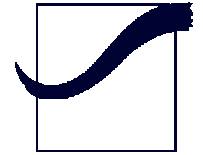


UNIVERSITÄT  
REGENSBURG



**KLINIKUM**

KLINIK UND POLIKLINIK FÜR INNERE MEDIZIN I

# Therapy of Hepatitis B

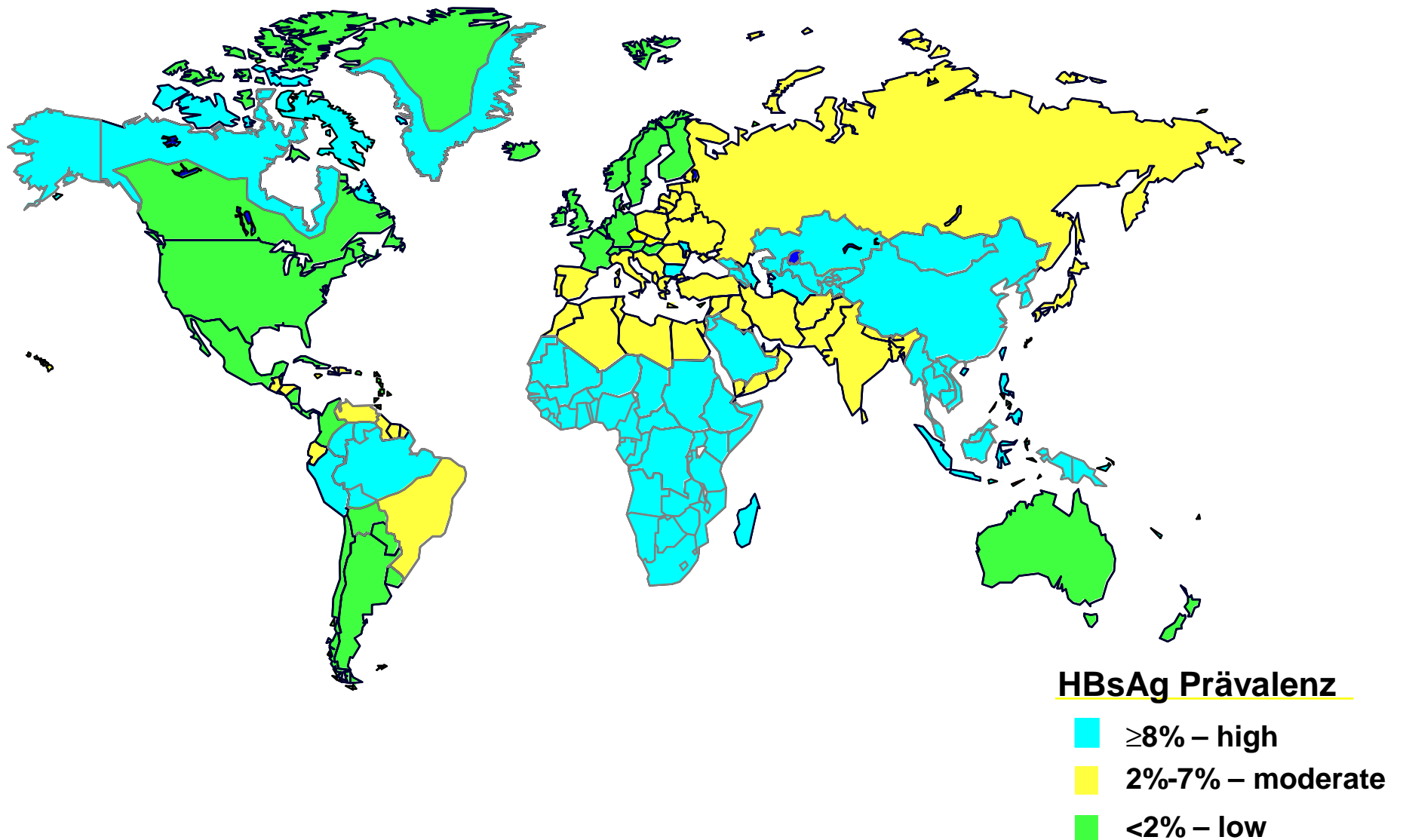
B. Salzberger

Klinik und Poliklinik für Innere Medizin I  
Klinikum der Universität Regensburg

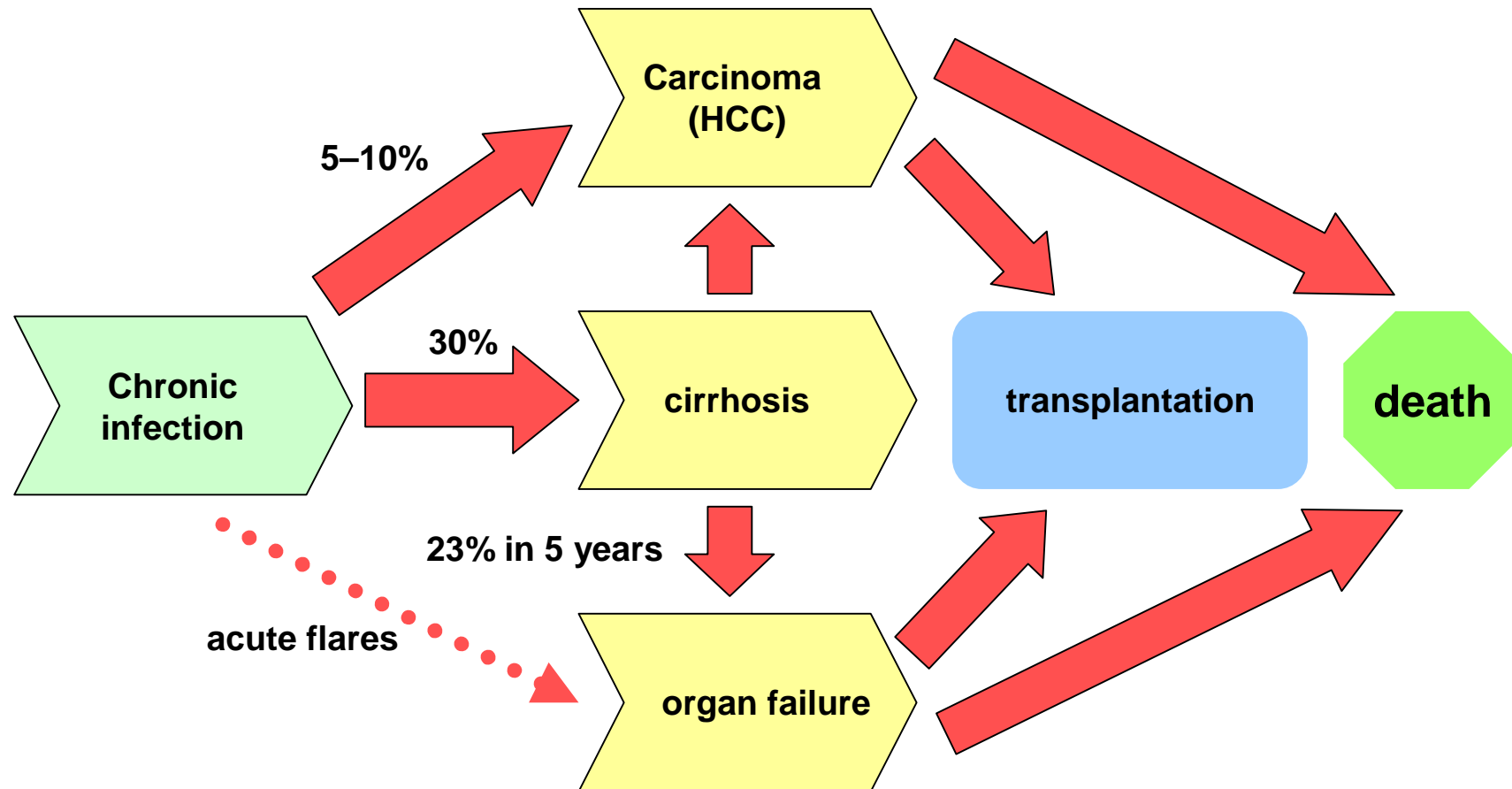
# Epidemiology

- about 40% of world population are anti-HBc positive
- 500.000 - 1.2 million deaths per year, number 10 cause of death worldwide
- 350 million HBV-chronically infected
  - 4 millions in West Europe
  - ca. 500 000 in Germany

