# Therapy of Hepatitis B

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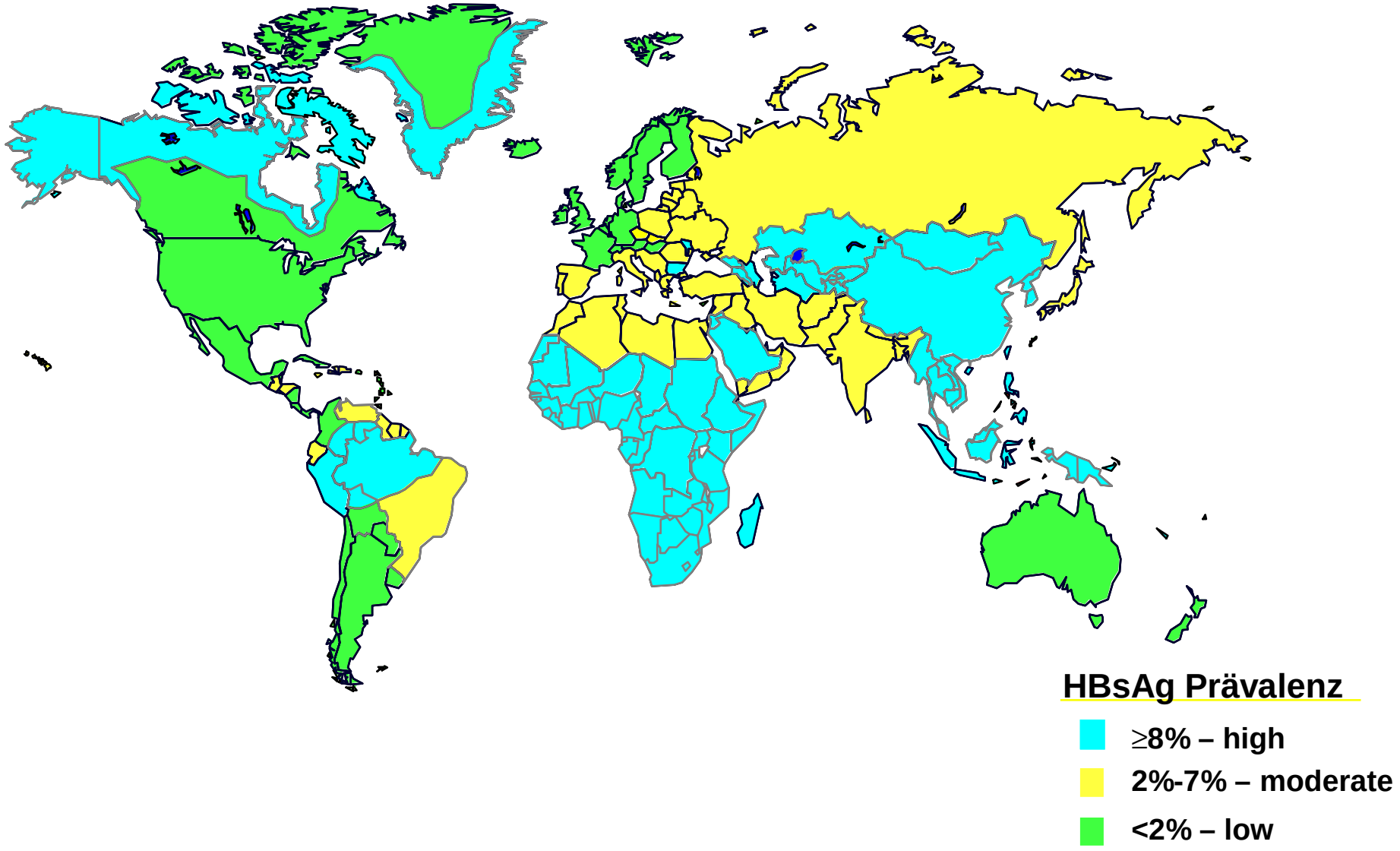
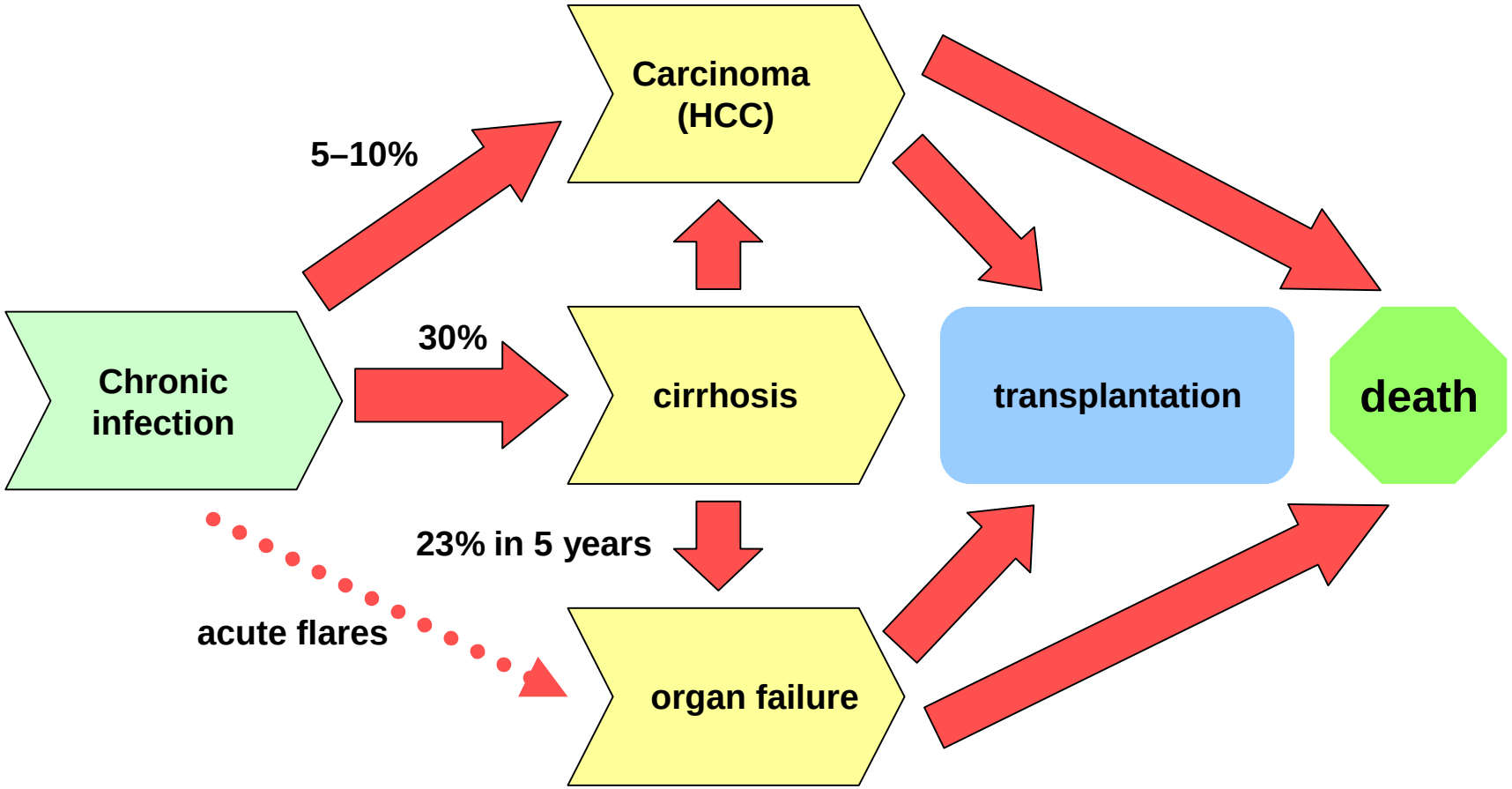
# Epidemiology

