29th Viral Hepatitis Prevention Board Meeting

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Treatment of chronic hepatitis B

José M. Sánchez-Tapias
Liver Unit
Hospital Clínic
University of Barcelona
Spain

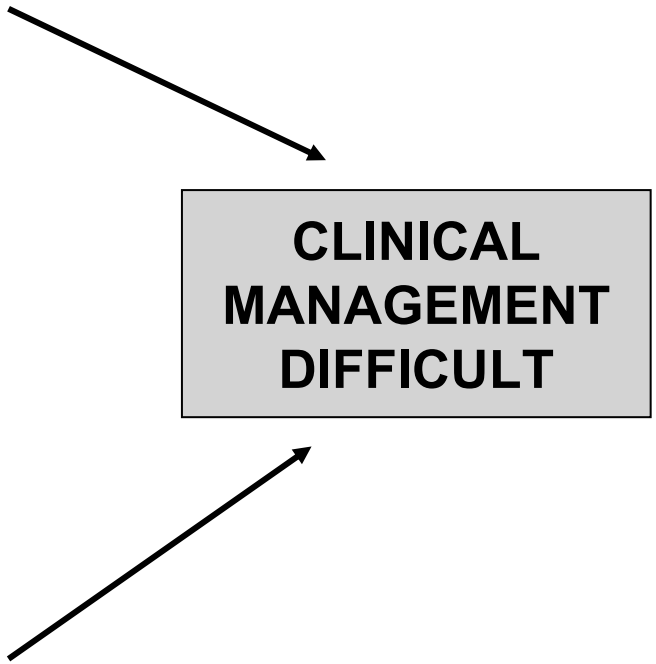
CHRONIC HBV INFECTION

THE DISEASE

- Highly heterogeneous at presentation
- Variable outcome on long-term
- Long-term prognosis uncertain

THE TREATMENT

- Valuable therapies available but
  - Limited efficacy
  - Prolonged administration
  - Viral resistance
  - High cost



CHRONIC HEPATITIS B VIRUS INFECTION IS A VERY HETEROGENEOUS CONDITION

- Immuno-tolerant carriers
- Inactive (*healthy)* carriers
- Active carriers

Active HBV carriers

Defined by: Elevated ALT

Increased serum HBV-DNA

Liver inflammation and fibrosis: Mild

Moderate

Severe

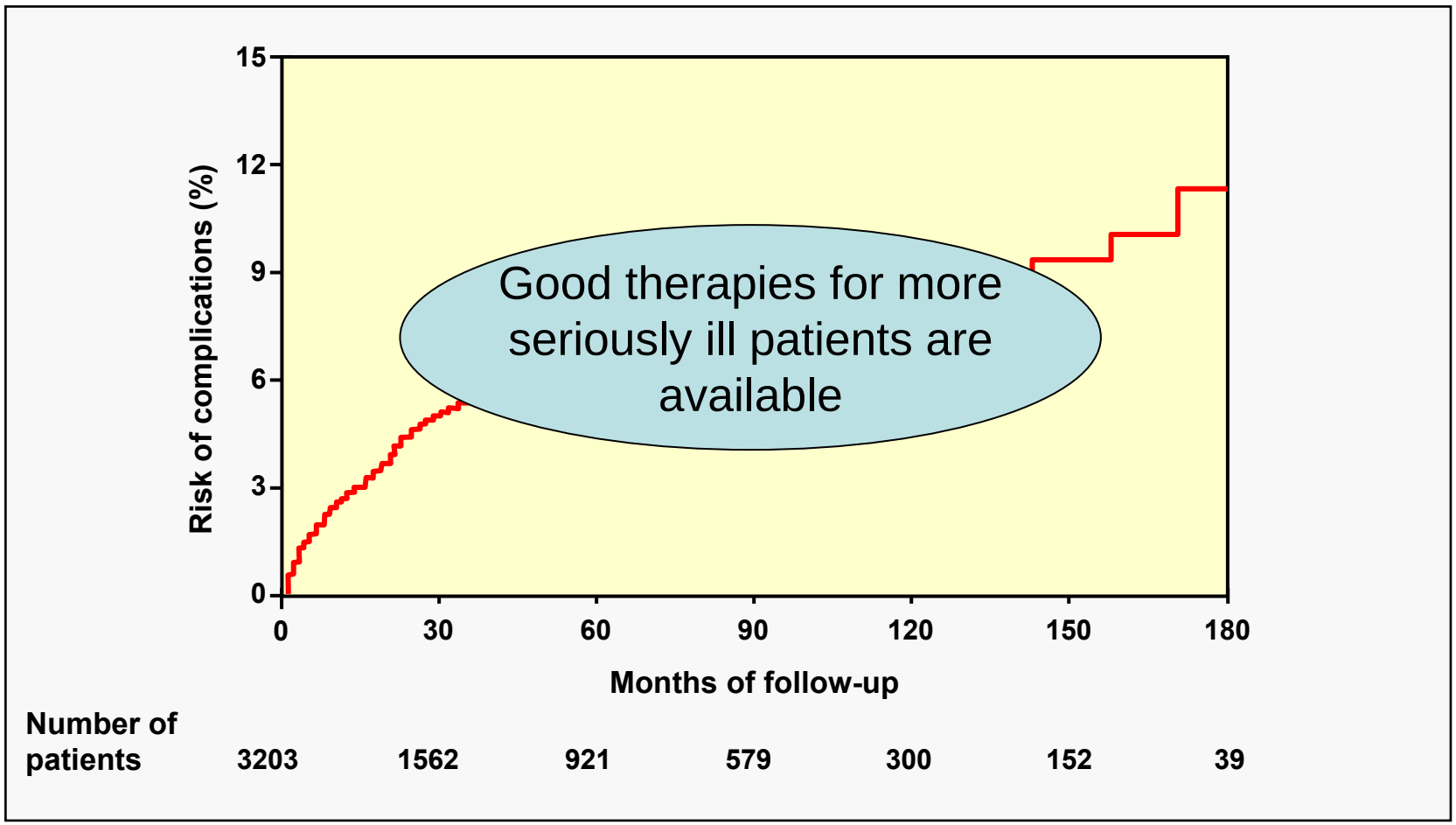
Outcome: Potentially (*but not necessarily*) progressive disease

