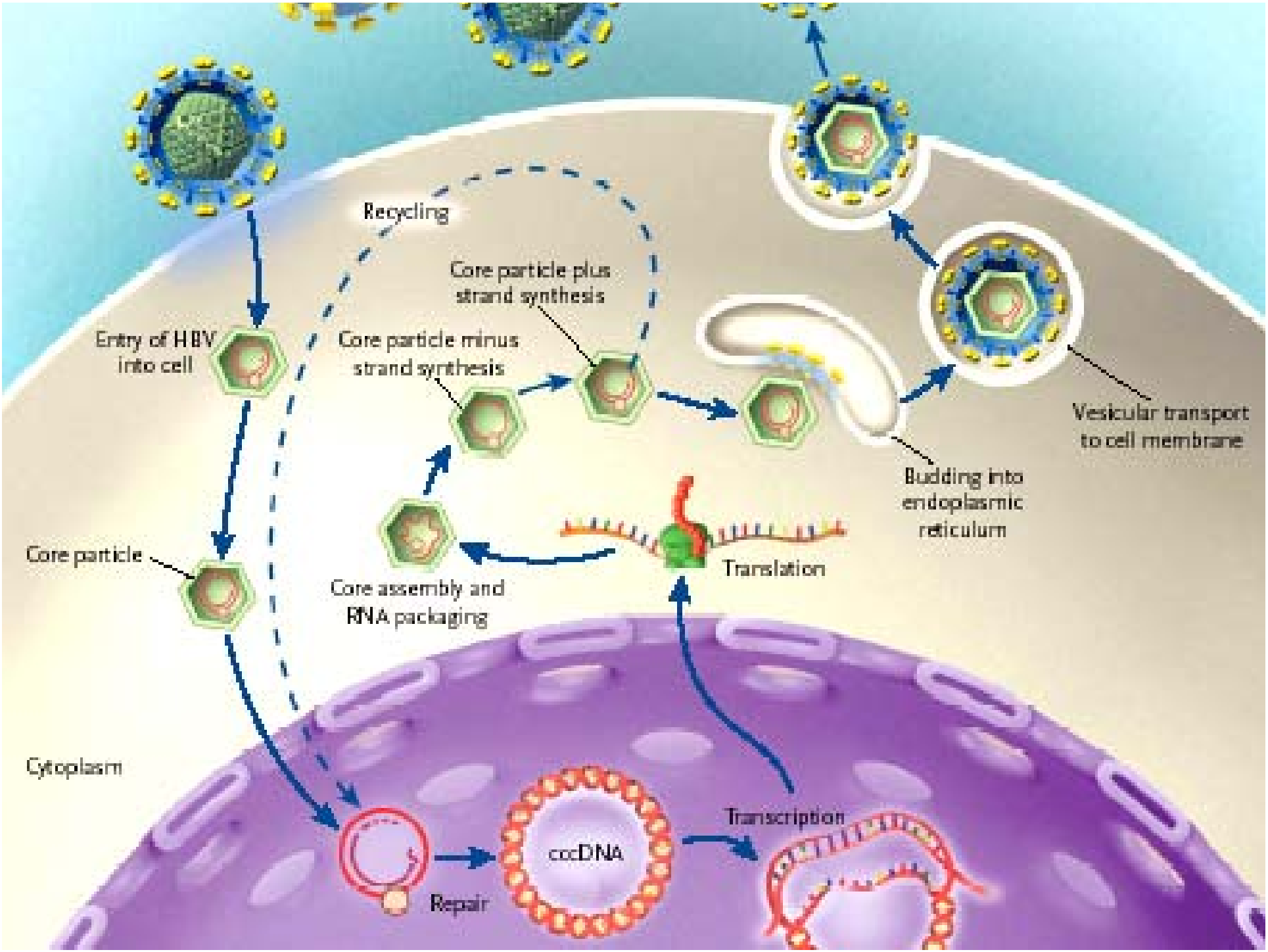
EPATITE B,
UNA EPIDEMIA SCONOCIUTA

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**

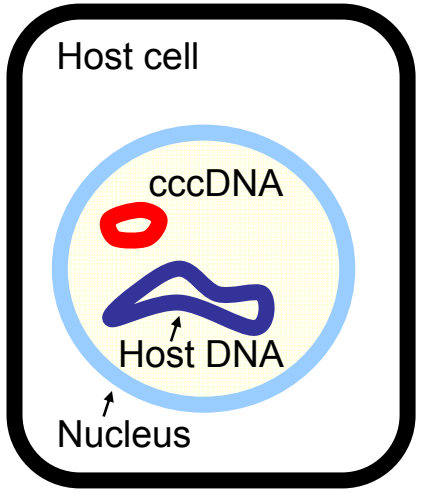

Recycling
Core particle plus strand synthesis
Entry of HBV into cell
Core particle minus strand synthesis
Vesicular transport to cell membrane
Budding into endoplasmic reticulum
Core particle
Translation
Core assembly and RNA packaging
Cytoplasm
Transcription
cccDNA
Repair