- 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*

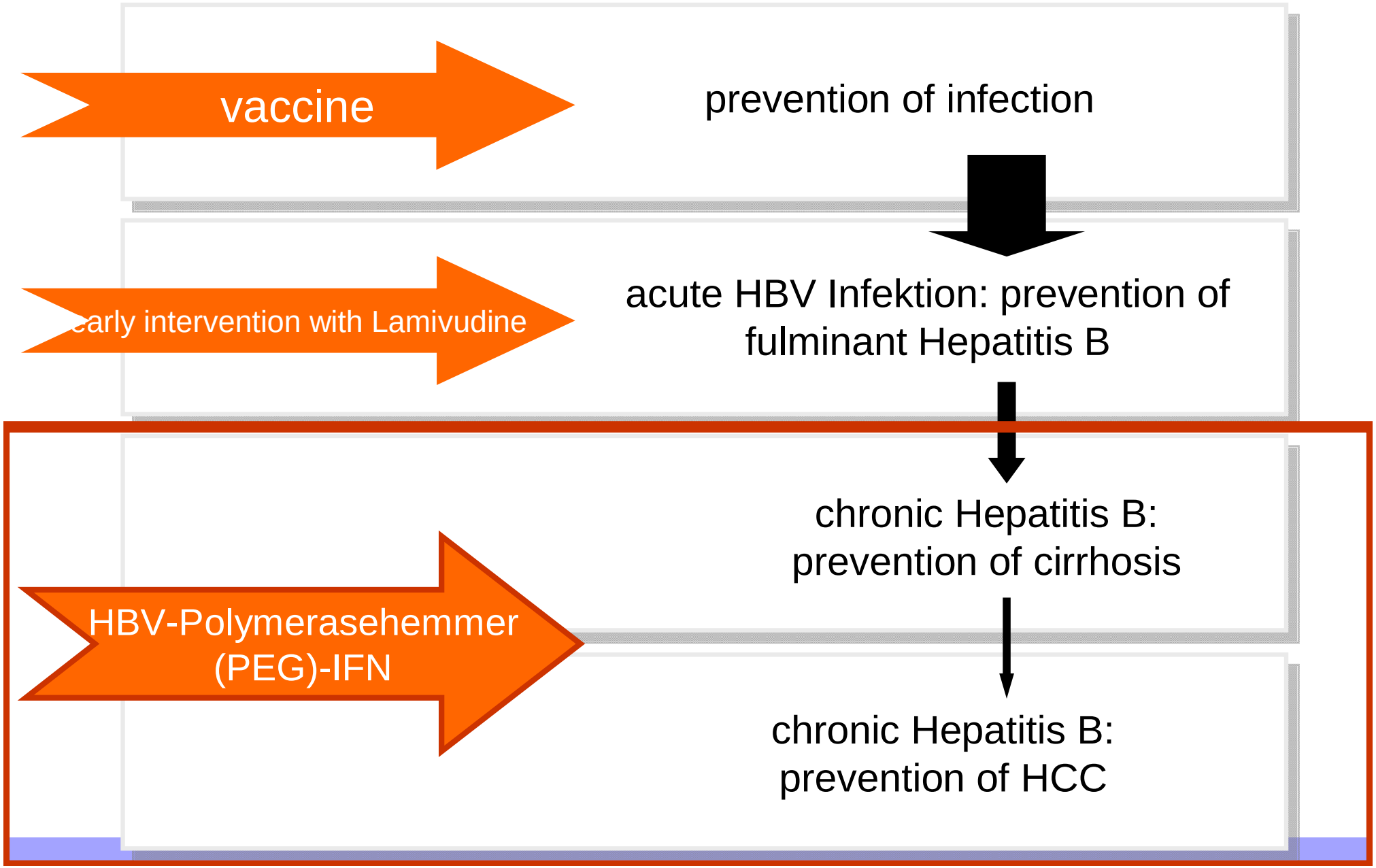


# Chronic Hepatitis B -infection: natural history




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

| | |
|---|---|
| **Lab values:** | **ALT↓(normalization)** |
| **Virology:** | **durable HBeAg-Seroconv. (WT)** |
| | **serum HBV-DNA↓ (<$10^4$ cp/ml)** |
| | **Loss of HBs-AG** |
| **Histology:** | **Inflammation (Grading)↓** |
| | **Fibrosis (Staging) ↓** |

# Diagnostic testing

# HBV- Infection

| | | | | | |
|---|---|---|---|---|---|
| HBsAg | + | + | + | + | - |
| anti-HBc | + | + | + | + | + |
| anti-HBs | - | - | - | - | + |
| HBV-DNA | ++++ | +++ | ++ | +/- | -/+ |
| HBeAg | + | + | +/- | - | - |
| anti-HBe | - | - | +/- | + | + |
| GPT | norm | +++ | ++ | +/norm | norm |
| | Immuno-tolerance | Hepatitis | | HBsAg-carrier-sttatus | cure |

# HBV- Infection

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

**„Hepatitis phase“**

**indication for antivirale therapy!**

# When and how to treat ?

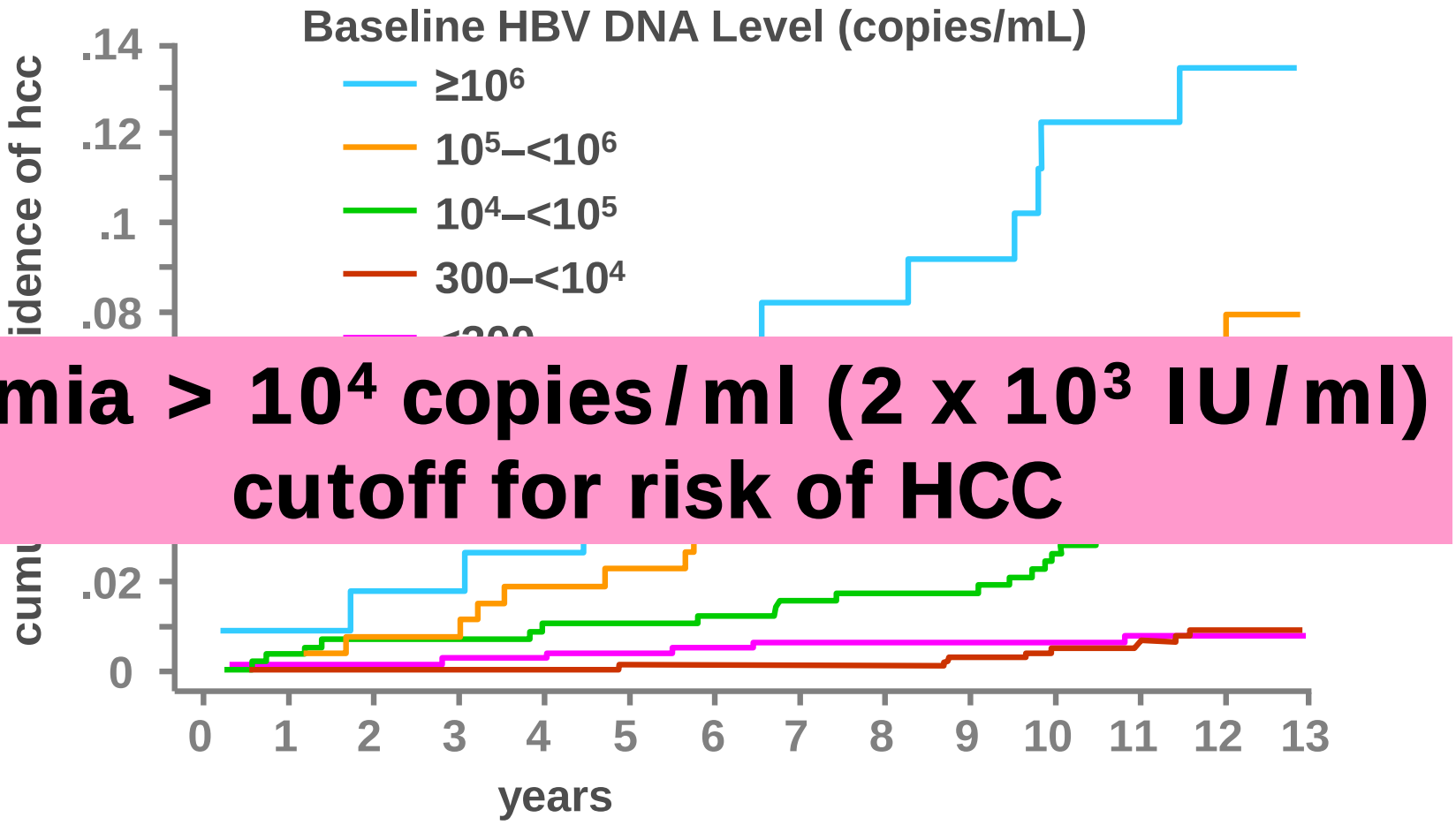
# Treatment in acute hepatitis B

- 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 ltx (20%) following lamivudine compared to historic controls (50-80%)

Kumar, Hepatology 2007; Tillmann, J. Viral Hep 2006

# REVEAL-HBV-Study: Chen et al., JAMA Jan 2006
# HCC-risk in pts. with normal liver enzymes

HBeAg(-) pts. with normal GPT, no cirrhosis (n=2,925)




**viremia > $10^4$ copies/ml ($2 \times 10^3$ IU/ml)**
**cutoff for risk of HCC**

# Hepatitis without cirrhosis

***Elevated*** **GPT (>2xNorm)**
**and**
**viremia > $10^4$ copies/ml (2 x $10^3$ IU/ml)**

**New:**

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

**=> treat**

# What if ?

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

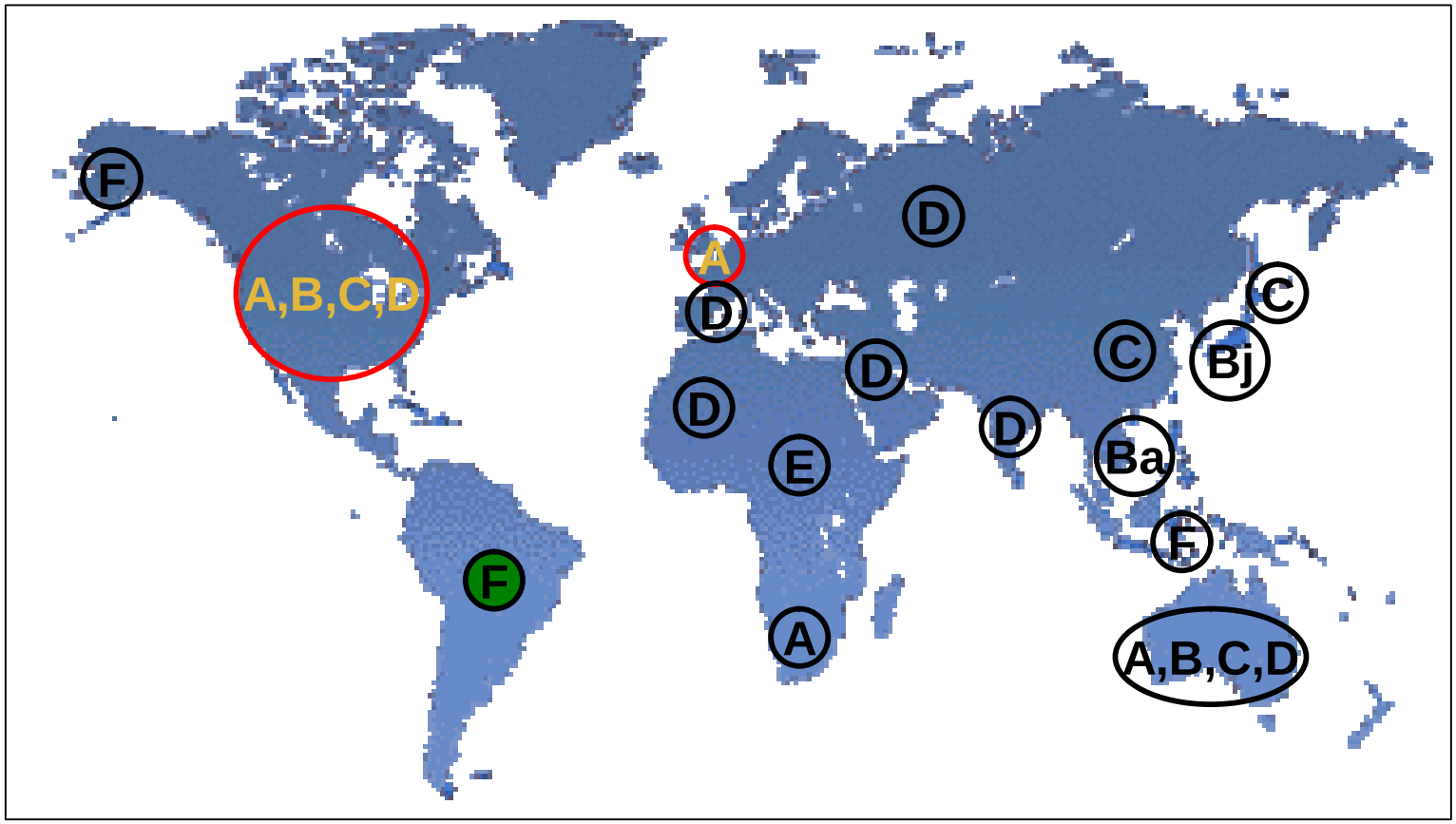
## HBV-Polymeraseinhibitors (nucleos(t)ide-analogues)