Spontaneous remission possible

Should all active carriers be treated?

Prognostic determinants for chronic hepatitis B in Asians: Therapeutic implications

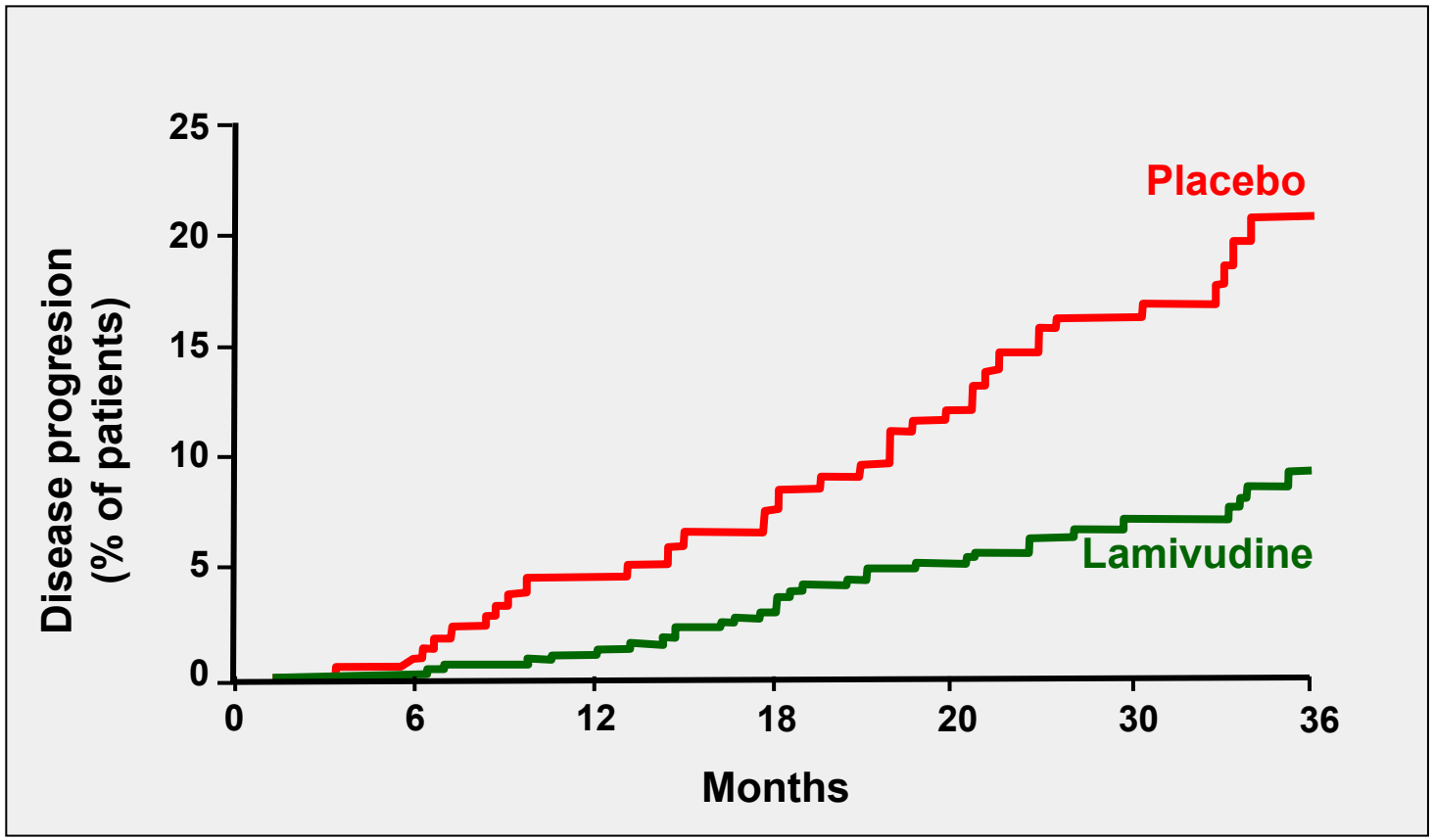
CUMULATIVE RISK OF DEVELOPMENT OF COMPLICATIONS



Yuen et al.
Gut 2005

Lamivudine for patients with chronic hepatitis B and advanced liver disease

Progression of the disease[1] according to therapy