# *Prevalence of chronic Hepatitis B-infection*



# Chronic Hepatitis B -infection: natural history

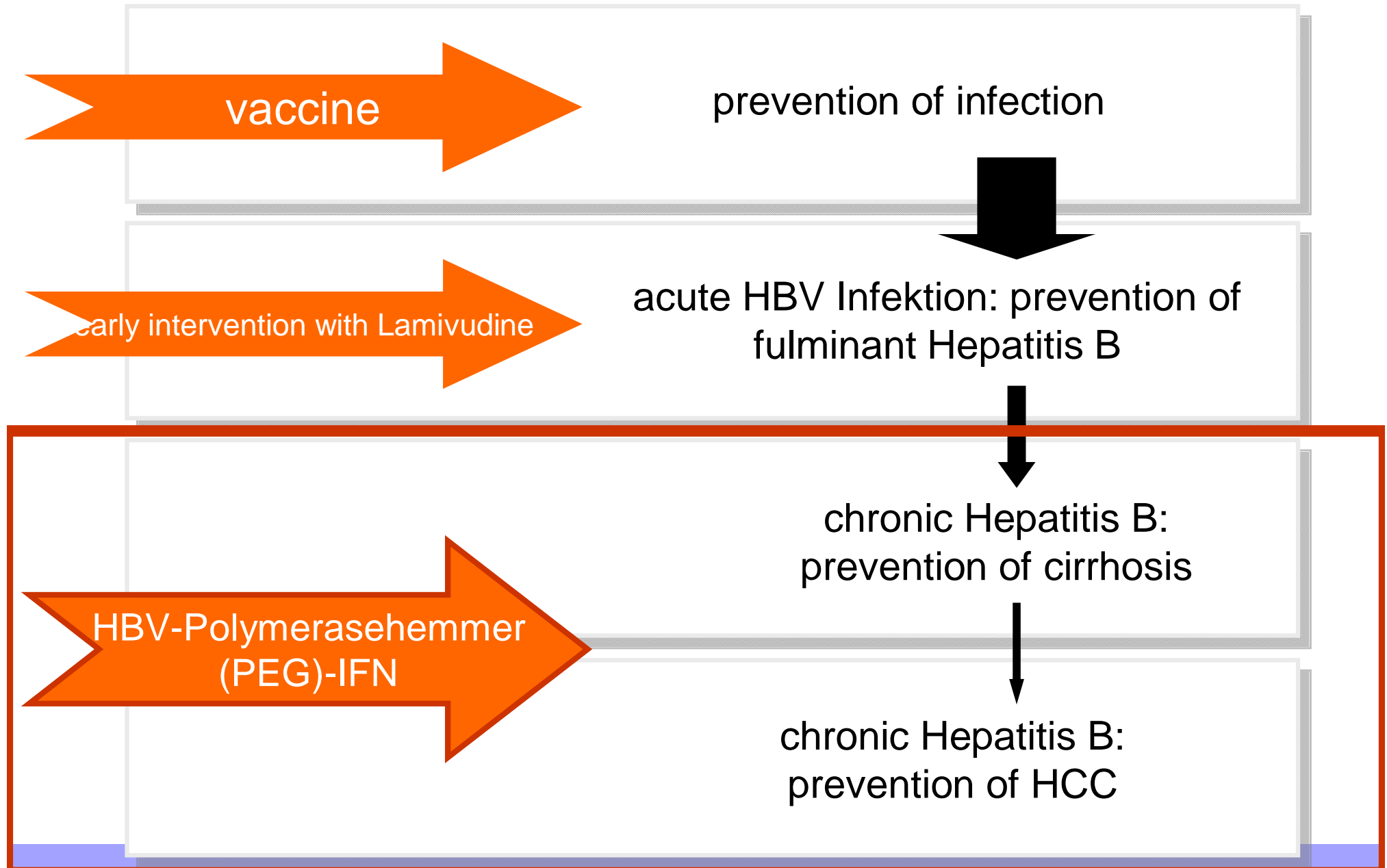


Torresi J *et al. Gastroenterology* 2000; **118**:S83–S103

Fattovich G *et al. Hepatology* 1995; **21**:77–82

Perrillo RP *et al. Hepatology* 2001; **33**:424–32

# Hepatitis B: therapeutic options



# Goals of antiviral therapy

---

<b>Lab values:</b>	<b>ALT↓(normalization)</b>
<b>Virology:</b>	<b> durable HBeAg-Seroconv. (WT)  serum HBV-DNA↓ (&lt;10<sup>4</sup> cp/ml)  Loss of HBs-AG</b>
<b>Histology:</b>	<b>Inflammation (Grading)↓  Fibrosis (Staging) ↓</b>

# Diagnostic testing

# HBV- Infection



<b>HBsAg</b>	+	+	+	+	-
<b>anti-HBc</b>	+	+	+	+	+
<b>anti-HBs</b>	-	-	-	-	+
<b>HBV-DNA</b>	+++++	+++	++	+/-	-/+
<b>HBeAg</b>	+	+	+/-	-	-
<b>anti-HBe</b>	-	-	+/-	+	+
<b>GPT</b>	norm	+++	++	+/norm	norm
	Immuno-tolerance	Hepatitis		HBsAg-carrier-status	cure

# HBV- Infection



<b>HBsAg</b>	+	+	+	+	-
<b>anti-HBc</b>	+	+	+	+	+
<b>anti-HBs</b>	-	-	-	-	+
<b>HBV-DNA</b>	++++	+++	++	++	+
<b>HBeAg</b>	+	+	+/-	+/-	-
<b>anti-HBe</b>	-	-	+/-	+/-	-
<b>GPT</b>	norm	+++	++	++	+
<b>cirrhosis</b>	-	+++	++	++	+
<b>HCC-risc</b>	-	++++	++	++	+

**„Hepatitis phase“**

**indication for antivirale therapy!**

**When and how to treat ?**

# Treatment in acute hepatitis B

- high spontaneous seroconversion in acute Hepatitis B in adults (95-99%)
- in a small randomized trial no positive effect for lamivudine in regard to HBs-Ag-seroconversion (92.5% with lamivudin vs. 97.5% with placebo at month 18) was detected
- in small series with fulminant hepatitis lower rate of Itx (20%) following lamivudine compared to historic controls (50-80%)



# Hepatitis without cirrhosis

**Elevated GPT ( $> 2 \times \text{Norm}$ )  
and  
viremia  $> 10^4$  copies/ml ( $2 \times 10^3$  IU/ml)**

**New:**

**no difference whether HBe-Ag positive or  
negative**

**= > treat**

# What if ?

**normal GPT (<2xNorm)  
and  
viremia > 10<sup>4</sup> copies/ml (2 x 10<sup>3</sup> IU/ml)**

**=> biopsy**

**with inflammation or  
significant fibrosis (>F1)**

**treat**

**no inflammation or  
significant fibrosis (≤F1)**

**wait and watch: GPT/GOT  
and HBV-DNA every 3-6  
months**

# How to treat ?

# Antiviral drugs

licensed until 2004

Interferon-alpha

Lamivudin

Adefovir

licensed in 2005/6

PEG-IFNa-2a

Entecavir

active against HBV,  
licensed only for HIV

Tenofovir

in some countries licensed

Telbivudin

Phase II/III-Studies

Clevudin

Pradefovir

# IFN vs. Polymerase-Inhibitors

## (PEG)-INTERFERON ALPHA

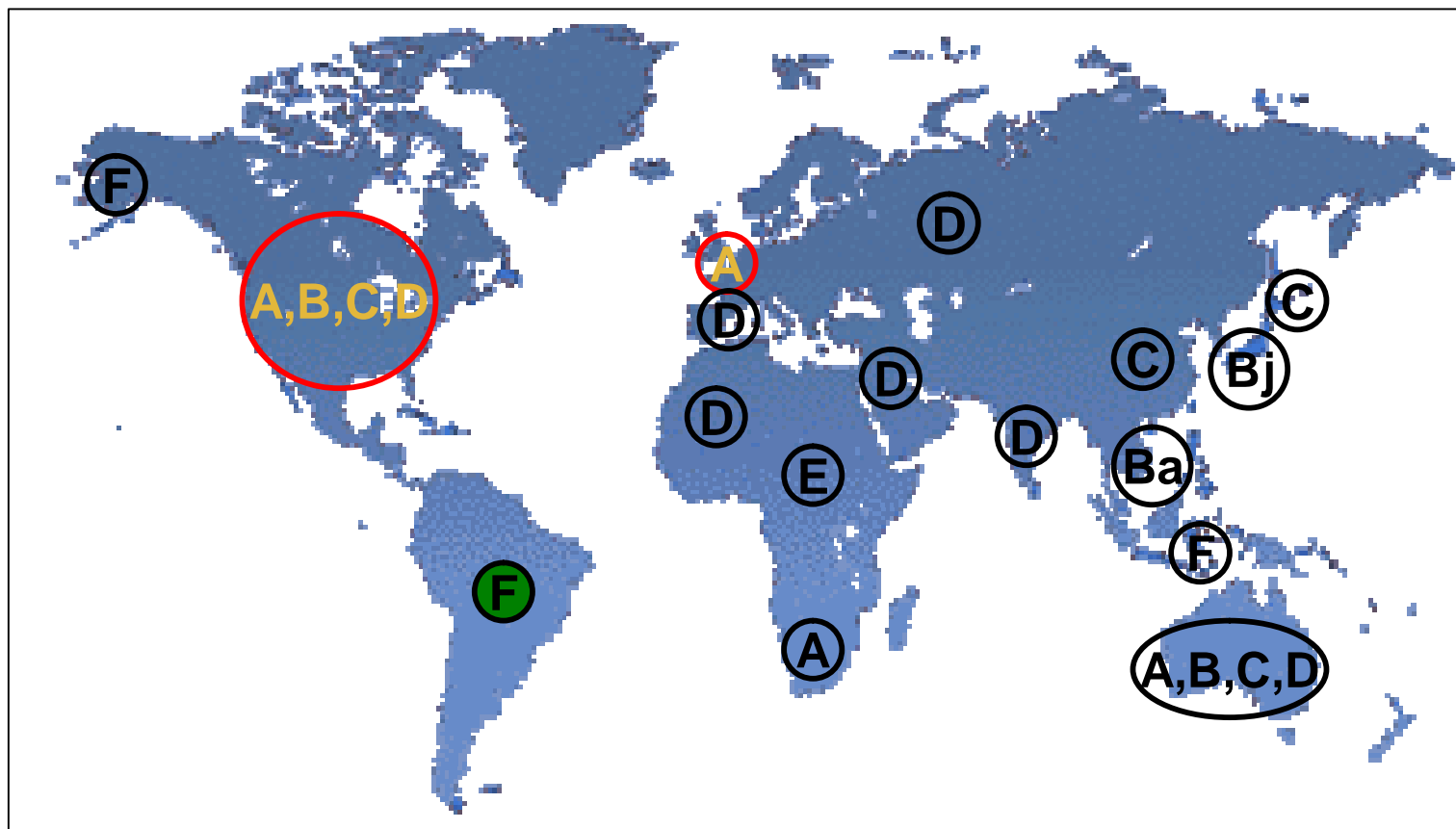
- HBs-seroconversion up to 10%
- HBe-seroconversion up to 50% in HBV-Genotype A
- no resistance (?)
- defined treatment duration
- adverse effects, contraindications (eg. advanced cirrhosis)
- low effectivity with high HBV-DNA and low activity (ALT)

## HBV-Polymeraseinhibitors (nucleos(t)ide-analogues)

- high antiviral potency
- few adverse effects
- no constraints in patients with advanced cirrhosis
- development of resistance
- relapse with stopping drug
- long term therapy may be necessary

