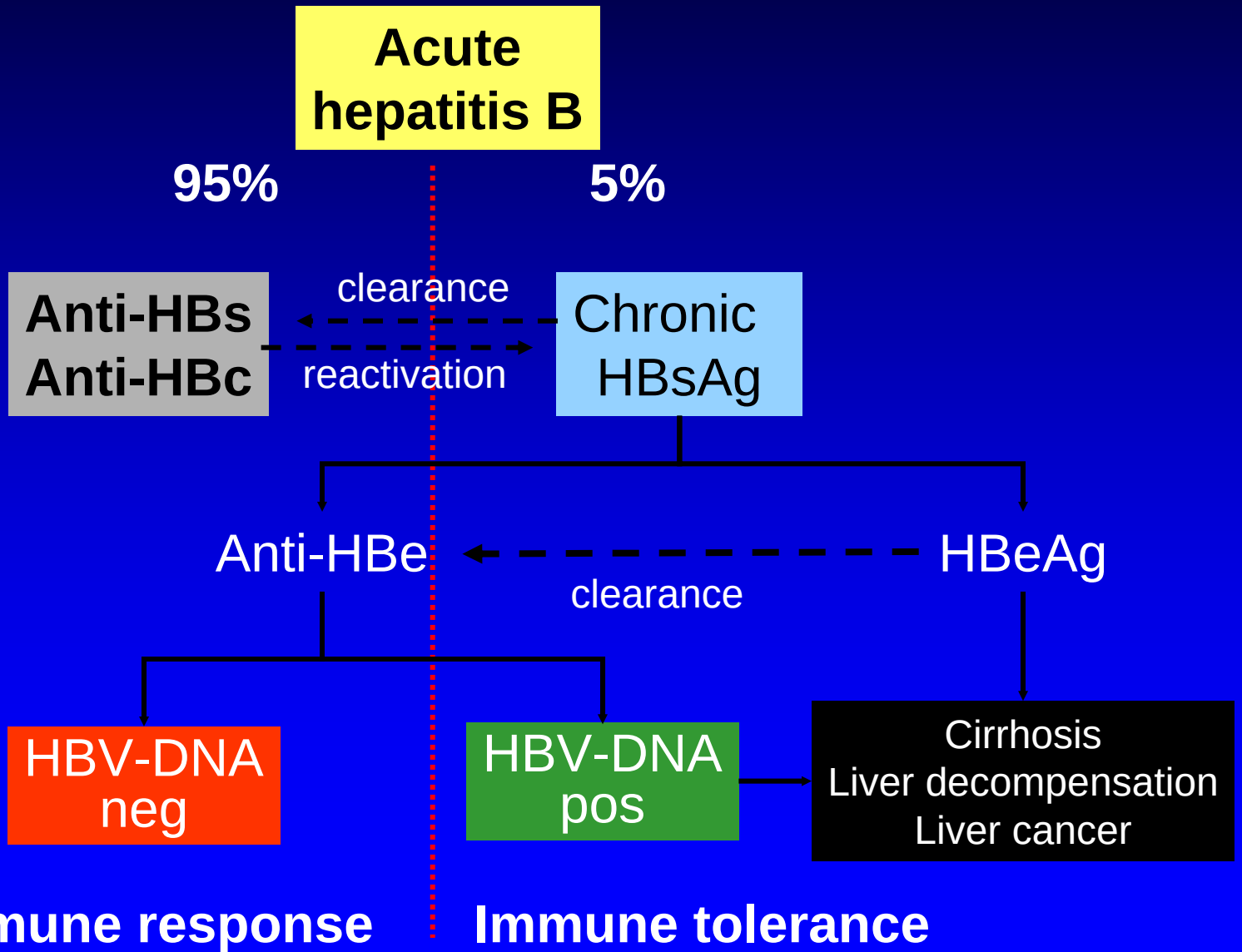
Geographic Distribution of Chronic HBV Infection



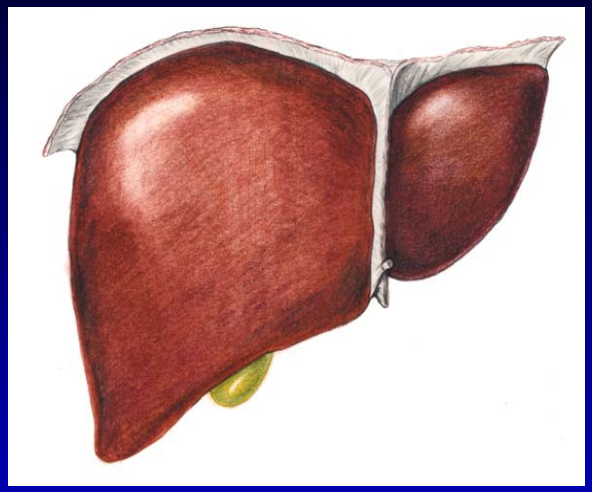
Hepatitis B: Genotypes



Natural history of HBV infection

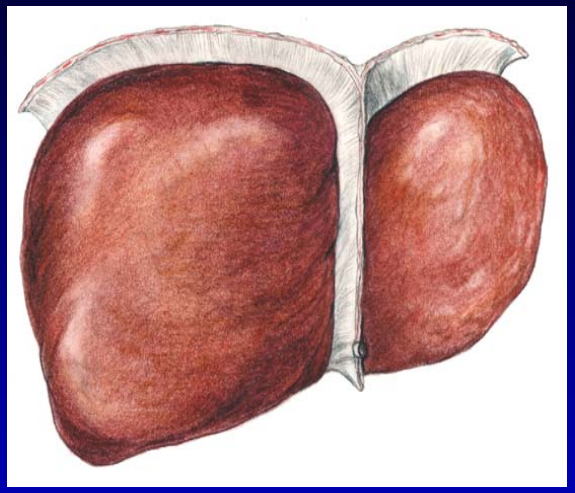


HBV infection



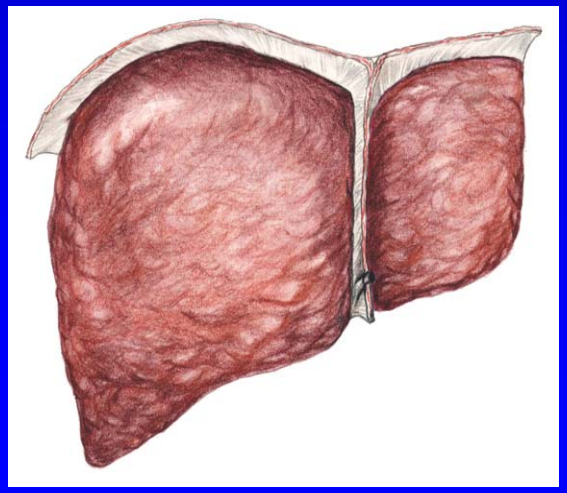
5-10% of all infected adults

chronic hepatitis

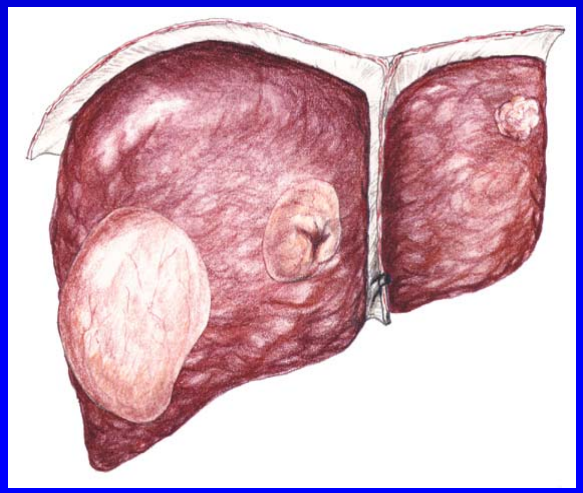


30%

cirrhosis



HCC



470.000 deaths yearly

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

Keeffe EB, Dieterich DT et al. 2006;4(8):936-62;

Chronic Hepatitis B

cut-off HBV DNA Viral load

REVEAL Study (prospective cohort study, Tawain)

Recruitment

1991 / 1992

Persons from 7 cities in Taiwan
(30-65 years, n = 89.293)

Voluntary participation
(n = 23.820)

Inclusion criteria
(HBsAg+, HBV DNA Test, no HCC, no HCV: n=3.653)
(in addition no cirrhosis: n=3.582)

Follow-up / Analyses

Juni 2004

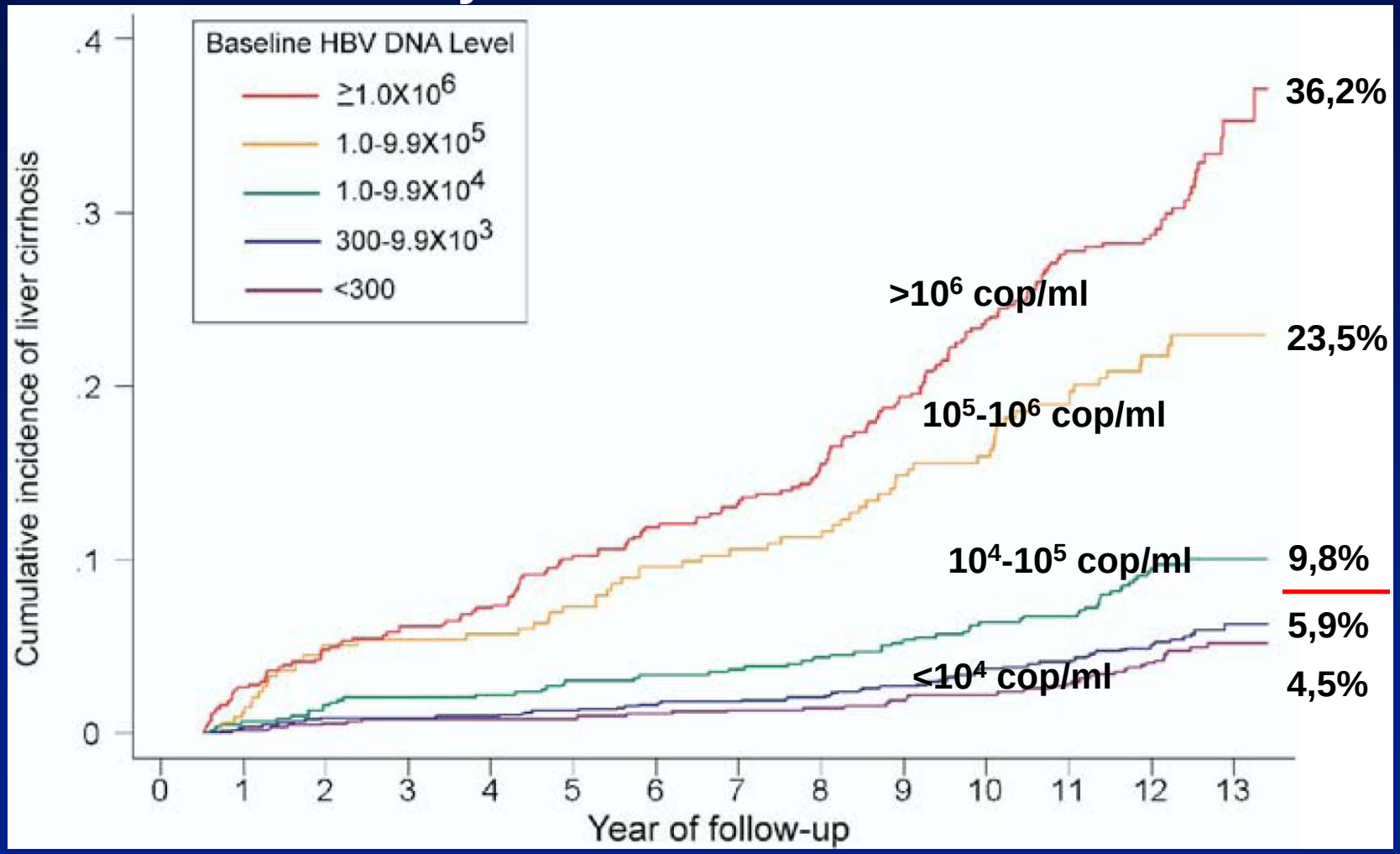
Analyses evaluating occurance of cirrhosis/ HCC
(Ultrasound Liver)
Restrictions: peri-/postnatal Infection, GT: B/C

