

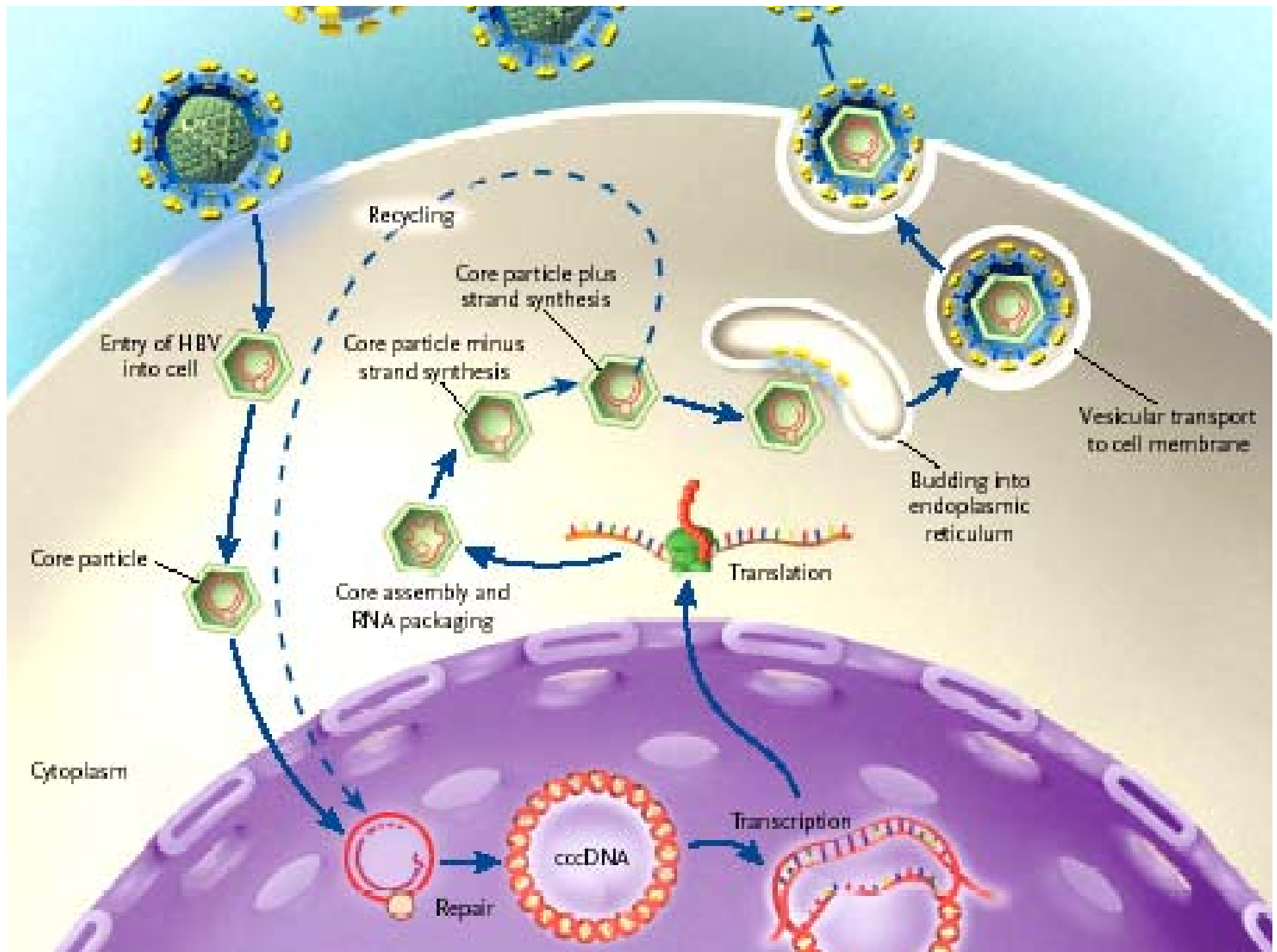
# **EPATITE B, UNA EPIDEMIA SCONOCIUTA**

***Maurizio KOCH***

**Azienda Ospedaliera San Filippo Neri  
U.O.C. Gastroenterologia ed Epatologia**

# Hepatitis B Virus

- **Hepadnavirus**
- **100 volte più infettivo di HIV**
- **Si trova nel sangue e nei fluidi corporei**
- **Sopravvive più di 7 giorni nel sangue essiccato**

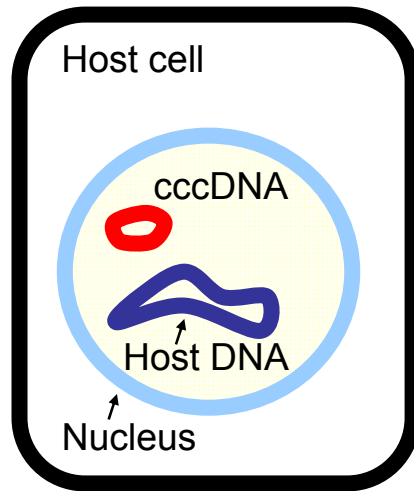


# Different virus replication strategies



## different treatment goals

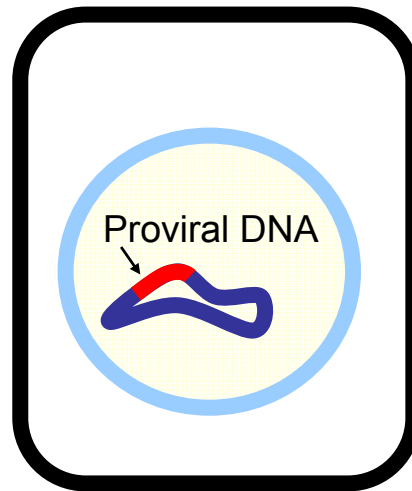
**HBV**



**TREATMENT**

**Long-term reduction of viral replication to lowest possible level<sup>1</sup>**

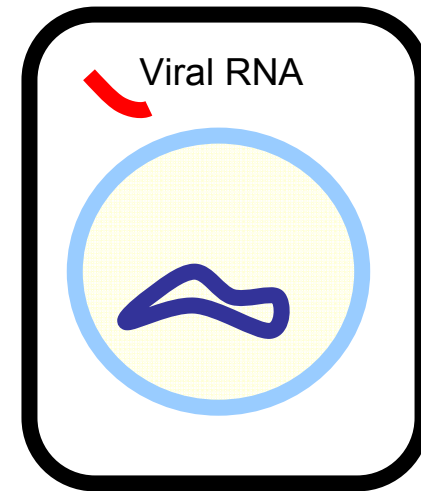
**HIV**



**TREATMENT**

**Lifelong suppression of viral replication<sup>2,3</sup>**

**HCV**



**TREATMENT**

**Definitive viral clearance<sup>1</sup>**



**SVR possible for HCV<sup>1</sup>**

1. Pawlotsky JM. *J Hepatol* 2006;44:S10-S13; 2. Siliciano JD, Siliciano RF. *J Antimicrob Chemother* 2004;54:6-9;

3. Lucas GM. *J Antimicrob Chemother* 2005;55:413-416

cccDNA = covalently closed circular DNA

# L'impatto della epatite B nel mondo è alto

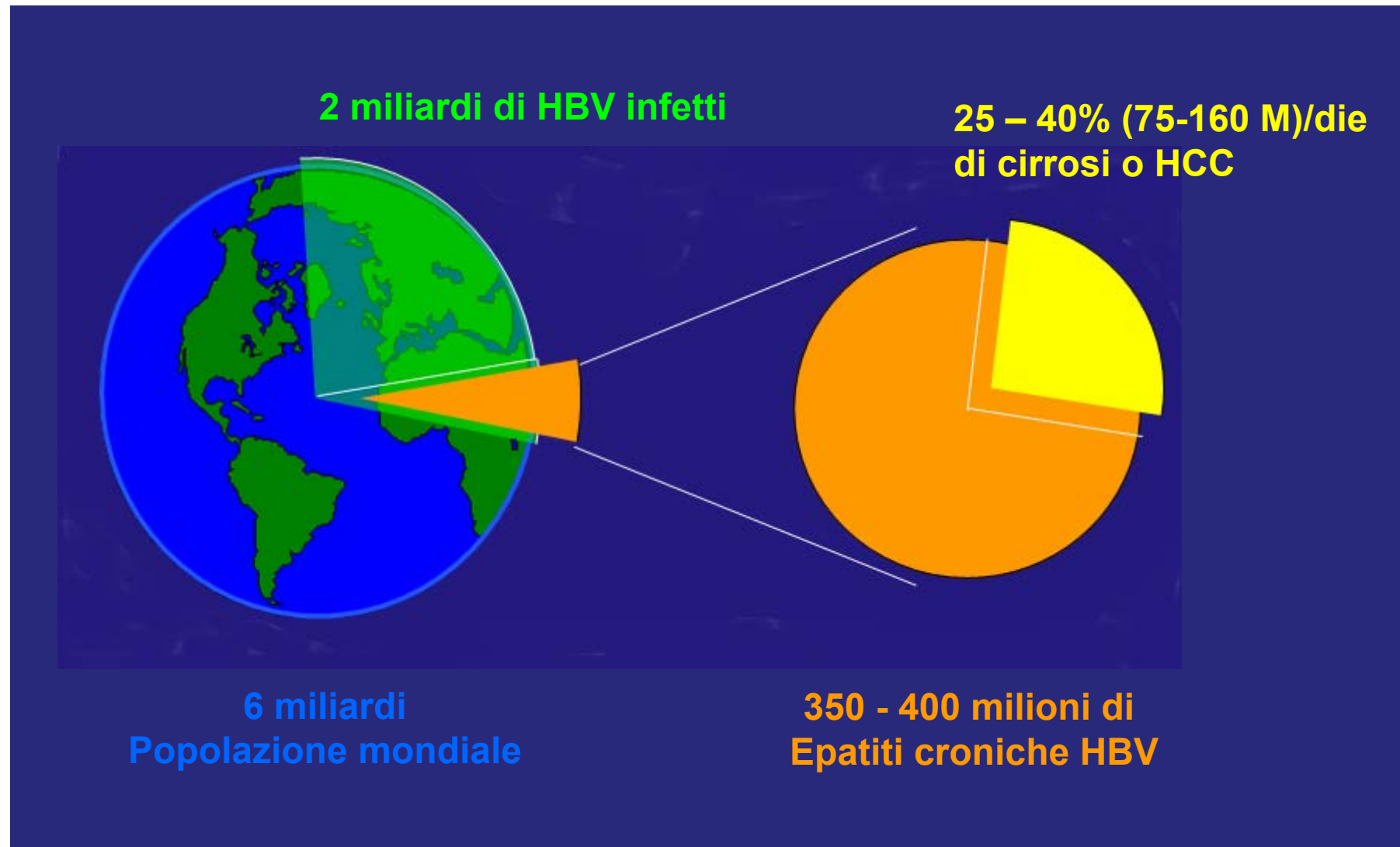
<b>Infetti presente/passato</b>	<b>~ 2 miliardi</b>
<b>Infezioni croniche</b>	<b>350-400 milioni</b>
<b>Morte</b>	<b>0.5-1.2 milioni/anno</b>
<b>Causa di morte per malattia</b>	<b>10° causa nel mondo</b>

*Lavanchy D, J viral Hepatol 2004  
Conjeevaram HS, J Hepatol 2003*



**Prevalenza HBsAg**

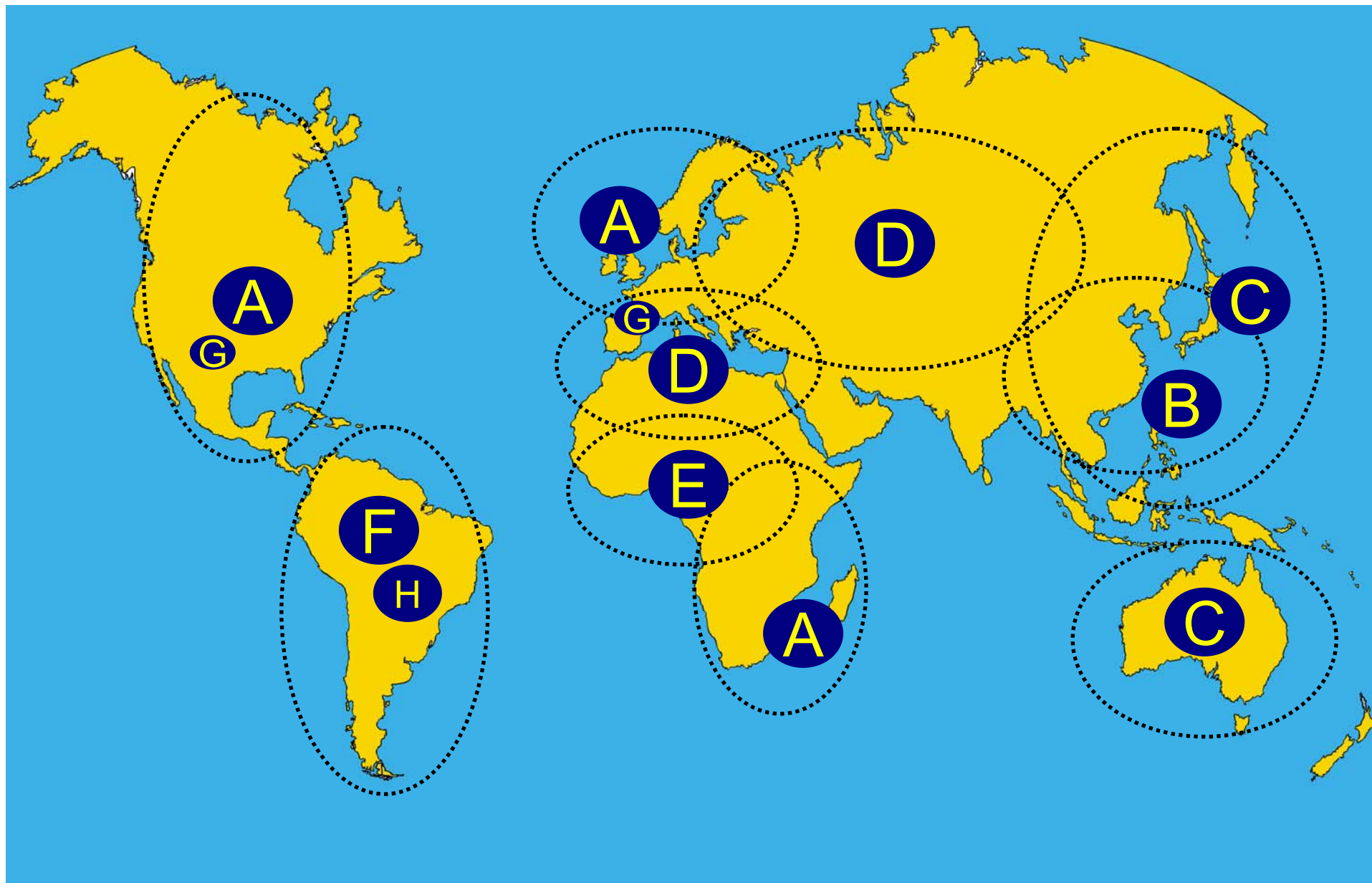
- $\geq 8\%$  = alta
- 2% - 7% = intermedia
- $< 2\%$  = bassa



# IMPATTO GLOBALE DELL'EPATITE B

*WHO Fact Sheets  
Conjeevaram HS, J hepatol 2003  
Lee WM N Engl J Med 1997  
Lok AS N Engl J Med 2002*

# HBV genotypes



# Le dimensioni del Problema in Italia

- **Ogni giorno in Italia muoiono 57 persone per epatocarcinoma o cirrosi**
  - 14 sono HBsAg+
- **600.000 -1.000.000 di portatori cronici di HBV (HBsAg+)**
- **1034 nuove infezioni all'anno notificate e ~ 10.000 stimate (il numero effettivo di nuove infezioni per anno è 5-10 volte il numero di casi denunciati)**
- **250.000 portatori tra cittadini immigrati**