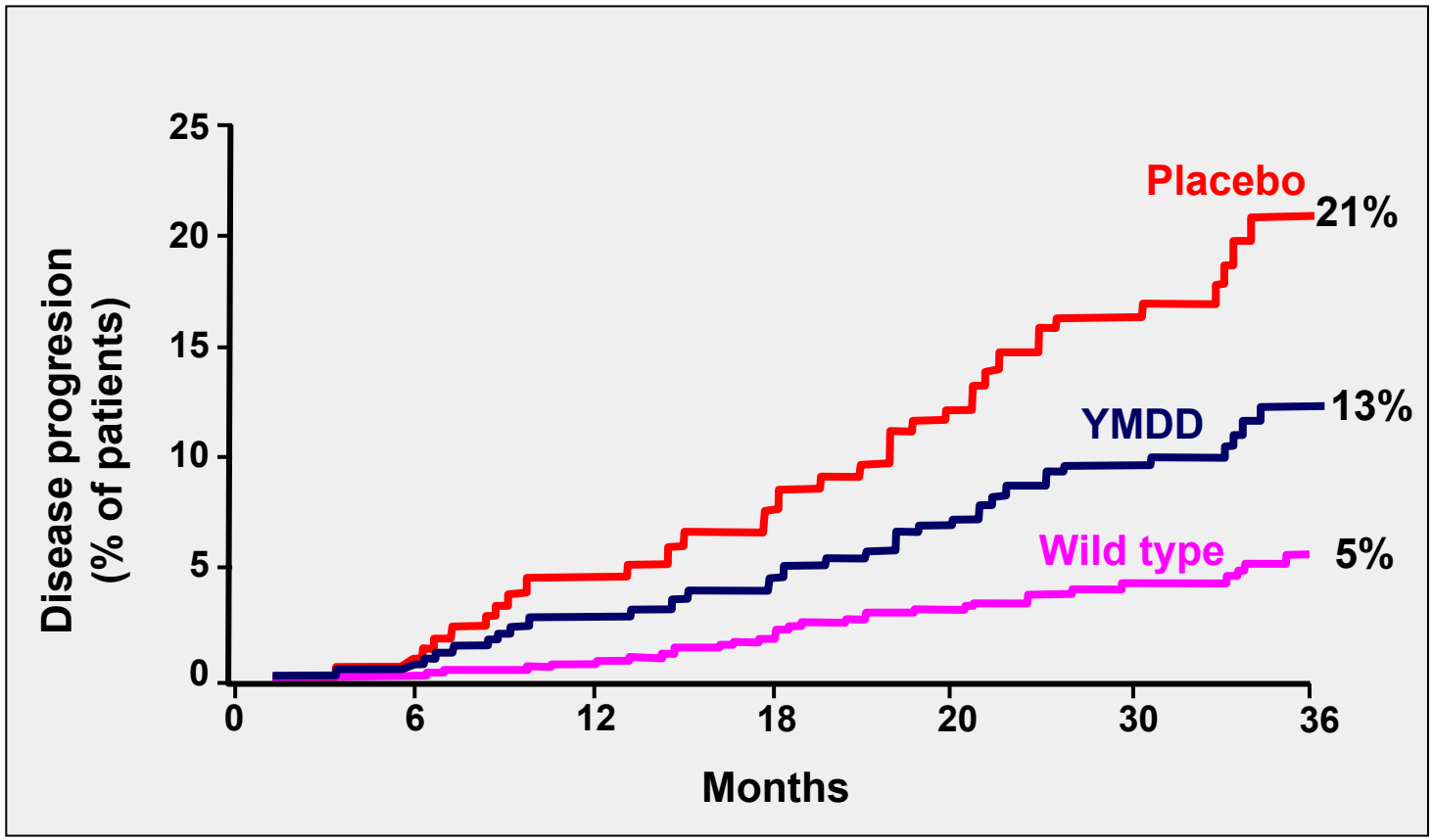


1: Includes worsening of Child score, clinical decompensation and HCC.

Liaw et al., NEJM 2004

Lamivudine for patients with chronic hepatitis B and advanced liver disease

Progression of the disease according to therapy and development of resistance to lamivudine



Liaw et al., NEJM 2004

Which patients should be treated?