Chen et al. JAMA 2006, Iloeje et al. Gastroenterology 2006

Chronic Hepatitis B

cut-off HBV DNA Viral Load

REVEAL Study: cumulative incidence cirrhosis

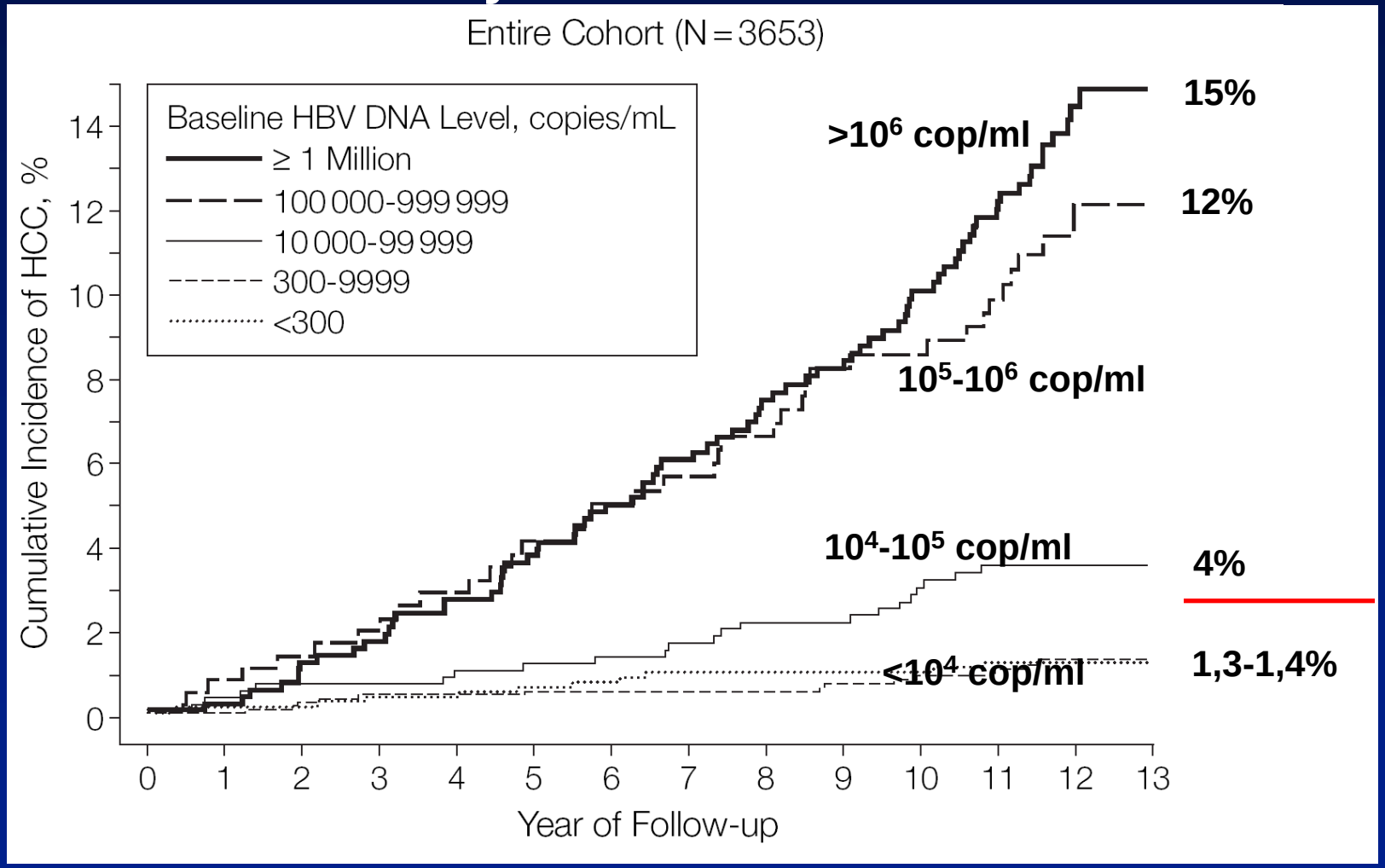


Iloeje,U.H. et al. Gastroenterology 2006

Chronic Hepatitis B

cut-off HBV DNA Viral Load

REVEAL Study: cumulative incidence HCC

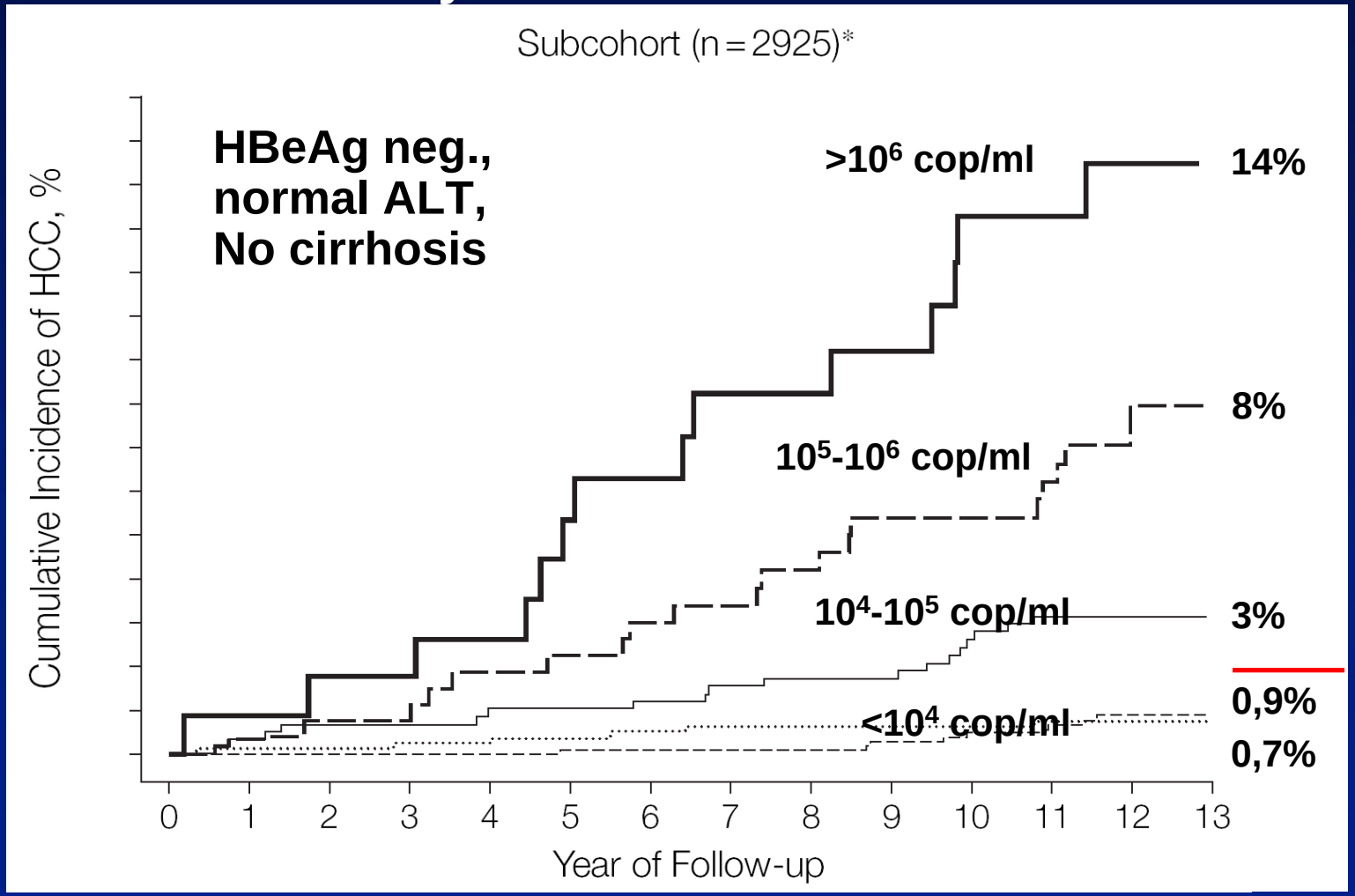


Chen et al. JAMA 2006

Chronic Hepatitis B

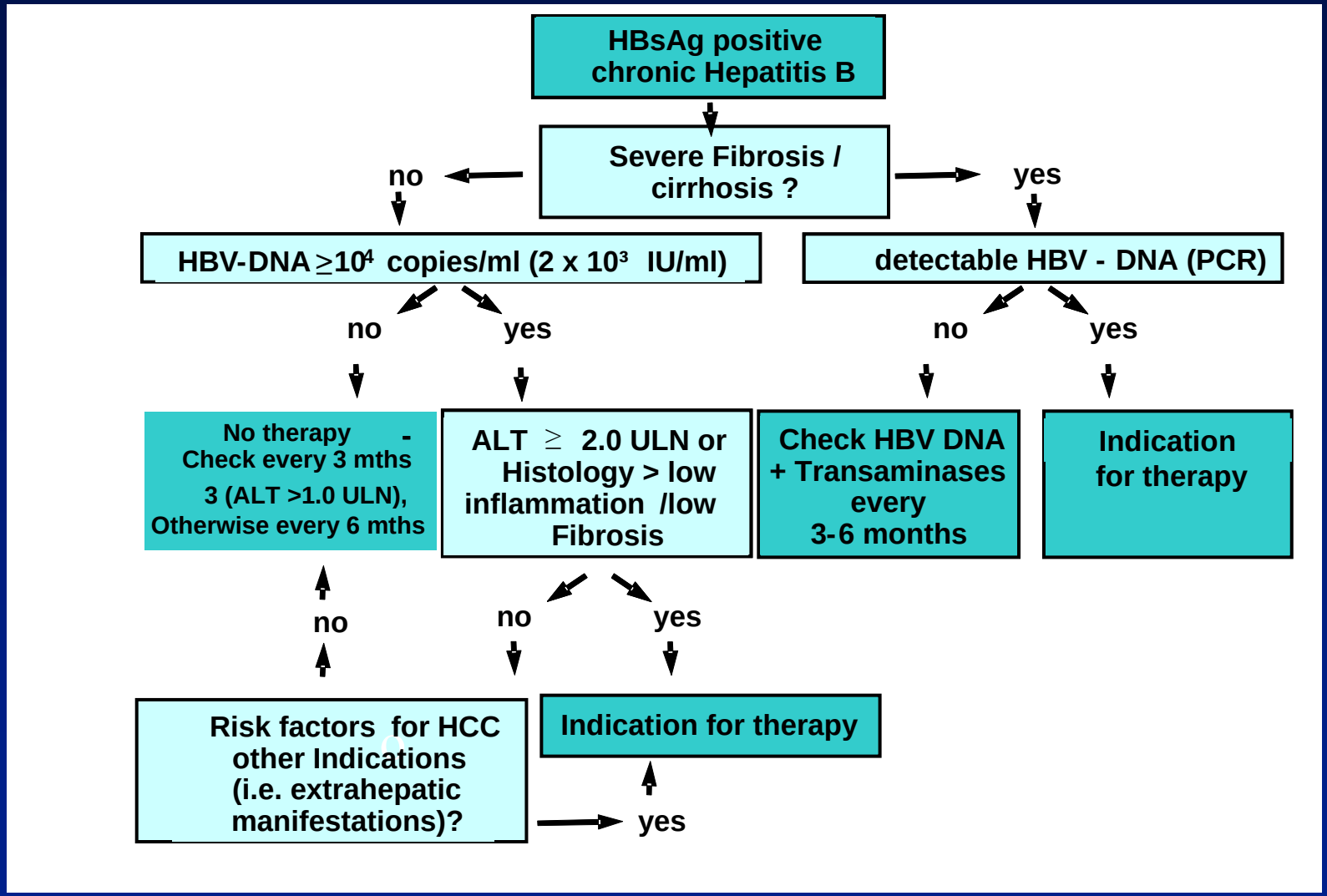
cut-off HBV DNA Viral Load

REVEAL Study: cumulative incidence HCC



Chen et al. JAMA 2006

Indication for chronic Hepatitis B Therapy



DGVS and GfV, Consensus Conference, Göttingen 2007

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:

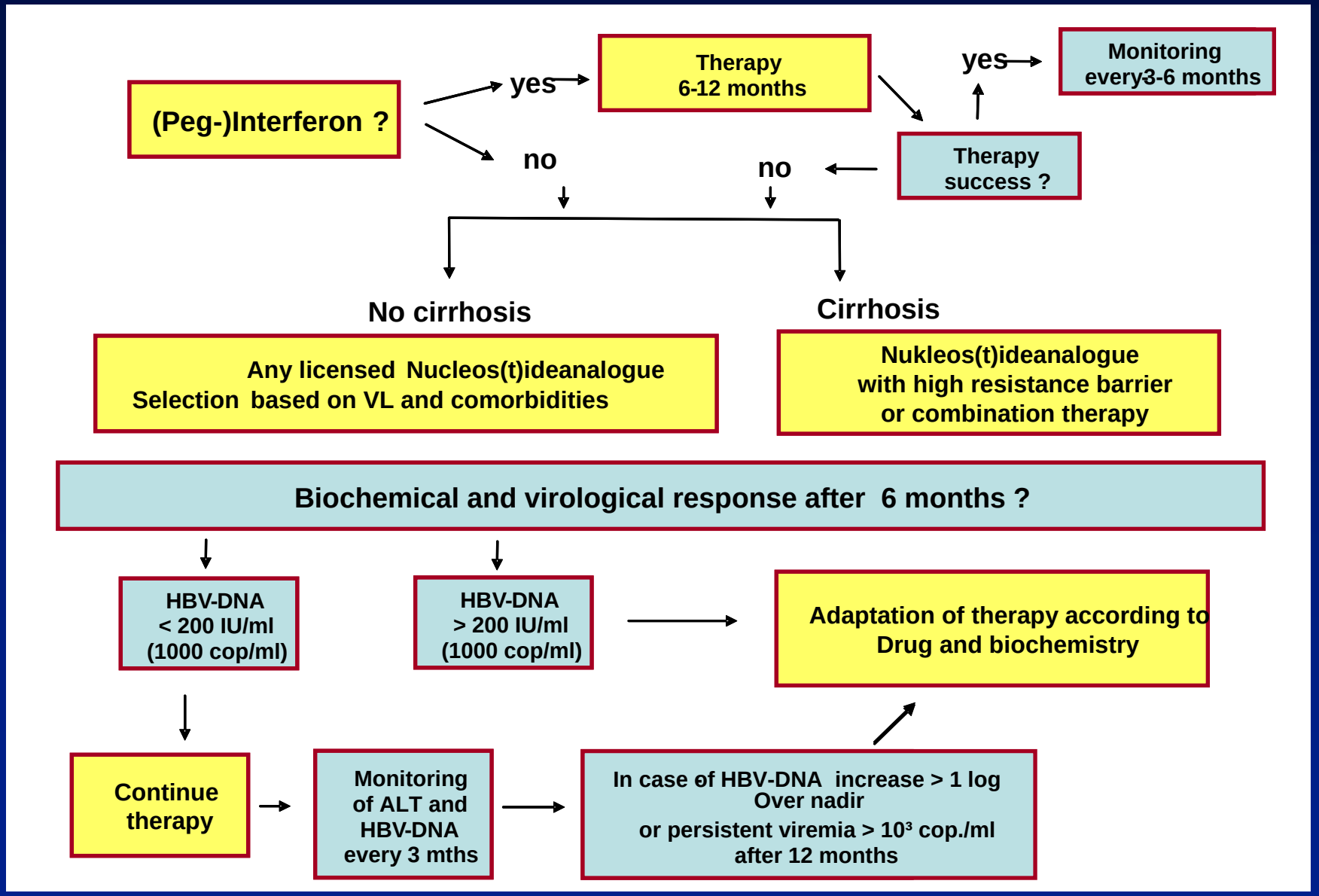
- HBV-DNA quantitative
- HBV-Genotyping (in case of therapeutic relevance)
- clinical-chemical Lab tests

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)