# Interferon

# HBV – genotypes



# HBV Genotypes

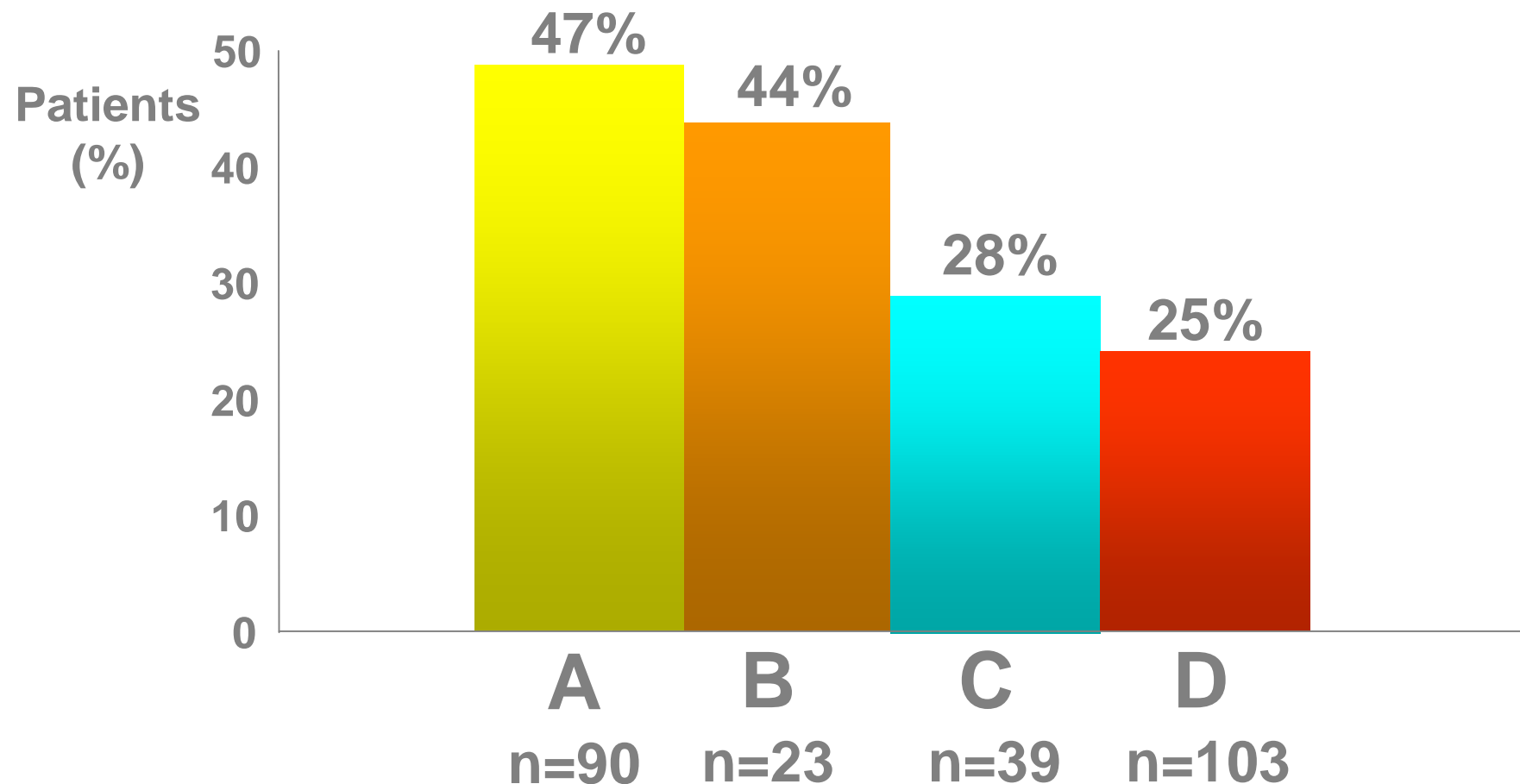
## spontaneous HBeAg seroconversion

with genotype B earlier and more frequent than with C

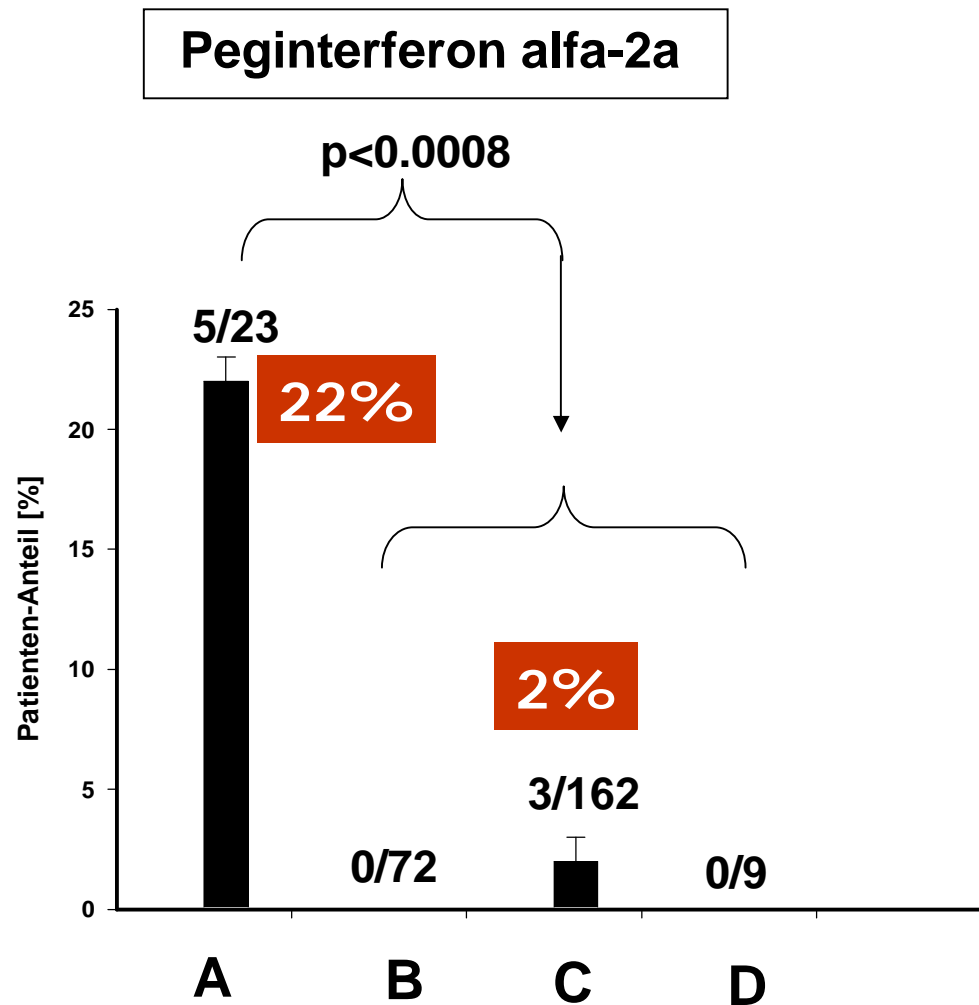
## inflammation and progression to cirrhosis

C > B (?), D > A

# PEG-IFNa-2b +/- Lamivudin: Loss of HBeAg by genotype



# HBsAg-seroconversion by genotype



# What influences response to — Interferon-a?

- HBV-genotype A
  - >20% HBsAg-seroconversion
- low viral load ( $<10^6$  copies/ml)
- ALT/AST at least 2xULN (even better 5x)
- not pretreated

# Contraindications for Interferon

- pregnancy, lactation period
- severe psychiatric comorbidity
- GPT (ALT)  $>10 \times \text{ULN}$ 
  - risk of acute flare
- advanced cirrhosis (Child B+C)
- thrombocytopenia ( $<50.000/\mu\text{l}$ ), leukopenia ( $<2.000/\mu\text{l}$ )
- autoimmune disease

# Standard-IFN versus PEG-IFN ?

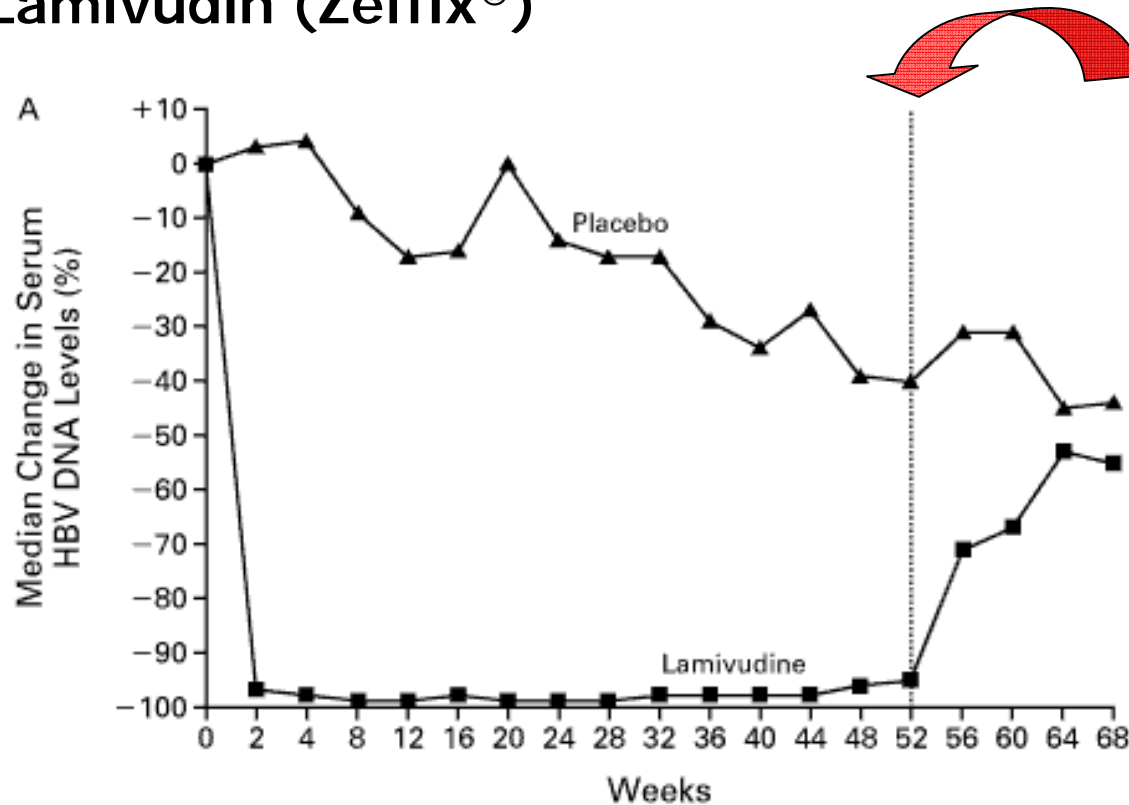
- Interferon alfa-2a (Roferon<sup>®</sup>)
  - (2,5-5 Mio. I.E./m<sup>2</sup> 3x/week)
- Interferon alfa-2b (Intron A<sup>®</sup>)
  - (5-10 Mio. I.E. 3x/week)
- Pegylated Interferon alfa-2a (Pegasys<sup>®</sup>)
  - (180µg/Woche s.c. for 48 weeks)