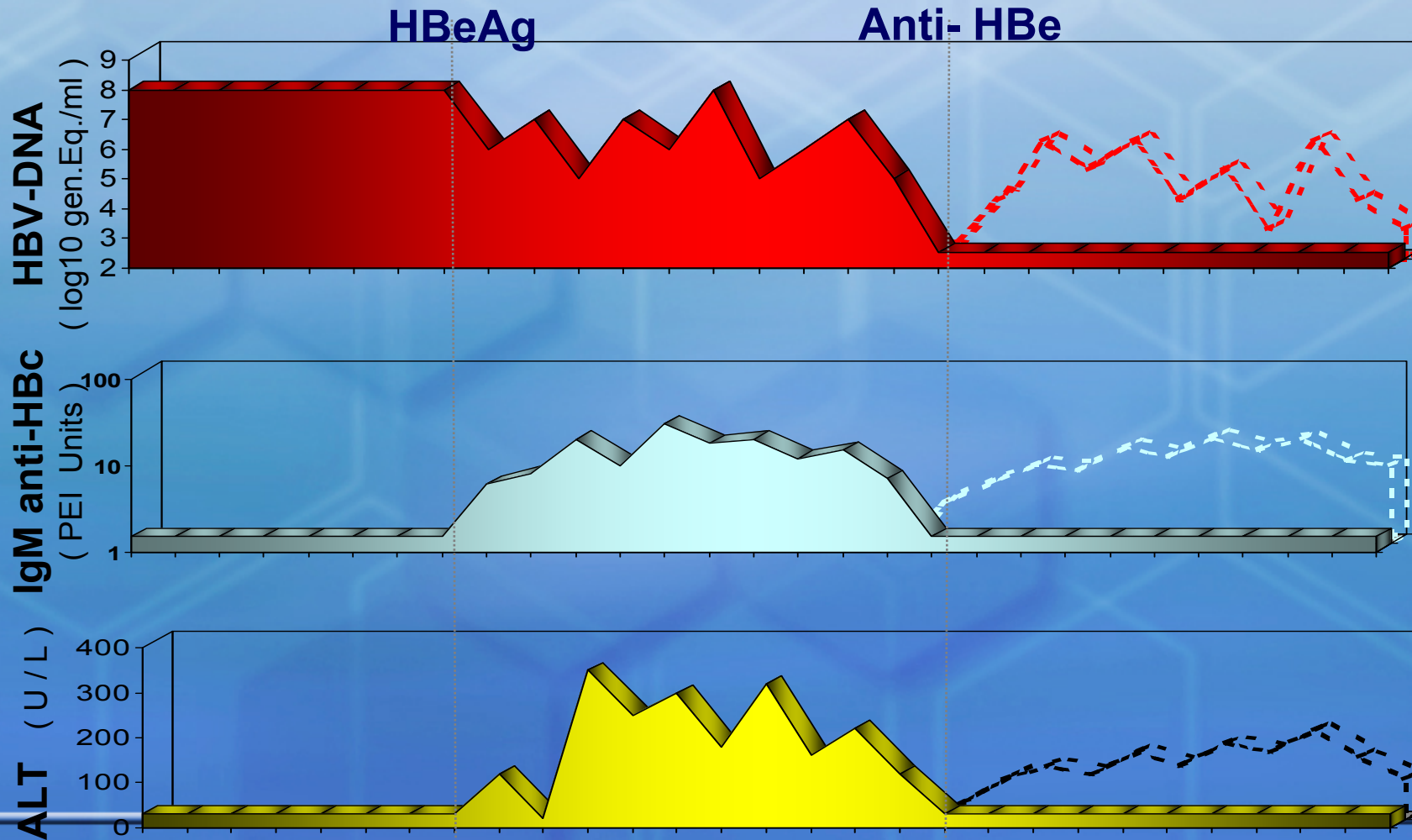
*WHO: Department of Communicable Diseases Surveillance and response 2002;  
AISF: documento conclusivo commissione sull' epidemiologia delle malattie epatiche*