DGVS and GfV, Consensus Conference, Göttingen 2007

Treatment algorithm

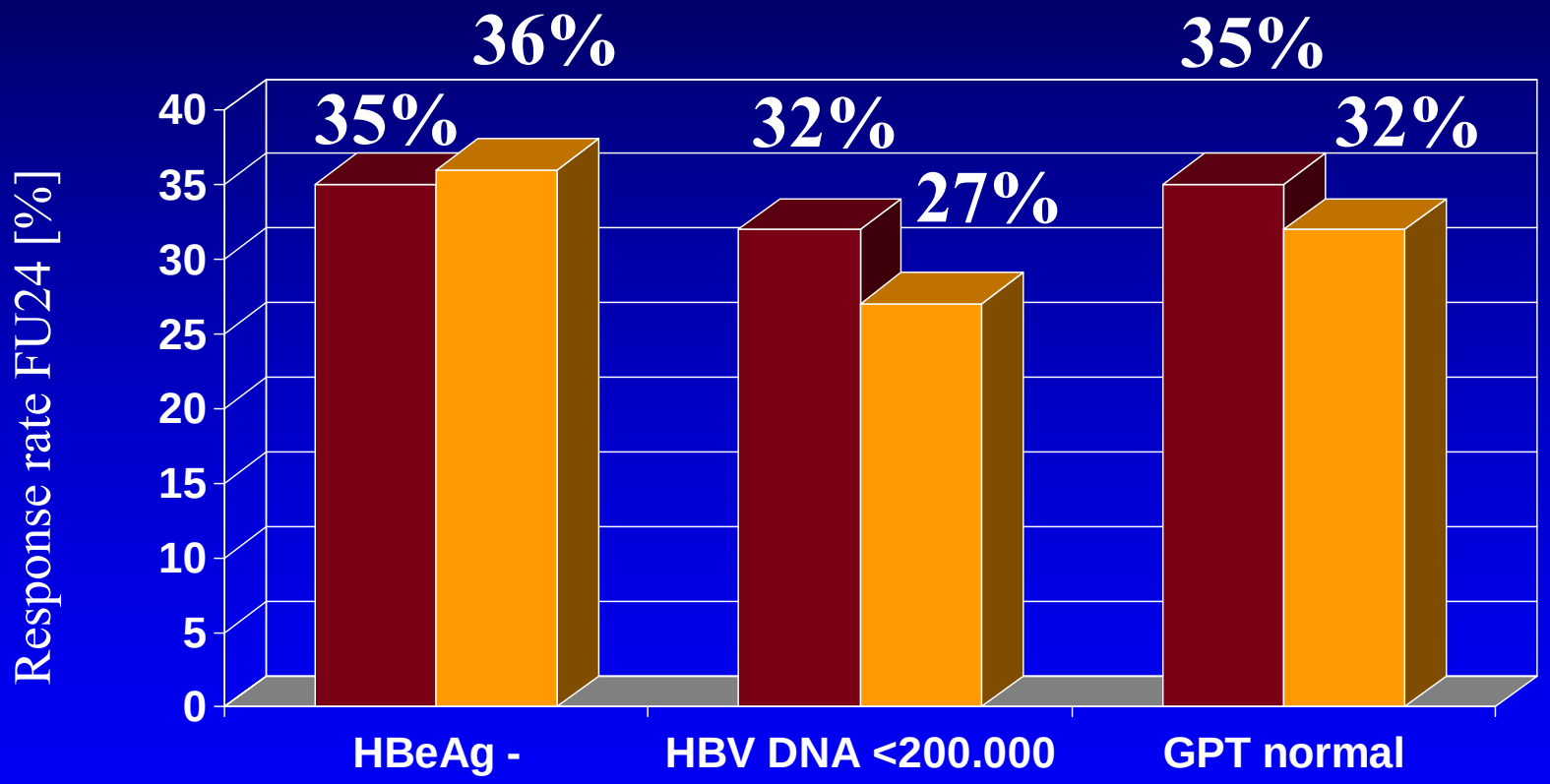


DGVS und GfV, Consensus Conference, Göttingen 2007

Treatment of HBV

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

Therapy of chronic Hepatitis B with PEG-IFN-α 2b
HBeAg pos.



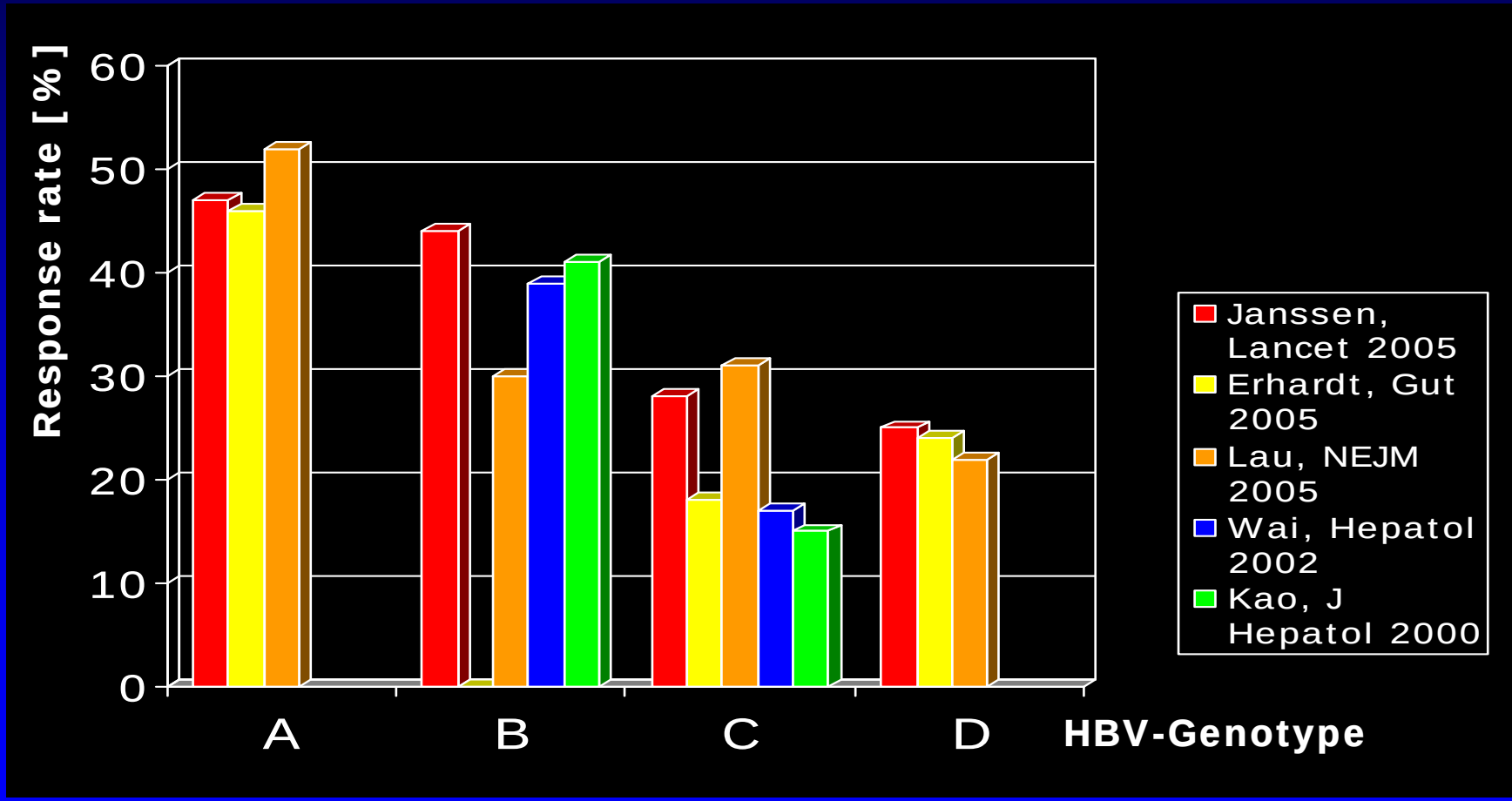
HBeAg pos.
n=266, 52 Weeks

PEG2b + Plac

PEG2b + Lami

Janssen et al., Lancet 2005

IFN Therapy in HBeAg+ Hepatitis B
Relevance of different HBV Genotypes

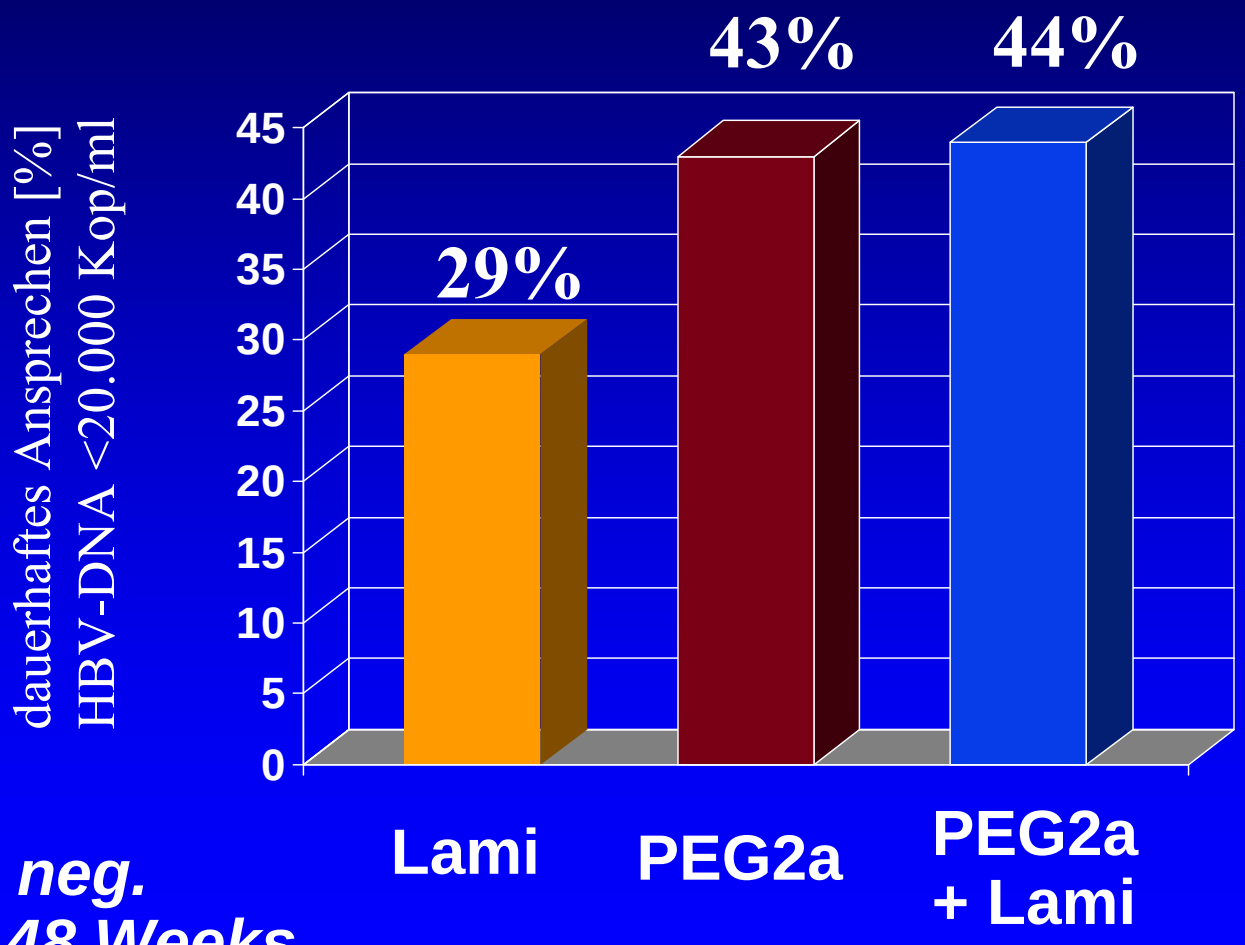


Favorable Factors for Interferon Therapy

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

Pegylated Interferon is the preferred interferon

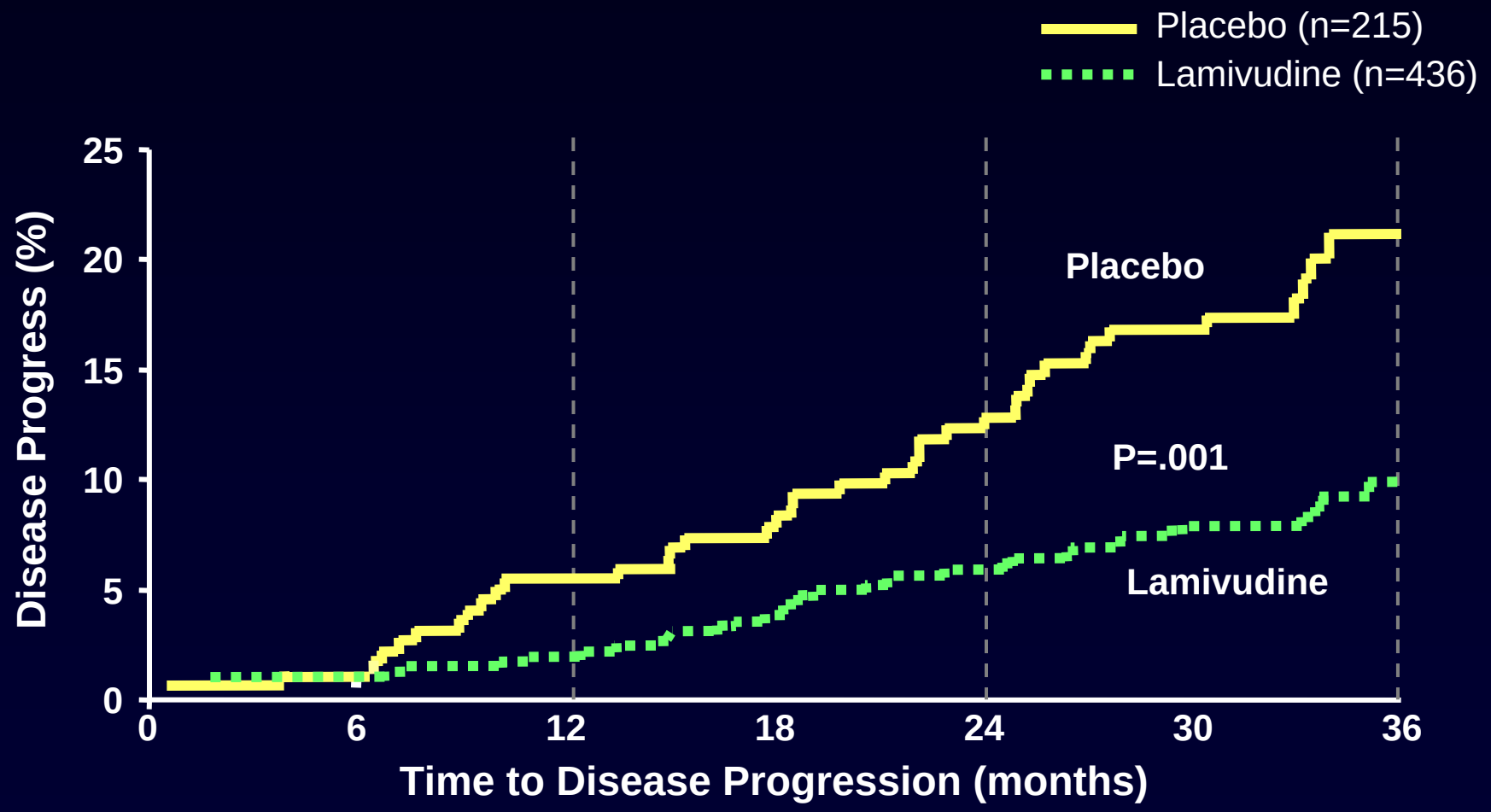
Therapy of chronic Hepatitis B with PEG-IFN-α 2a
HBeAg neg