- 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

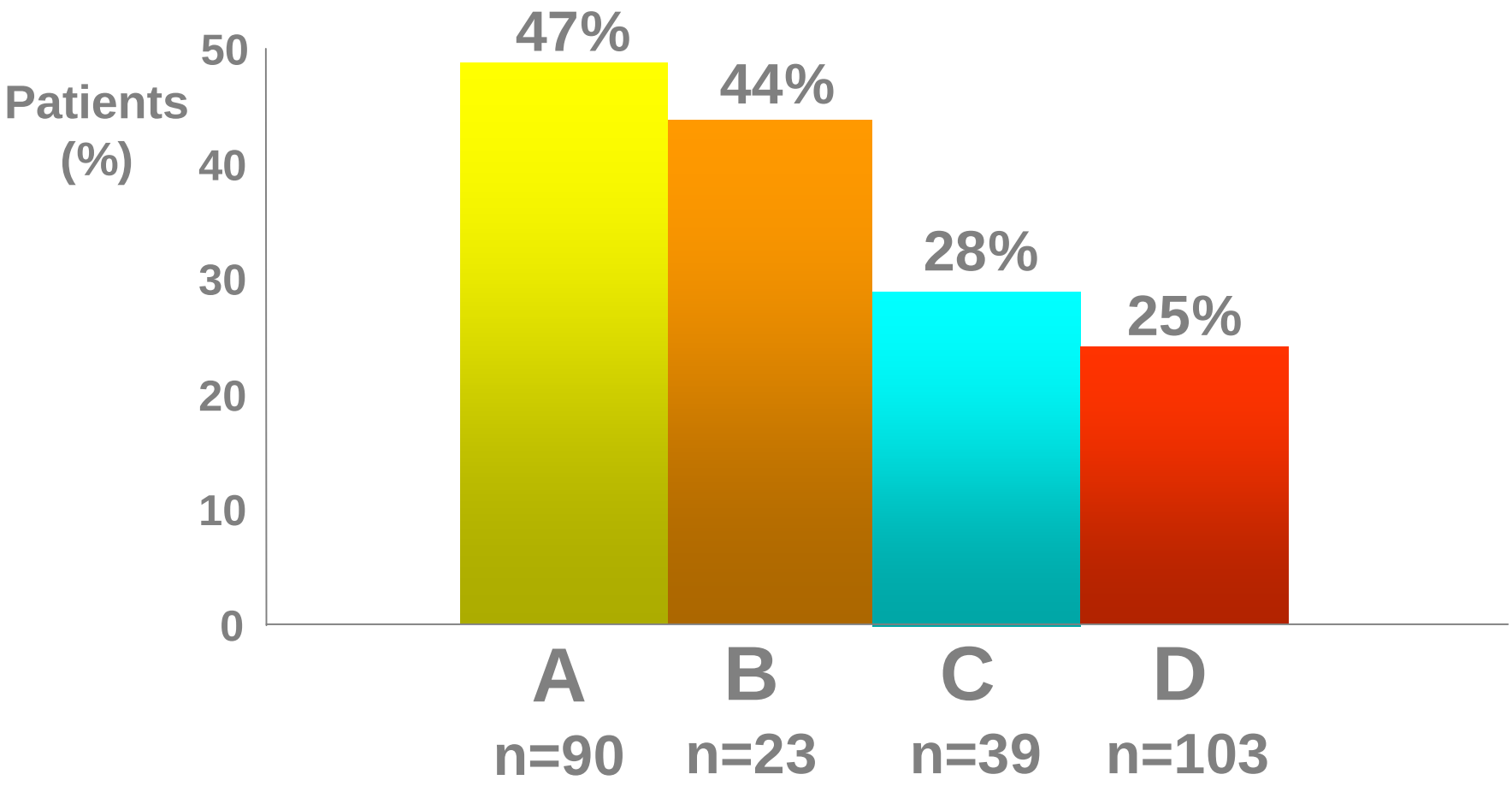
**spontaneous HBeAg seroconversion**

**with genotype B earlier and more frequent than with C**

**inflammation and progression to cirrhosis**

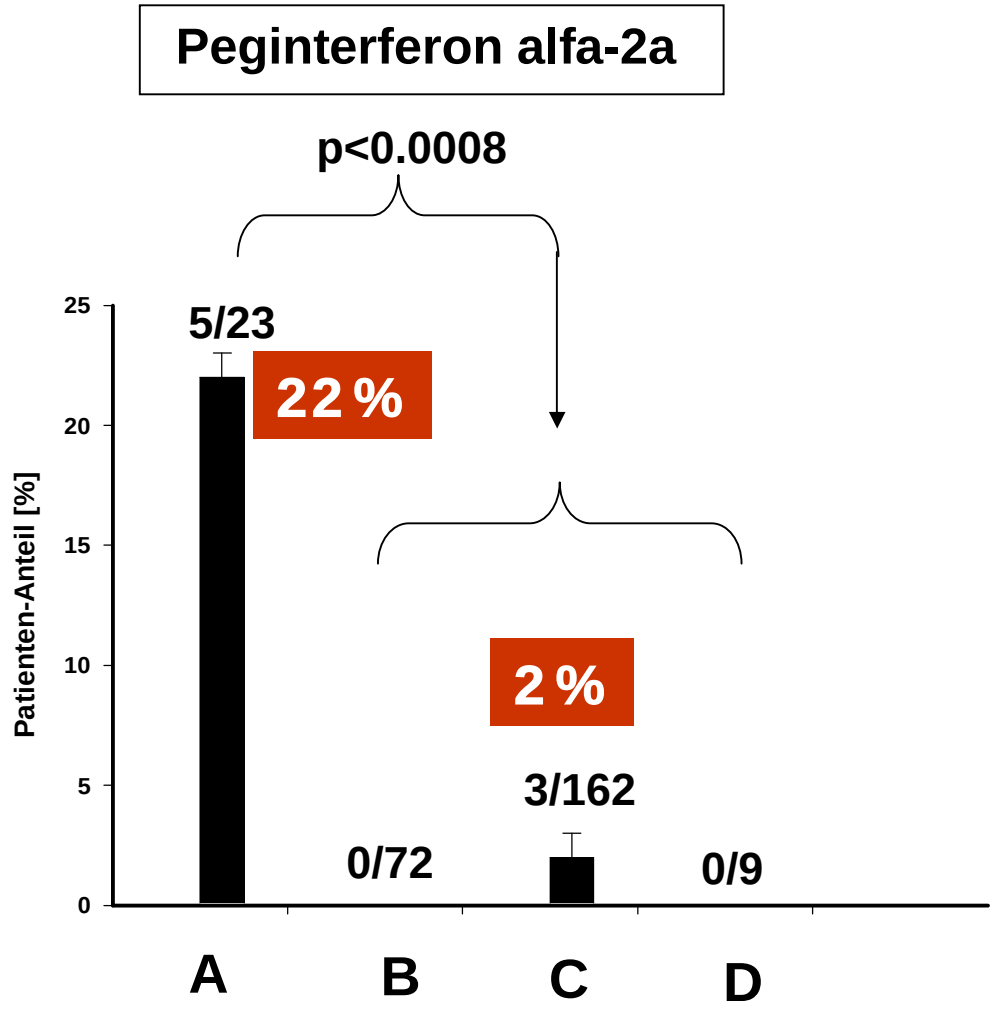
**C > B (?), D>A**

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




Janssen *et al*, Lancet 2005

# HBsAg-seroconversion by genotype




Tillmann HL et al. WJGastro 2007;7:125ff

# 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

# Contraindicationen for Interferon

- pregnancy, lactation period
- severe psychiatric comorbidity
- GPT (ALT) >10xULN
  - risk of acute flare
- advanced cirrhosis (Child B+C)
- thrombocytopenia (<50.000/µl), leukopenia (<2.000/µl)
- autoimmune disease

# Standard-IFN versus PEG-IFN ?

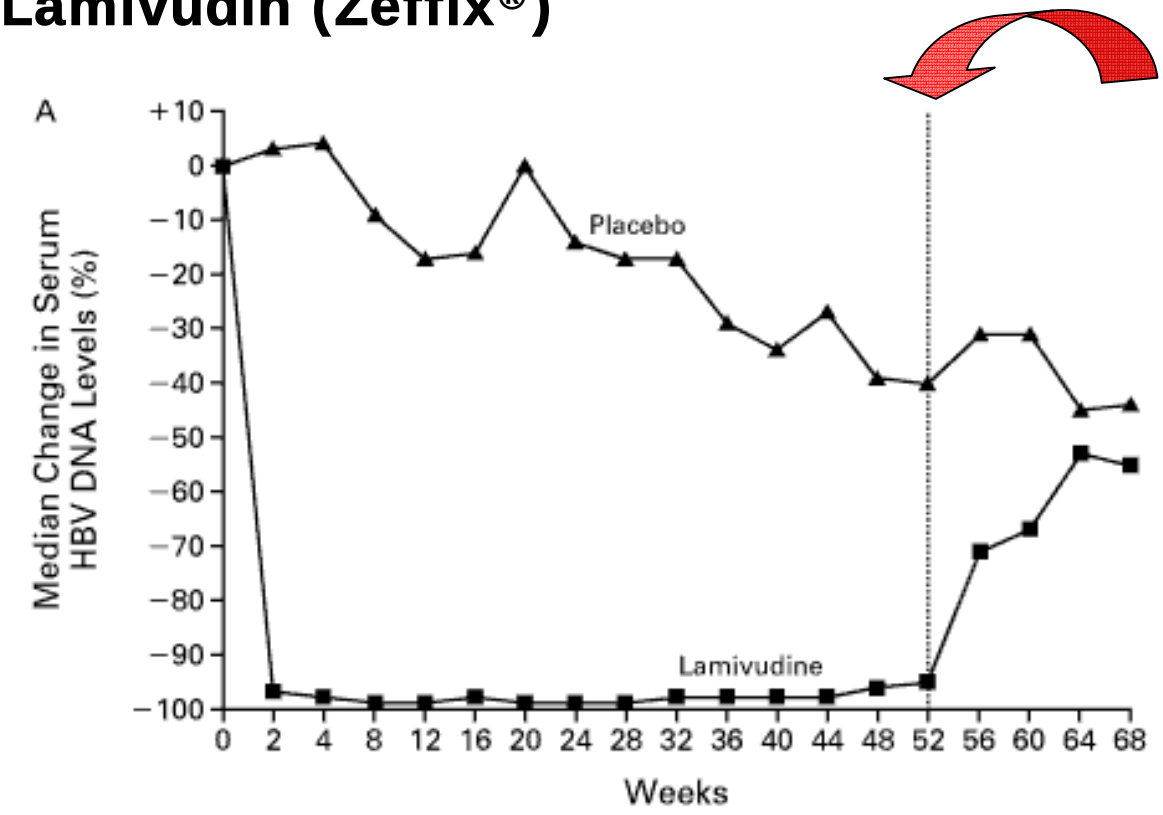
- Interferon alfa-2a (Roferon®)
  - (2,5-5 Mio. I.E./m2 3x/week)
- Interferon alfa-2b (Intron A®)
  - (5-10 Mio. I.E. 3x/week)
- Pegylated Interferon alfa-2a (Pegasys®)
  - (180µg/Woche s.c. for 48 weeks)