# Il paziente con epatite cronica HBeAg +: il ruolo della risposta immunitaria

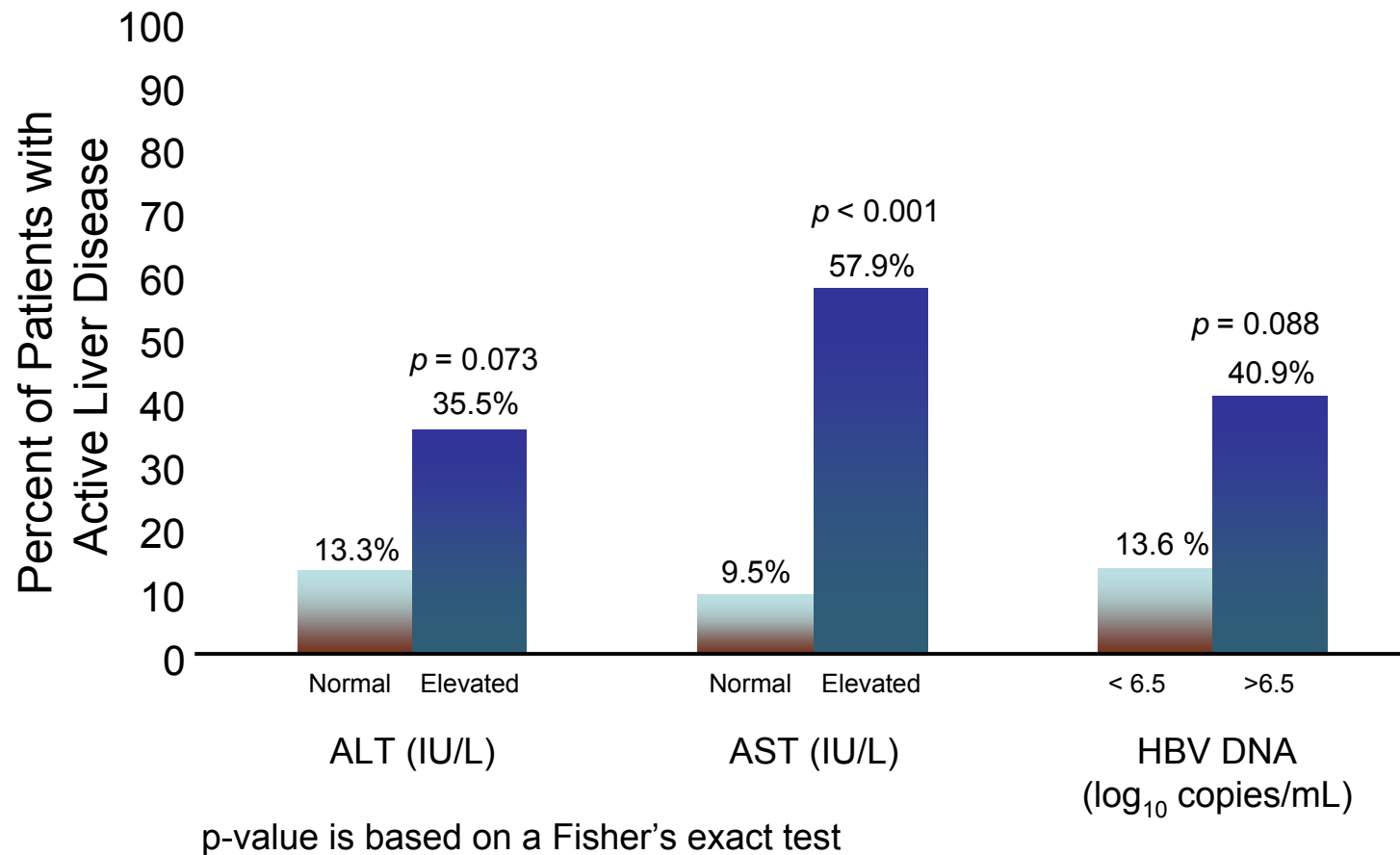
Immune-tolerance

Immune-activation

Immune-control



# Association of Liver Disease with Virological/Biochemical Parameters



# STORIA NATURALE

**Primary HBV  
Infection**

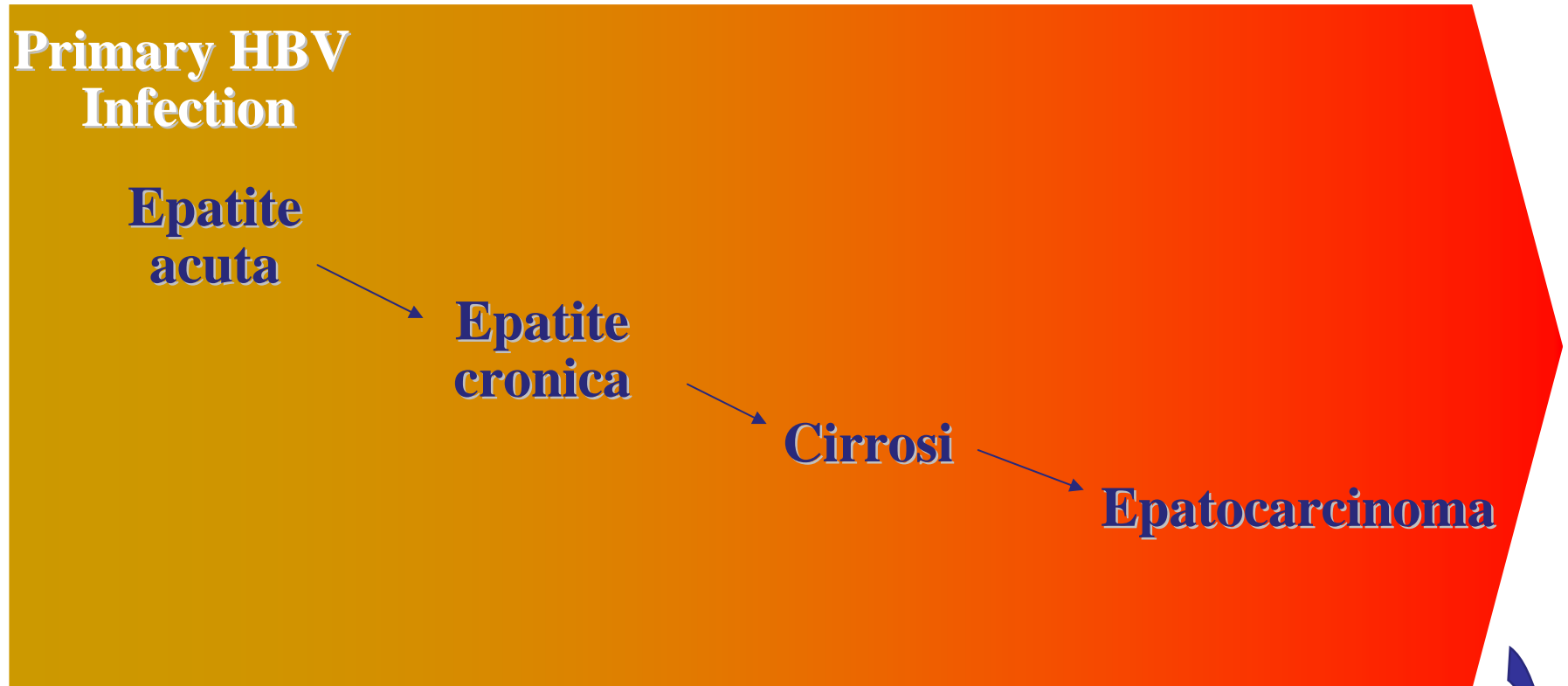
**Epatite  
acuta**

**Epatite  
cronica**

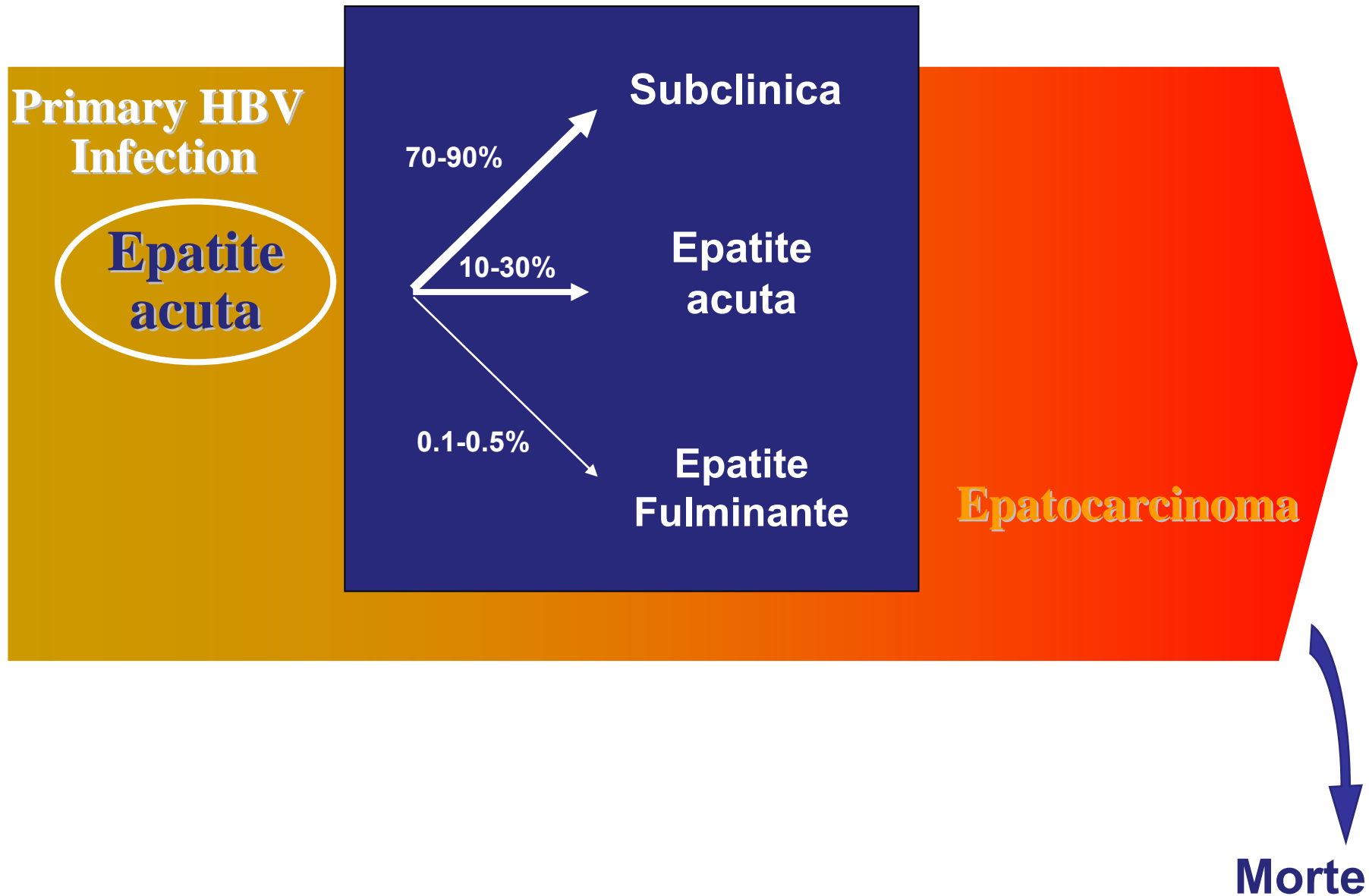
**Cirrosi**

**Epatocarcinoma**

**Morte**



# STORIA NATURALE



# STORIA NATURALE

**Primary HBV  
Infection**

**Epatite  
acuta**

**Epatite  
cronica**

95% neonati da madri  
HBsAg+/HBeAg+

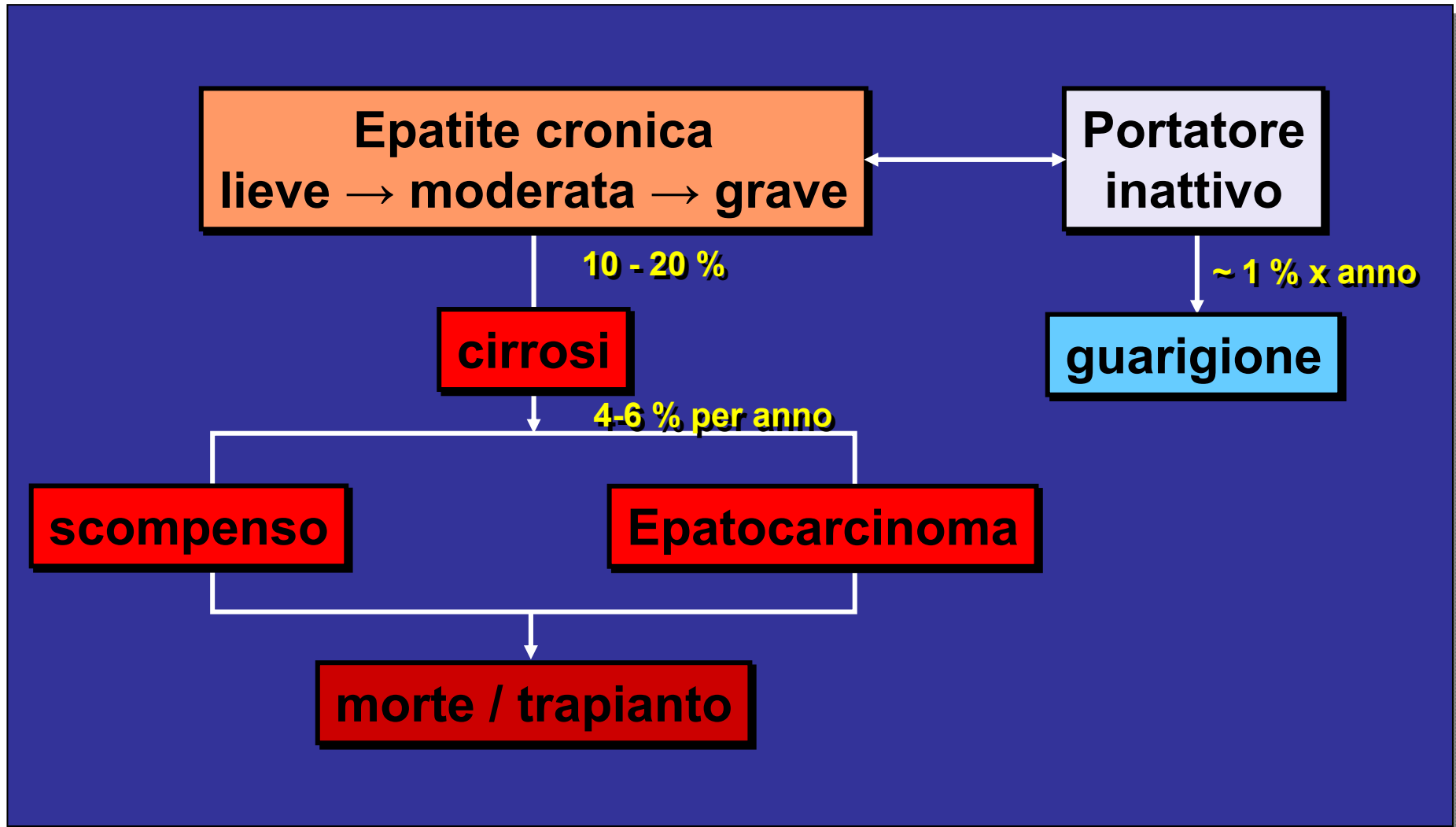
3% giovani  
18 – 24 anni

23 – 28%  
bambini 1 – 5 anni

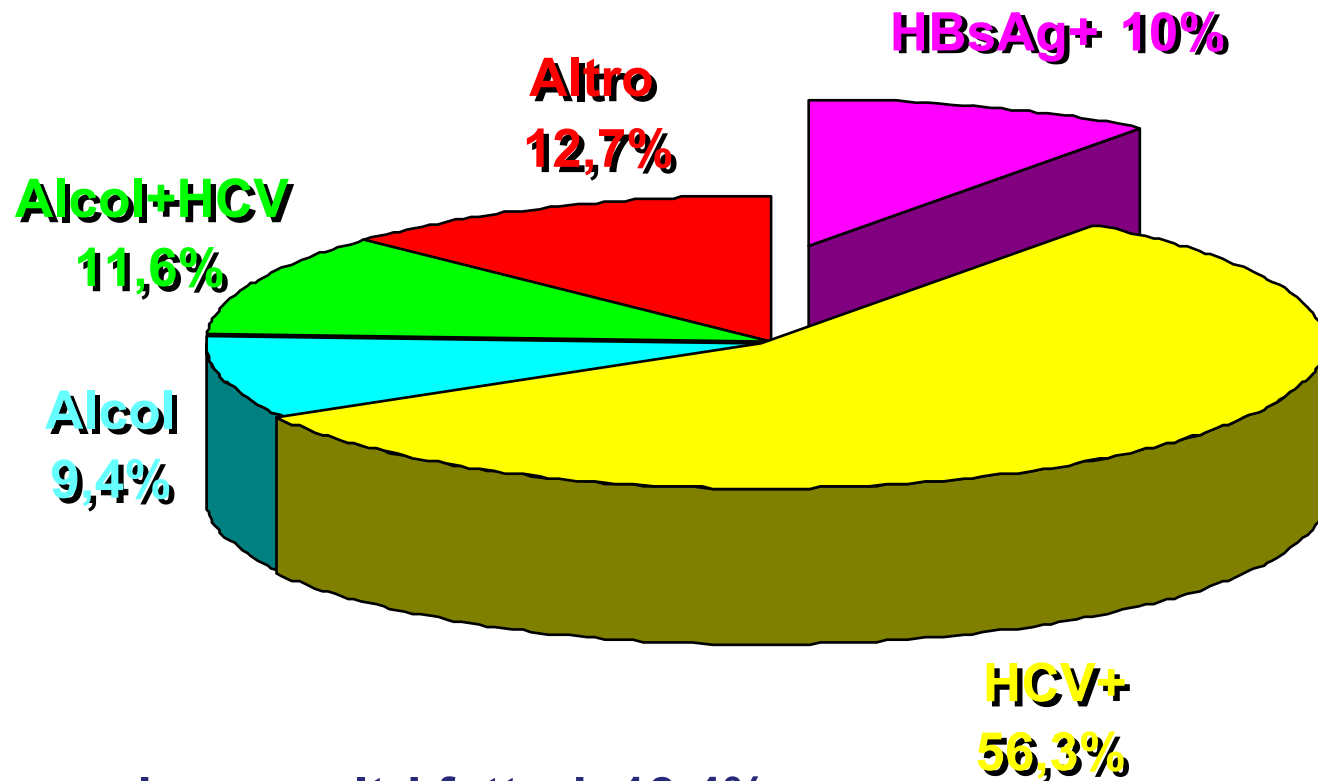
0.2% adulti  
immunocompetenti

**Morte**

# STORIA NATURALE



# Prevalenza dei diversi fattori eziologici in 9997 soggetti con epatopatia, Italia 2001

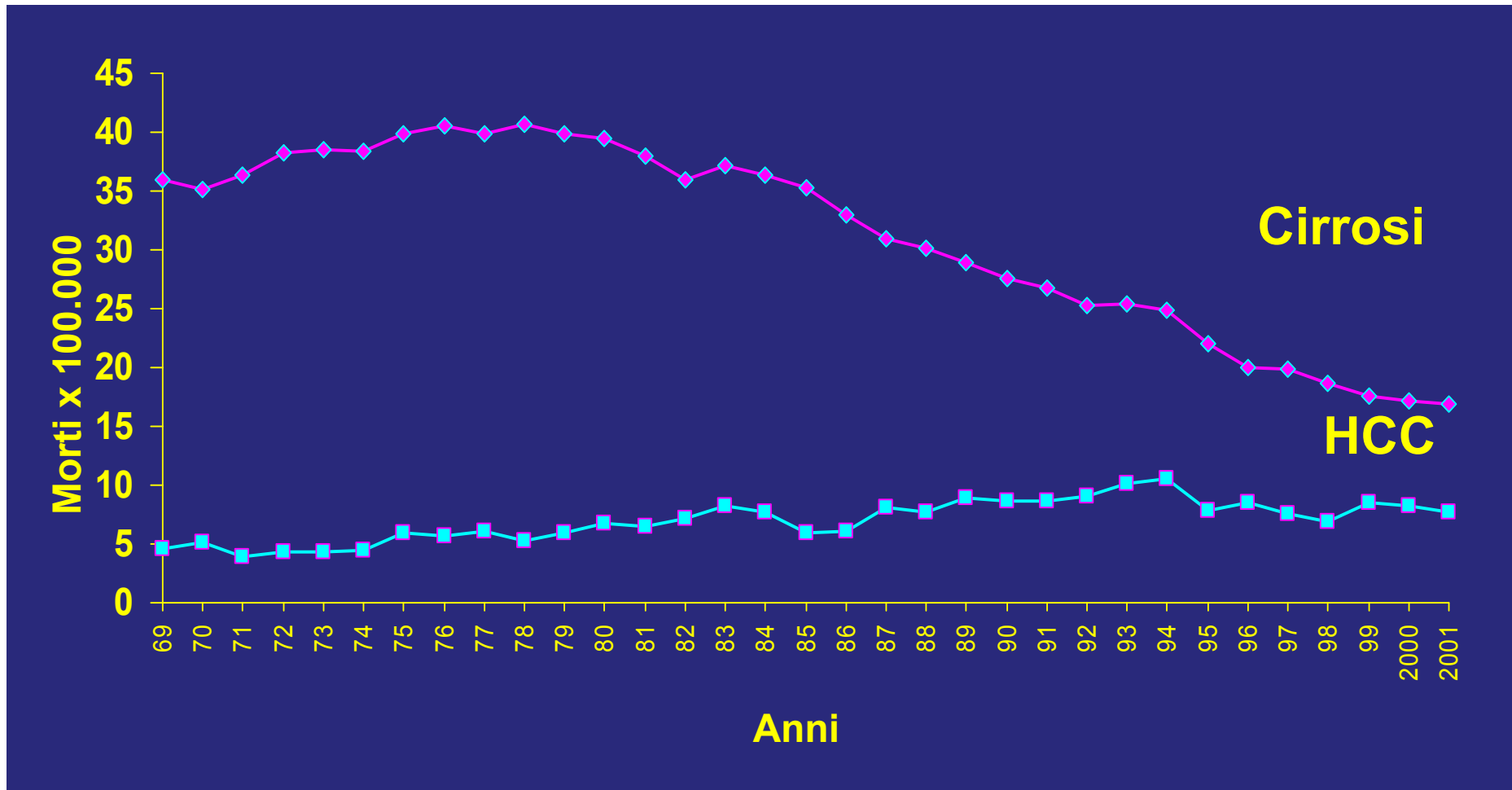


HBsAg anche con altri fattori=13,4%

HCV anche con altri fattori=69,9%

Alcol anche con altri fattori=23,0%

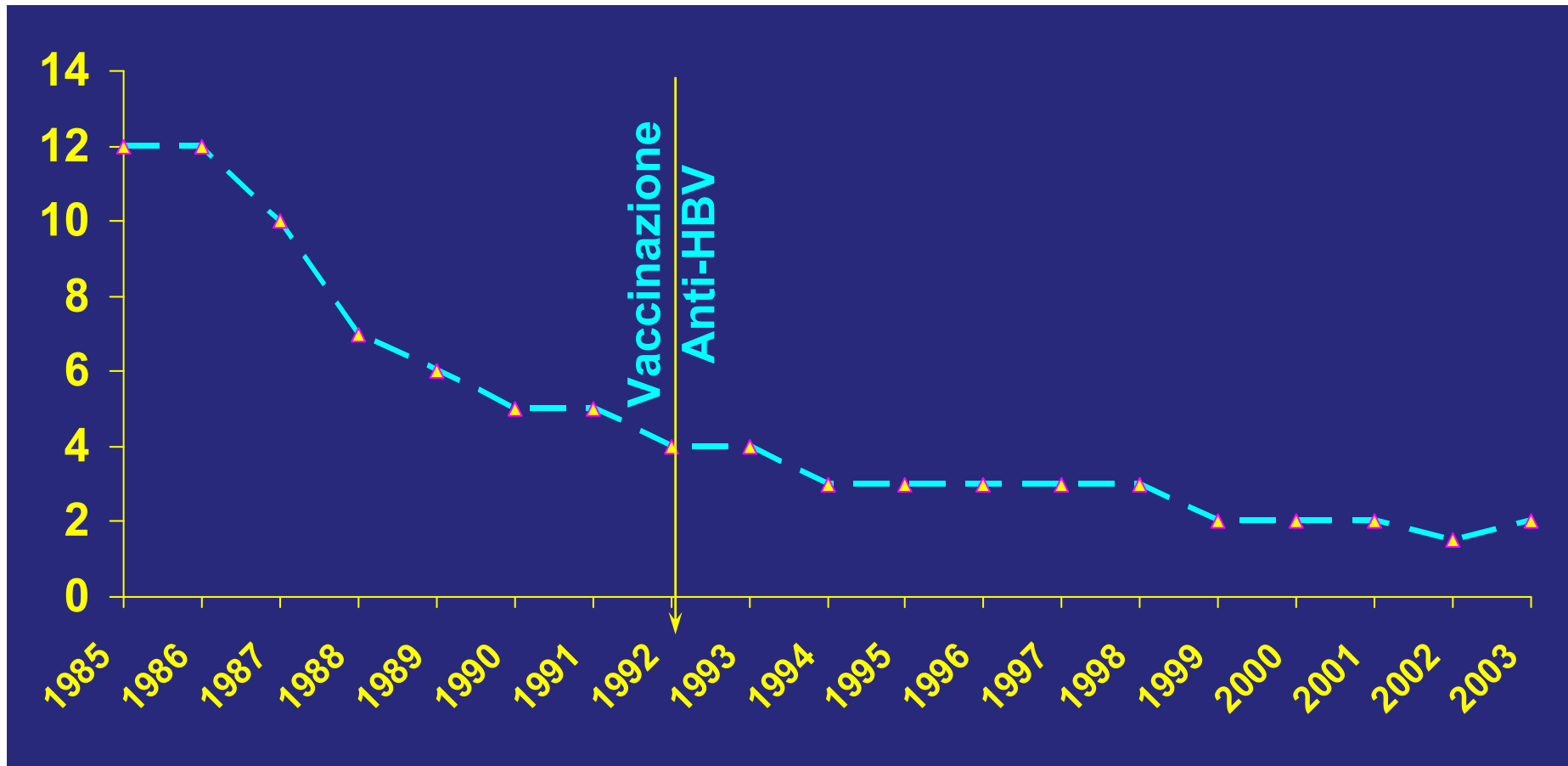
## Tasso di mortalità (decessi per 100.000 abitanti) per Cirrosi ed HCC in Italia 1969-2001



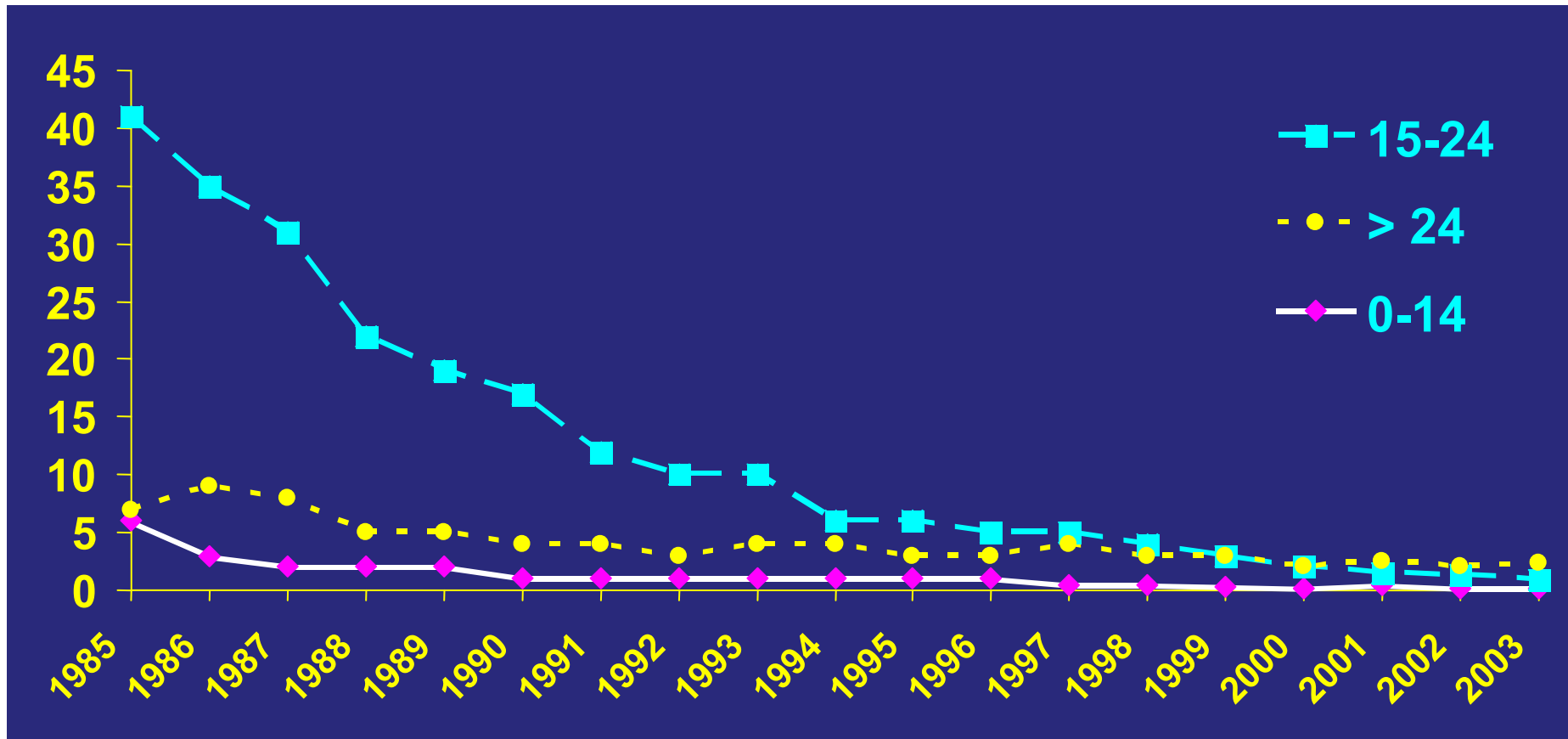
*Dati ISTAT*

**Perché vaccinare?**

# Incidenza di epatite B in Italia. SEIEVA 1985-2003



# Incidenza (per 100000) età specifica di epatite B in Italia. SEIEVA 1985-2003



**Perché  
sottoporre a screening?**

# Screening per epatite B: motivazioni

- **precoce identificazione e cura dei soggetti infetti**  
*(Valla et al 2003)*
- **Prevenzione della diffusione ad altri soggetti** *(Valla et al. 2003)*
- **Terapie antivirali efficaci sono in grado di rallentare la progressione della malattia nei soggetti con epatite cronica B e ritardare l'insorgenza della cirrosi** *(Liaw et al 2004)*
- **Per i pazienti con cirrosi in fase terminale l'unica possibile terapia è il trapianto di fegato**