HBeAg neg.
n=537, 48 Weeks

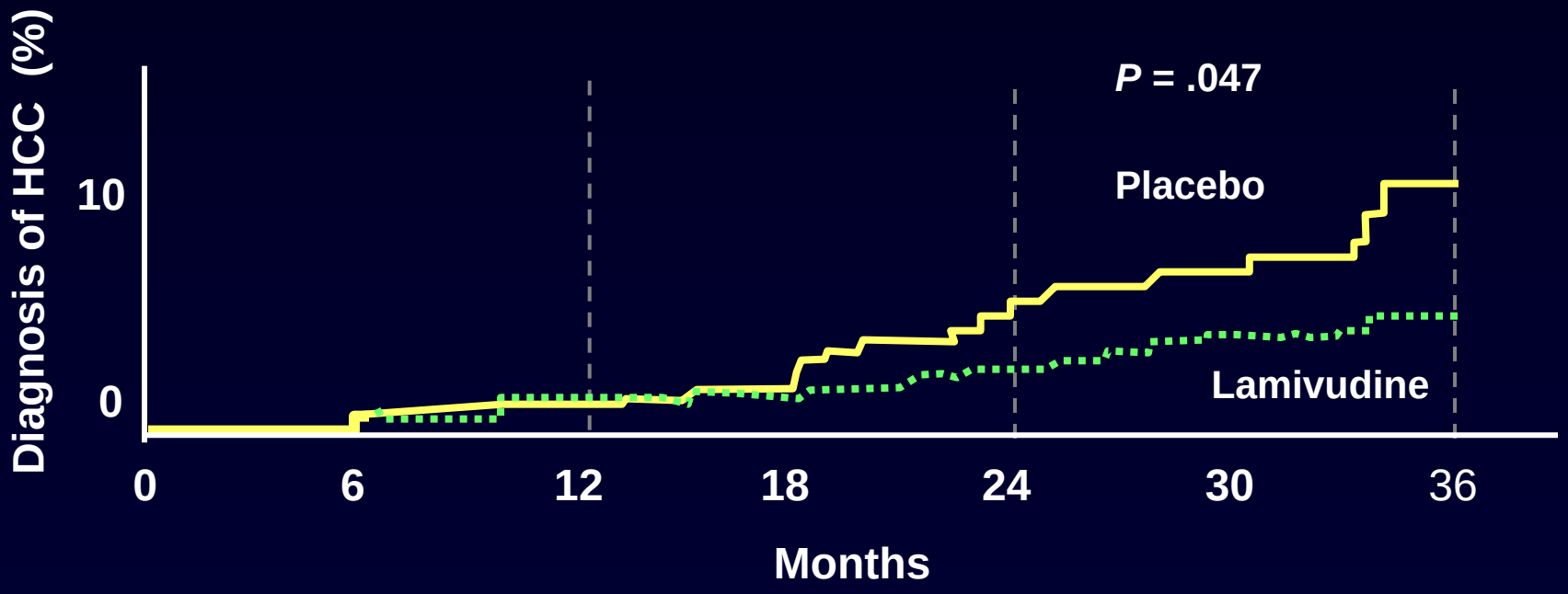
Marcellin et al., NEJM 2004

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



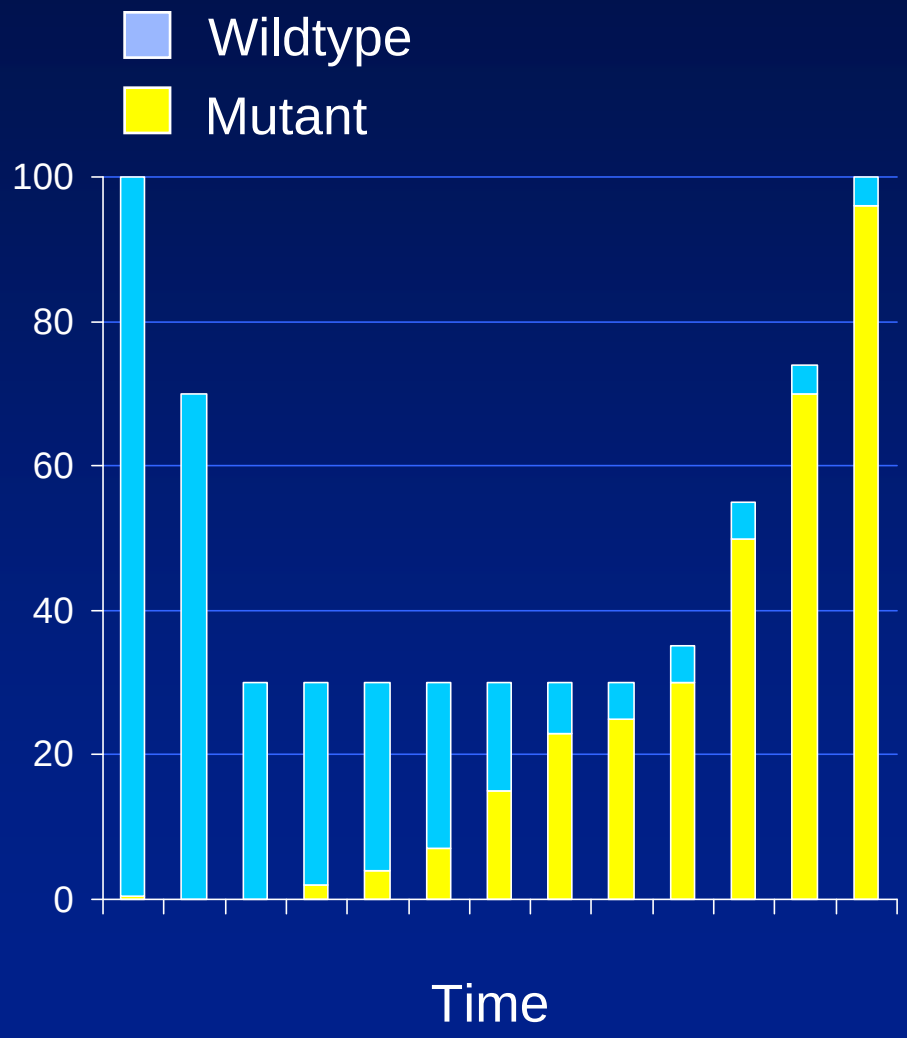
Liaw YF, et al. *N Engl J Med*. 2004;351:1521-1531.

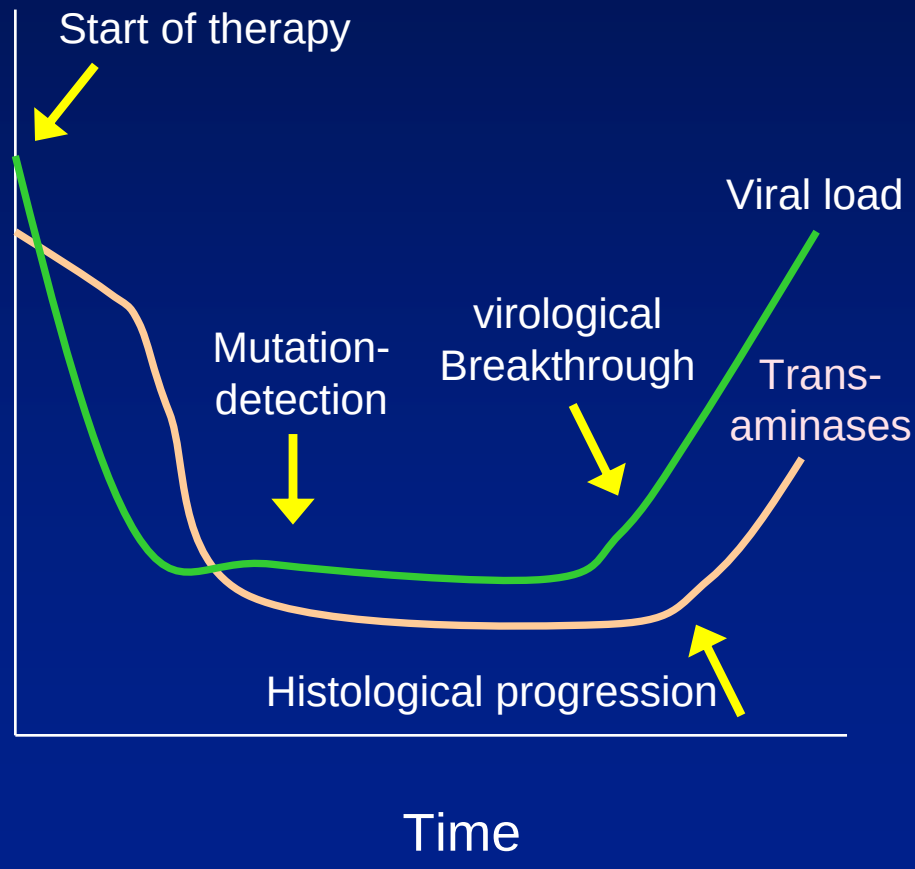
Effect of Rx (lam) on Incidence of HCC in Patients with Advanced Fibrosis



Liaw YF, et al. N Engl J Med. 2004;351:1521-1531.

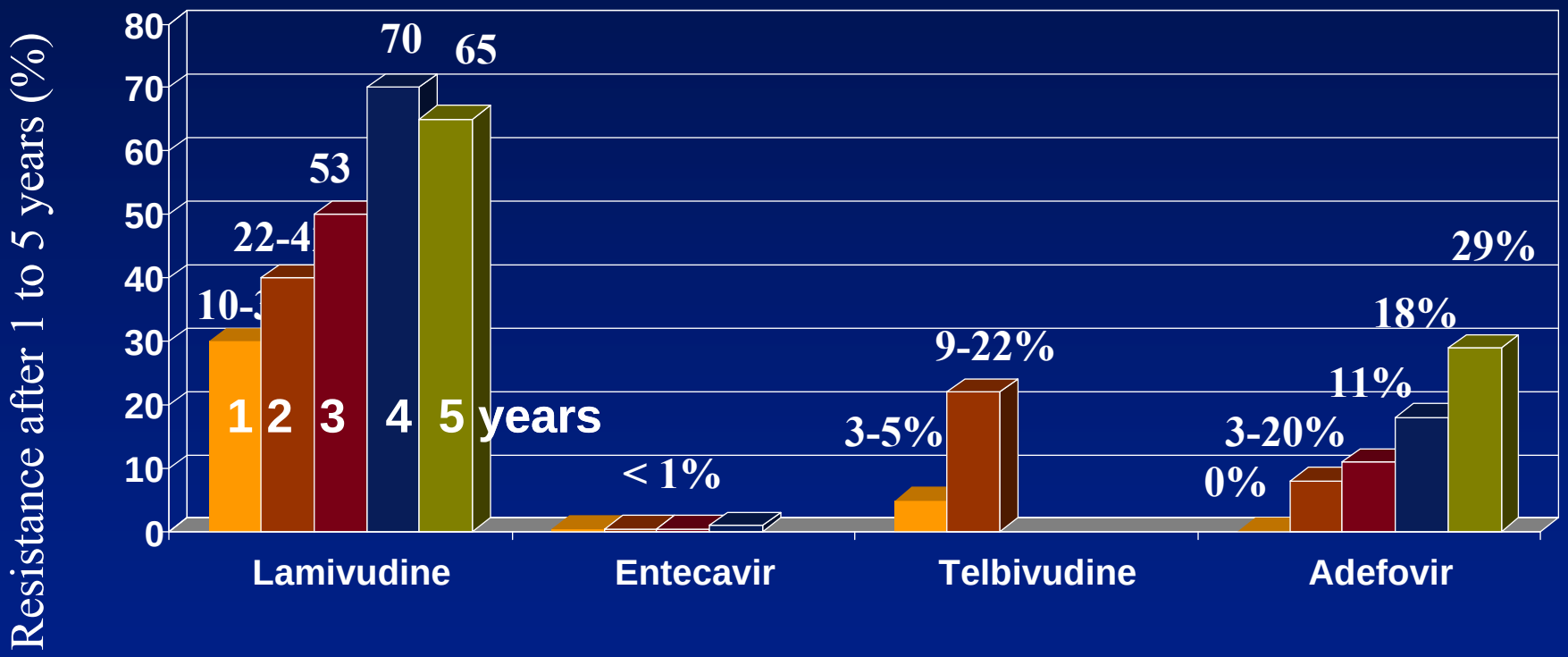
Development of antiviral resistance





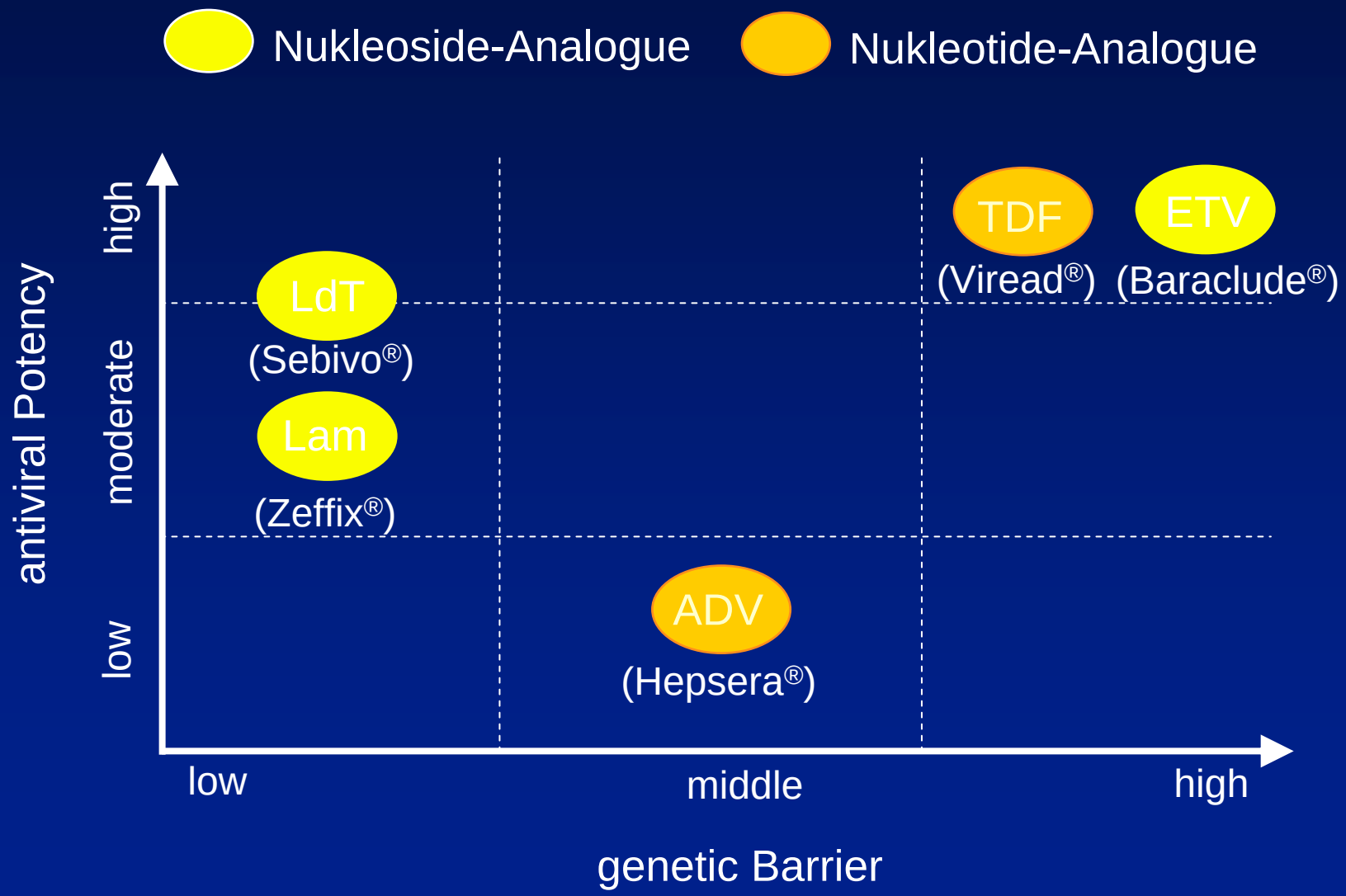
Therapy of chronic HBV with Polymersase Inhibitors