PEG-Interferon is generally preferable, noninferior in effectivity but more convenient (only 1x/week)

# Nukleos(t)ide- analogues

# Nucleos(t)idanalogueues - problems

## Lamivudin (Zeffix®)



No. EVALUATED

Placebo	65	62	61	59	64	61	62	59	56	58	59	55	56	54	56	50	48	50	53
Lamivudine	63	60	62	61	58	60	62	59	56	57	58	55	51	54	54	48	51	51	52

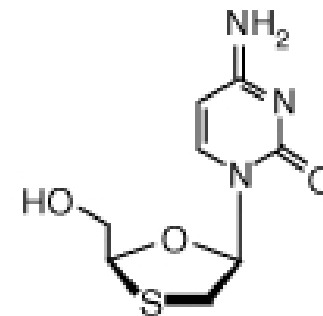
„It is easy to start

but,

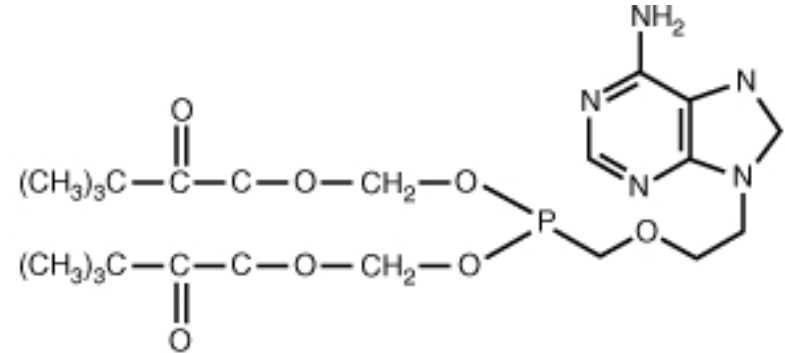
difficult to stop“

# Lamivudine (Zeffix, Epivir-HB, Epivir)

- Cytidine nucleoside analogue, initially developed for treatment of HIV-infection
- dose in HIV-infection 300mg/d, in Hepatitis B-infection 100mg/d
- high safety, low rates of adverse events  
resistance can rapidly emerge



# Adefovir (Hepsera)



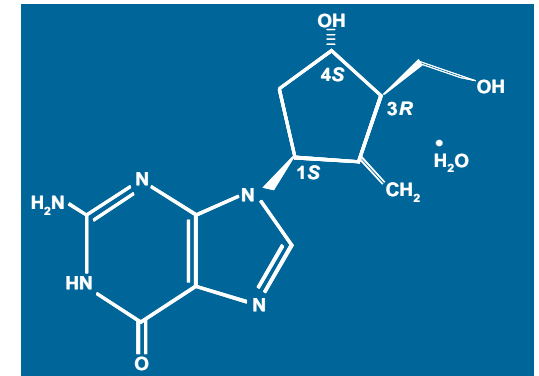
- adenine-nucleotide analogue, initially developed for HIV-infection
- doses evaluated in HIV-infection 60 and 120mg/d, nephrotoxic
- in Hepatitis B dose of 10mg daily effective
- lower rate of resistance development than lamivudine, primary resistance

# Entecavir (Baraclude®)

*Guanosin-Nukleosid*analogue

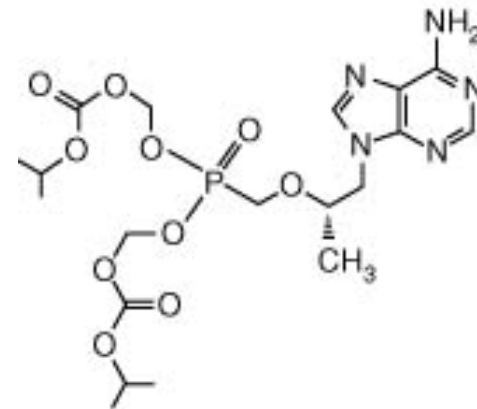
-> very high antiviral potency

- Ideal for pts. with
  - high HBV-DNA
  - cirrhosis
- development of resistance
  - in pts without previous Lamivudin: <1% in 3 years
  - can develop cross resistance to lamivudine in HIV-infection?



# Tenofovir (Viread)

- adenine- nucleotide analogue
- developed and licensed for HIV-infection
- low rate of resistance development
- second line drug
- dose 245 mg/d

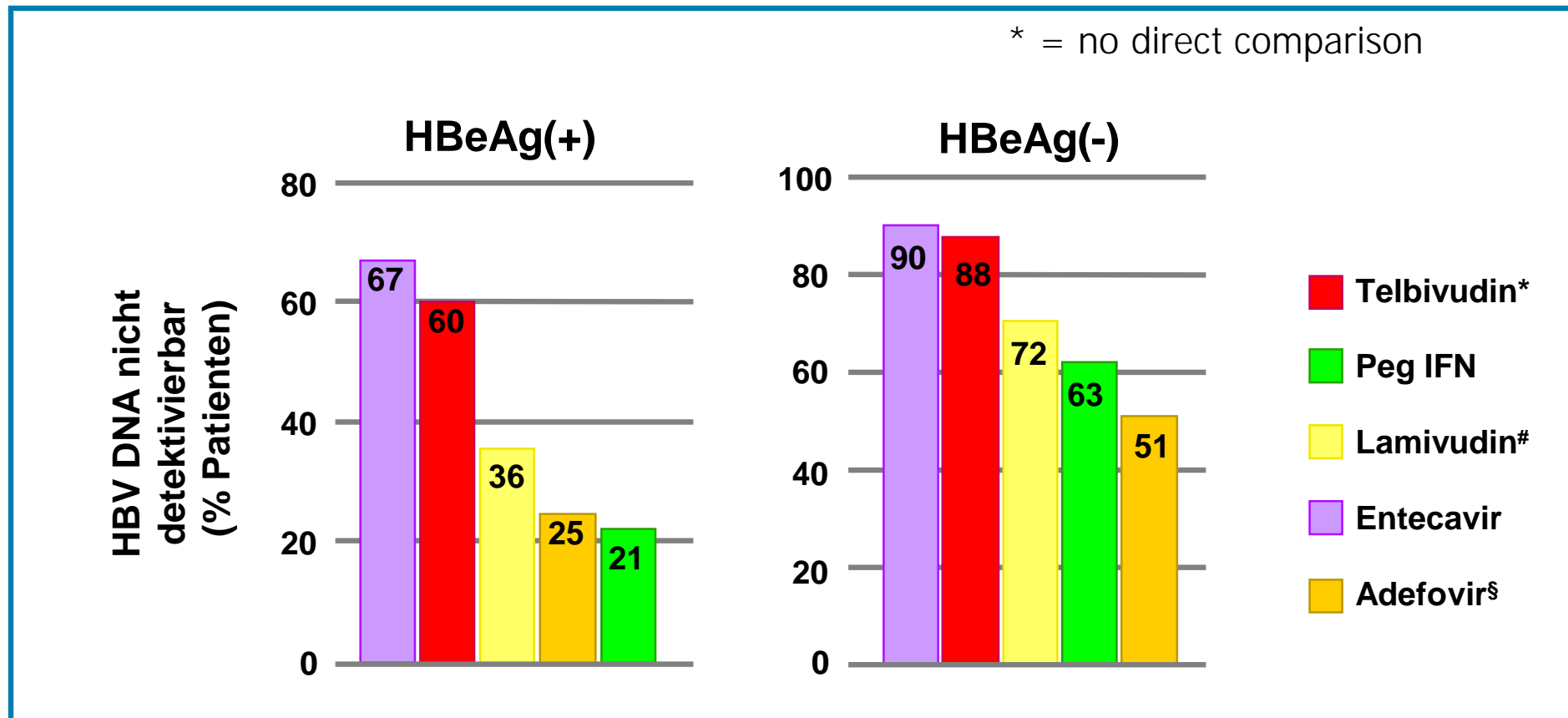


# Telbivudine (Tyzeka, Sebivo)

- Thymidine-Analogue, dose 600mg/d
- in randomized studies over 48 weeks superior to Adefovir in viral suppression
- cross resistance with lamivudine possible