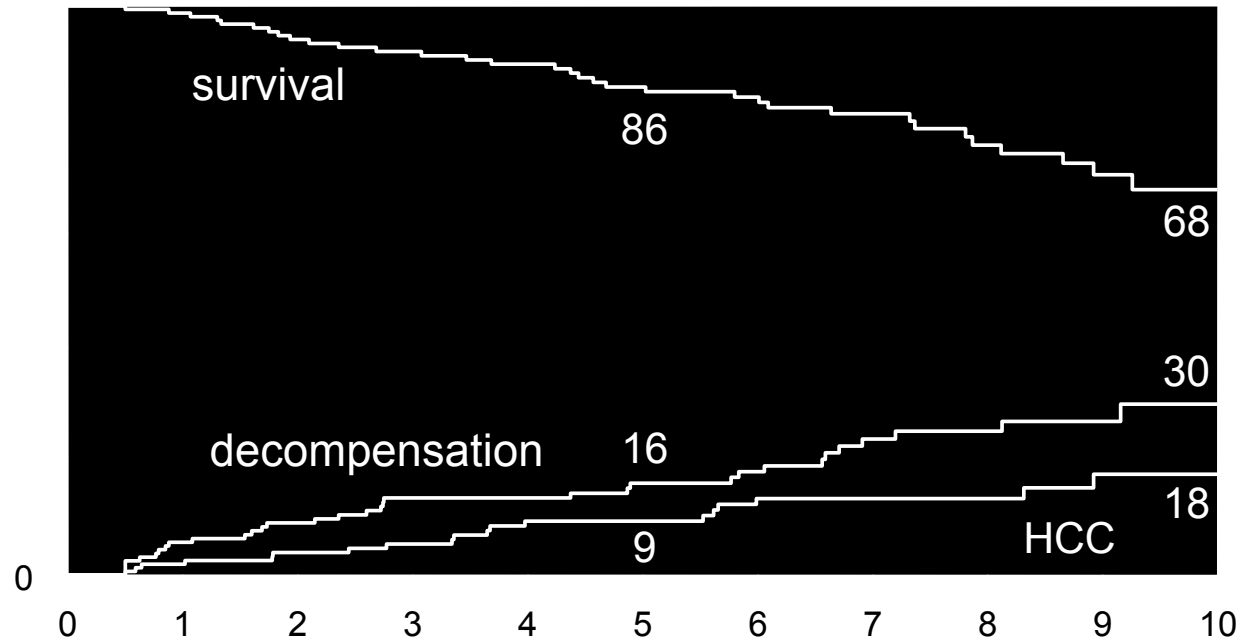
# **Dove dovrebbe essere disponibile lo screening per epatite B**

- **Carceri**
- **Strutture sanitarie ed in particolare:**
  - **Centri per malattie sessualmente trasmissibili**
  - **Centri per il trattamento della dipendenza da sostanze d'abuso**
  - **Centri trasfusionali**
  - **Centri per la terapia dell'HIV**
- **Centri per immigrati**
- **Agenzie internazionali per l'adozione**

**Perchè trattare?**

# Survival in compensated cirrhosis B

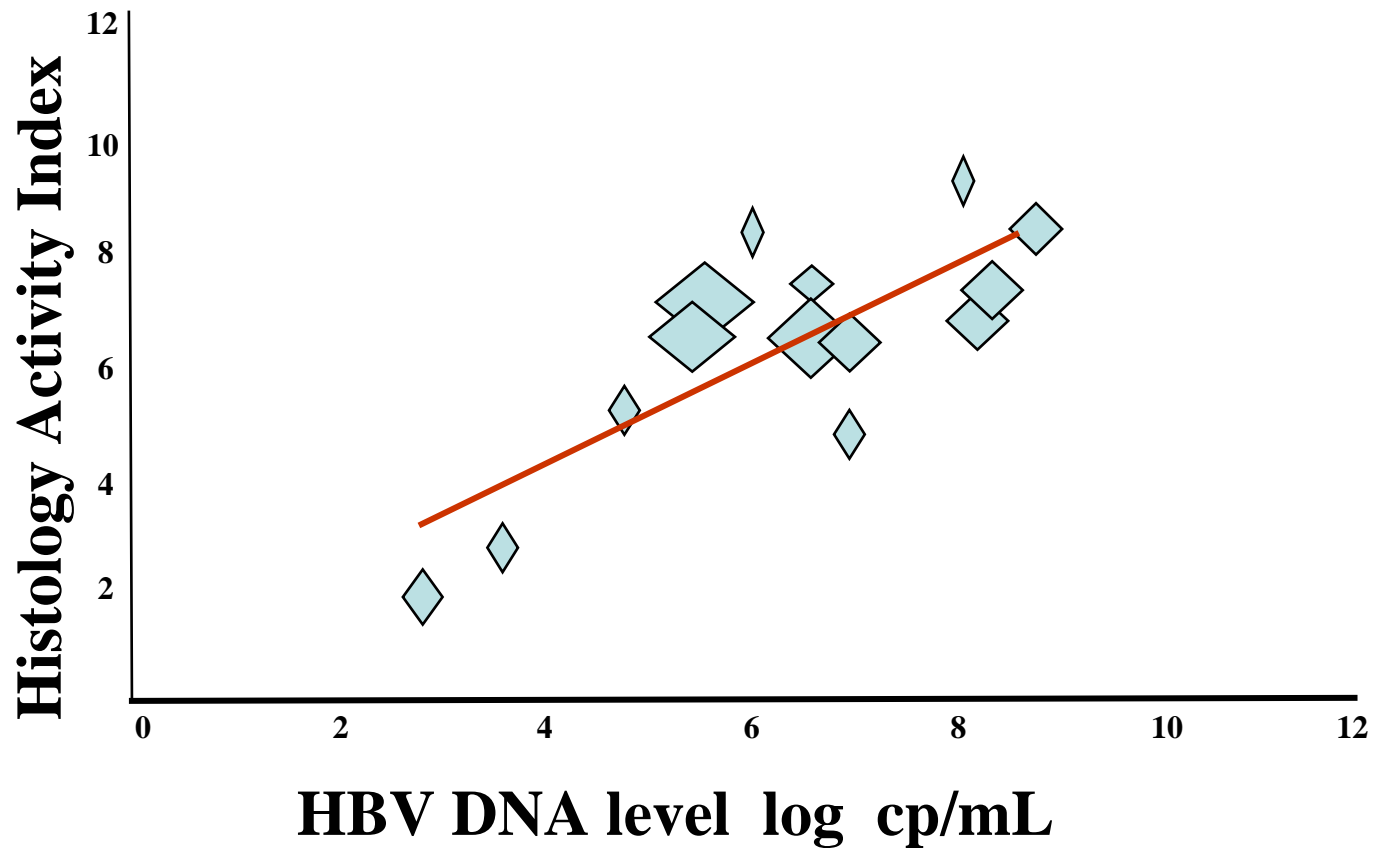
Reference		Pts (n)	Median age (yrs)	Follow-up yrs (range)
Liaw 1989	Asia	76	41	3 (1-7)
De Jong 1992	Europe	77	46	4 (2-17)
Fattovich 2002	Europe	161	48	6 (1-16)



*Fattovich, Am J Gastroenterol 2002; 97: 2886-95*

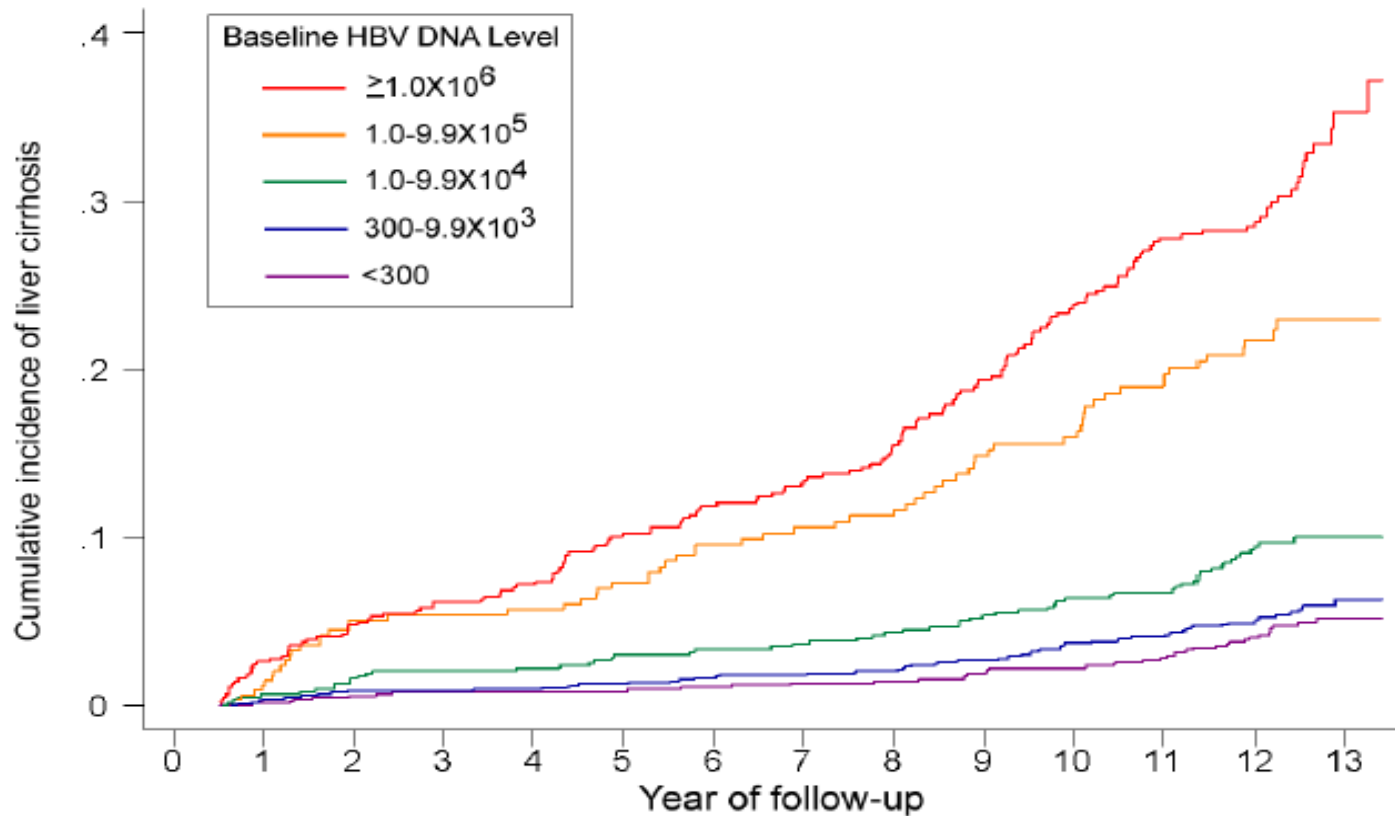
# Relazione tra livelli di HBV DNA e indice di attività istologica.

## Una review di 26 studi prospettici



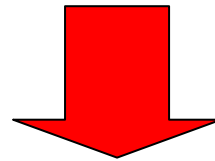
*From: Mommeja-Marin H, Hepatology. 2003.*

# Relazione tra livelli di HBV DNA e sviluppo di cirrosi



# Clinical benefits of HBeAg and HBsAg clearance

**HBeAg clearance**



**HBsAg clearance**

**Disease remission**

**HBsAg seroconversion**

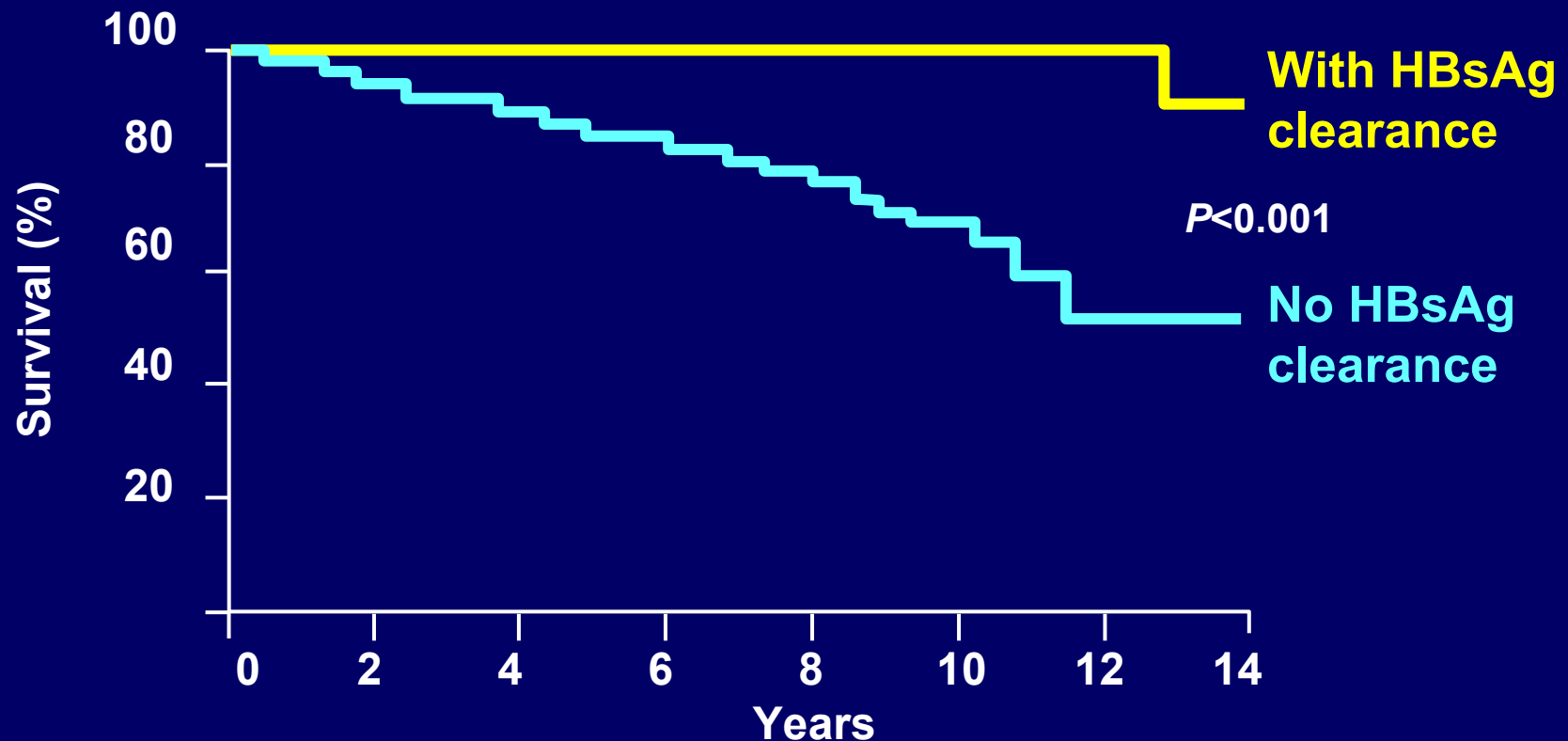
**Prevention of HCC**

**Increased survival**

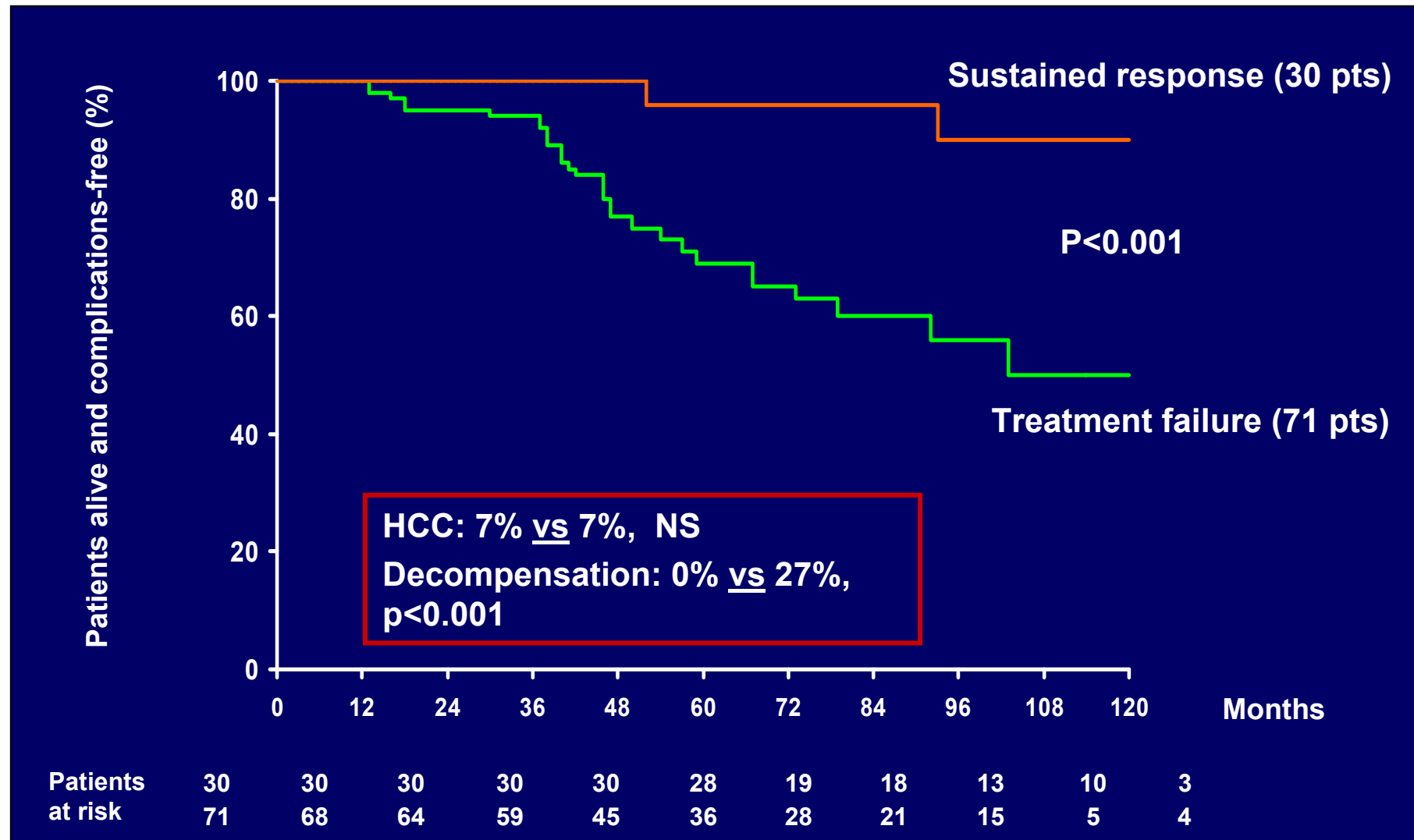
# HBsAg clearance improves survival rates