HBeAg neg.: genetic Barrier

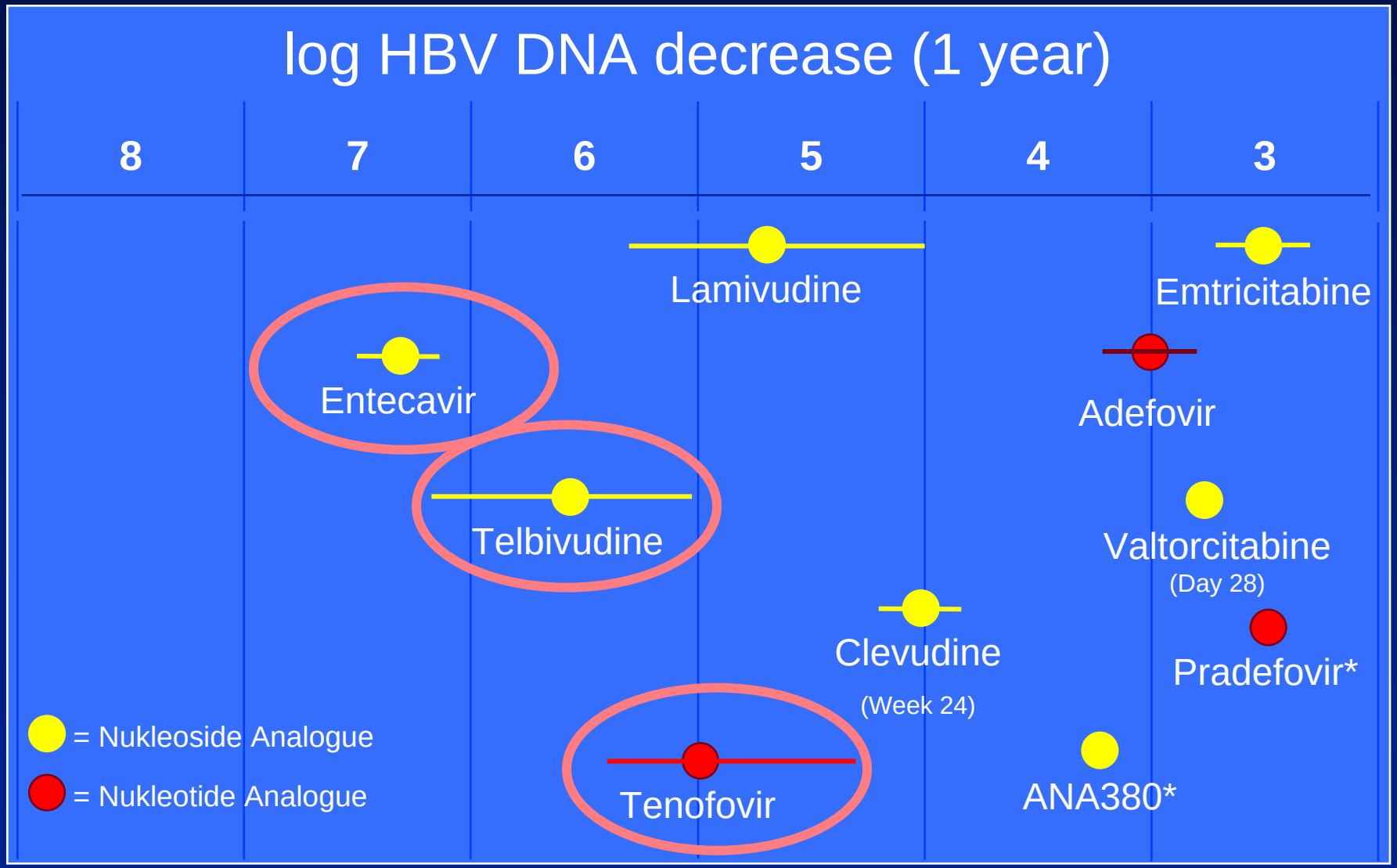


Lai et al., AASLD 2005
Marcellin et al., NEJM 2003
van Bömmel et al., Hepatology 2004
Lai CL et al., NEJM 2006
Colonno et al. EASL 2007

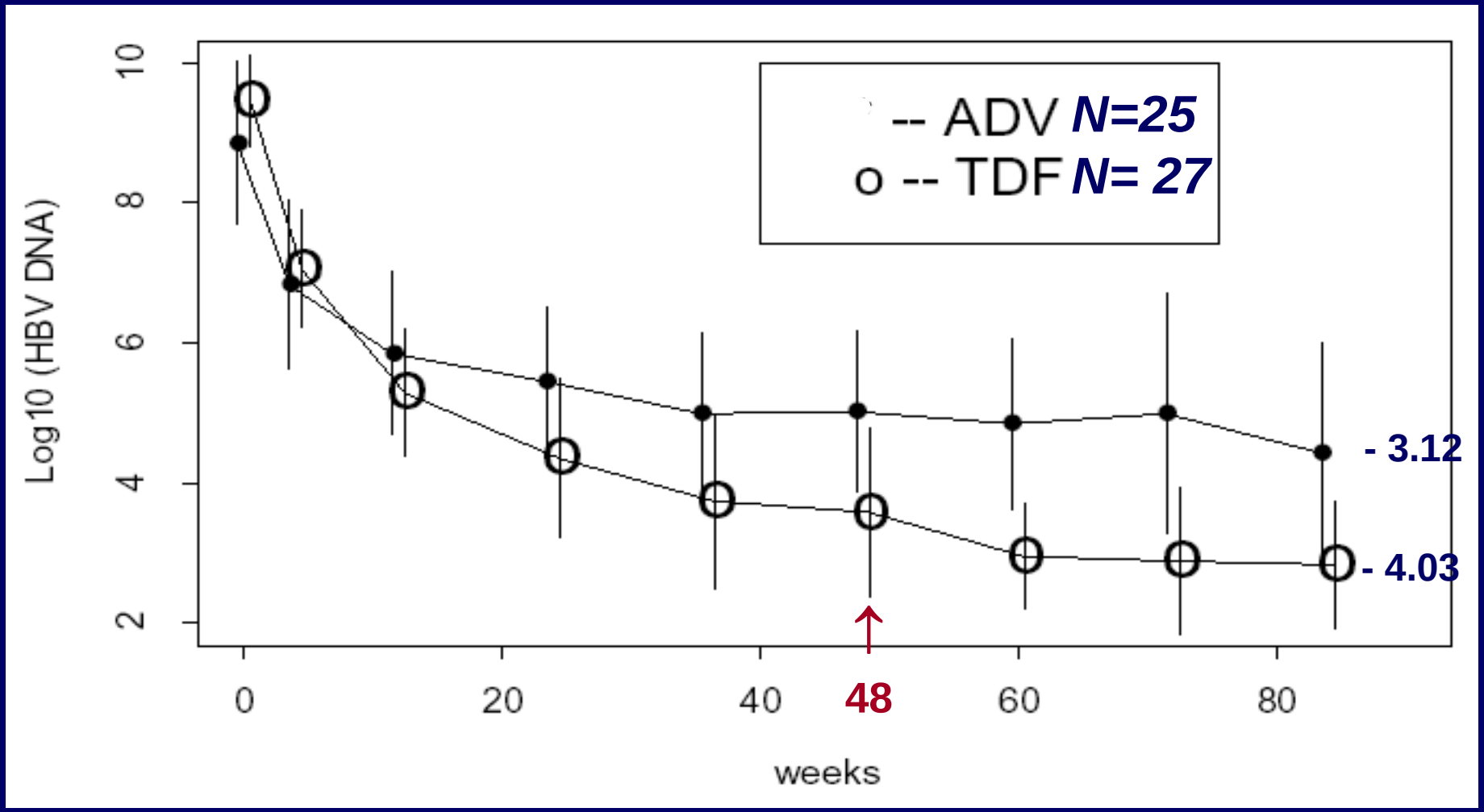
Characteristics of different Nukleos(t)ide-Analogues