" Therapy should be reserved for those who need to be treated –those with active disease examplified by raised serum aminotransferases, by clinical or histological evidence of progressive disease, or both. The decision to start therapy should not be made on the basis of HBV-DNA levels alone….."

Jay H. Hoofnagle

NEJM, March 2006

CRITERIA FOR TREATMENT

- Chronic infection
- HBsAg positive
- Serum HBV-DNA > 10^5 copies/mL
- Increased ALT
- Liver inflamation (HAI >4)

AASLD, EASL, APASLD Consensus Conferences

Treatment of chronic hepatitis B

Drugs

LICENSED:

- **Interferons (alfa-interferon, pegylated α-2a interferon)**

- **Nucleos(t)ide analogues: Lamivudine, adefovir, entecavir, tenofovir (HIV).**

ON THE WAY: **Telbivudine, clevudine, emtricitabine, pradefovir, valtorcitabine, ANA380….**
Combinations

FAR AWAY: **Immunostimulants, therapeutic vaccines, gene therapy**

Advantages and disadvantages of available agents

INTERFERON

Advantages	Disadvantages
Finite duration of treatment	Side effects. Injection
Durable response	Low response rate
Loss of HBsAg	Expensive
No resistance	

ANALOGUES

Excellent tolerance	Long or indefinite treatment duration
Oral administration	Drug resistance
Potent inhibition of viral replicacation	Low rate of HBsAg clearance
Less expensive than IFN	Expensive if administered long-term

Peginterferon in HBeAg-positive chronic hepatitis B

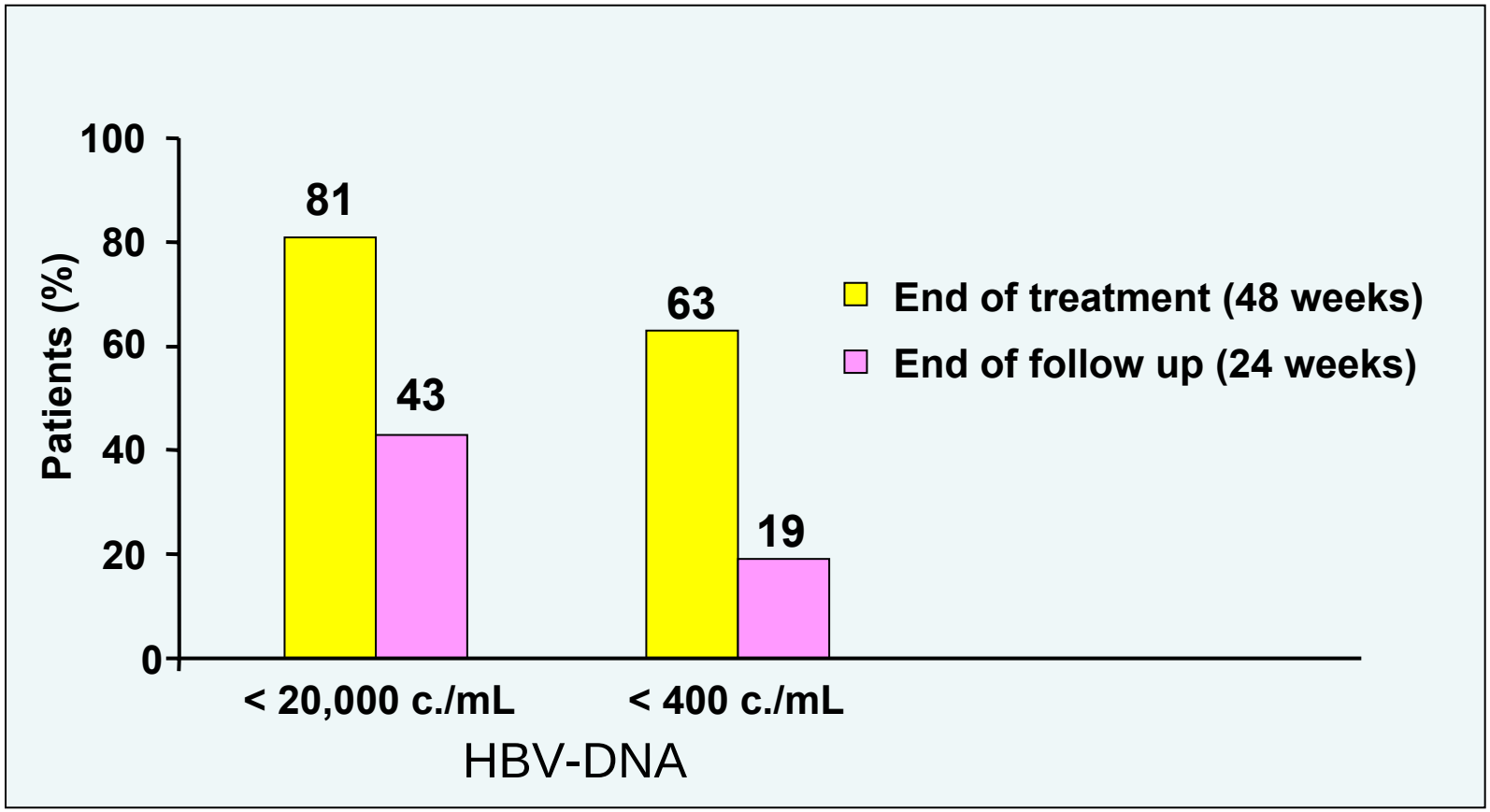
- Three large controlled trials [1-3]
- More efficient than lamivudine (48 weeks), but less well tolerated
- HBe seroconversion in 30%
- Response sustained in 90% of responders
- HBsAg seroconversion in 3%
- More efficacy in patients with higher ALT, lower serum HBV-DNA and genotype A or B