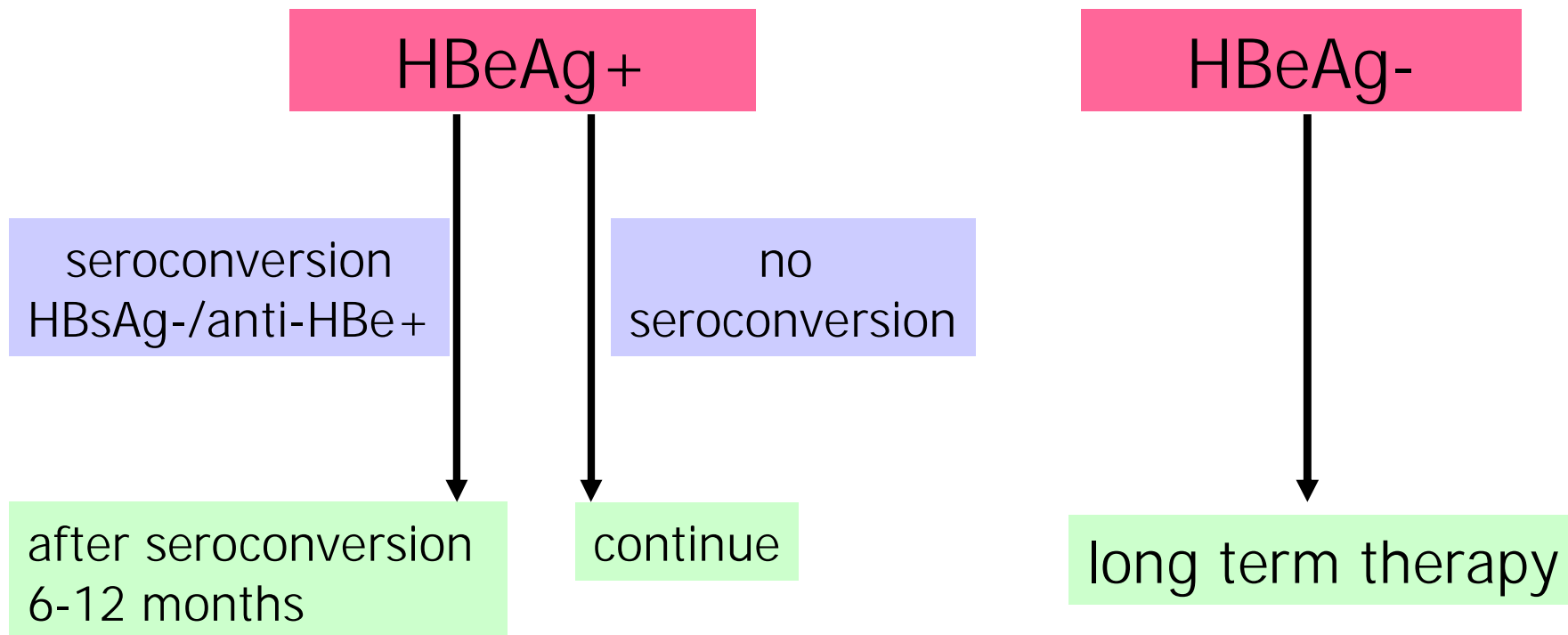


# HBV DNA Suppression within one year in nucleoside-naïve patients\*



\* Non detectable <300 Kopien/mL  
 # Non detectable <400 Kopien/mL  
 § Non detectable <1000 Kopien/mL

# Nukleos(t)ide-analogues: Duration



Stop therapy with HBsAg-Seroconversion with anti-HBs > 100 IU/l

# **Development of resistance How to react ?**

# Resistance: Definition

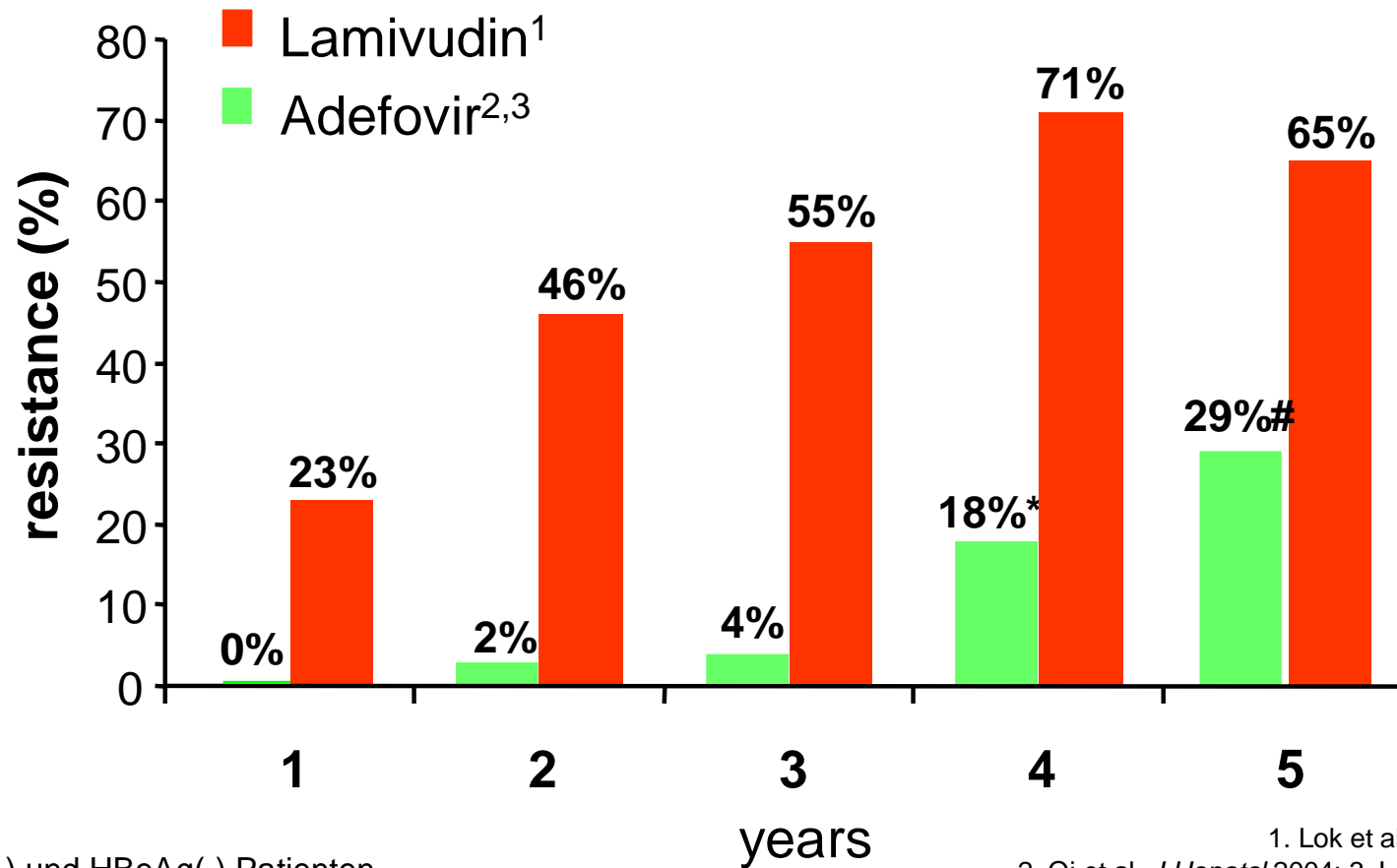
## Primary resistance

- with no drop in HBV-DNA by at least 1 log in 3 months

## Secondary resistance

- with a rise in HBV-DNA by at least 1 log on therapy

# Development of resistance

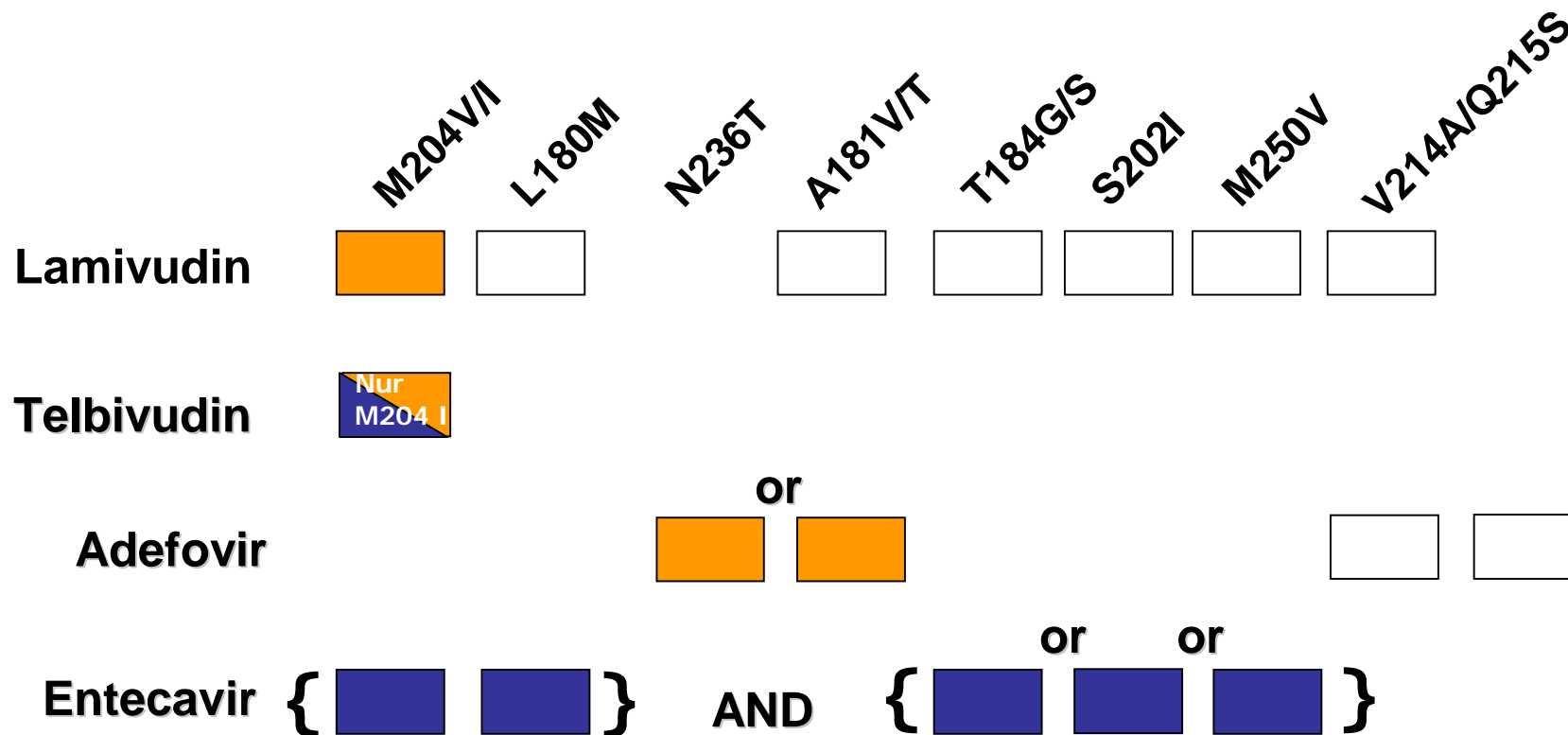


\*HBeAg(+) und HBeAg(-) Patienten

1. Lok et al. *Gastroenterology* 2003;  
2. Qi et al. *J Hepatol* 2004; 3. Locarnini et al. *EASL* 2005  
# K. Borroto-Esoda, *DDW* 2006.