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

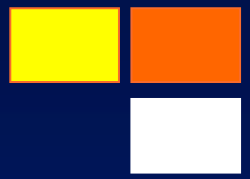


ADV vs TDF in HIV/HBV co-infected patients
Mean serum HBV DNA



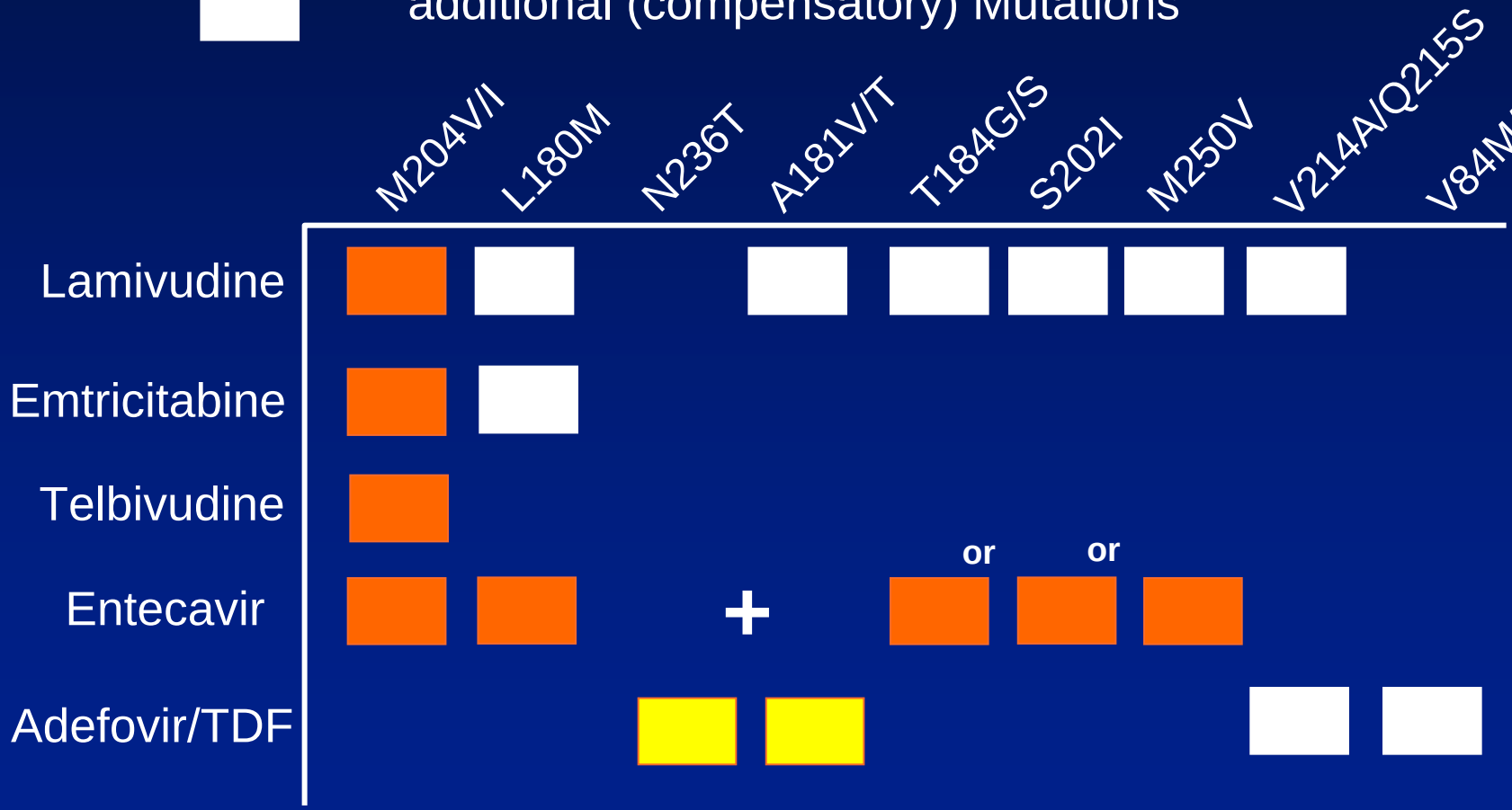
Peters M et al. CROI 2005

Nukleos(t)id-Analogue Resistance-associated Mutations



Mutations associated with virological breakthrough

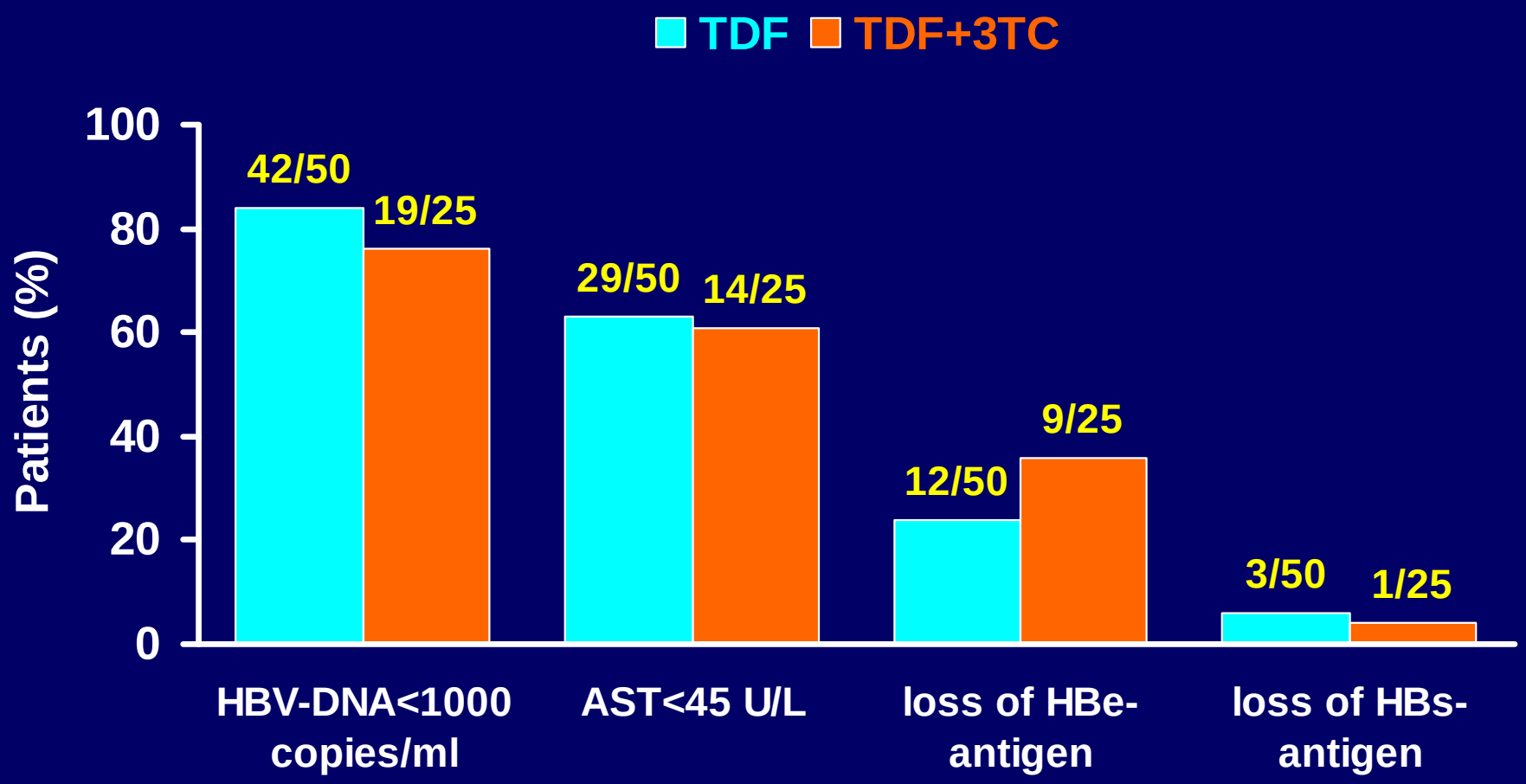
additional (compensatory) Mutations



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

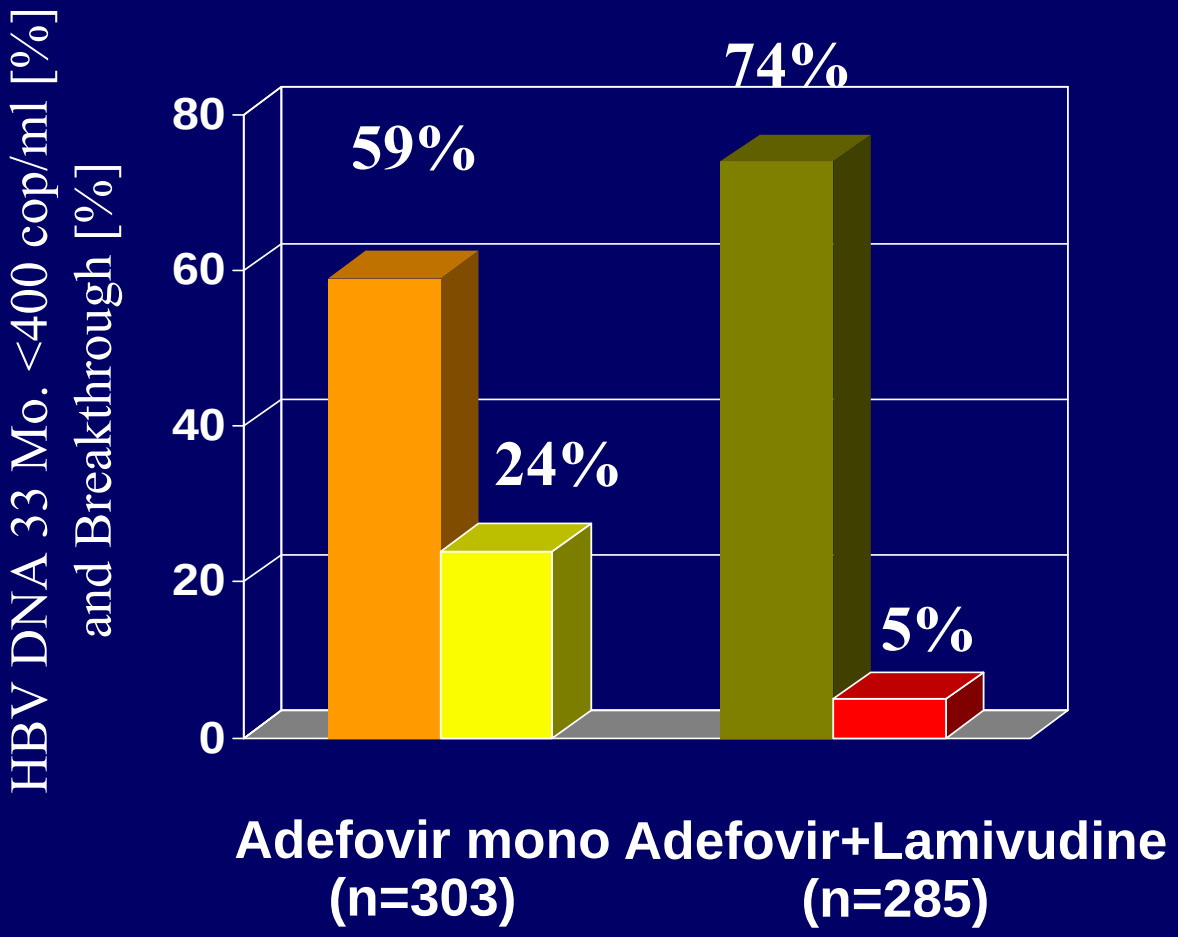
Tenofovir vs. Tenofovir + Lamivudin

(HBV/HIV-coinfection)



Schmutz G. et al. AIDS 2006

Lamivudin-Resistence
Switch to Adefovir versus Add-on



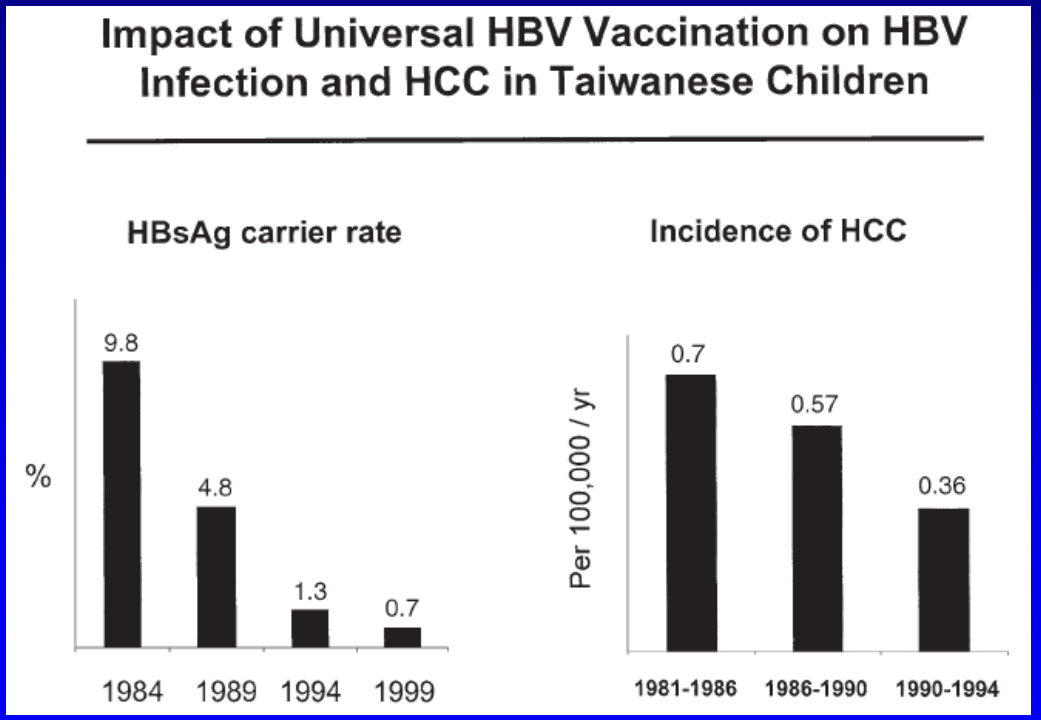
- HBe-Ag neg.
- n=588
- Lam.-Resistance
- switch vs. add-on
- Mean follow-up 33 Months
- Kreatinine increase in 8% of cases

Lampertico et al. AASLD 2006

Treatment goal and duration

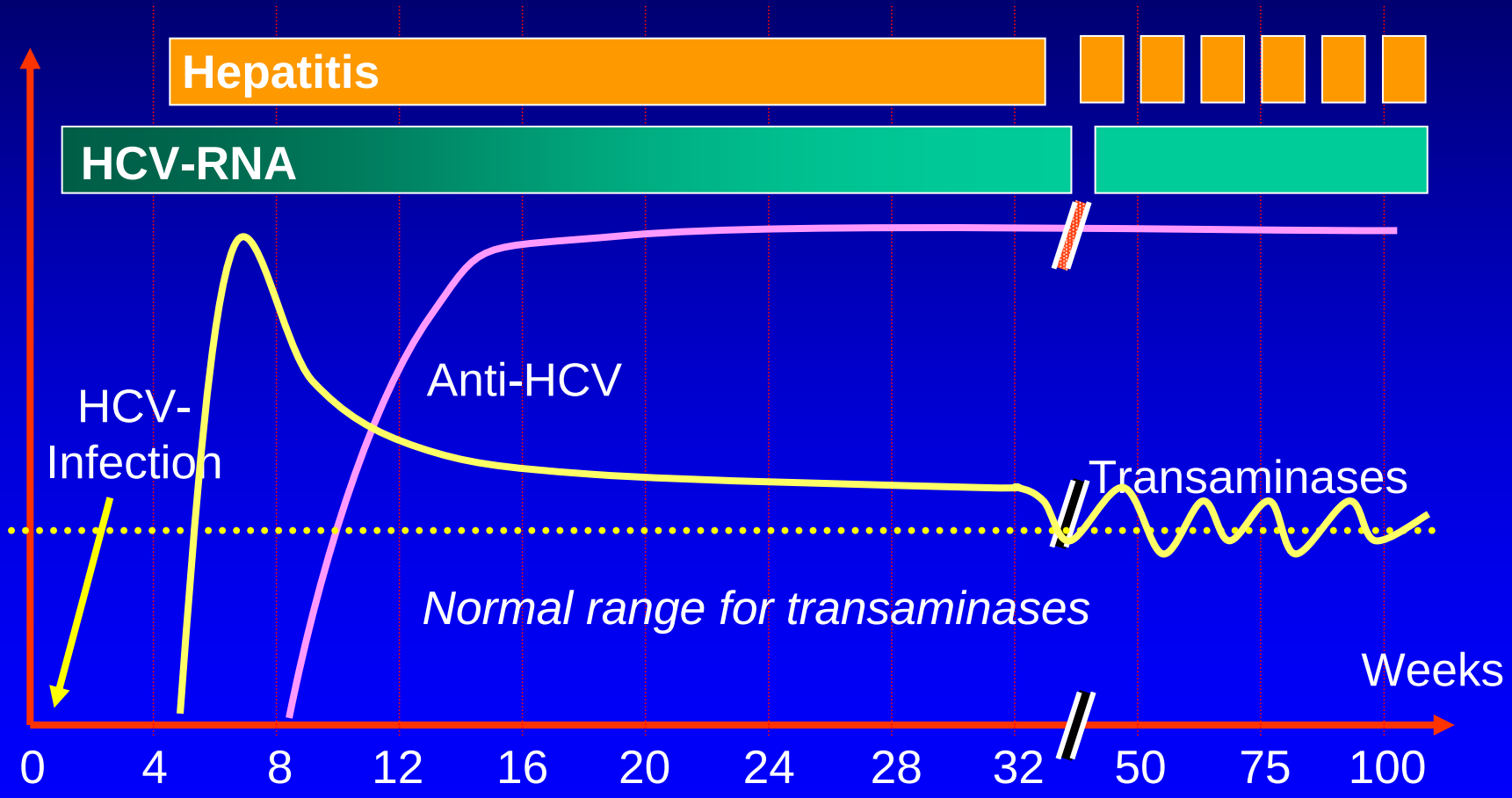
- IFN: **treatment length 48 weeks for PEG INF; goal HBe and HBs-Ag seroconversion**
- **for the nucleoside analogues: HBsAg seroconversion + 6-12 mths.**
- **anti-HBV therapy may be stopped cautiously in HBeAg+ patients who have achieved HBe-seroconversion or HBs-seroconversion for at least six months**
- 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 herapy 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