## Probability of survival in patients with and without HBsAg clearance

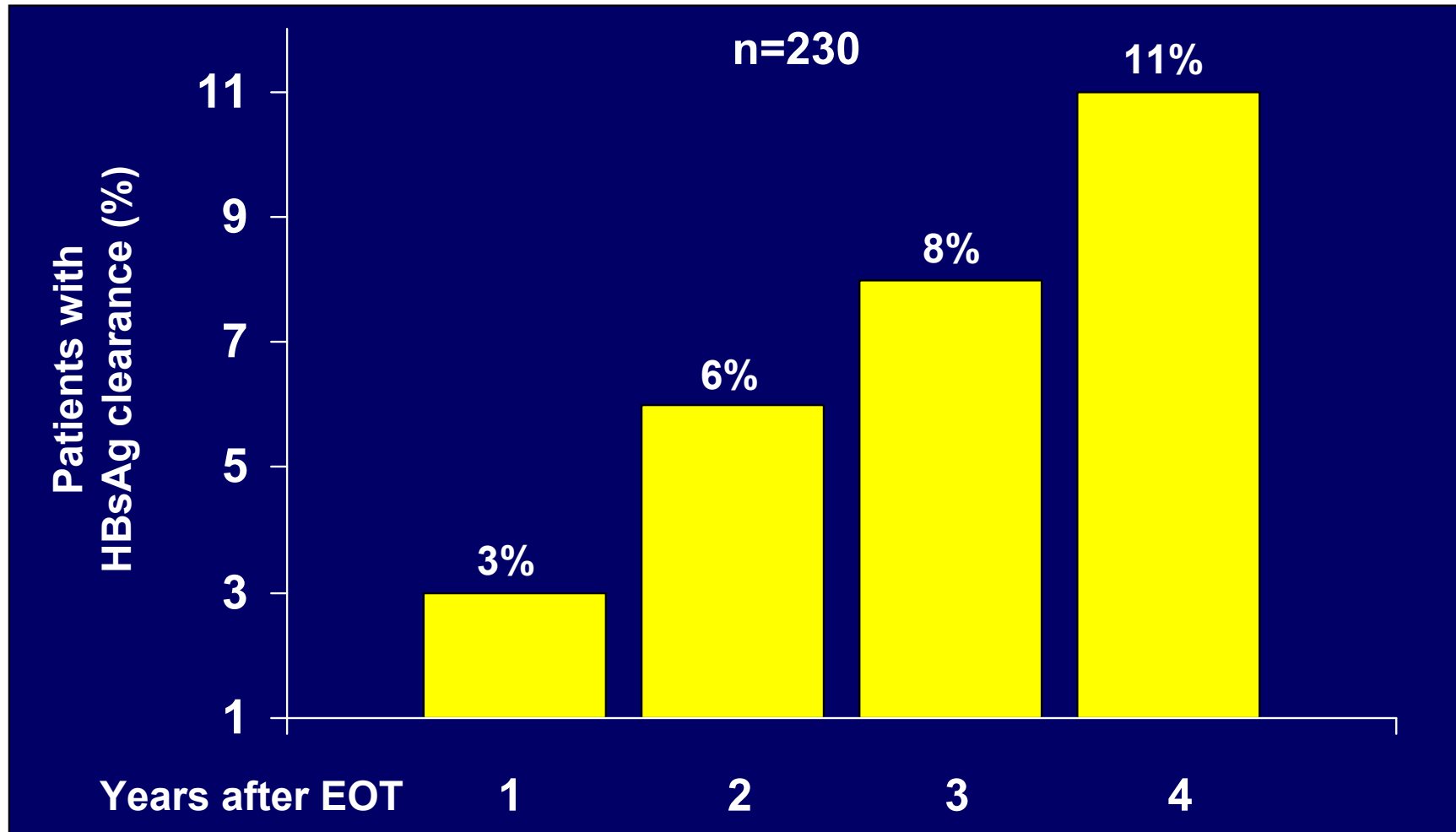
Retrospective study of 309 patients over mean follow-up of 5.7 years



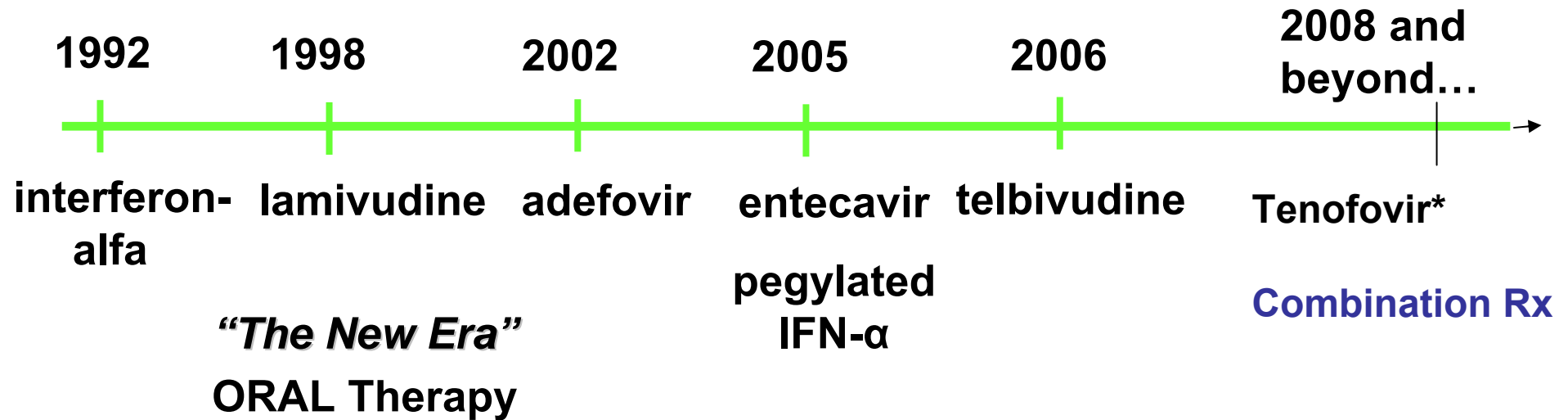
# Cumulative probability of complications-free survival in 101 HBeAg negative patients treated with IFN for 2 years



# HBsAg clearance continues to increase **after therapy** in HBeAg-negative patients treated with PEG-IFN



# Therapy for Chronic Hepatitis B: 2008



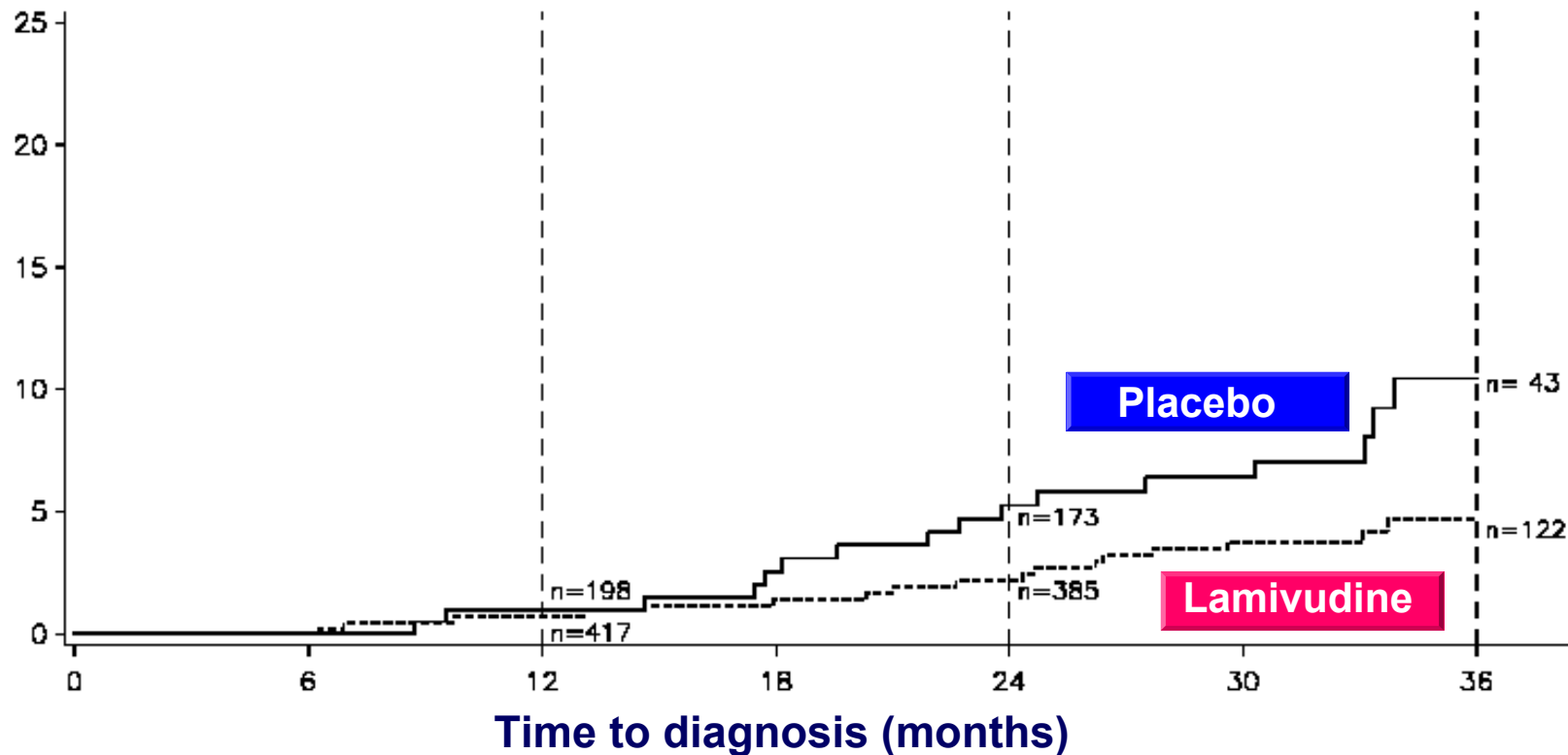
\*FDA-approved for HIV and in review by FDA for HBV indication

\*\* in phase III trial

# Lamivudine in compensated cirrhosis

## Time to diagnosis of HCC

Percentage with diagnosis

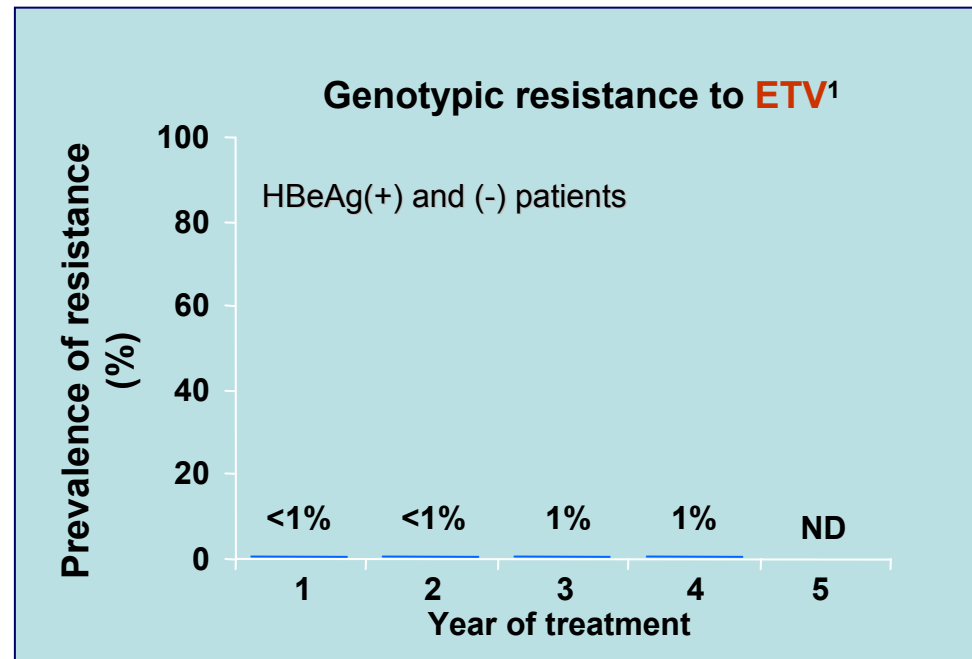
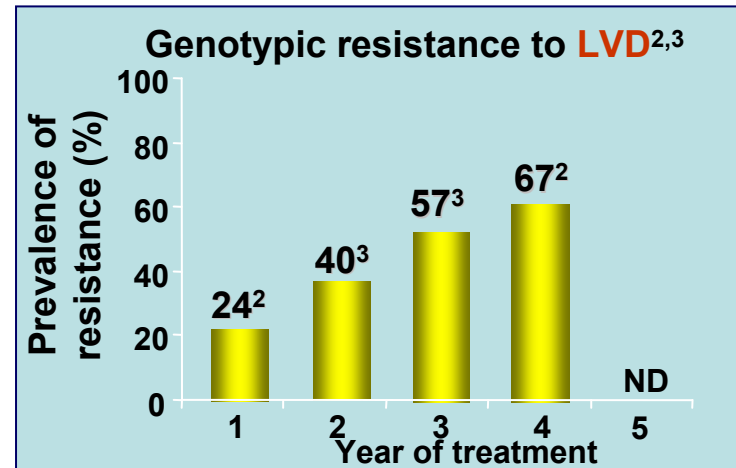
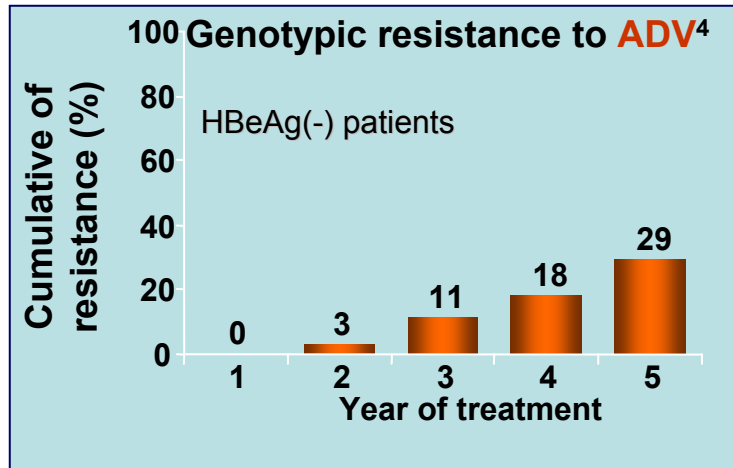


Excluding 5 cases in yr1: HR=0.47; P=0.052

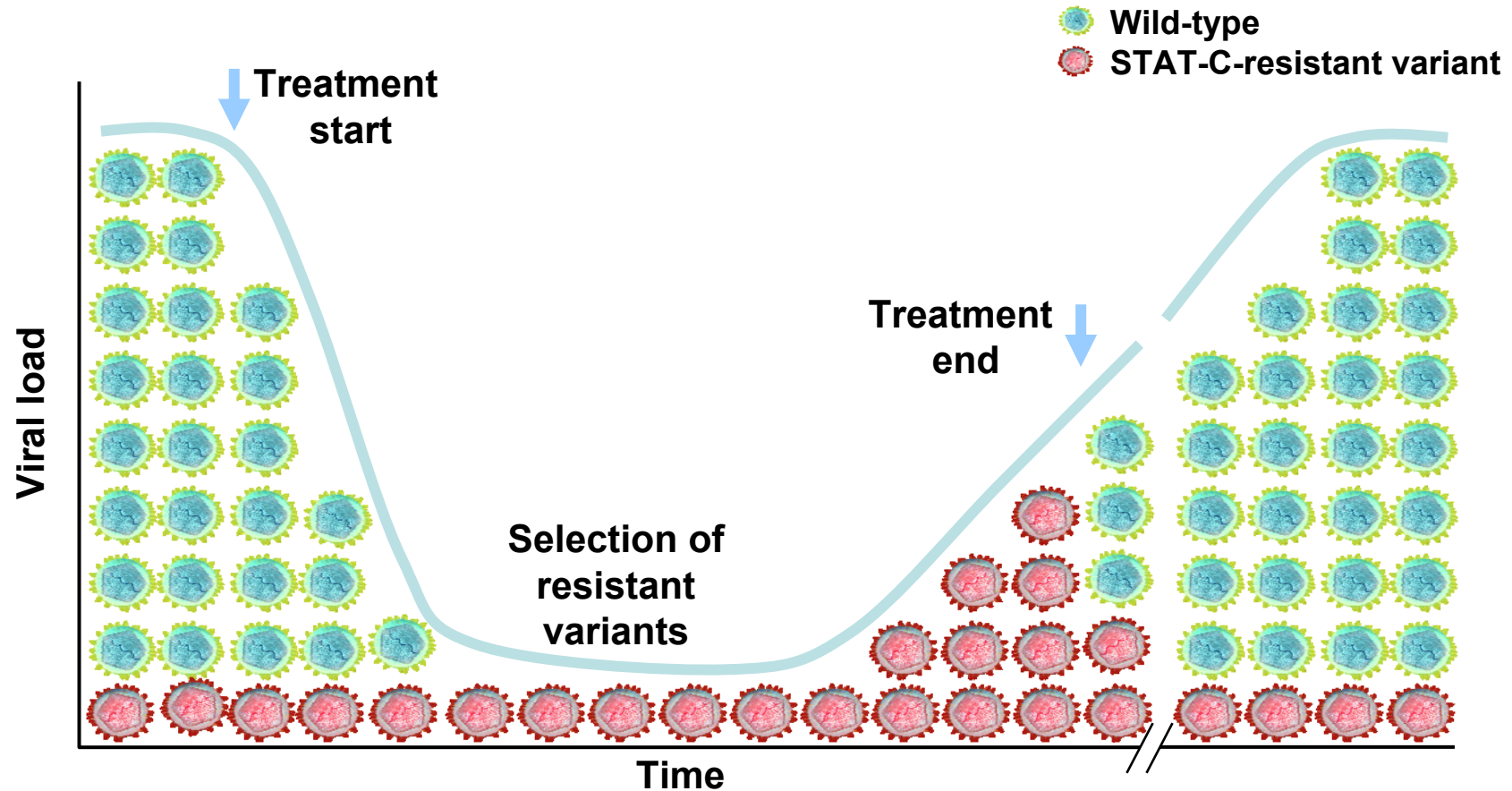
- Placebo (n=215)
- - - - - Lamivudine (n=436)