1) Janssen et al, Lancet 2005

2) Lau et al, NEJMed 2005

3) Yuen-Chan, Ann Intern Med 2005.

Peginterferon alfa-2a in patients with HBeAg-negative chronic hepatitis B



Marcellin *et al. N Engl J Med* 2004; 351:1206-17

Peginterferon alfa-2a in patients with HBeAg-negative chronic hepatitis B

- **116 patients**

  With biochemical response* after 24 weeks on no therapy.

  Followed for an additional 18 months (24 months off-therapy)

Normal ALT:	**44 (38%)**	**(25%)****
ALT <50 IU/L and HBV-DNA < 100x10^3 c./mL:	**47 (41%)**	**(27%)****
HBsAg seroconversion:	**6 (5%)**	**(3%)****

***: Defined by ALT below 50 IU/L**

****: Percent of the whole treated population**

Marcellin *et al. EASL 2006 (Abstract 743)*

NUCLEOS(t)IDE ANALOGUES

Activity:

Block HBV-DNA polymerase
Chain termination

Effects of one year therapy:

Marked reduction (suppression) of viral replication

Improved ALT, histology and liver function

Well tolerated

Benefits usually not sustained after discontinuation

Prolonged therapy is necessary

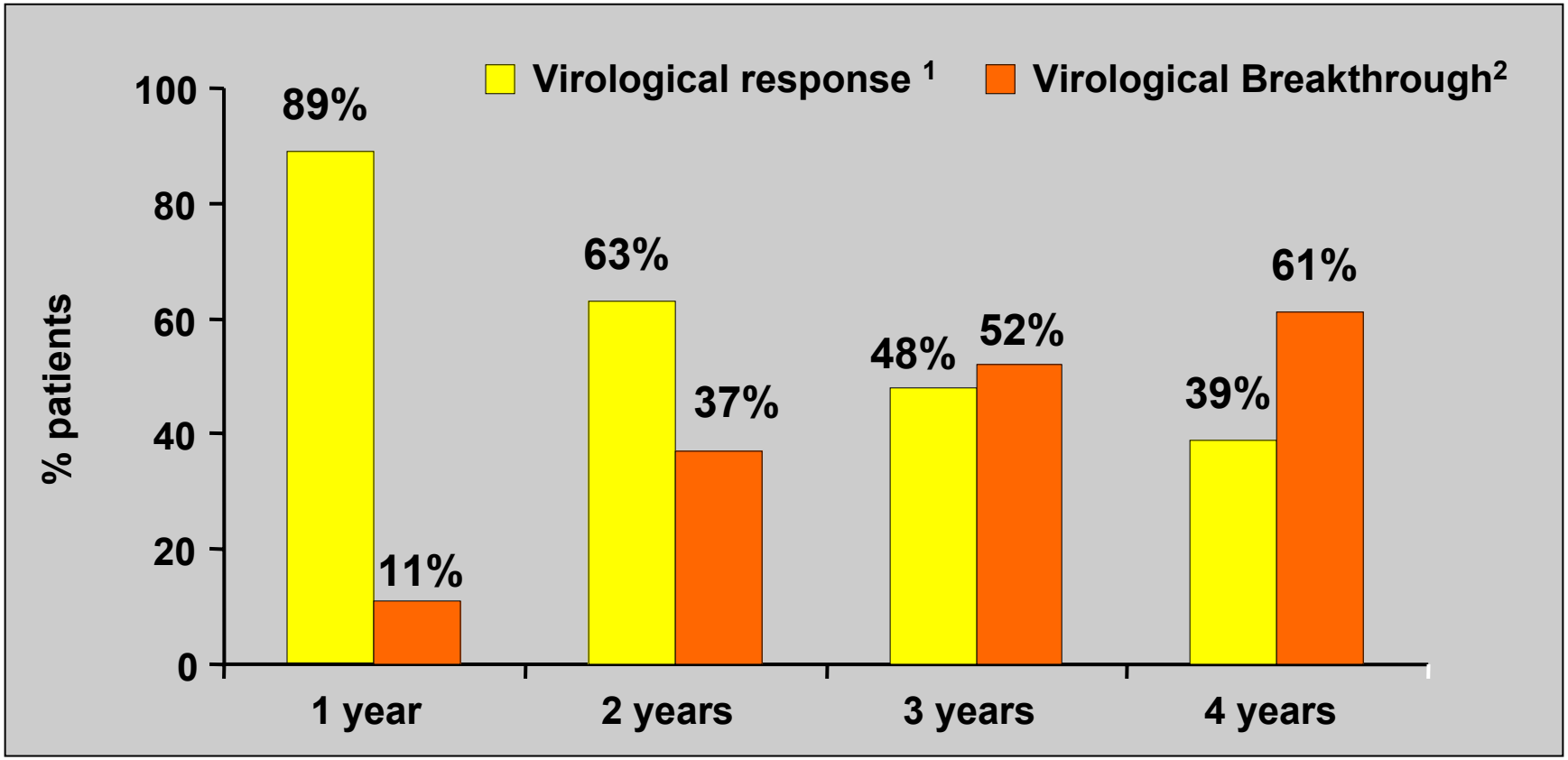
For how long?