Nach Lok et al. Gastroenterology 2004

Natural Course of Hepatitis C Infection



Symptoms of Hepatitis C

- Fatique
- Inefficiency
- Abdominal pain or discomfort
- Arthritis

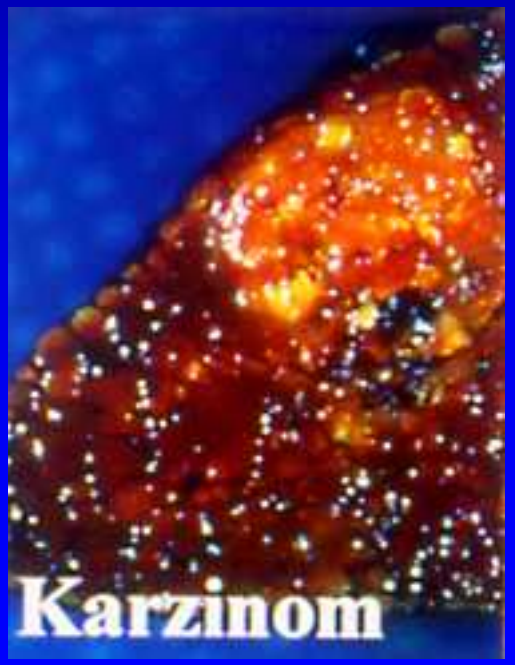
Mostly mild and unspecific

Chronic Hepatitis with Fibrosis 50%

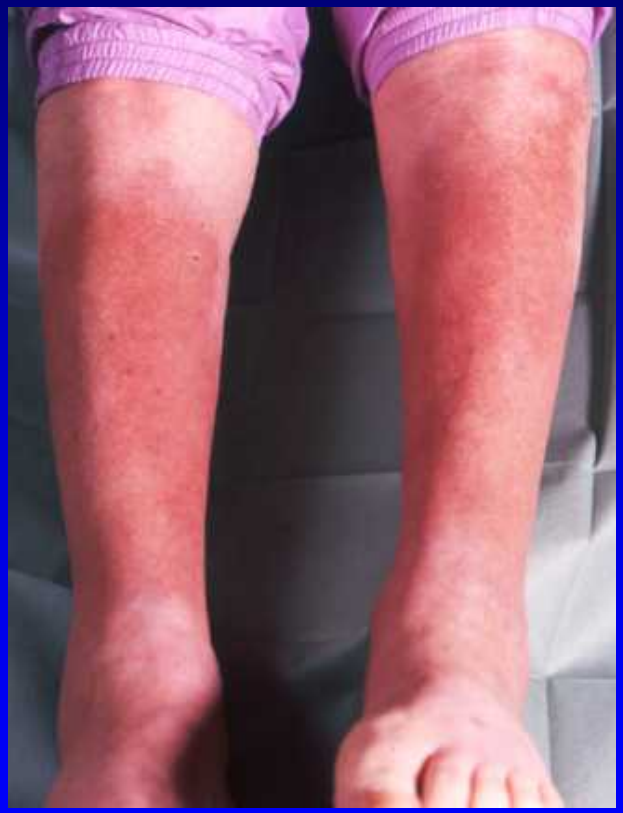
50-80% chronic Infection

Chronic Hepatitis without Fibrosis 50%

3-5 % / Year



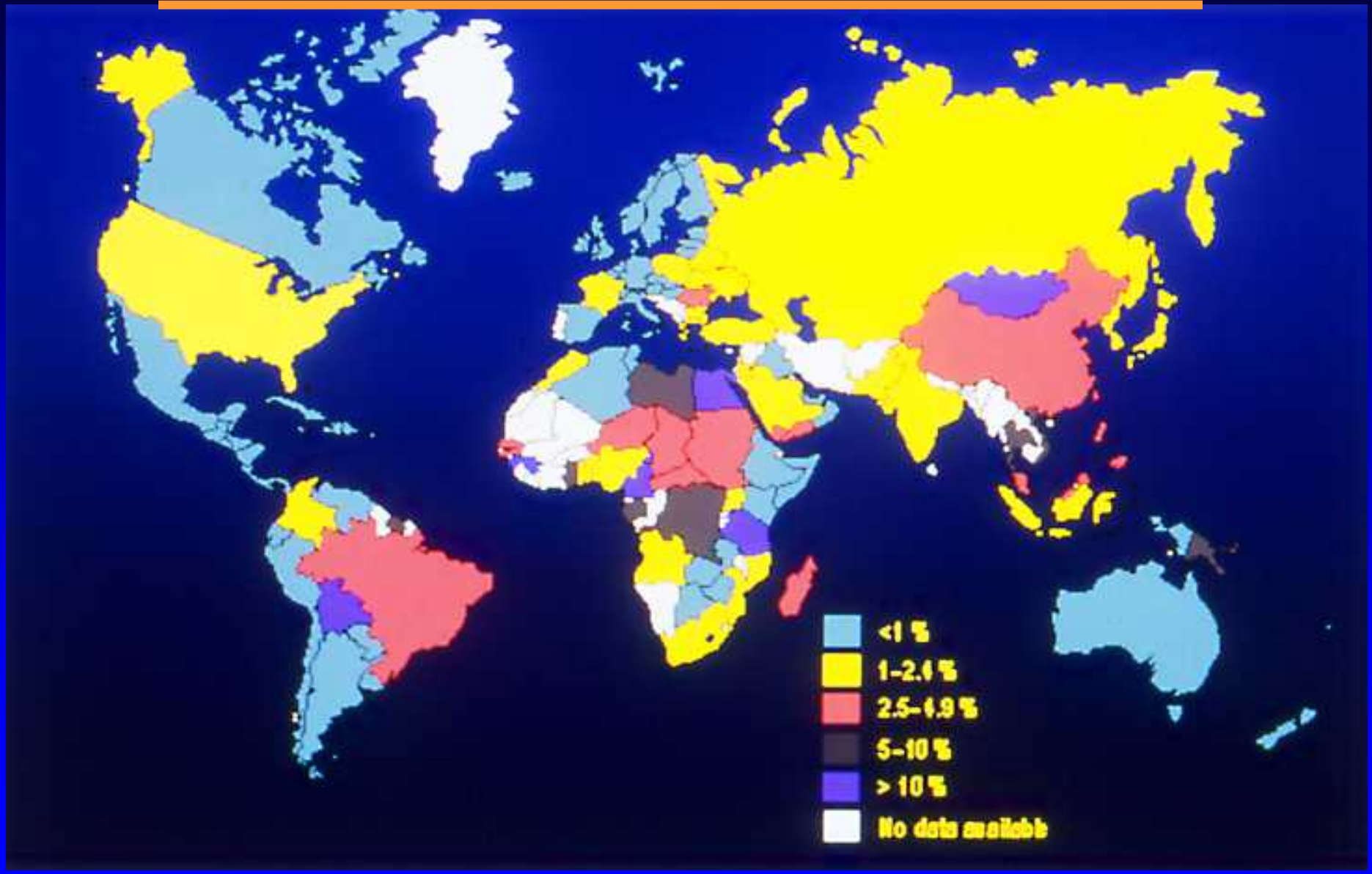
Extrahepatic Manifestations of Hepatitis C
Essential mixed cryoglobulinemia



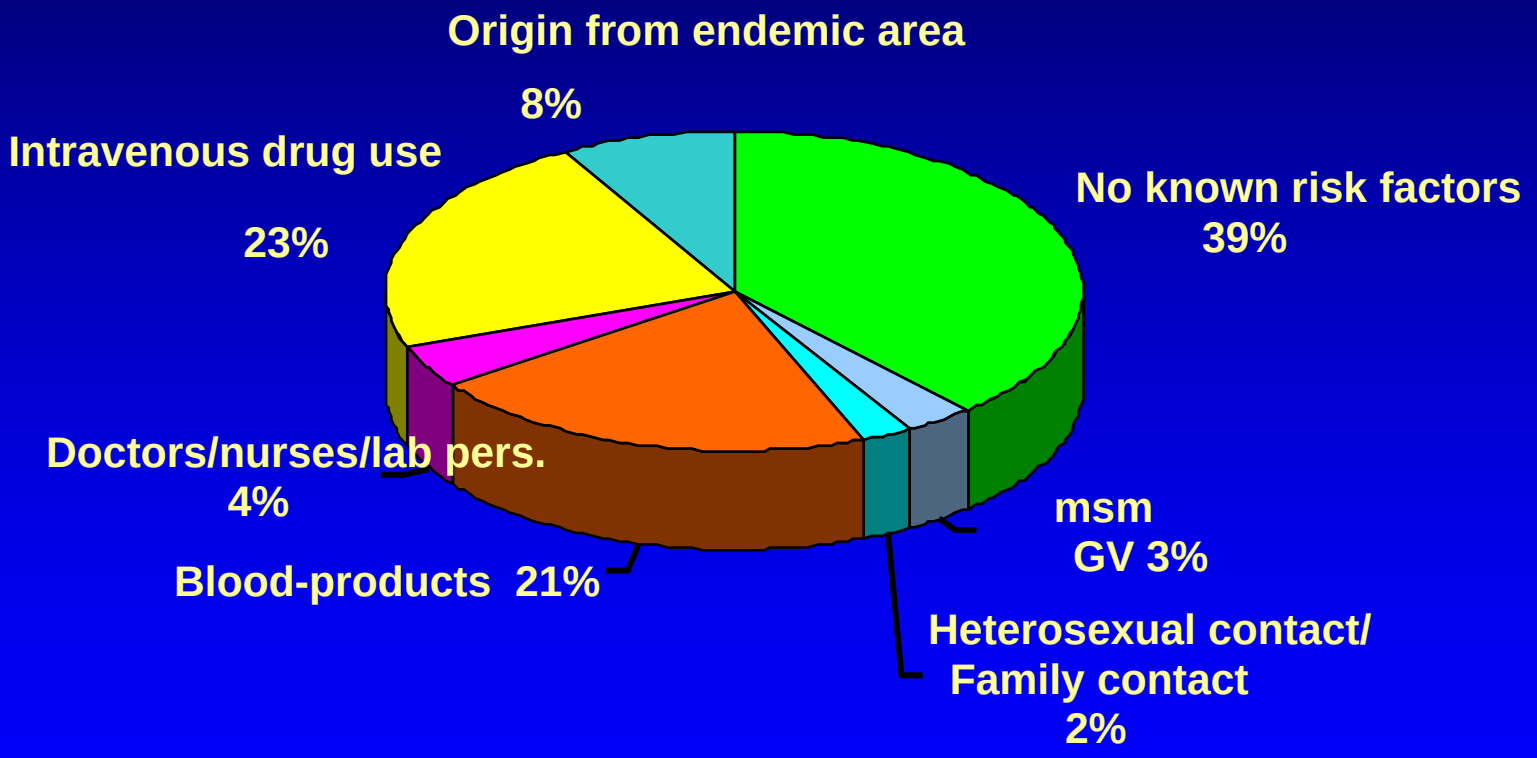
- Palpable Purpura
- Arthralgia
- weakness