*Liaw et al, NEJM 2004*

# Resistance Rates in Naïve Patients



# Monotherapy exerts pressure on replicating virus



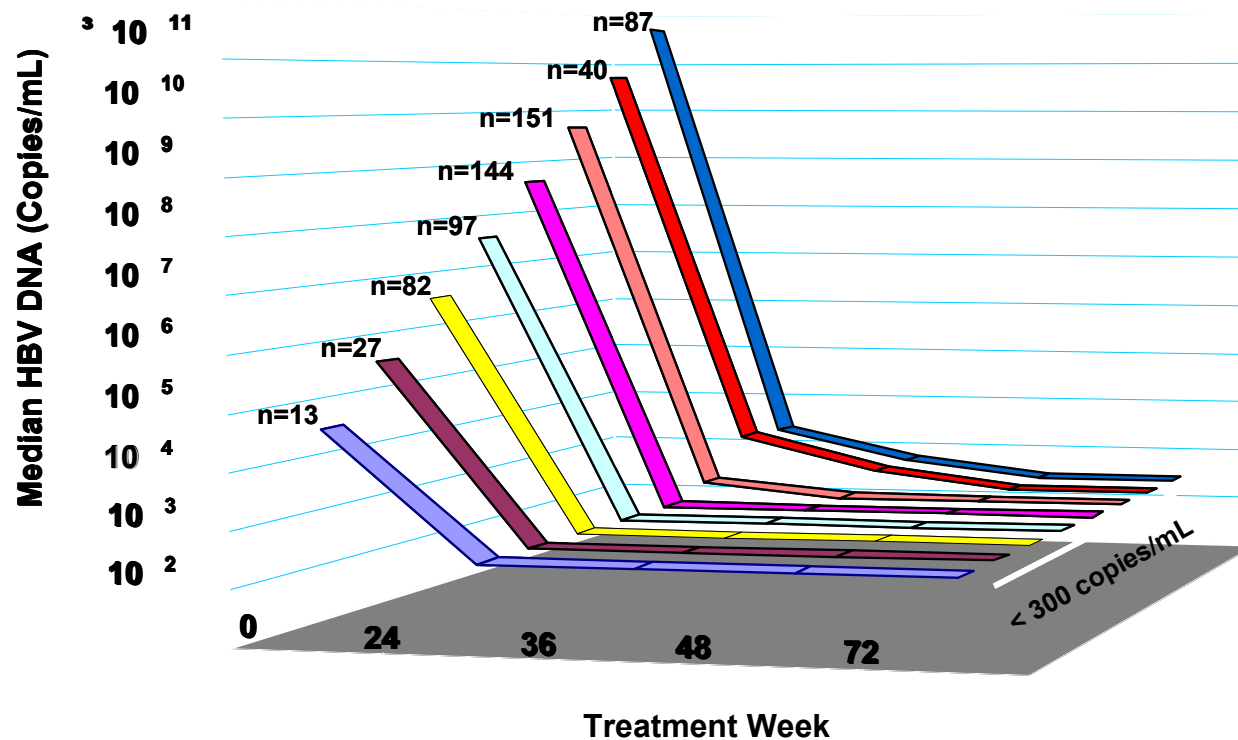
**Hypothetical representation** based on information from Sarrazin C, et al. *Gastroenterology* 2007;132:1767-1777; Hinrichsen H, et al. *Gastroenterology* 2004;127:1347-1355

# Potent viral load suppression with entecavir even from high baseline levels

- Average intracellular entecavir tri-phosphate drug concentrations are approximately 50 times greater than the IC50 of wild-type HBV<sup>1</sup>

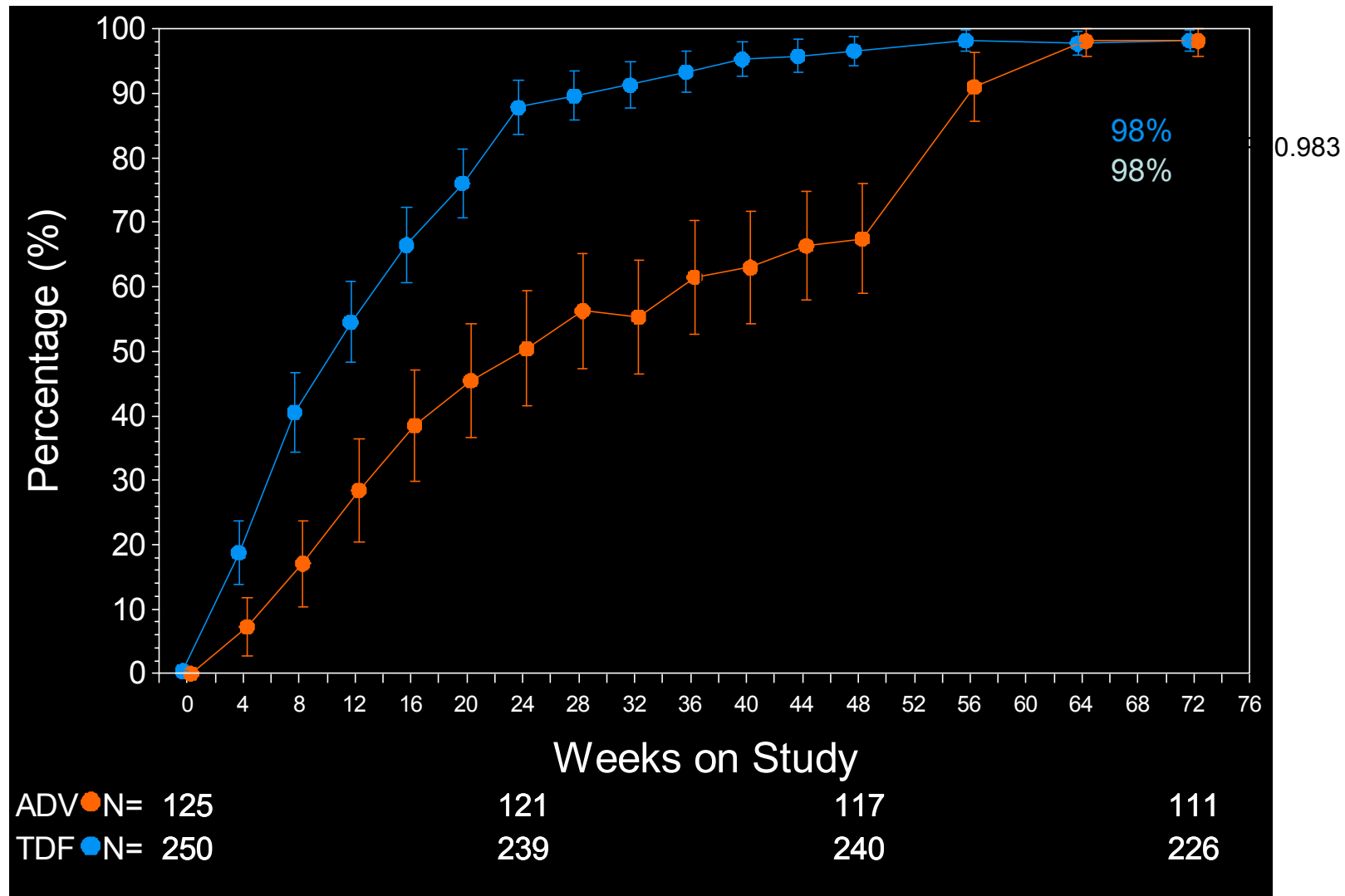
## HBV DNA reductions by baseline DNA level<sup>2</sup>

Nucleoside naïve, HBeAg(+) and (-) patients



1. Tenney DJ, et al. Antimicrob Agents Chemother. 2007;51:902-911. Colonna R. ISVHLD 2006; Oral presentation O200

# Patients with HBV DNA <400 c/mL

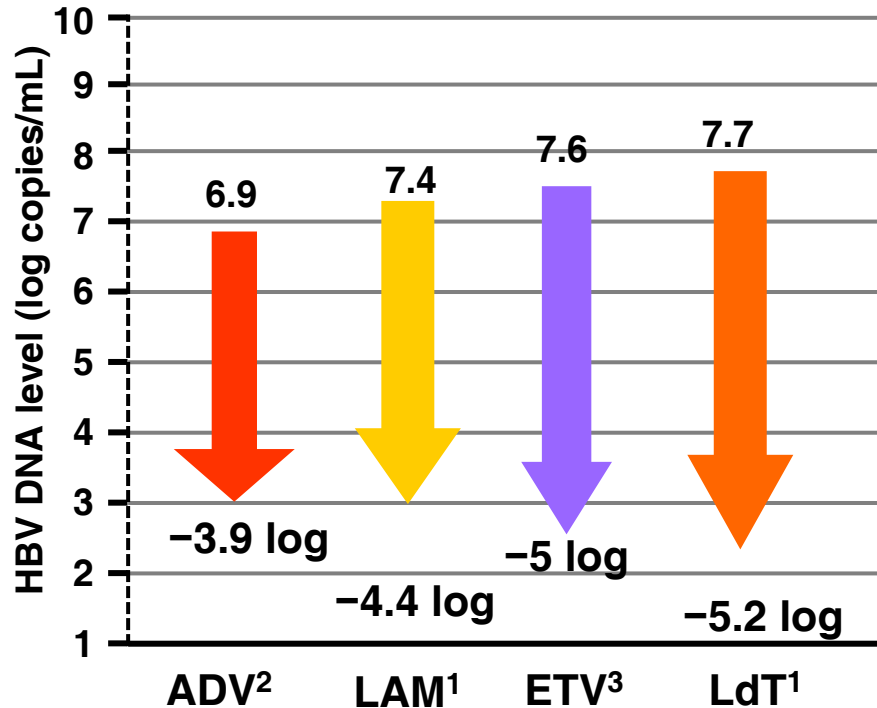


Observed Data

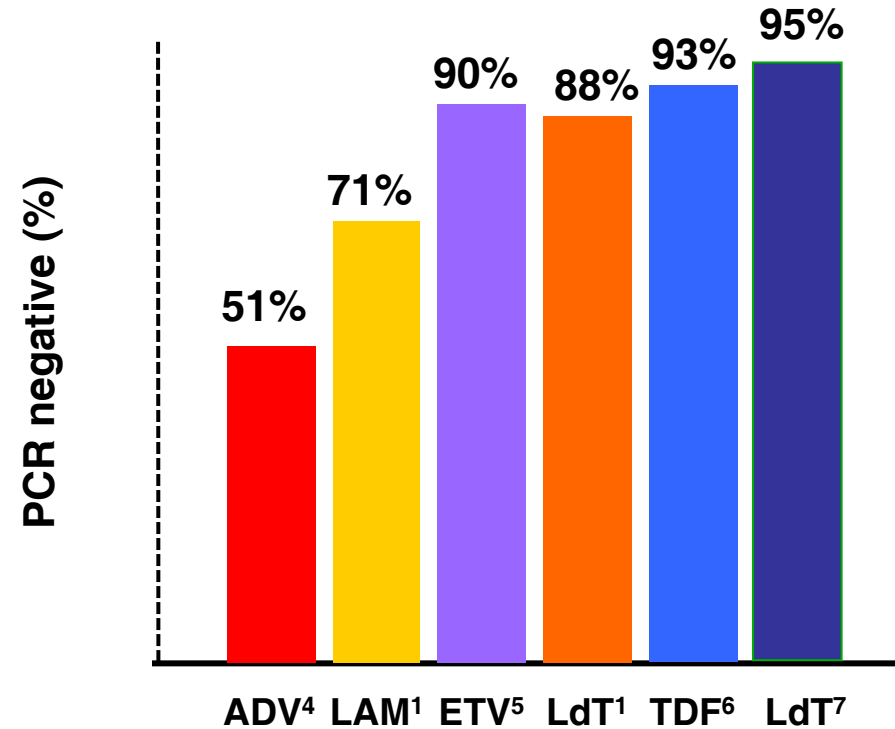
Marcellin P, et al. 43rd EASL; Milan, Italy; April 23-27, 2008. Abstract 57.

# Efficacy Varies among Nucleos(t)ide Analogs

HBV DNA mean reduction at 1 year  
HBeAg-negative patients



HBV DNA PCR negativity at 1 year  
HBeAg-negative patients

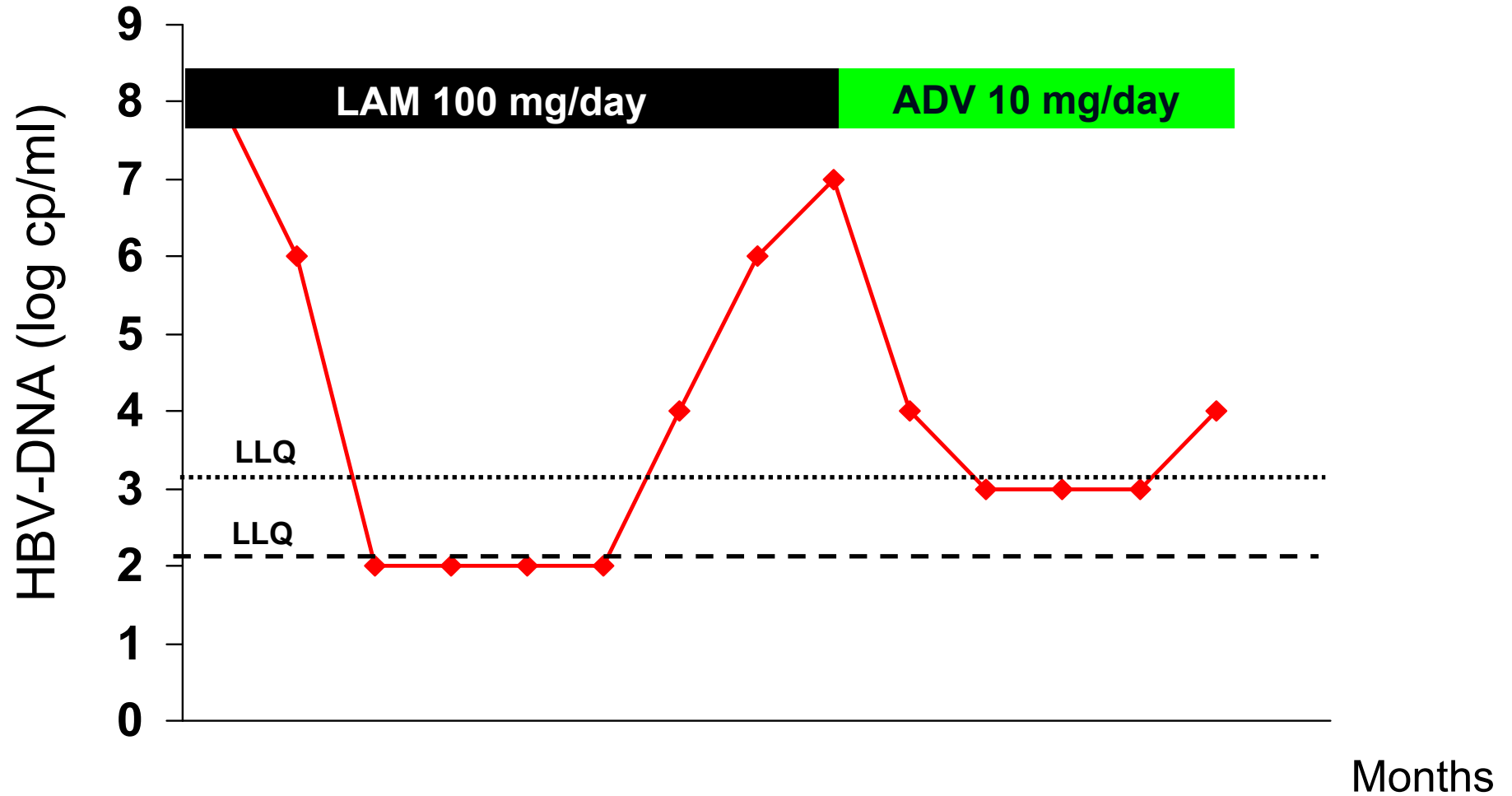


**Data not from head-to-head studies. Design, inclusion and evaluation criteria may differ.  
HBV DNA thresholds: 1000 copies/mL (ADV); 300 copies/mL (LAM, LdT, ETV); 400 copies/mL (TDF)**

1. Lai CL et al. *N Engl J Med.* 2007;357:2576-2588;
2. Chang TT et al. *N Engl J Med.* 2006;354:1001-1010;
3. Lai CL et al. *N Engl J Med.* 2006;354:1011-1020;
4. Hadziyannis SJ et al. *N Engl J Med.* 2003;348:800-807;  
5. Lai CL et al. *N Engl J Med.* 2006;354:1011-1020;
6. Marcellin P et al. *Hepatology.* 2007;46 (S1):290-291A;
7. Globe study: data on file.