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

# Nukleos(t)ide-analogues

# *Nucleos(t)idanalogues - 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,**

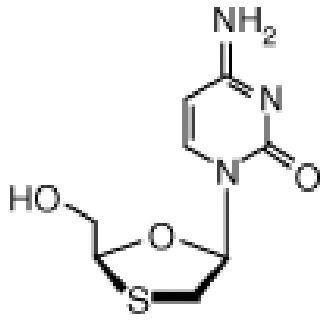
**difficult to stop“**

**Dienstag et al. NEJM 1999**

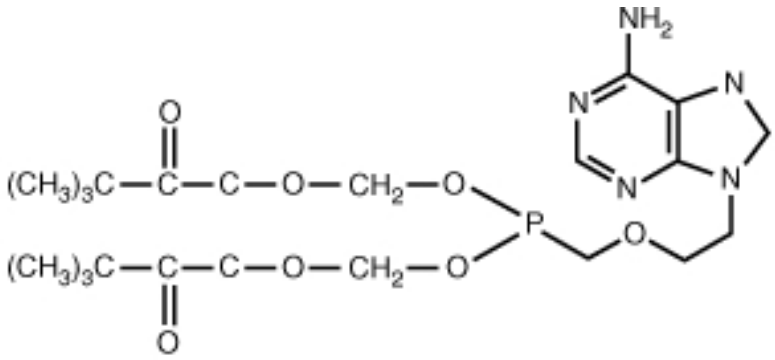
**J. Hofnagle personal note**

# Lamivudine (Zeffix, Epivir-HB, Epivir)

- Cytidine nucleoside analogue, initially developped 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)

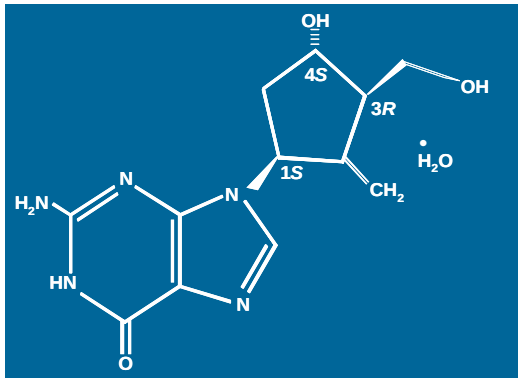


- adenine-nucleotide analogue, initially developped for HIV-infection
- doses evaluated in HIV-infection 60 and 120mg/d, nephrotoxic
- in Hepatitis B dose of  10mg daily effective
- lower rate of resistance development thand lamivudine,  primary resistance

# Entecavir (Baraclude®)

*Guanosin*-Nukleosidanalogue

-> very high antiviral potency

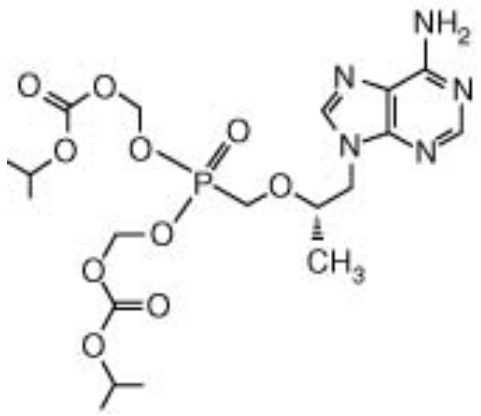



- Ideal for pts. with
  - high HBV-DNA
  - cirrhosis

- development of resistance
  - in pts without previous Lamivudin: <1% in 3 years
  - can develop cross resistance to lamivudine in HIV-infection?

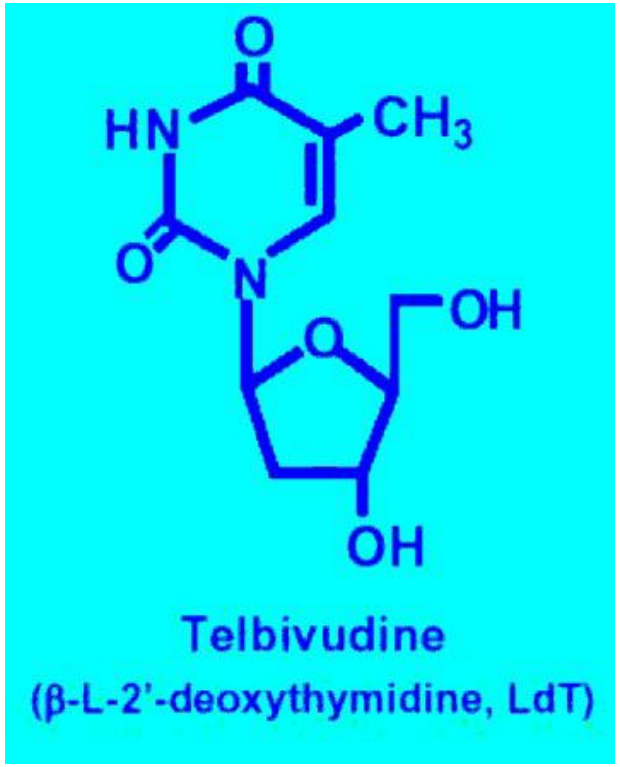
# Tenofovir (Viread)