Different virus replication strategies

➔

different treatment goals

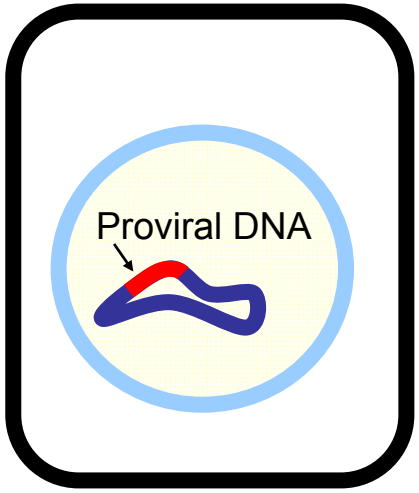
HBV



TREATMENT

Long-term reduction of viral replication to lowest possible level[1]

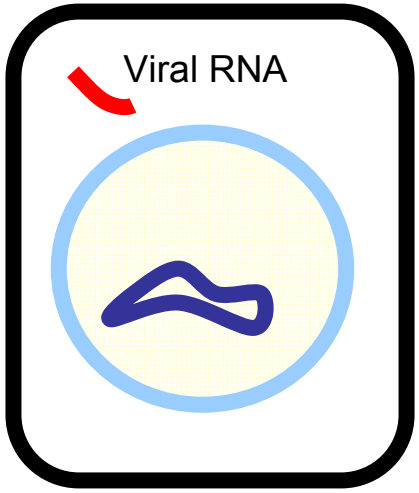
HIV



TREATMENT

Lifelong suppression of viral replication[2,3]

HCV



TREATMENT

Definitive viral clearance[1]

↓

SVR possible for HCV[1]

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

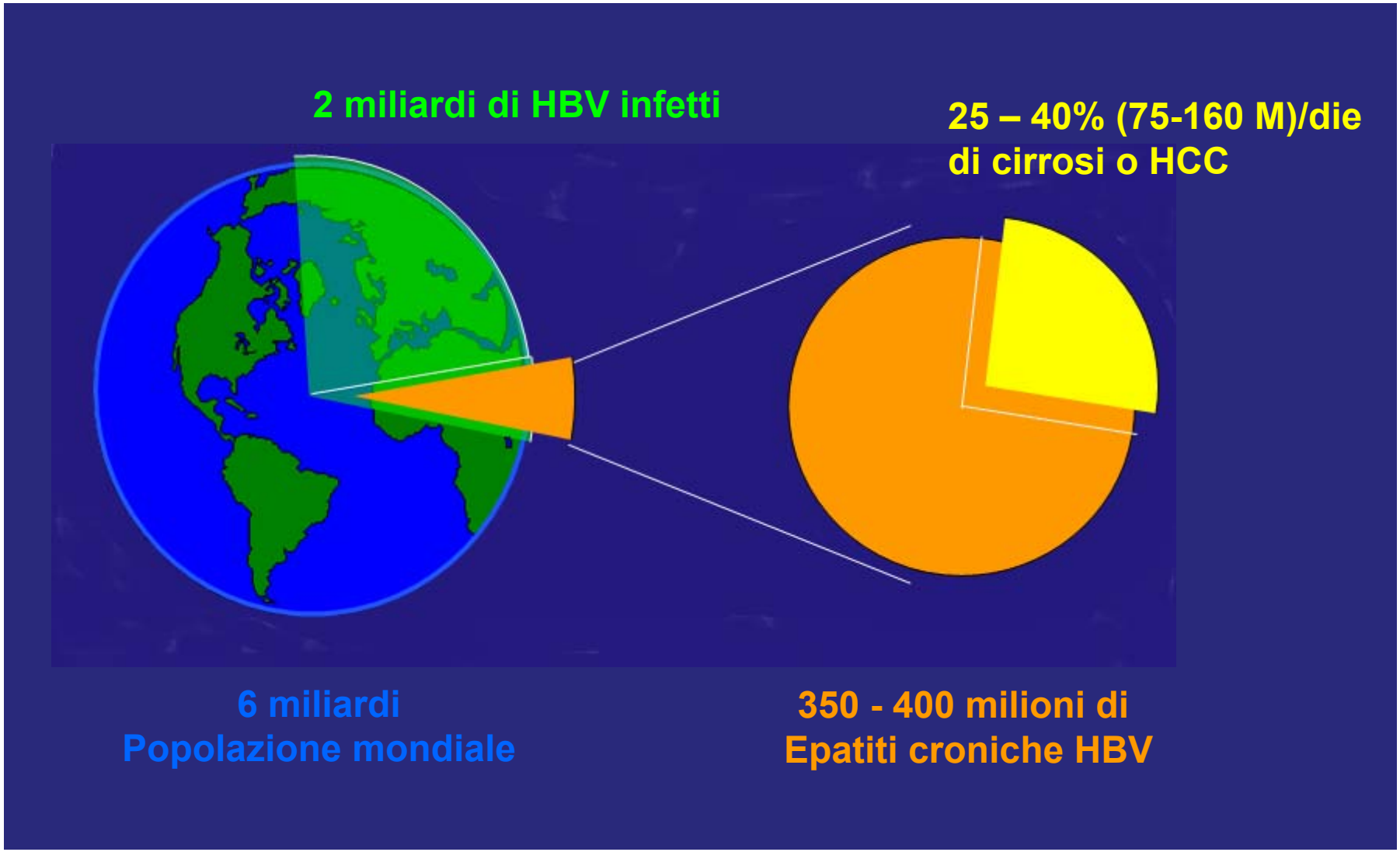
Infetti presente/passato	~ 2 miliardi
Infezioni croniche	350-400 milioni
Morte	0.5-1.2 milioni/anno
Causa di morte per malattia	10° causa nel mondo