# Patterns of Resistance

Mutations seen in viral breakthrough



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

# How to react to resistance to Lamivudine?

“Add on” or “switch” ?

Lamivudin

Nukleotid (Adefovir)

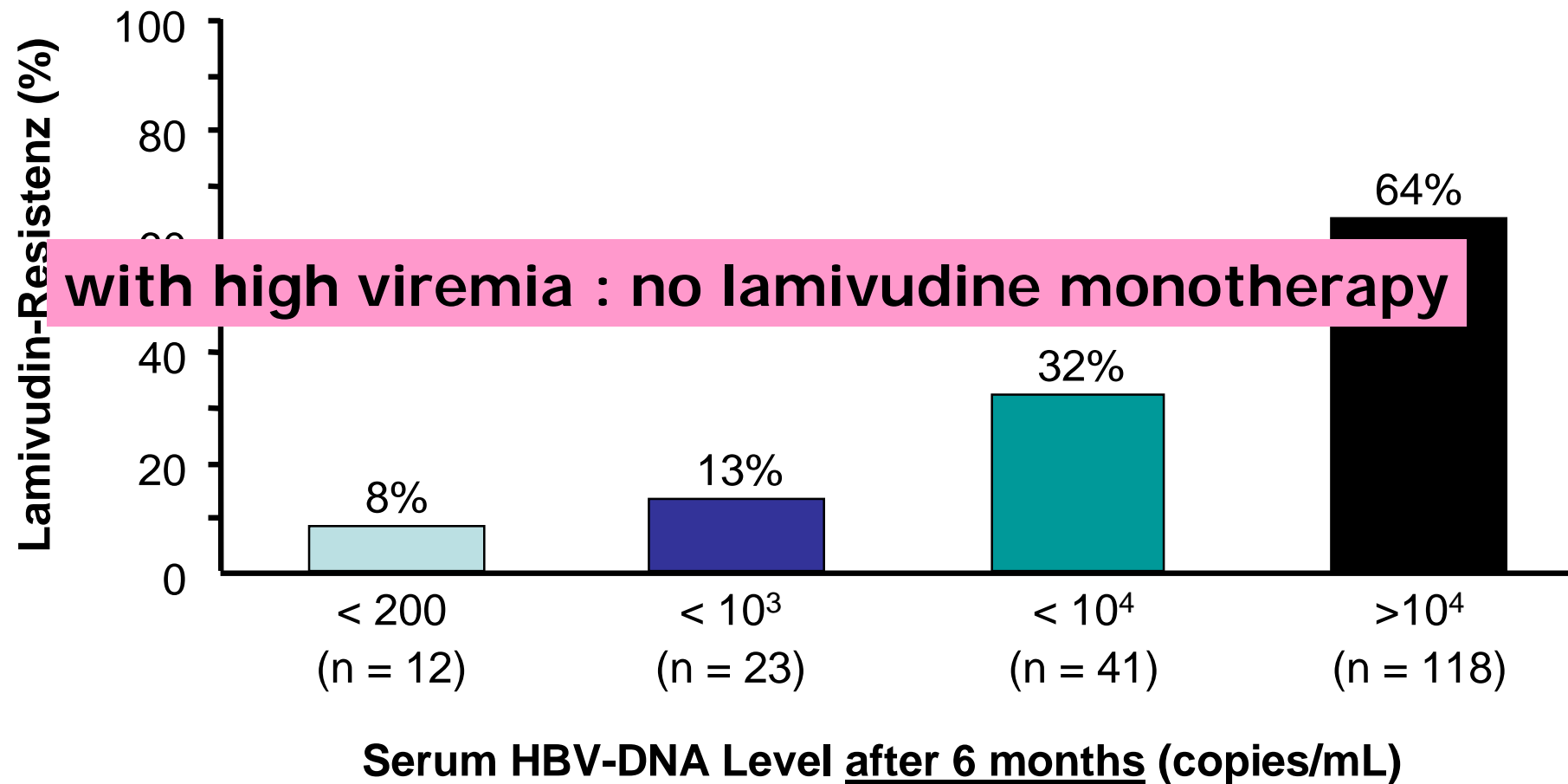
~~Lamivudin~~

~~Nukleotid (Adefovir)~~

Lamivudin

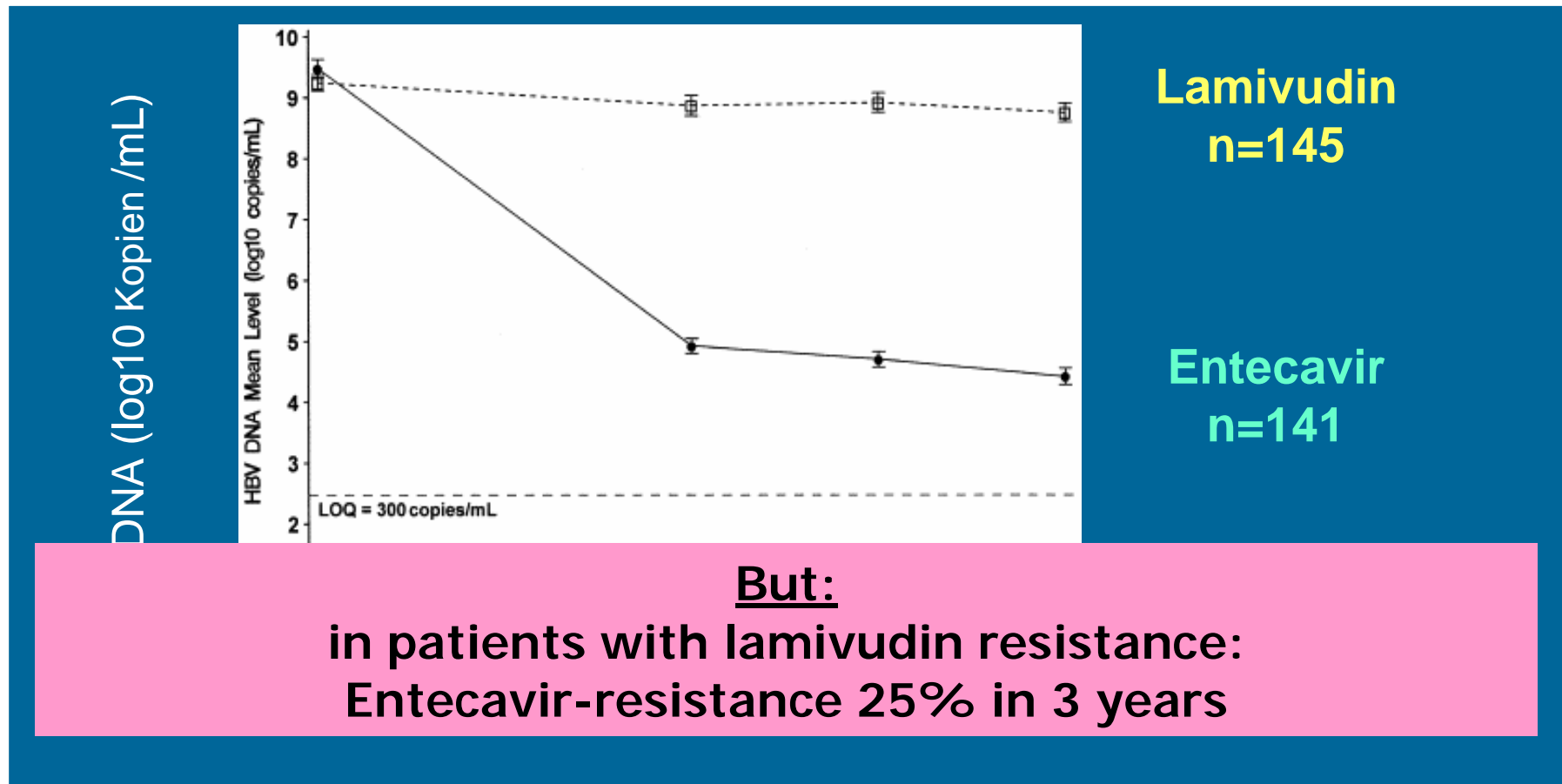
Nukleosid (Entecavir)

## Risk of Lamivudine-Resistance higher with more viral replication



\*Median follow-up: 29.6 months.