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

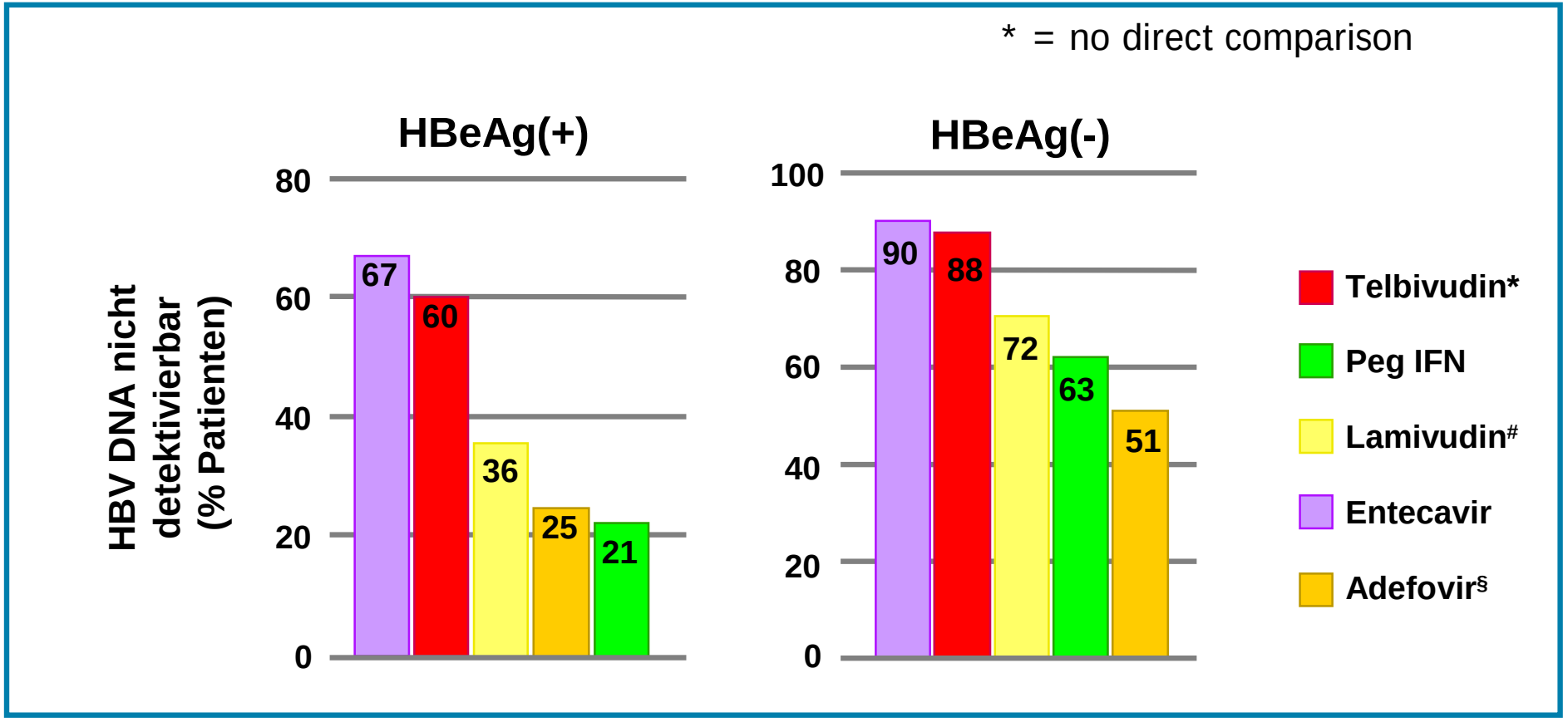


# Telbivudine (Tyzeka, Sebivo)

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



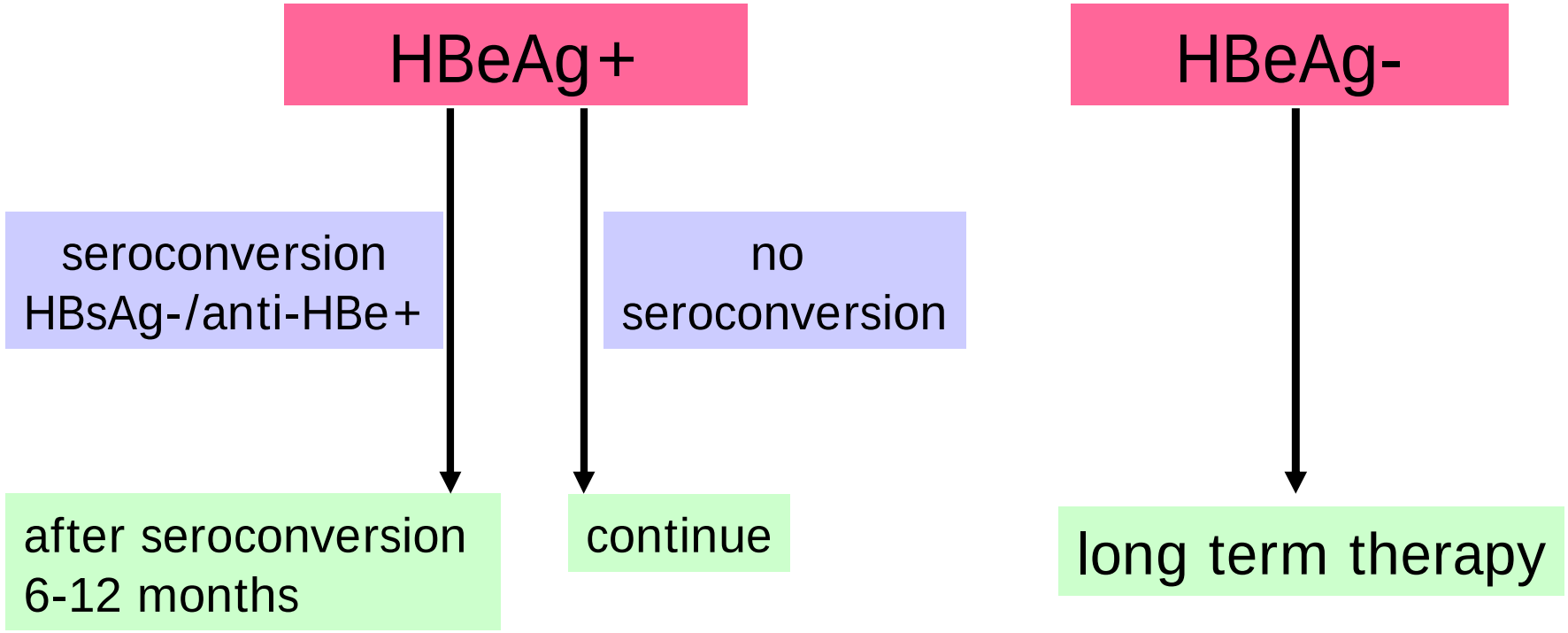
# HBV DNA Suppression within one year in nucleoside-naïve patients*




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

Lai CL, et al. *Hepatology* 2005; 42:748A (AASLD abstract LB01); Lau G, et al. *NEJM* 2005; 352:2882–2695; Chang T-T, et al. *NEJM* 2006; 354:1000–1010; Marcellin P, et al. *NEJM* 2003;348:808–816