- Involvement of nerves and kidney possible

Distribution of HCV

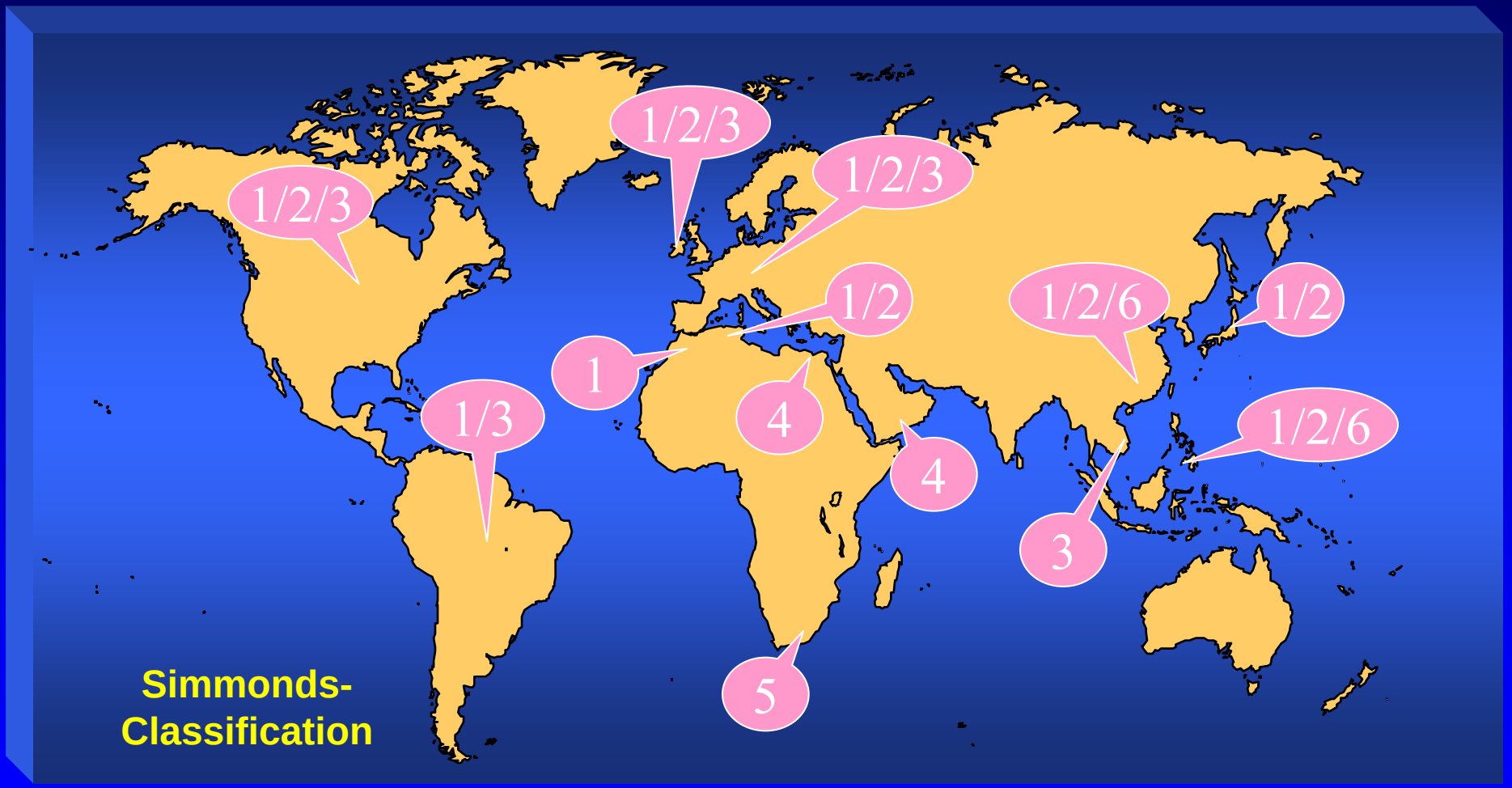


Hepatitis C - Possible transmission risk factors

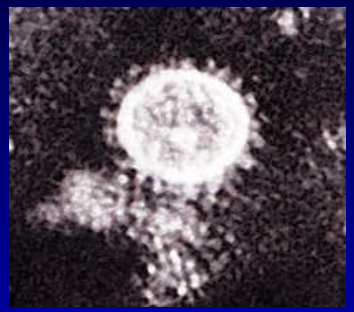


Niederau: Dtsch. Med. Wochensch 2000;127;563-566

Hepatitis C
Distribution of HCV-Genotypes



Structure of the Hepatitis C Virus



Drugs for treatment of Hepatitis C

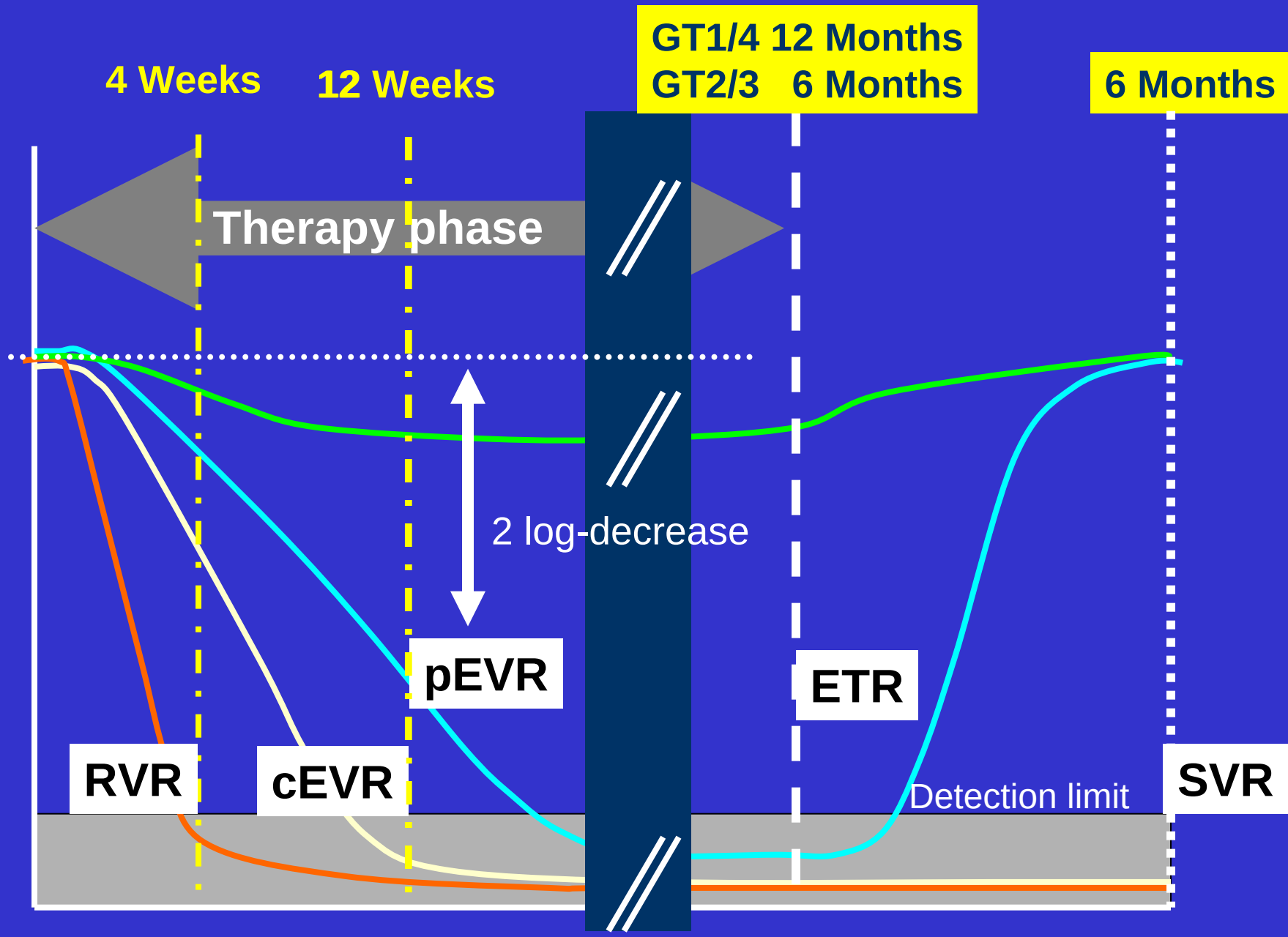
Pegylated Interferon alfa

1 x weekly

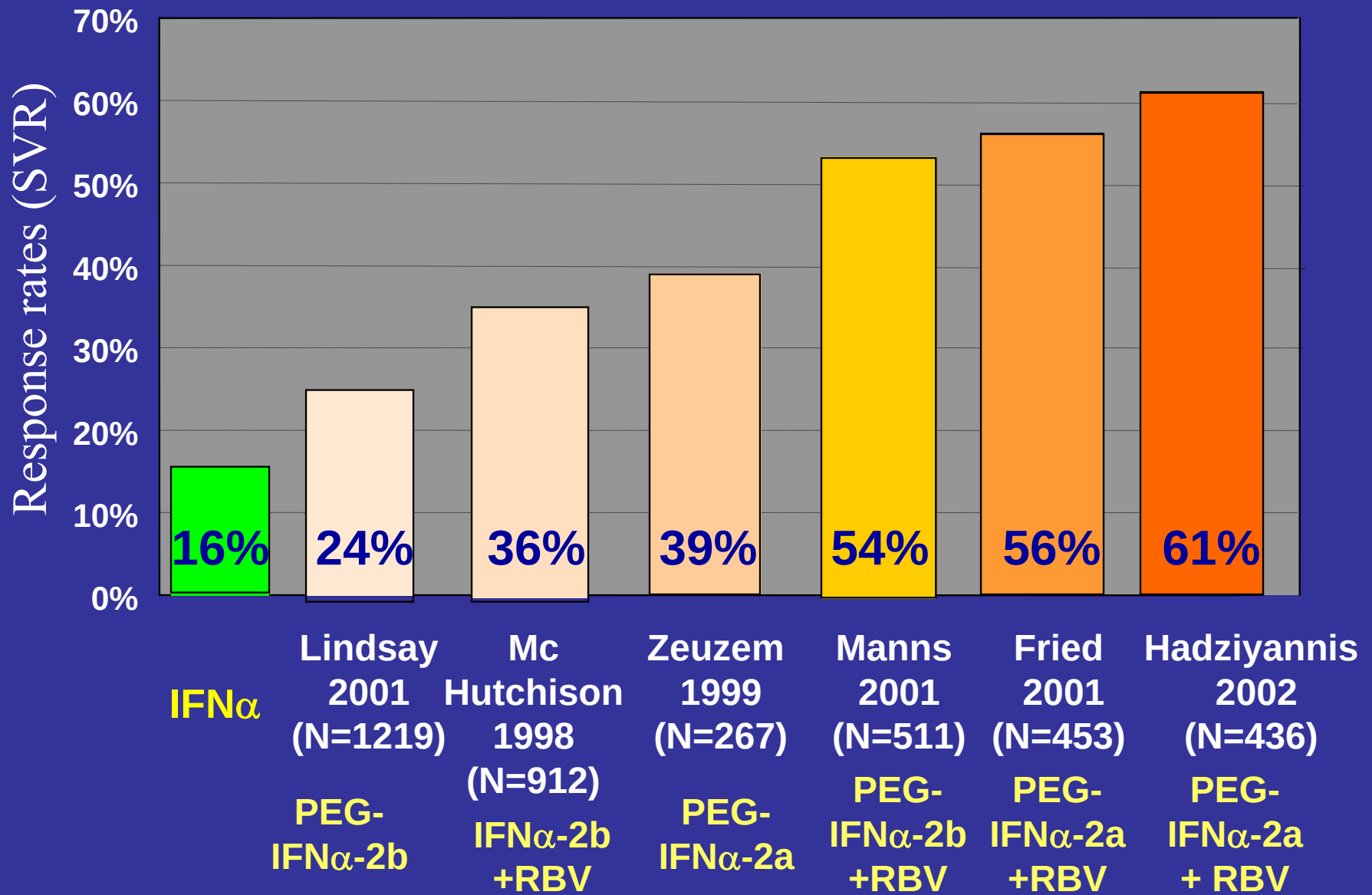
Ribavirin

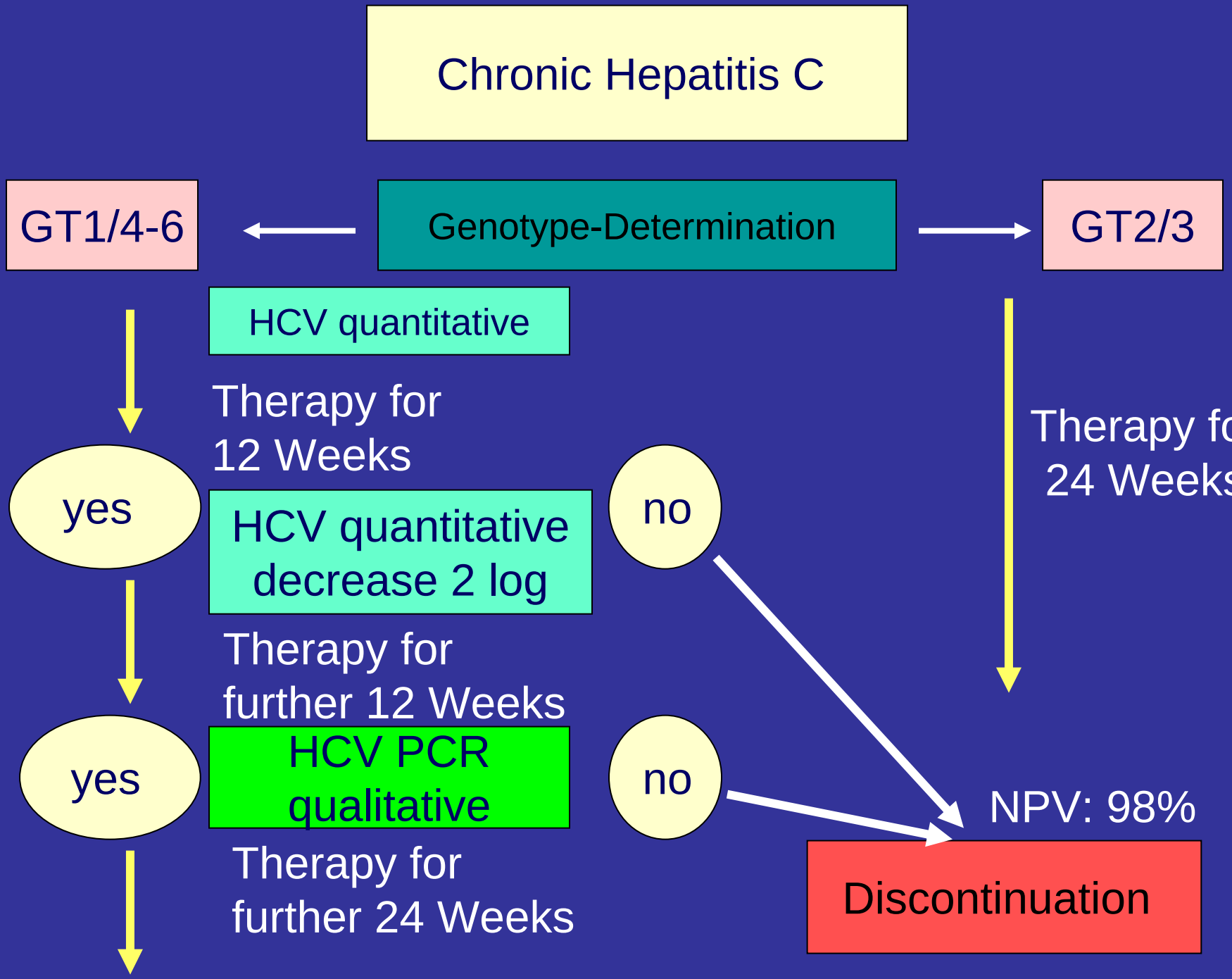
2 x daily

HCV Therapy


GT1/4 12 Months
GT2/3 6 Months
4 Weeks
12 Weeks
6 Months
Therapy phase
2 log-decrease
pEVR
ETR
RVR
cEVR
Detection limit
SVR

Interferon and Ribavirin for treatment of Hepatitis C




Chronic Hepatitis C
GT1/4-6
Genotype-Determination
GT2/3
HCV quantitative
Therapy for
12 Weeks
Therapy for
24 Weeks
yes
HCV quantitative
decrease 2 log
no
Therapy for
further 12 Weeks
yes
HCV PCR
qualitative
no
NPV: 98%
Therapy for
further 24 Weeks
Discontinuation

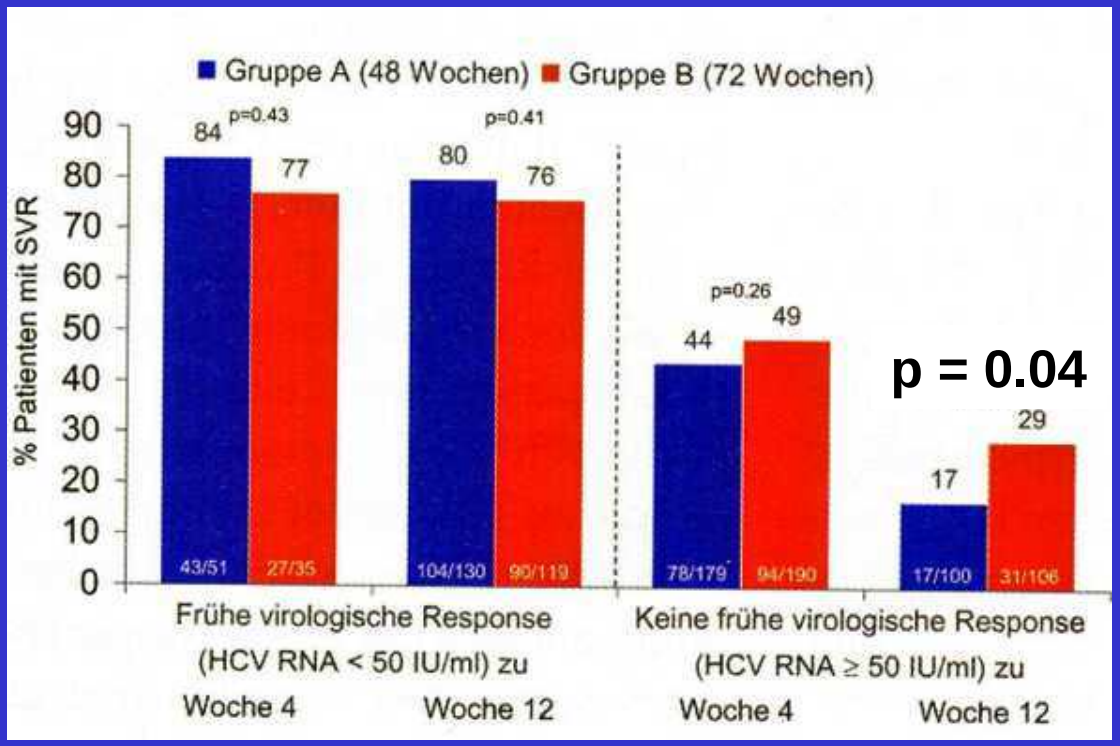
Individualisied HCV-Therapy

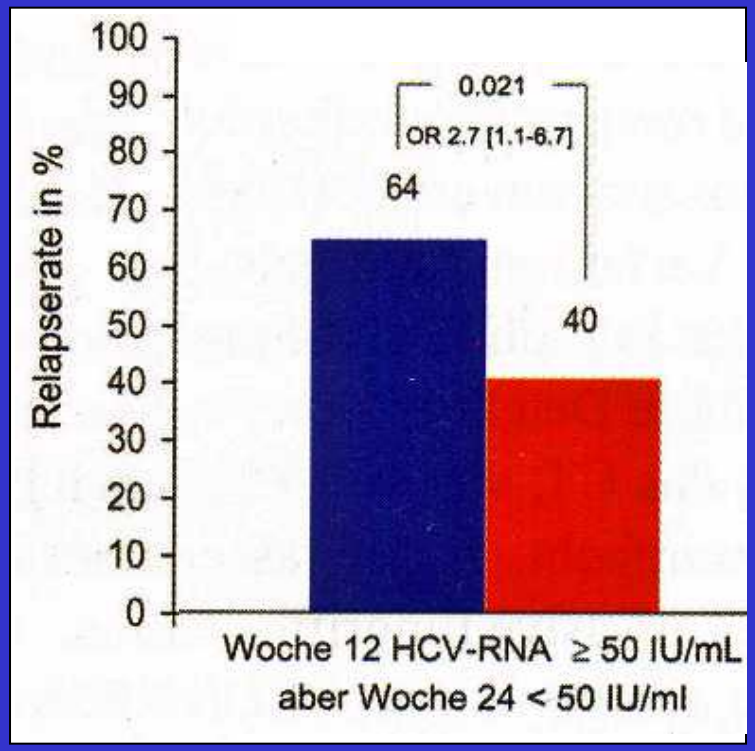
Shortened treatment duration in the presence of RVR and/or low baseline viral load

Genotype 1:			
Zeuzem et al.	J Hepatol 2006	24 vs. 48 W	89%
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%**

Individualised HCV-Therapy

Prolonged treatment duration
in the presence of delayed response





Berg et al. Gastroenterology 2006; 130: 1086

Sanchez-Tapiaz et al. 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)	Nucleosite 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% Risik reduction if >2 cups/ d

Wakai et al. 2007 (111 000 Persons)		HCV+	HCV-
Risik reduction:	1 cup /d	21%	38%
	>2 cup /d	61%	37%