# Entecavir in Lamivudin-Resistance

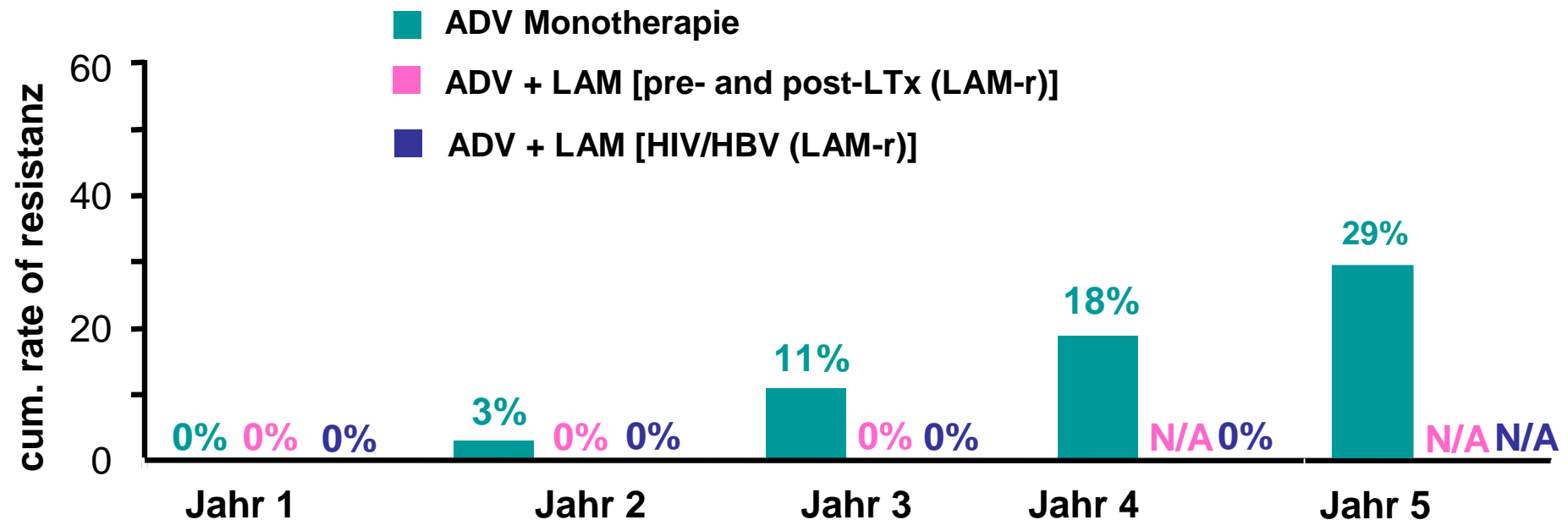


Naive HBe-Ag positive pts: -6.9 log  
LAM-R HBe-Ag positive pts: -5.1 log

## How to react to Adefovir-Resistance?

- **no lamivudin-pretreatment:**
  - Entecavir
  - Lamivudin („add on“)
  - Tenofovir (only licensed for HIV)
  - Telbivudin (limited to some countries)
- **lamivudin-pretreatment:**
  - Tenofovir (only licensed for HIV)

# Adefovir-resistance in pts treated with Adefovir + Lamivudin\*



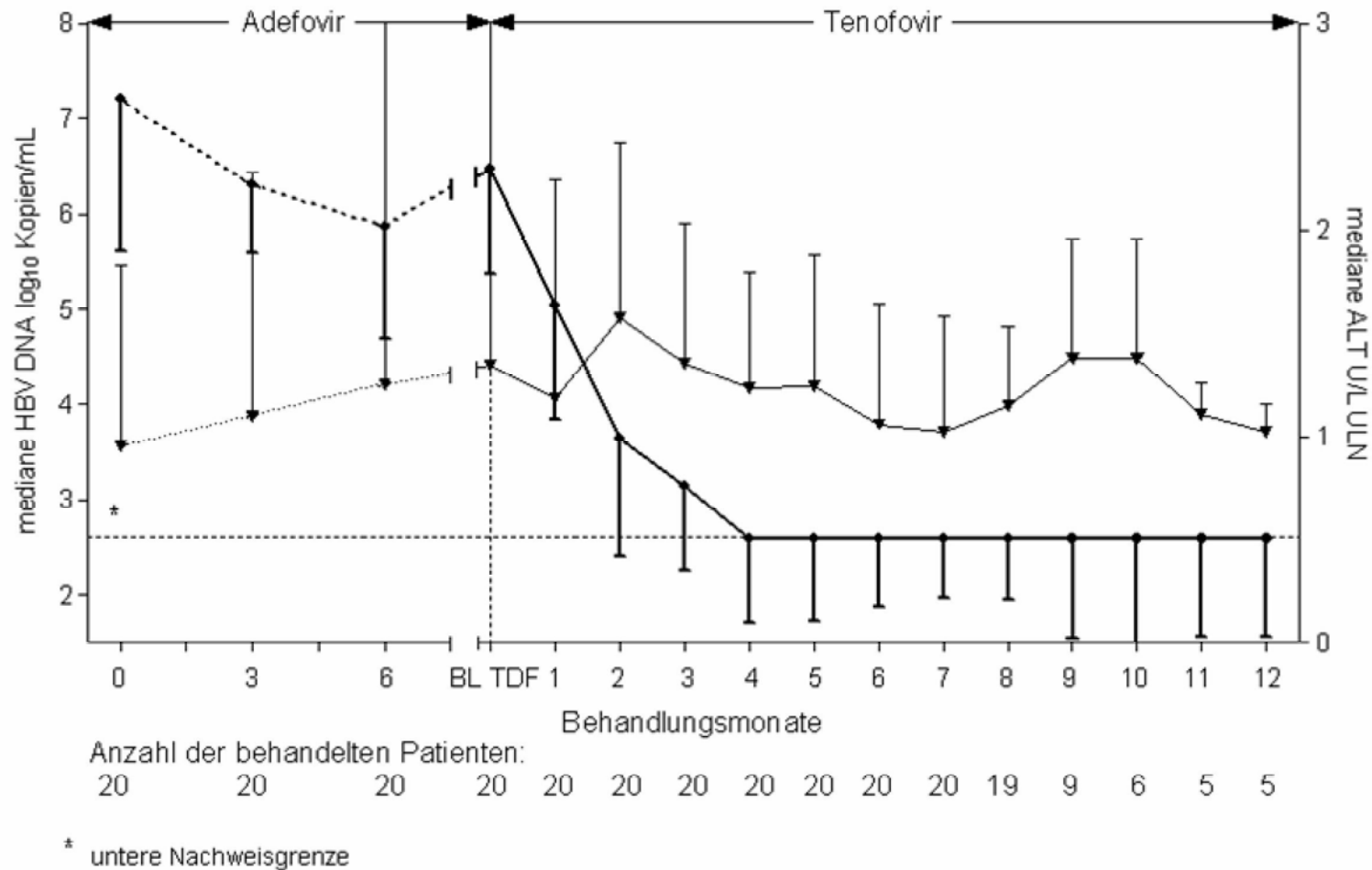
\*Based on experience in controlled clinical trials.

†2 patients enrolled in Study 435, initially on combination therapy with ADV + LAM, and subsequently selected ADV resistant mutation N236T. However, they were on ADV monotherapy when ADV resistance mutation was detected.

Hadziyannis S, et al. Hepatology. 2005;42(suppl 1):754A.

Lampertico P. EASL 2006. Abstract 499.

# Tenofovir in pts with incomplete response to Adefovir



**19/20 Patienten with HBV DNA < 400 cop/ml  
nach 4 (1-8) Monaten**

*Van Bömmel, Berg et al.  
Hepatology August 2006*

## How to react to Entecavir-resistance?

treat with Nukleotide-analogue

- Adefovir

- or Tenofovir

# Combinationtherapy: (PEG)-Interferon plus Nukleos(t)ideanalogue?

= > Currently not recommended

# Prophylactic Therapy

# Prophylaxis with high dose chemotherapy or immunosuppression

rate of reactivation in HBsAg-pos. pts.: 15-50%

- HBsAg-+ Pts
  - treat prophylactically
    - high viremia: Entecavir or Lamivudin+Adefovir
    - low or negative viremia: Lamivudin
  - continue for at least. 3-6 Mon. after chemotherapy
- Anti-HBc-+, HBsAg-neg. pts:
  - watch closely
  - antivirale therapy with rise of HBV-DNA or development of HBs-AG