# Nukleos(t)ide-analogues: Duration




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

# Development of resistance
# How to react ?

# Resistance: Definition

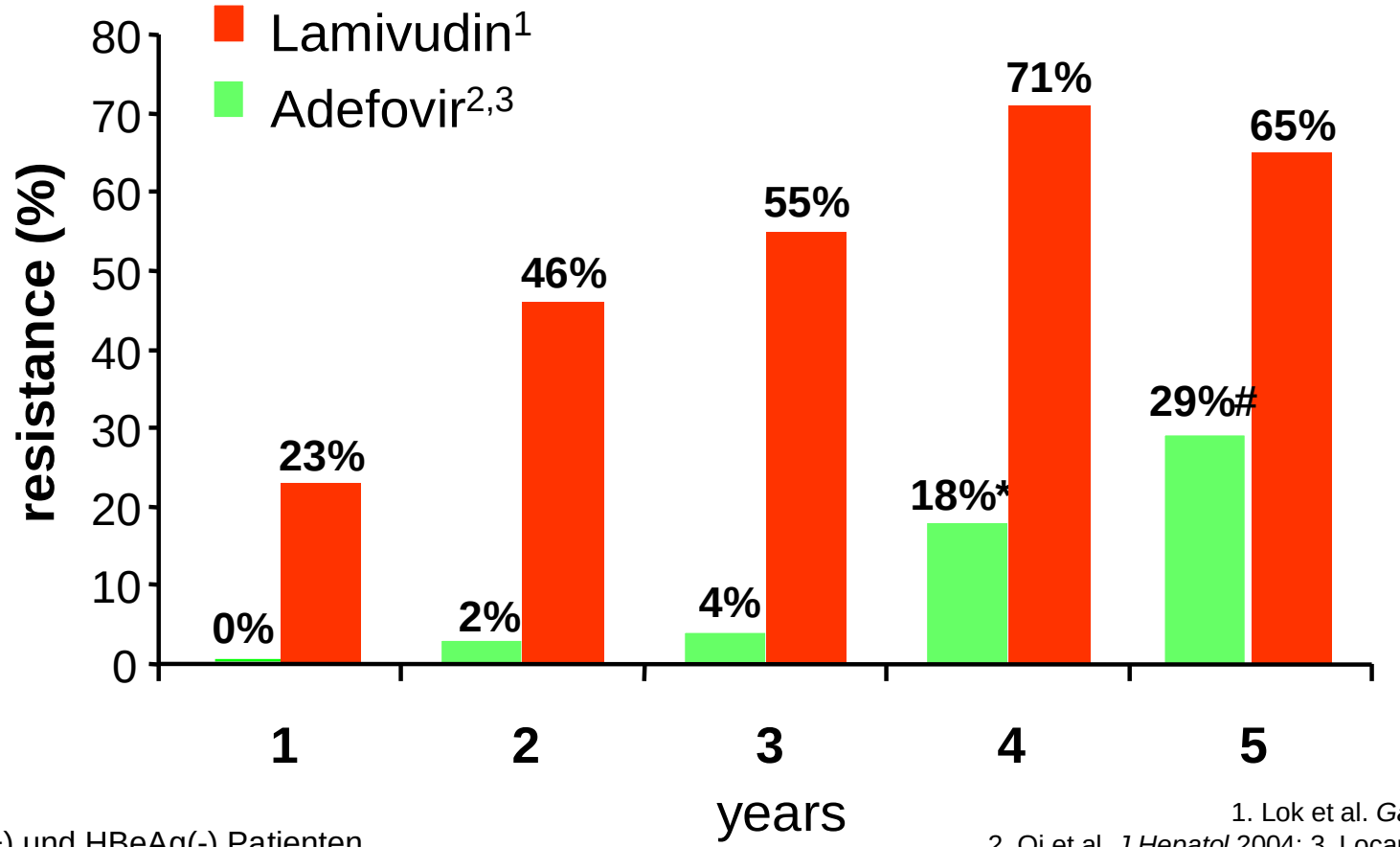
## Primary resistance

– 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

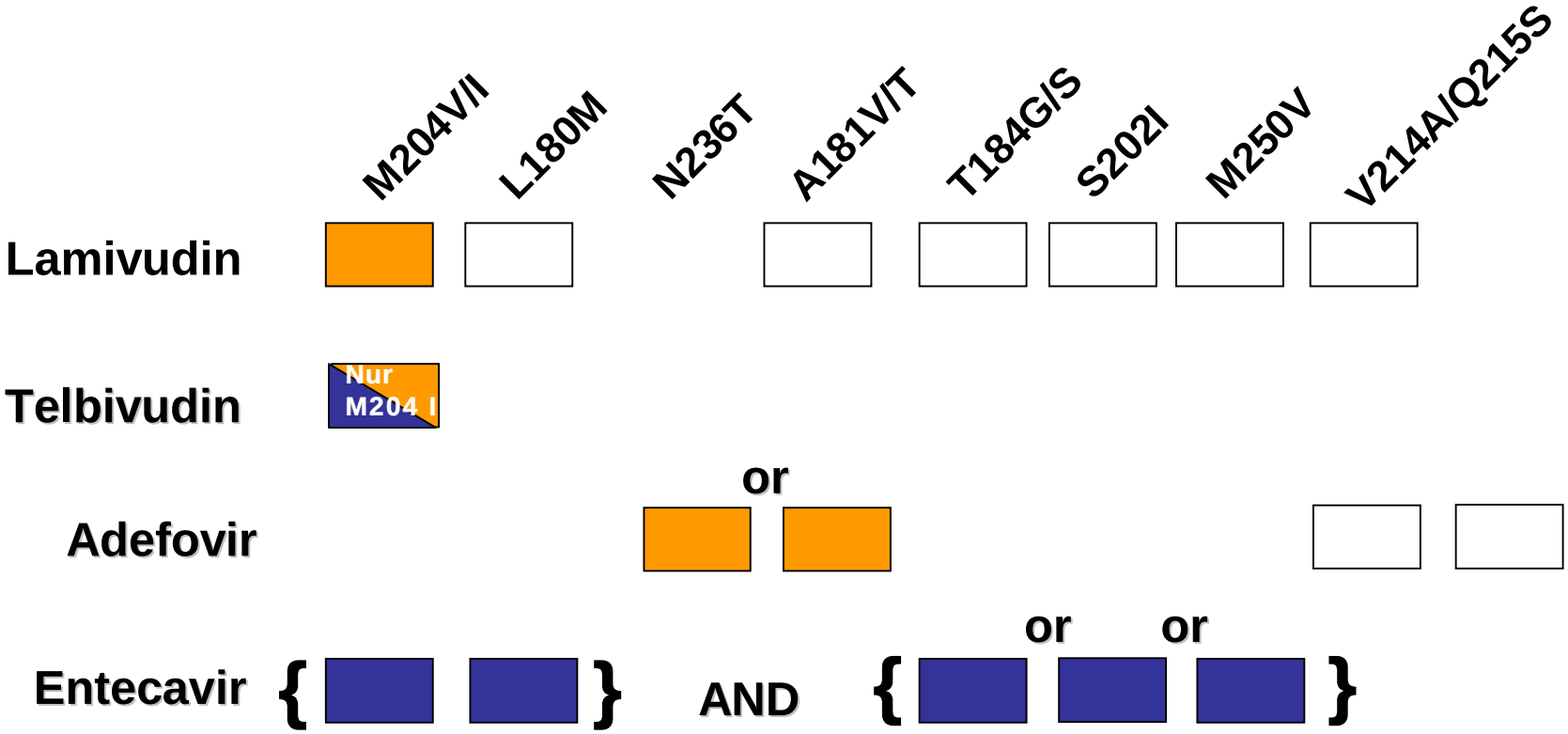



*HBeAg(+) und HBeAg(-) Patienten

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

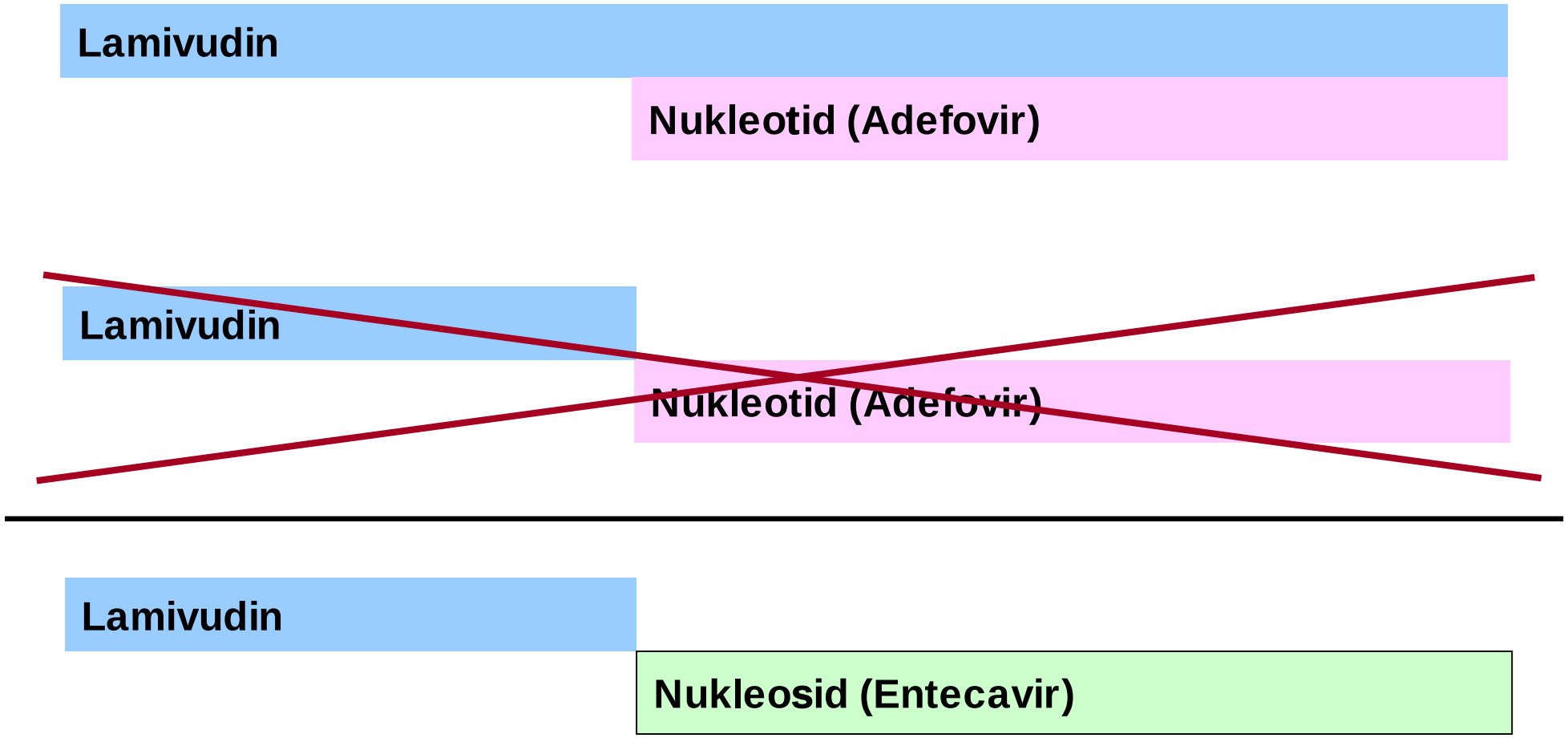
## Mutations seen in viral breakthrough



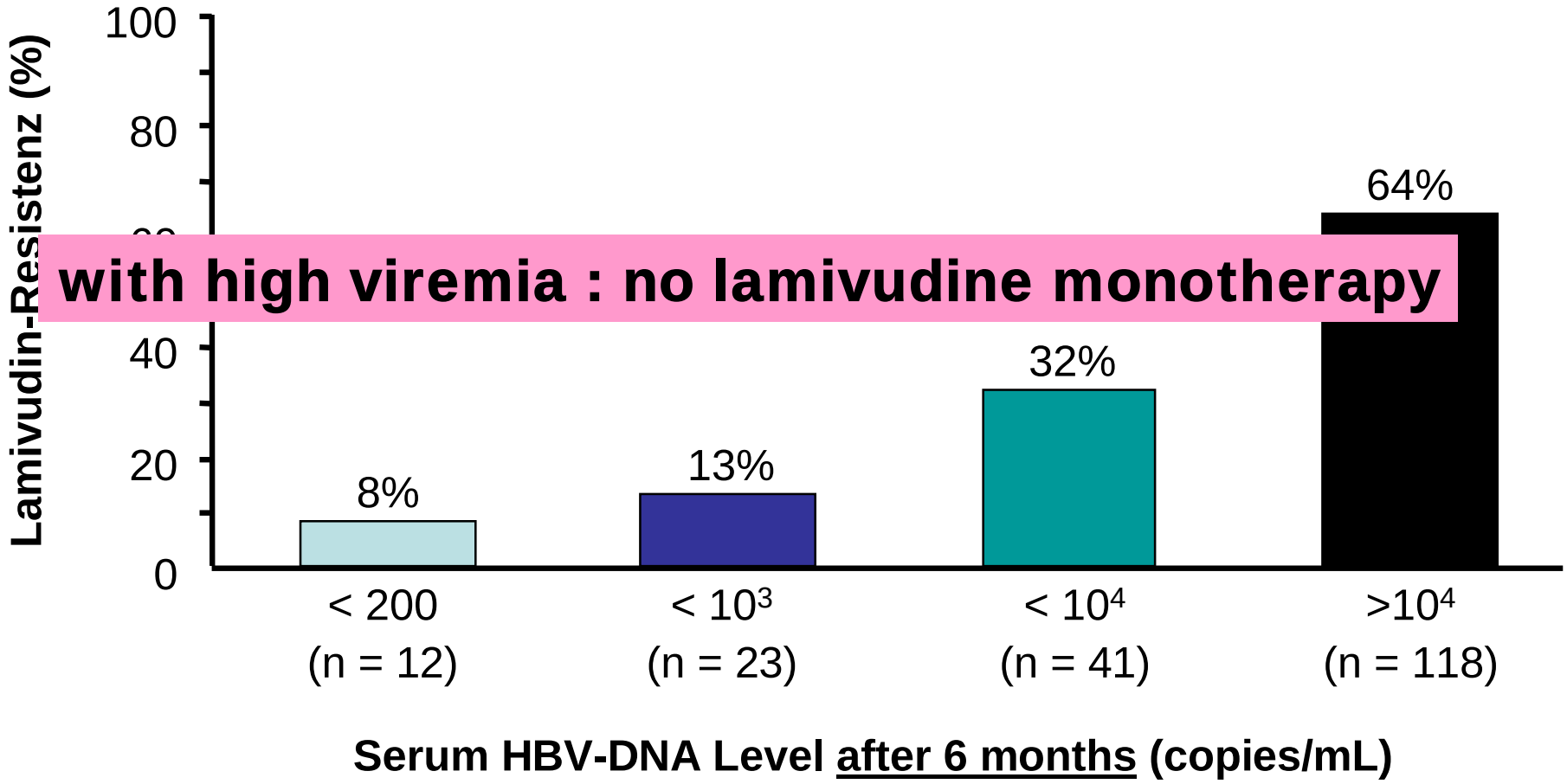

Adapted from Locarnini. Monothematic Conference, Istanbul, Turkey, 6-8 October 2005; Yuen et al. *Expert Rev Anti Infect Ther*. 2005;3:489-94; Adapted from Locarnini et al. *Antivir Ther* 2004;9:679-93