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



Prevalenza HBsAg

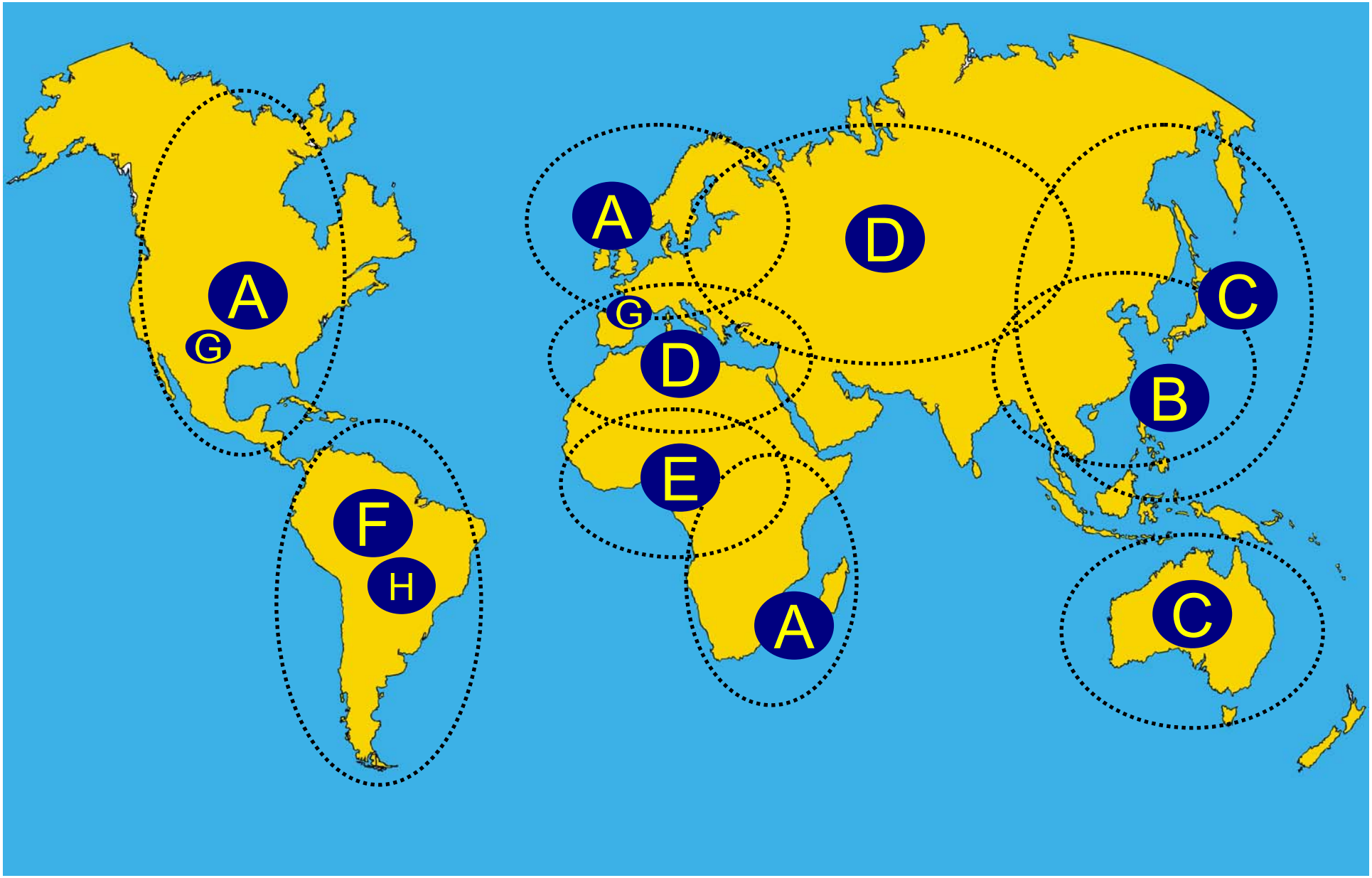
- ≥ 8% = alta
- 2% - 7% = intermedia
- <2% = bassa