# May 2003 – May 2005

ALT	206	60	25	40	426	182	40	41
IgM anti-HBc	1.75	0.85	0.05	0.10	1.30	-	0.05	0.04



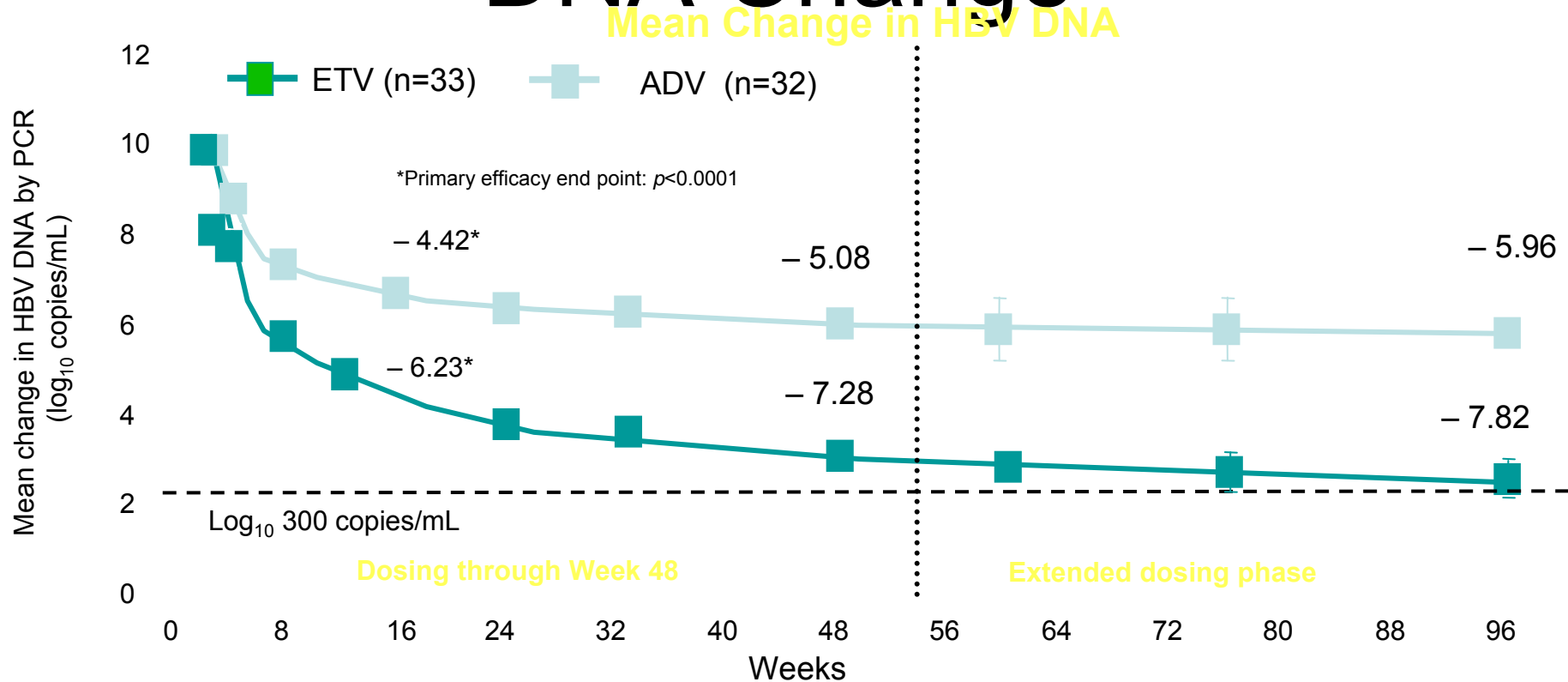
SOGNI D'ORO, E CERCA  
DI NON FARTI  
PRENDERE  
DAL PANICO.





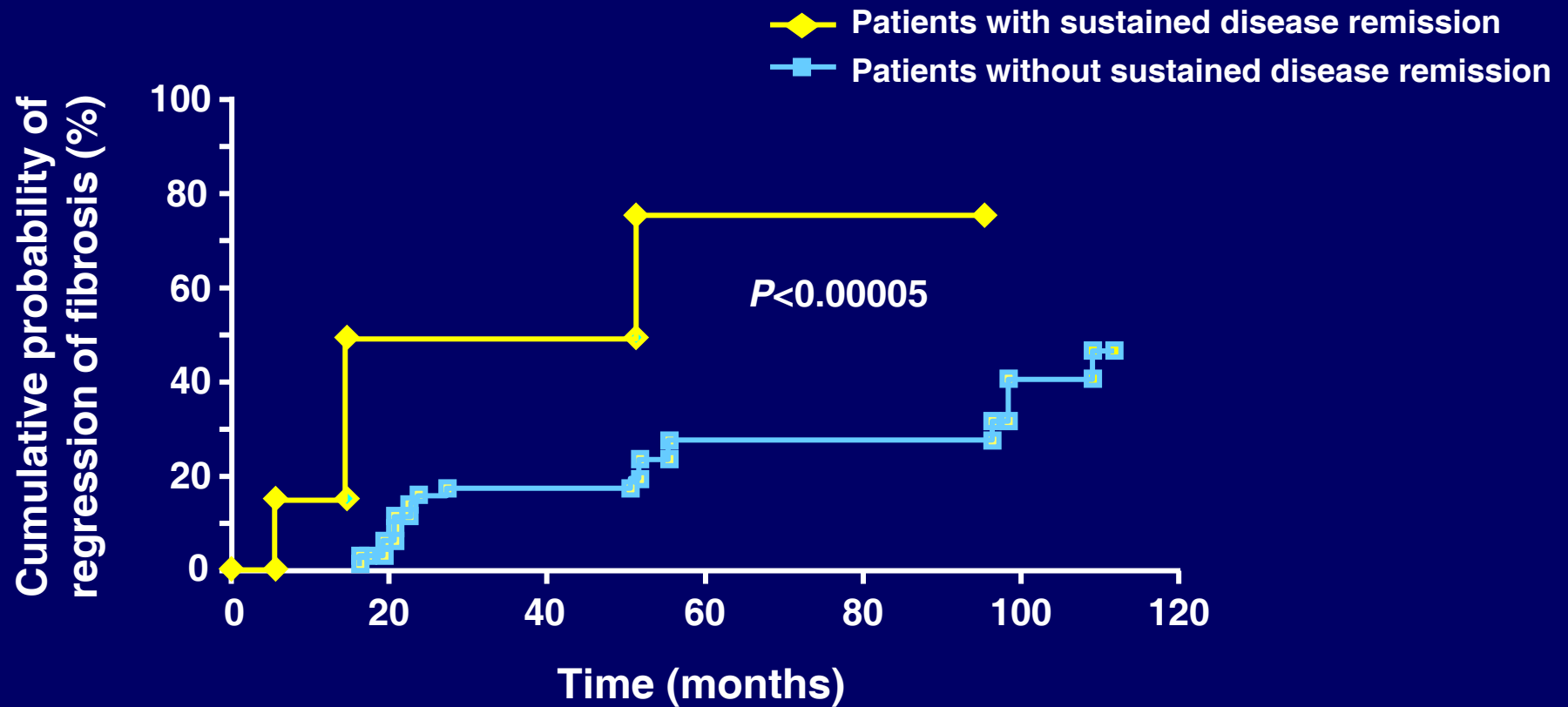
O.DONNELL

# E.A.R.L.Y. Study: Mean HBV DNA Change

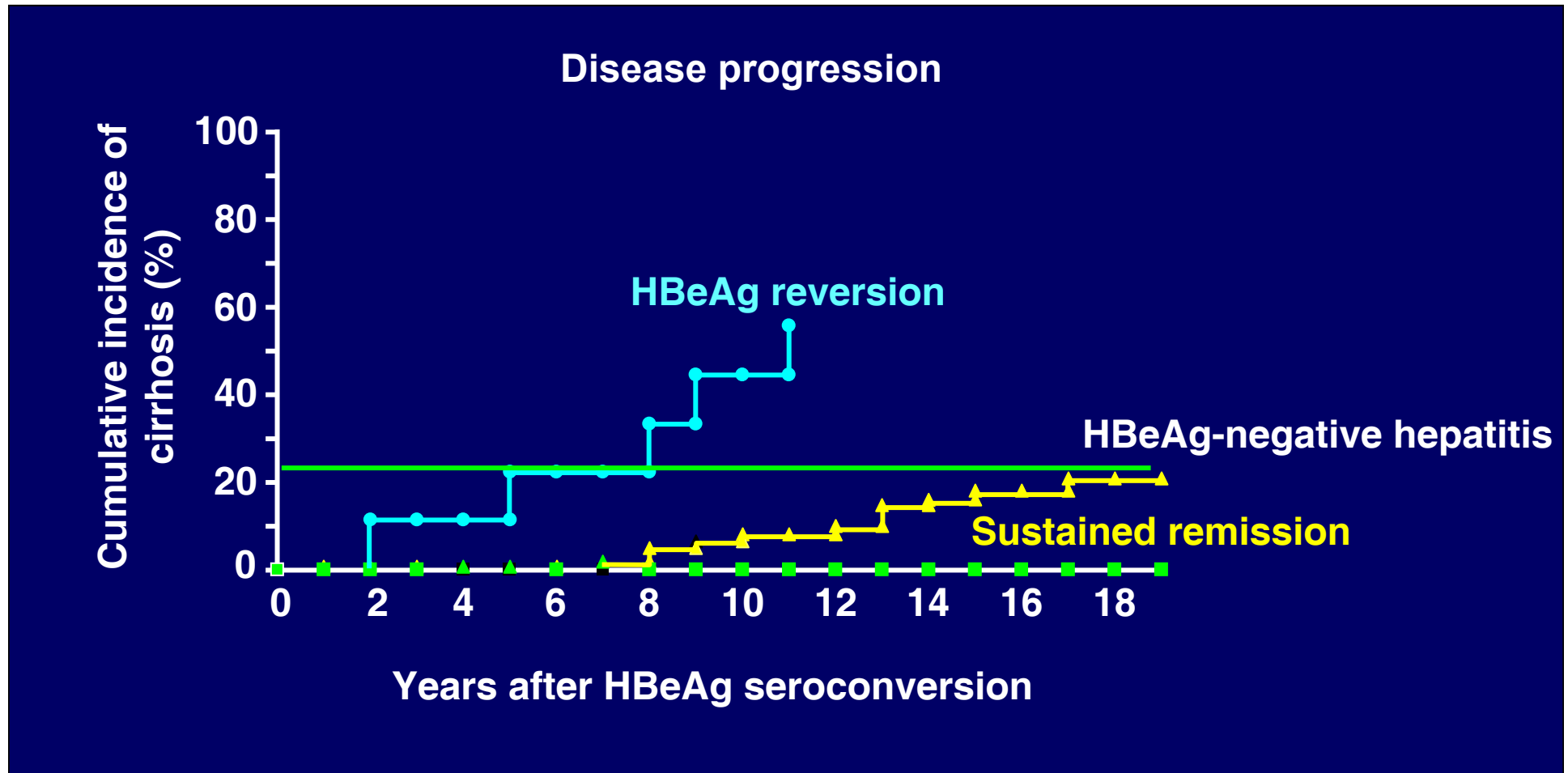


**Other Results at Week 96:**  
 Normal ALT: 97% vs. 85%  
 HBe Seroconversion: 24% vs. 25%  
 Discontinuation due to AE: 0% vs. 3%

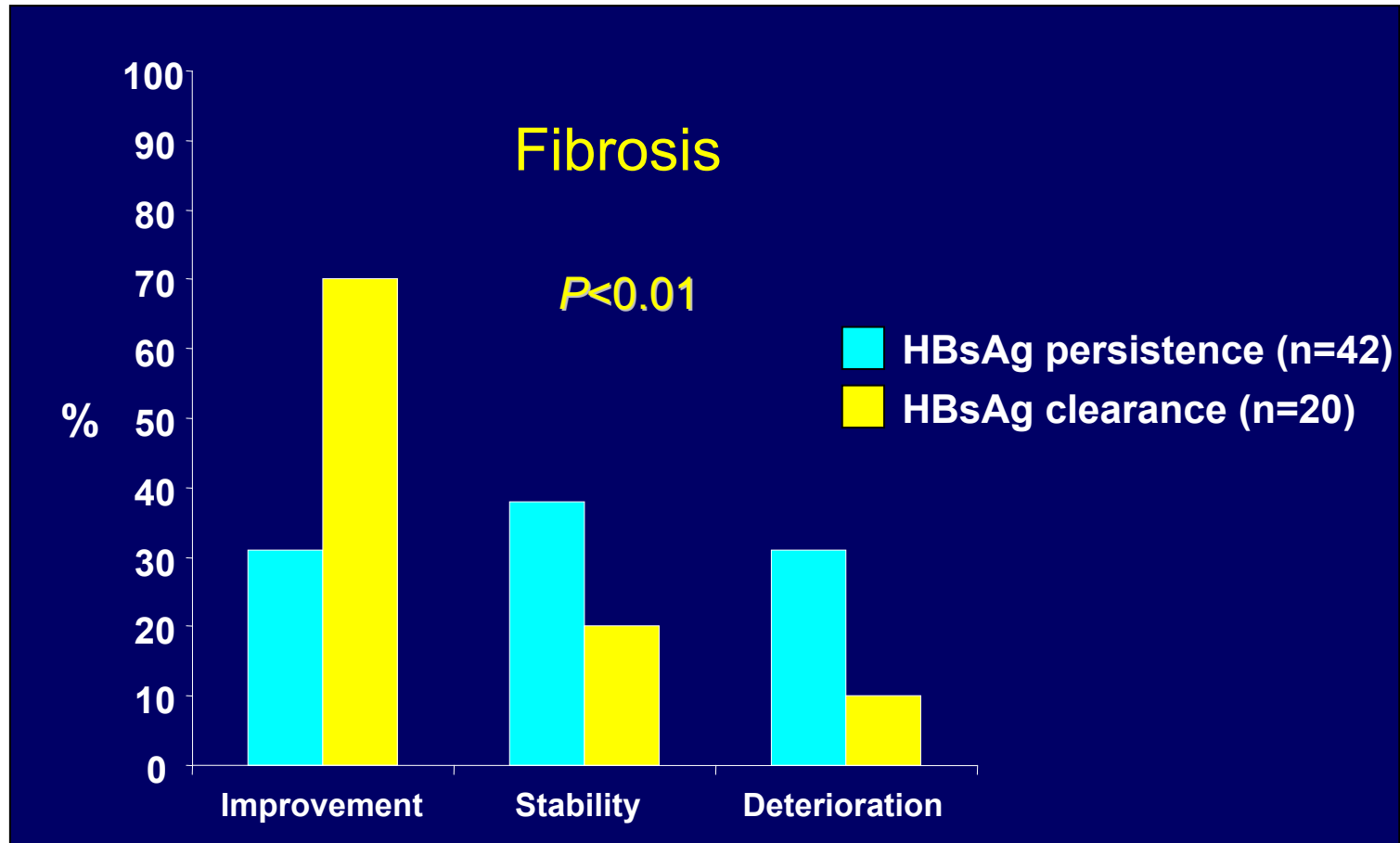
# Spontaneous HBeAg seroconversion: reduces fibrosis progression