# How to react to resistance to Lamivudine?

## “Add on” or “switch” ?



# Risk of Lamivudine-Resistance higher with more viral replication

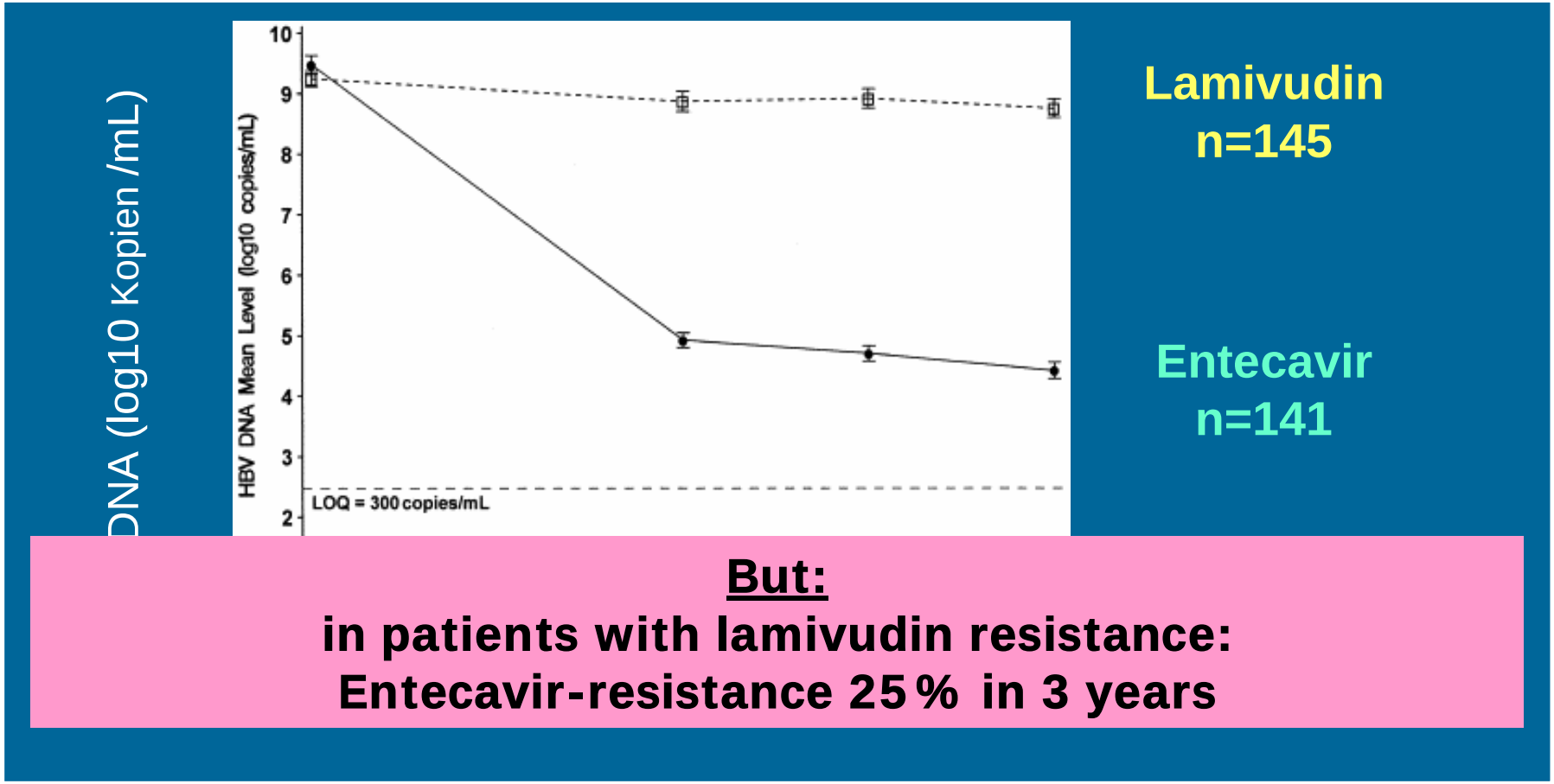



**with high viremia : no lamivudine monotherapy**

*Median follow-up: 29.6 months.

Yuen MF, et al. Hepatology. 2001;34:785-791.

# Entecavir in Lamivudin-Resistance




**But:**
**in patients with lamivudin resistance:**
**Entecavir-resistance 25 % in 3 years**

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

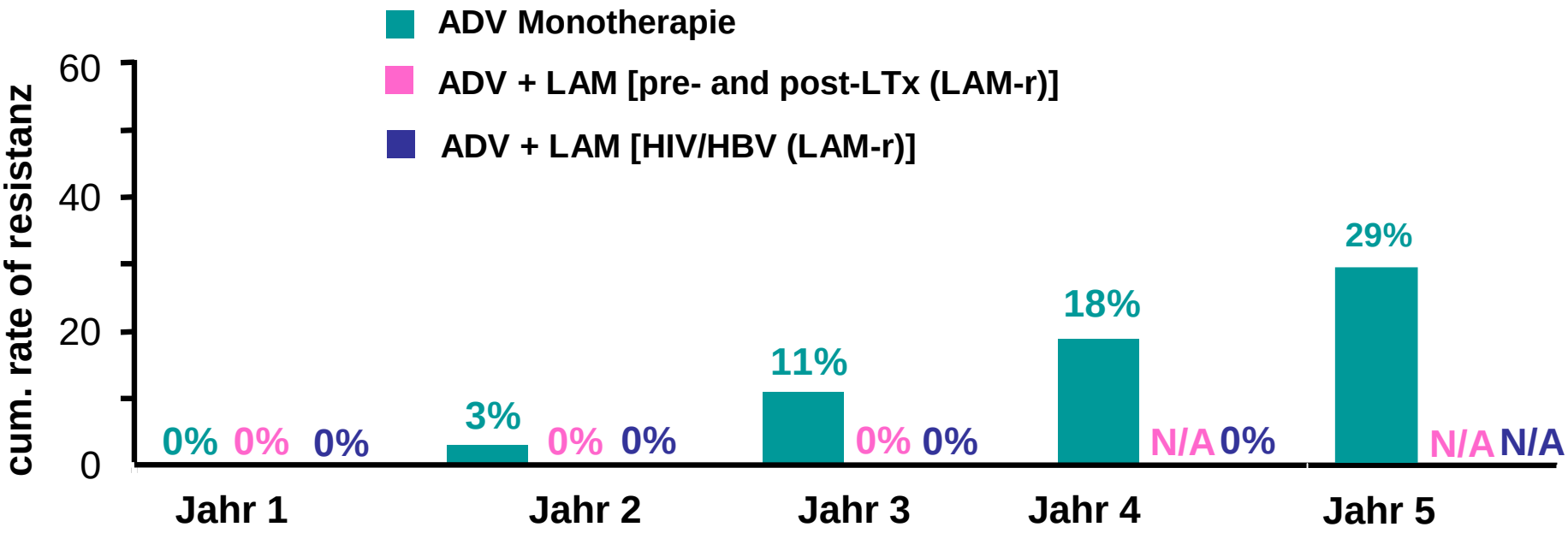
Sherman M. et al., Gastroenterology 2006;130: 2039-2049

# 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)**

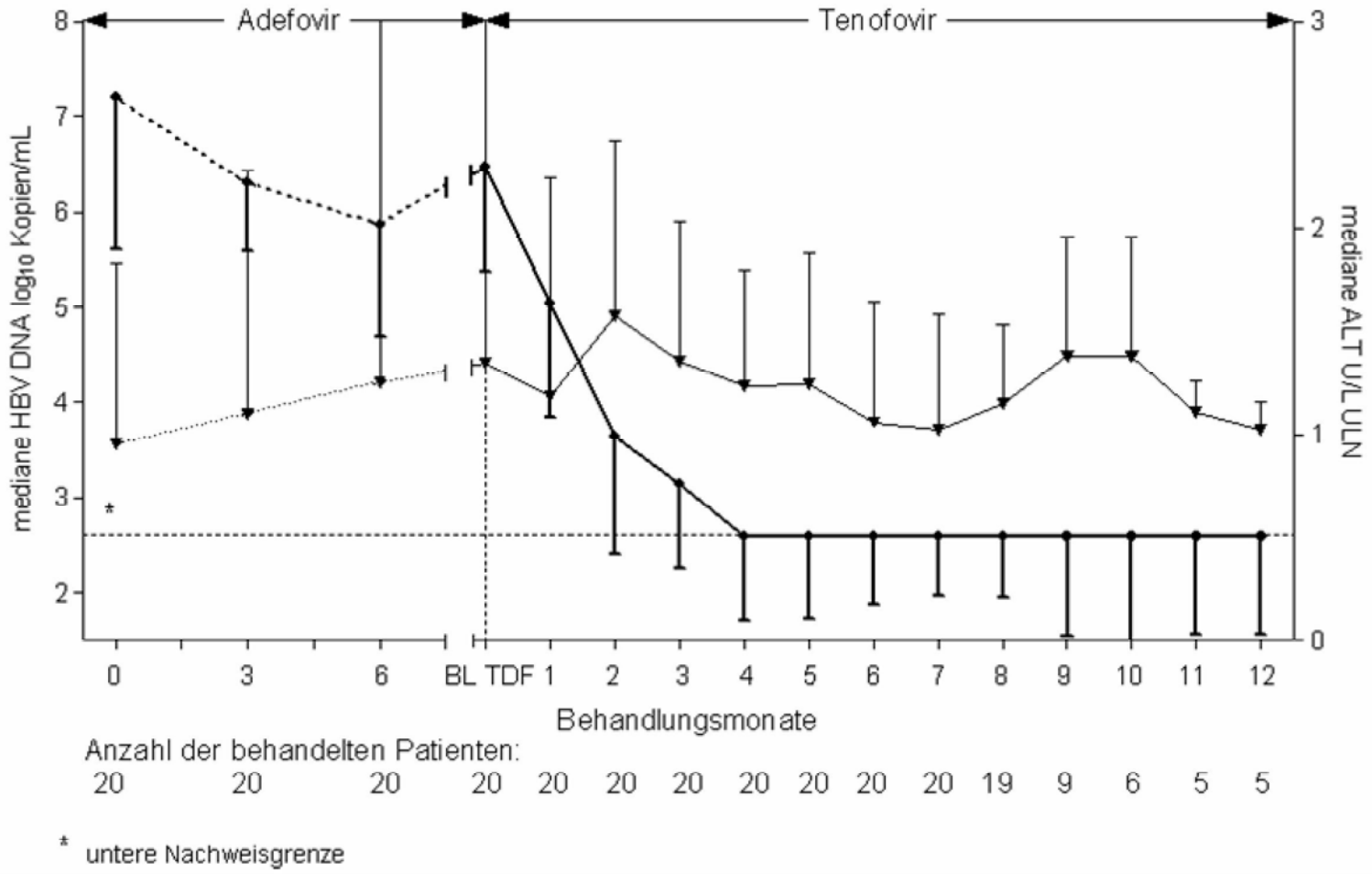
# Adefovir-resistance in pts treated with Adefovir + Lamivudin*




*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-analague**
**- Adefovir**

**- or Tenofovir**

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

**=> Currently not recommended**

# Prophylactic Therapy

# Prophylaxis with high dose chemotherapy or immunesuppression

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 ?