Resistance may occur

Consequences of viral resistance

- Virologic and biochemical breakthrough
- Loss of initial virologic, biochemical, and histologic response
- Hepatitis flares, hepatic decompensation, and death

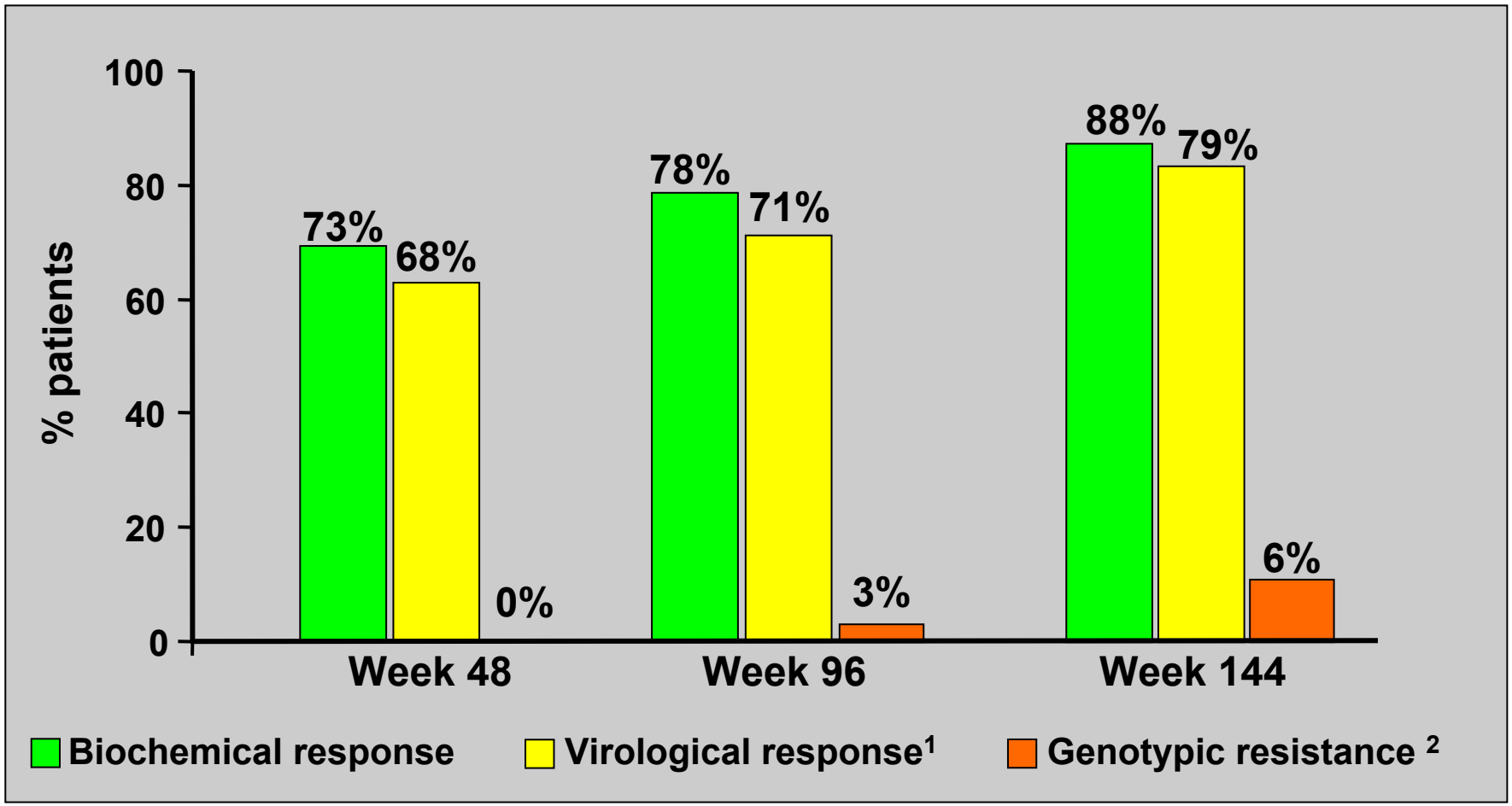
Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine



1. HBV DNA < 10^5 copies/mL by Digene Hybrid Capture II or bDNA Bayer assay
2 . Reappearance of HBV DNA by non PCR assay or > 10^5 copies/mL by PCR assay

AISF Lamivudine Study Group
Di Marco et al. Hepatology 2004; 40: 883-91

Long term therapy with Adefovir dipivoxil for HBeAg negative chronic hepatitis B



1. HBV DNA < 1000 copies/mL by Roche Amplicor Monitor PCR assay

2. Detection of ADV-resistance associated mutations

Hadziyannis et al.
NEJM 2005

SUSTAINED BIOCHEMICAL AND VIROLOGICAL REMISSION AFTER DISCONTINUATION OF 4 TO 5 YEARS OF ADEFOVIR DIPIVOXIL TREATMENT IN HBeAg-NEGATIVE CHRONIC HEPATITIS B

33 Patients with HBeAg neg chronic hepatitis B (genotype D)

- **In sustained remission under ADV therapy for 4-5 years**

  Normal LFT
  Undetectable HBV-DNA
  No genotypic resistance
  Improved histology

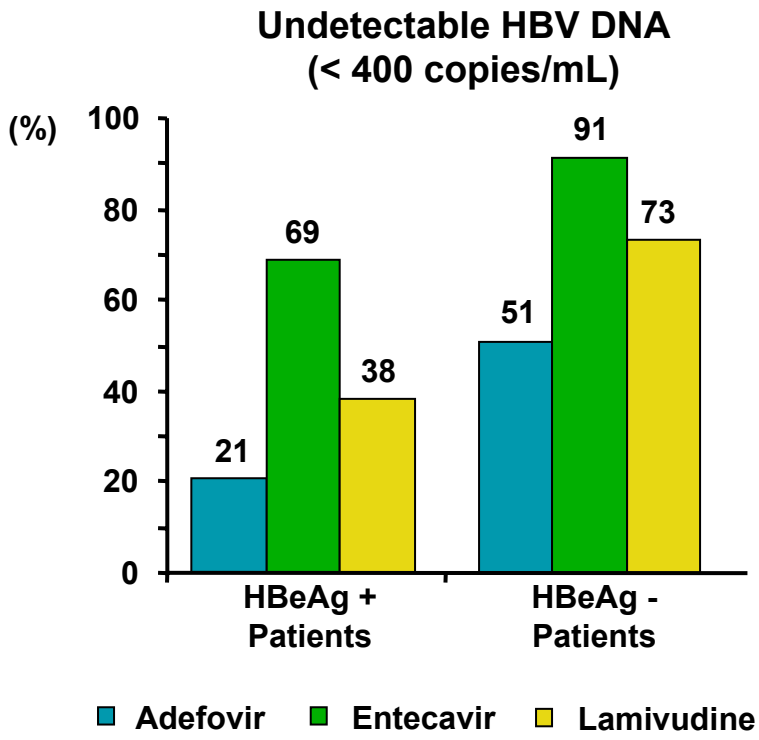
- **Followed for 18 months after treatment withdrawal**

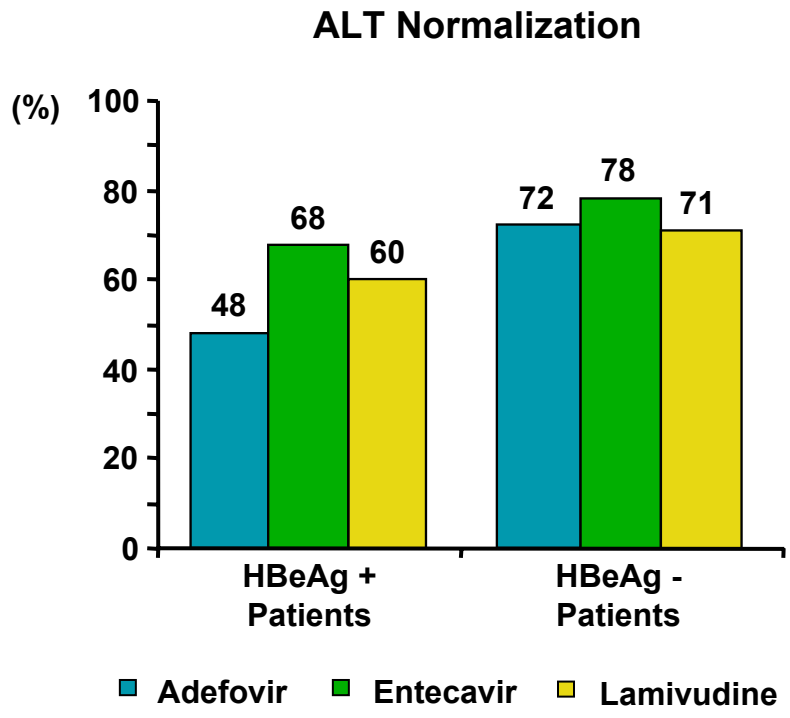
22 (67%) maintained remission (Inactive HBV carriers)