# Therapy in Pts. with Cirrhosis ?

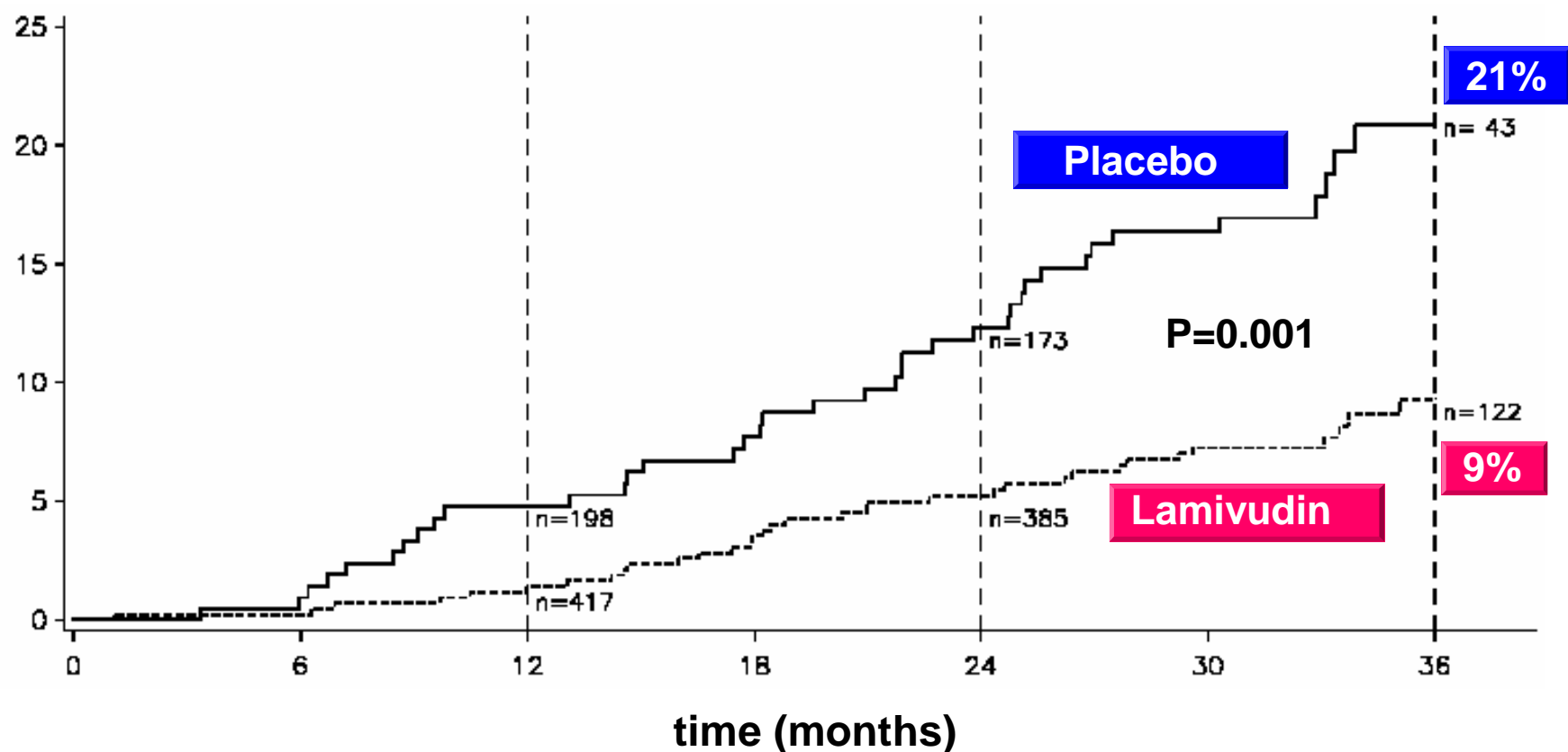
# Cirrhosis and chron. Hepatitis B

With positive viremia

= > treat always

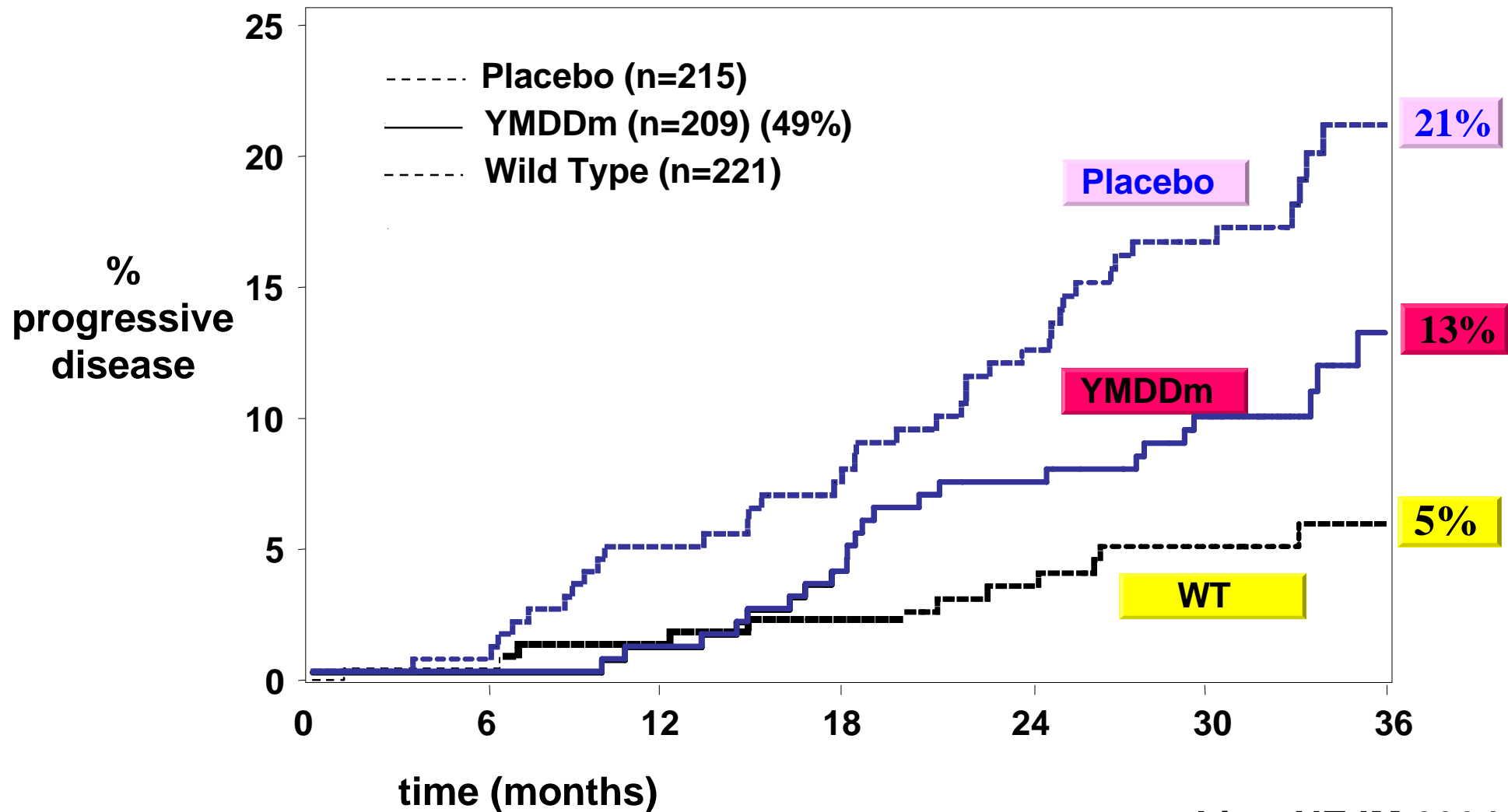
# Lamivudin in pts. with HBV-assoc. cirrhosis: organ failure and HCC

progression to organ  
failure or hcc

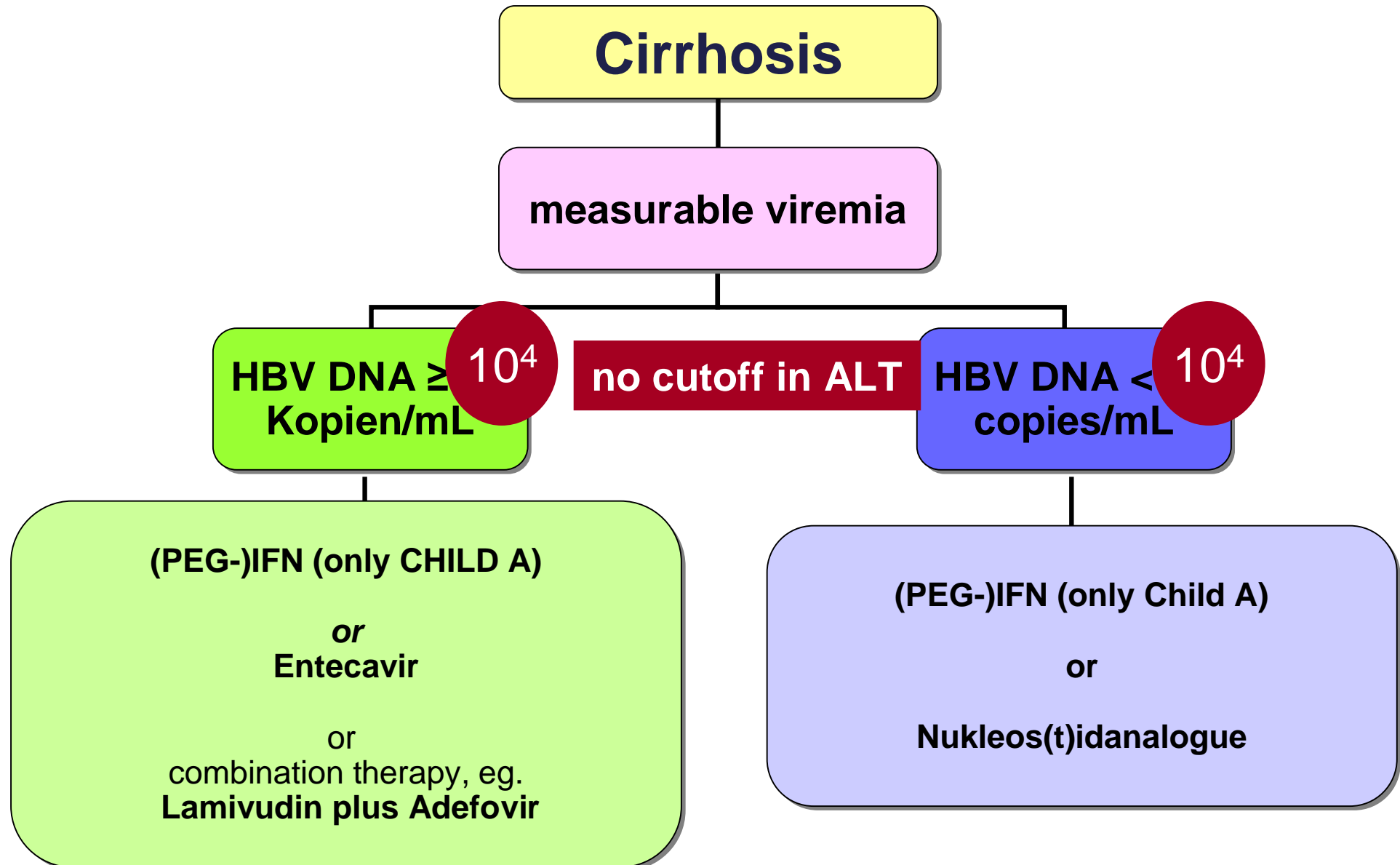


— Placebo (n=215)  
..... Lamivudin (n=436)

# Lamivudin in pts with HBV-assoc. cirrhosis: YMDD-Mutation



# Therapy of Hepatitis B with Cirrhosis



# Conclusions I

## pts. without cirrhosis:

- elevated GPT/AST (>2x ULN) and viremia > 10<sup>4</sup> copies/ml
  - treat
- normal GPT/AST (<2x ULN) and viremia > 10<sup>4</sup> copies/ml
  - biopsy
  - with inflammation or fibrosis >F1 => treat

## pts **with** advanced fibrosis or cirrhosis:

- with positive viremia
  - treat

## pts. with high-dose chemotherapy or immune suppression:

- HBsAg-positive pts
  - treat prophylactically (at least until 3-6 Mon. after chemotherapy)

**PEG-IFNa-2a**: Jyounger patients; GPT >ULN; low viral load (<10<sup>6</sup> copies/ml); genotype A; duration (6-)12 months

**Lamivudin**: long term safety - problem development of resistance  
- in resistance: add on adefovir  
- cave: cross-resistance with Telbivudin, Entecavir (partial), Tenofovir

**Adefovir**: add-on in lamivudine resistance, combination with lamivudin in selected patients

**Tenofovir**: with primary or secondary resistance to Adefovir, not yet licensed for HBF

**Entecavir**: preferred in Lam-naiven pts. with advanced fibrosis/cirrhosis  
with high viral load  
higher dose (1 mg statt 0,5 mg) in Lam-resistant pts.

**Telbivudin**: licensed only in some countries