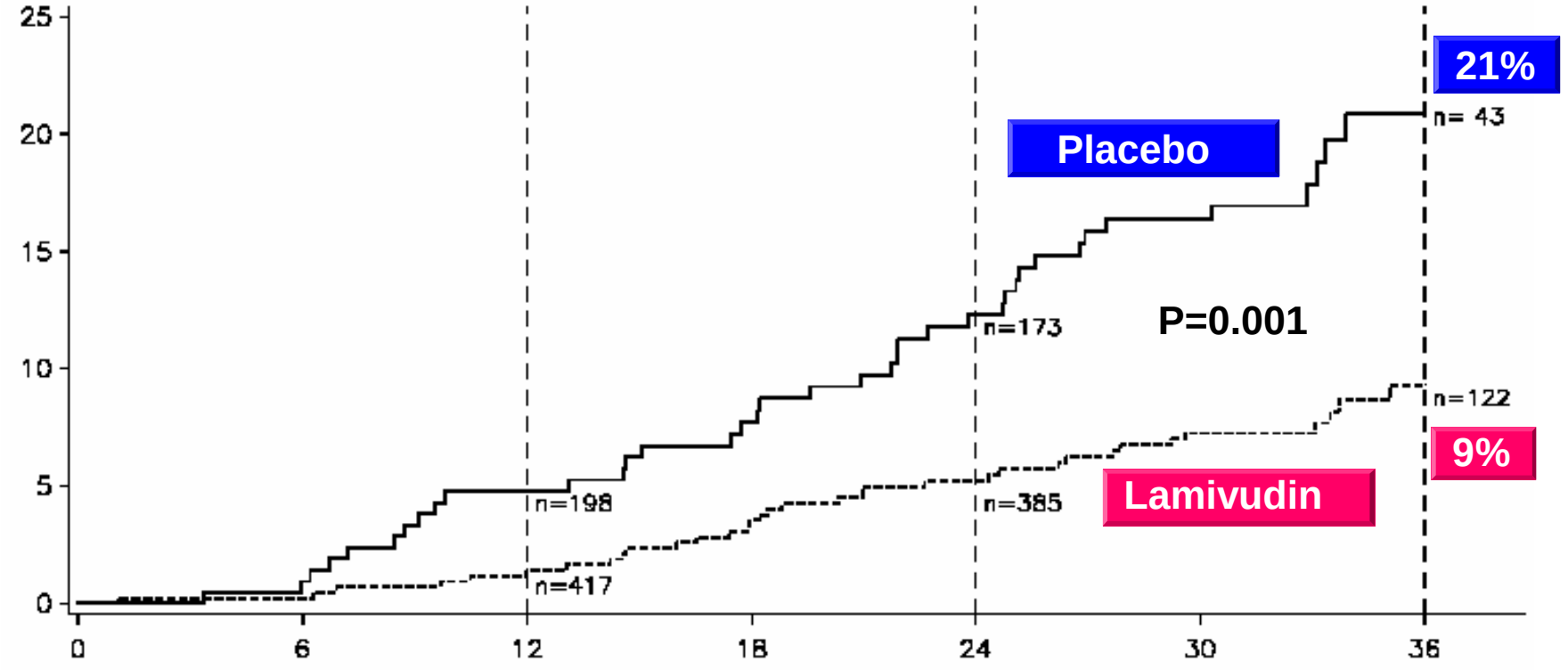
# Cirrhosis and chron. Hepatitis B

With positive viremia

=> treat always

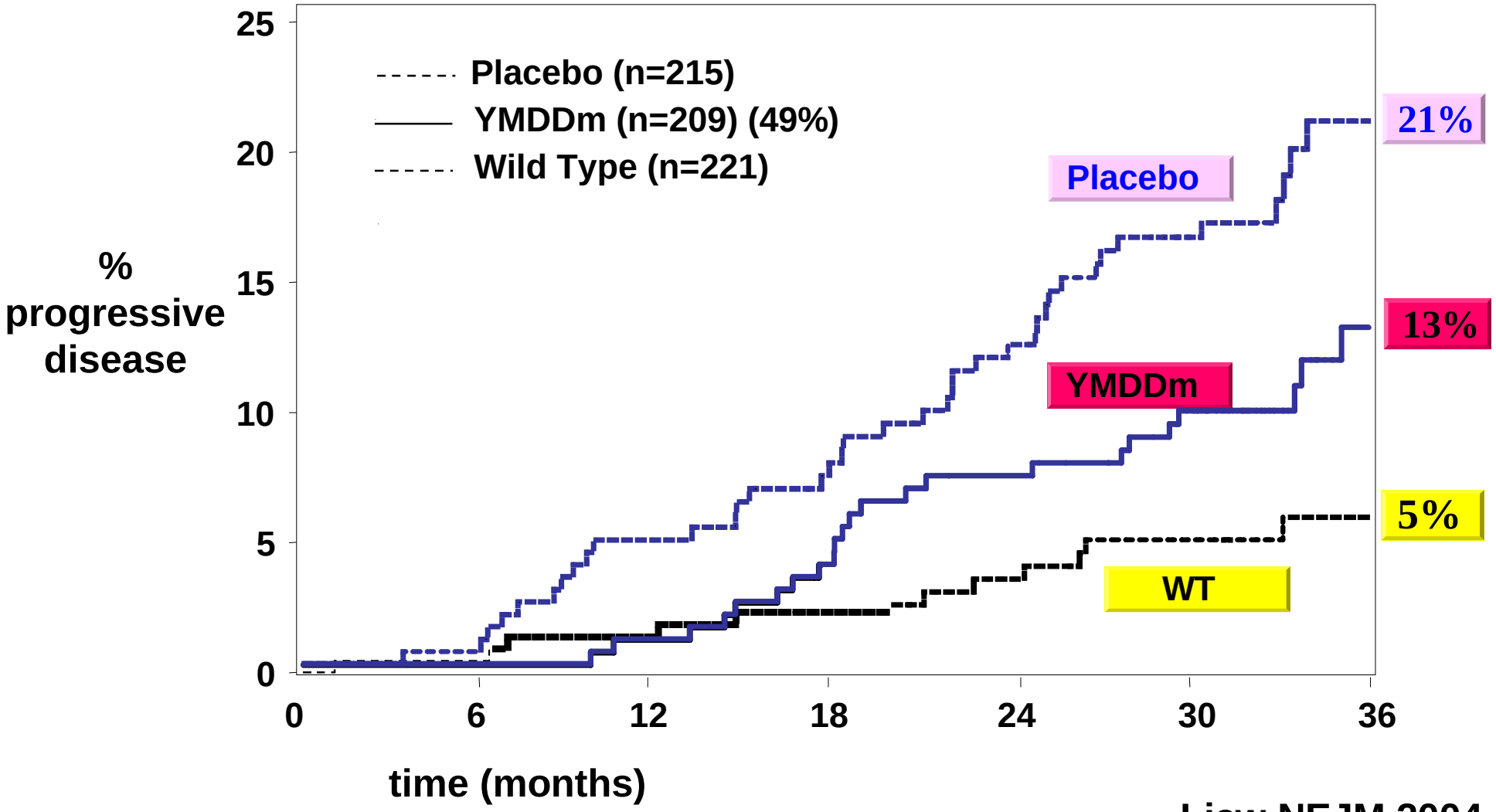
# Lamivudin in pts. with HBV-assoc. cirrhosis: organ failure and HCC

**progression to organ failure or hcc**



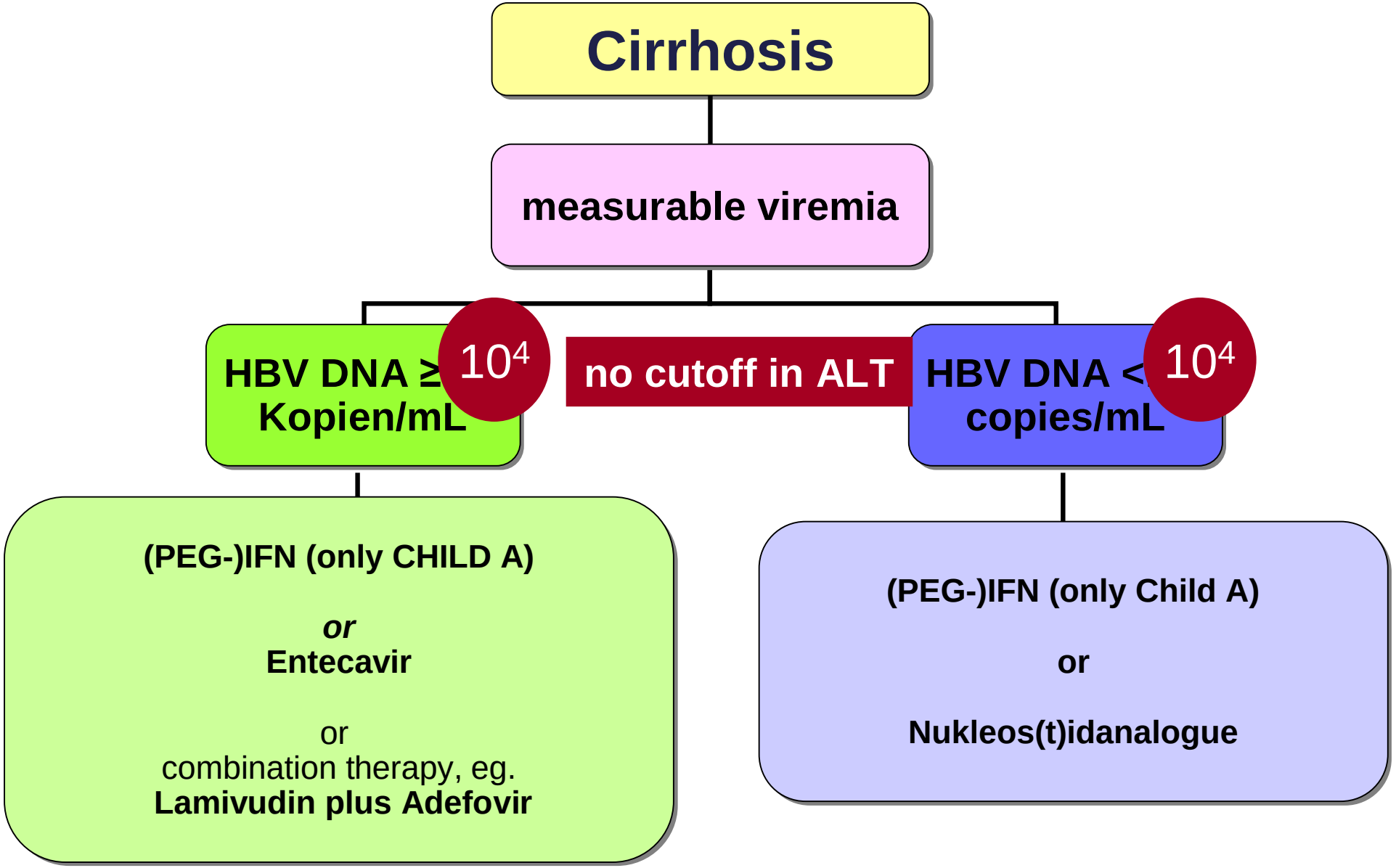

Liaw NEJM 2004

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




Liaw NEJM 2004

# Therapy of Hepatitis B with Cirrhosis



# Conclusions I

## pts. without cirrhosis:

- elevated GPT/AST (>2x ULN) and viremia > $10^4$ copies/ml
  - treat
- normal GPT/AST (<2x ULN) and viremia > $10^4$ 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 (<$10^6$ 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