11 (33%) relapsed witin 3 months.
Responded to re-treatment

Hadziyannis et al., AASLD 2006, (Abst 114)

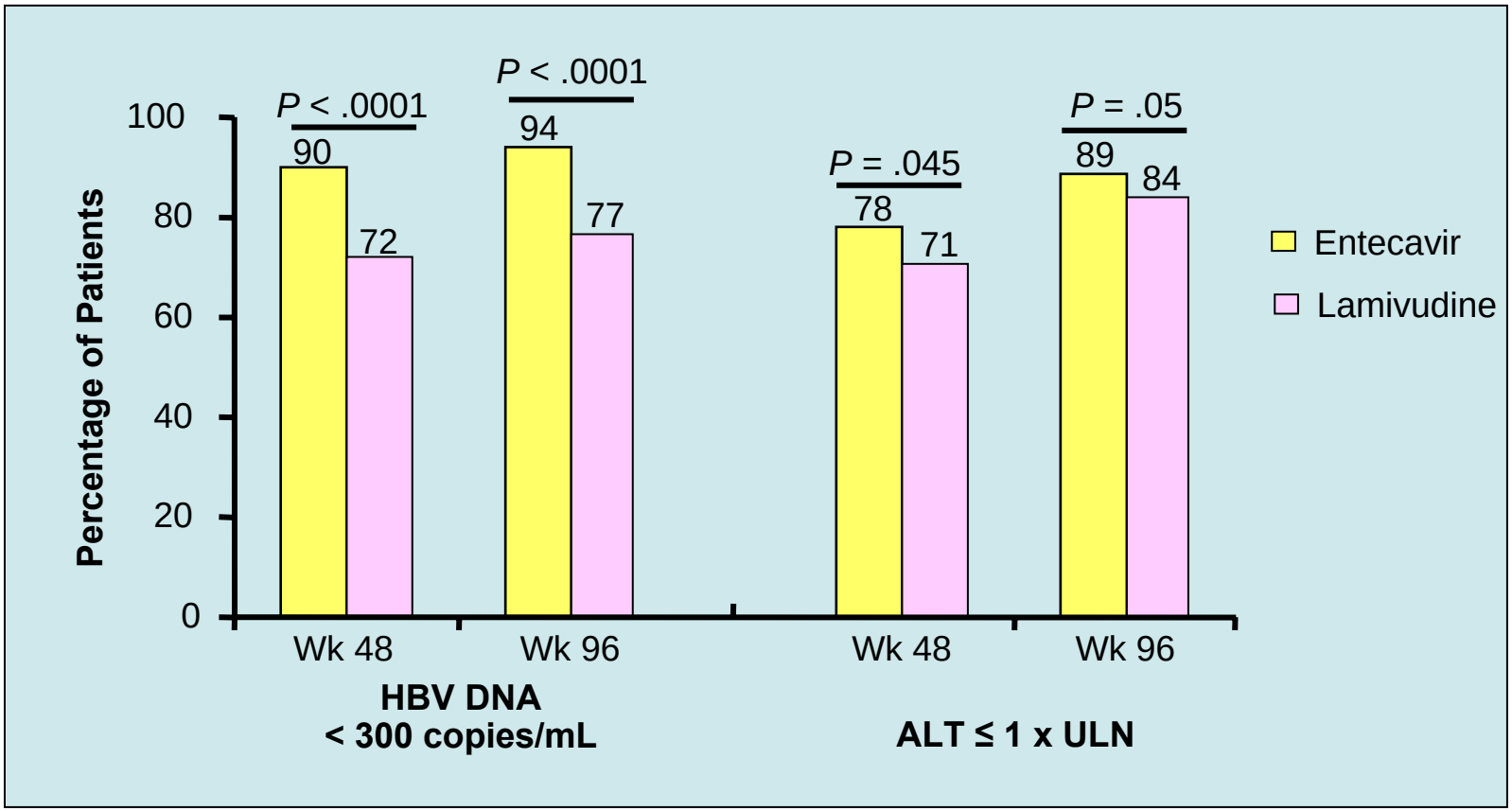
Efficacy of one year therapy with nucleosid(t)e analogues for Hepatitis B





Entecavir in HBeAg(-) Patients: Week 96

Cumulative Response Outcomes



Shouval D, et al. EASL 2006. Abstract 45.

CURRENT TREATMENT OF CHRONIC HBV INFECTION

- Still evolving
- Effective therapies available
- Optimal therapeutic options partially identified
- Many questions pending