# Spontaneous HBeAg seroconversion: reduces incidence of cirrhosis



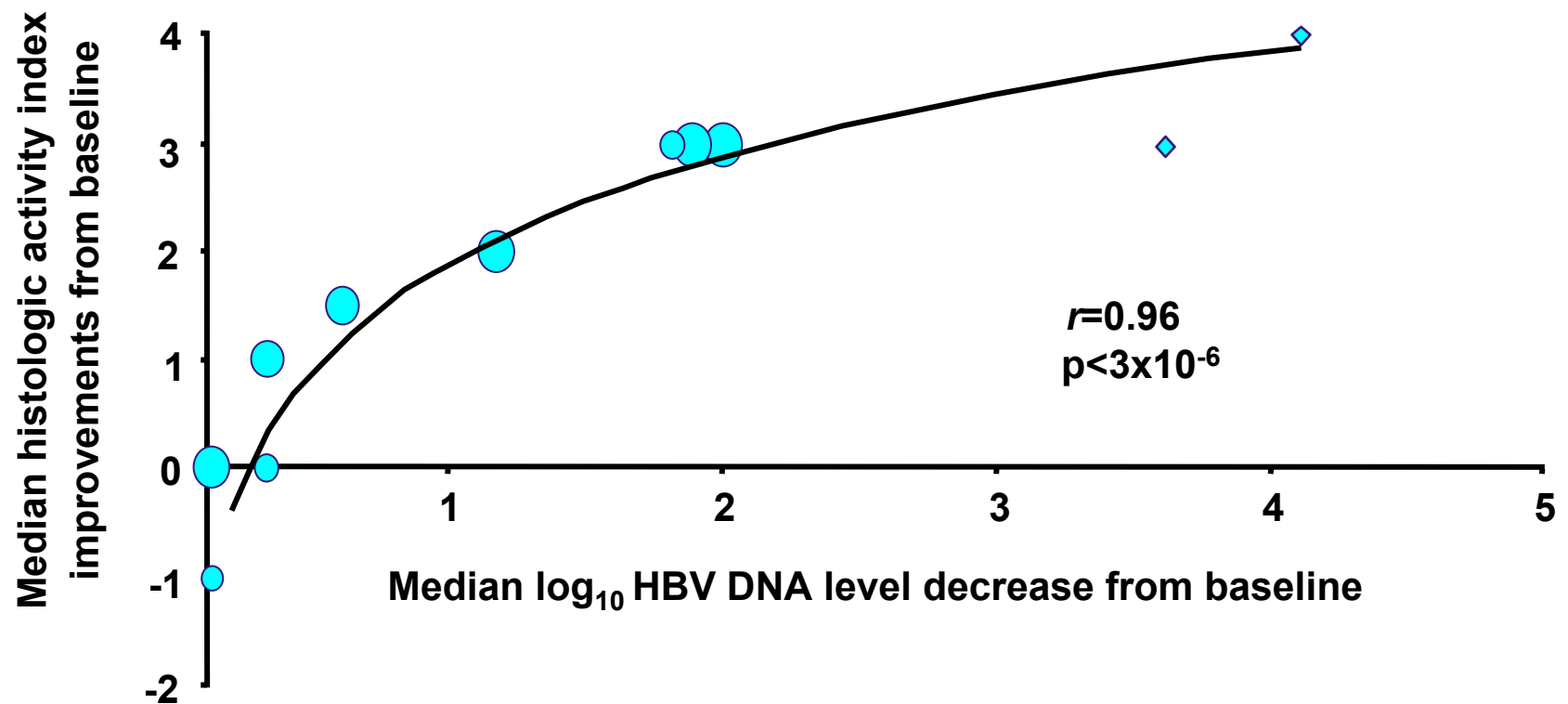
# Histological outcome



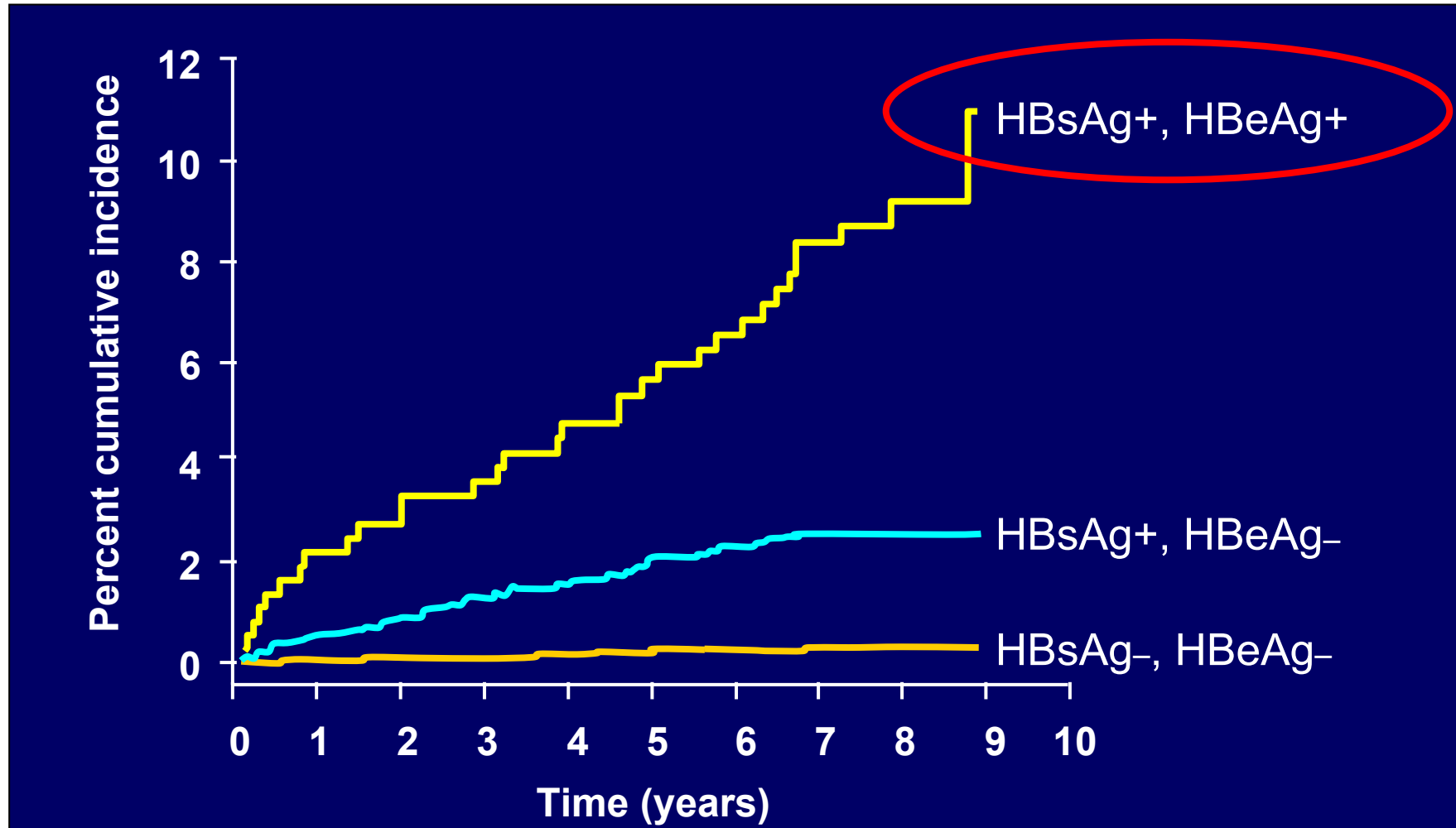
*Korevaar et al. AASLD 2007*

# Relazione tra decremento di HBV DNA terapia indotto e miglioramento dell'istologia epatica

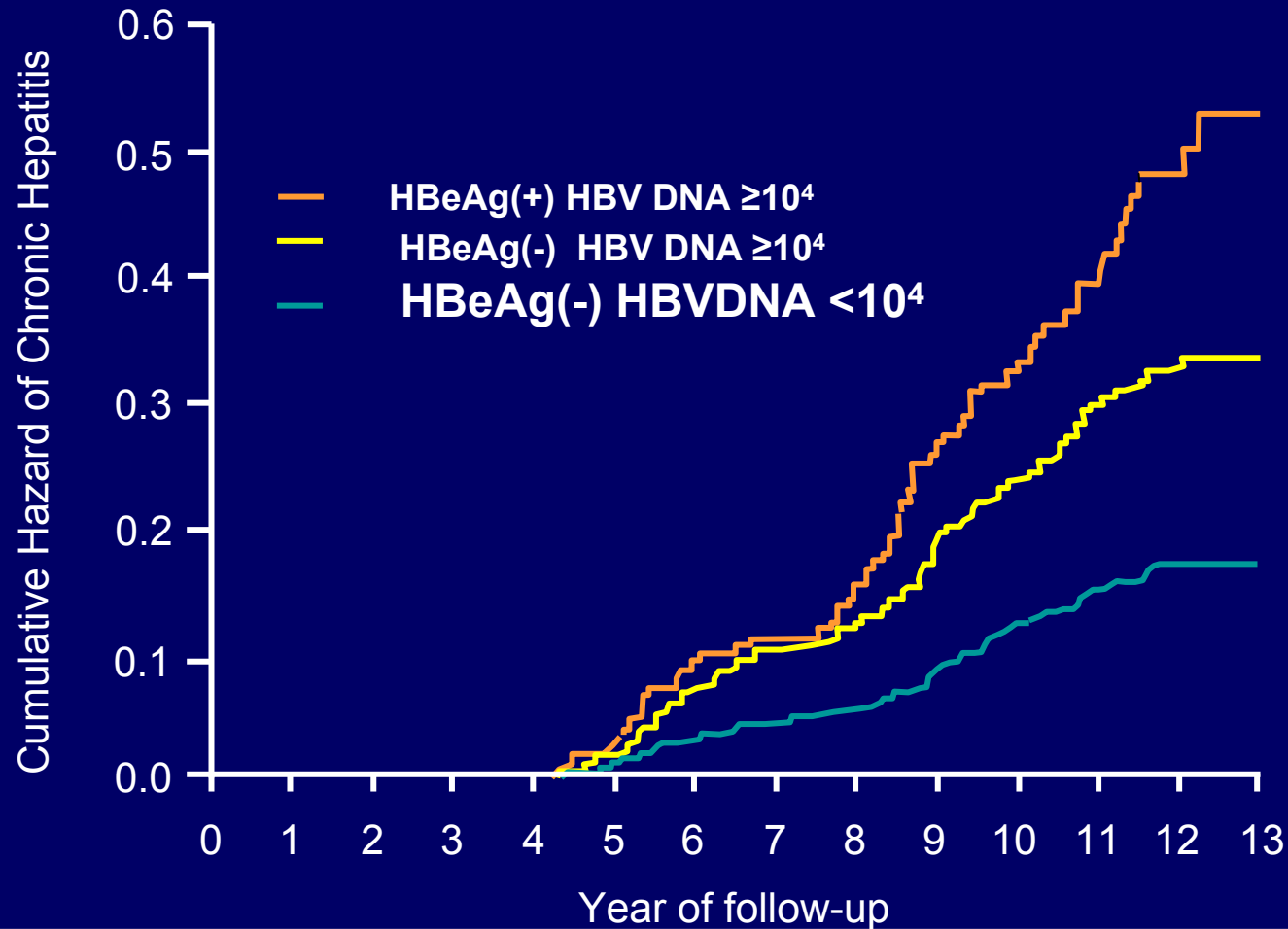
Literature analysis of 26 prospective clinical studies  
Predominantly Caucasian patient population



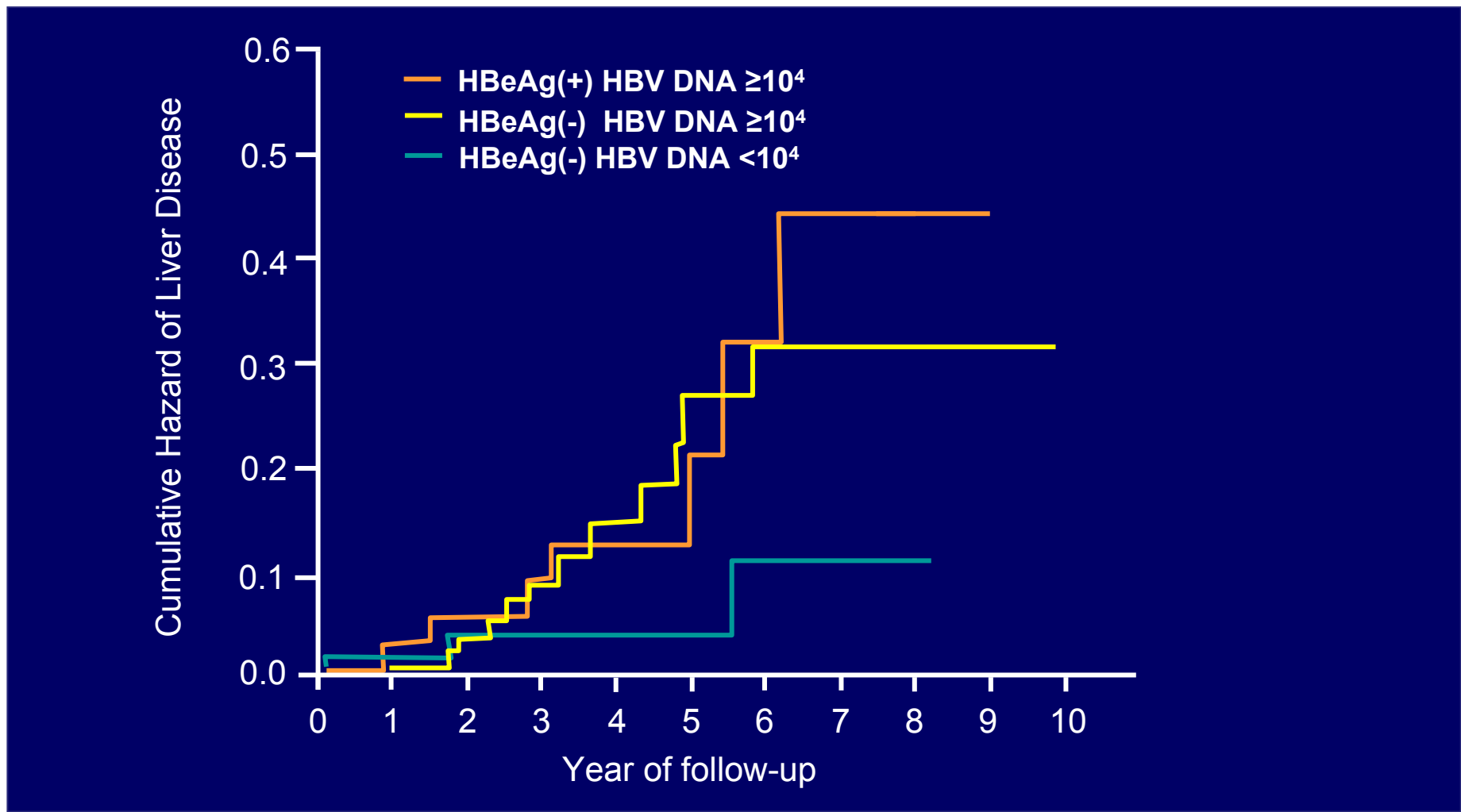
# Hepatitis B and risk of HCC



# Cumulative Hazards of Progression from Asymptomatic CHB to Chronic Hepatitis



# Cumulative Hazards of Progression from Chronic Hepatitis to Cirrhosis



# Il trattamento dell'epatite cronica B

## Stresa 2007

Ishak: S2 —————> S4 —————> S6



Interferone Peghilato (6-12 mesi)

Lieve

Moderata

Grave

Cirrosi

Cirrosi scompensata

NUC (per 5 anni o 6 mesi success. perdita HBs)

HBeAg pos

HBV DNA > 20.000IU/mL



> 200 IU/mL

HBeAb pos

HBV DNA > 2.000IU/mL



> 200 IU/mL

# Treatment of chronic hepatitis B

## Summary

	PegInterferon	Lamivudine	Adefovir	Entecavir
<b>Response in Yr 1</b>				
HBe Ag+(seroconversion)	27%	16%-21%	12%	21%**
HBe Ag+ (HBV DNA neg <sup>1</sup> )	25%	40%-44%	40%*	67%**
HBe Ag- (HBV DNA neg <sup>1</sup> )	63%	60%-70%	51%	90%***
<b>Duration of treatment</b>				
HBe Ag+	1 yr	>1 yr	>1 yr	> 1yr
HBe Ag-	1 yr	>>1 yr <sup>2</sup>	>>1 yr <sup>2</sup>	>>1 yr <sup>2</sup>
<b>Durability of response<sup>3</sup></b>				
HBe Ag+ <sup>4</sup>	NA	50%-80%	91%	69%
HBe Ag- <sup>5</sup>	~20%	<10%	~5%	NA

1 PCR assays  
 2 indefinite therapy  
 3 24 weeks post-treatment  
 4 HBe Ag seroconversion  
 5 undetectable HBV DNA

\* Ann Intern Med 200  
 \*\* NEJM 2006  
 \*\*\* NEJM 2006

# Treatment of chronic hepatitis B

## Summary 2-5 yr

	PegInterferon	Lamivudine	Adefovir	Entecavir
<b>Response in Yr 2</b>				
HBe Ag+(seroconversion)		12-14%*	11%***	
HBe Ag+ (HBV DNA neg <sup>1</sup> )			81%***	
HBe Ag- (HBV DNA neg <sup>1</sup> )	34% <sup>o</sup>	71%**		
<b>Response in Yr 5</b>				
HBe Ag+(seroconversion)		50%§		
HBe Ag+ (HBV DNA neg <sup>1</sup> )				
HBe Ag- (HBV DNA neg <sup>1</sup> )			67% §§	
<sup>1</sup> PCR assays			<sup>o</sup> Hepatol 2005 <sup>*</sup> NEJM 2003 <sup>**</sup> NEJM 2005 <sup>***</sup> NEJM 2006 <sup>§</sup> Gastroenterol 2003 <sup>§§</sup> Hepatol 2005	

# Decline of HBV cccDNA During LdT and LAM Therapy

- **38 patients on LdT and 32 patients on LAM**
- **Intrahepatic HBV DNA and cccDNA were measured by a previously validated real-time PCR assay**
- **Greater reduction of HBV DNA with LdT; no differences in CCC or intrahepatic DNA between groups**