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+**

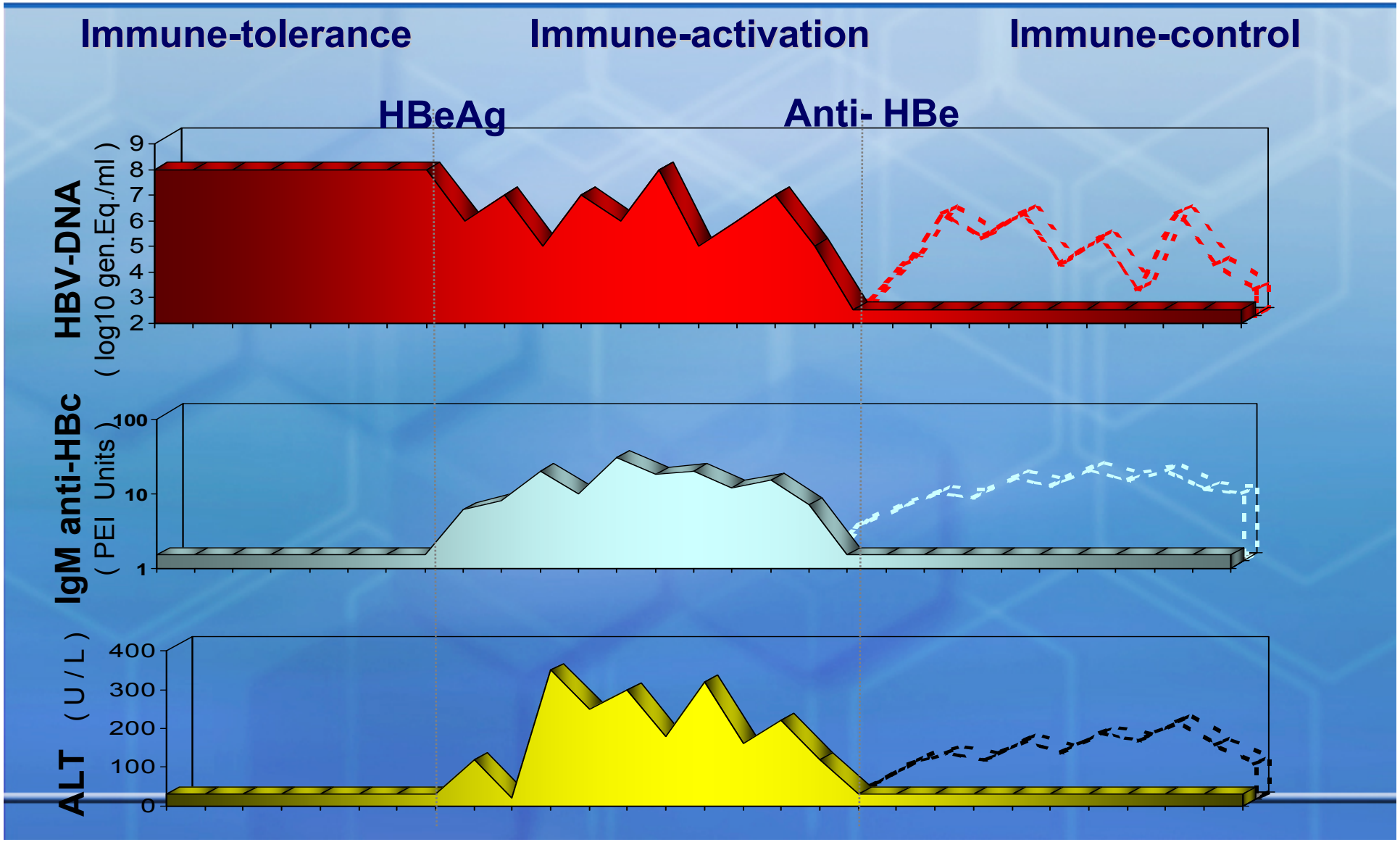
- **600.000 -1.000.000 di portatori cronici di HBV (HBsAg+)**

- **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)***

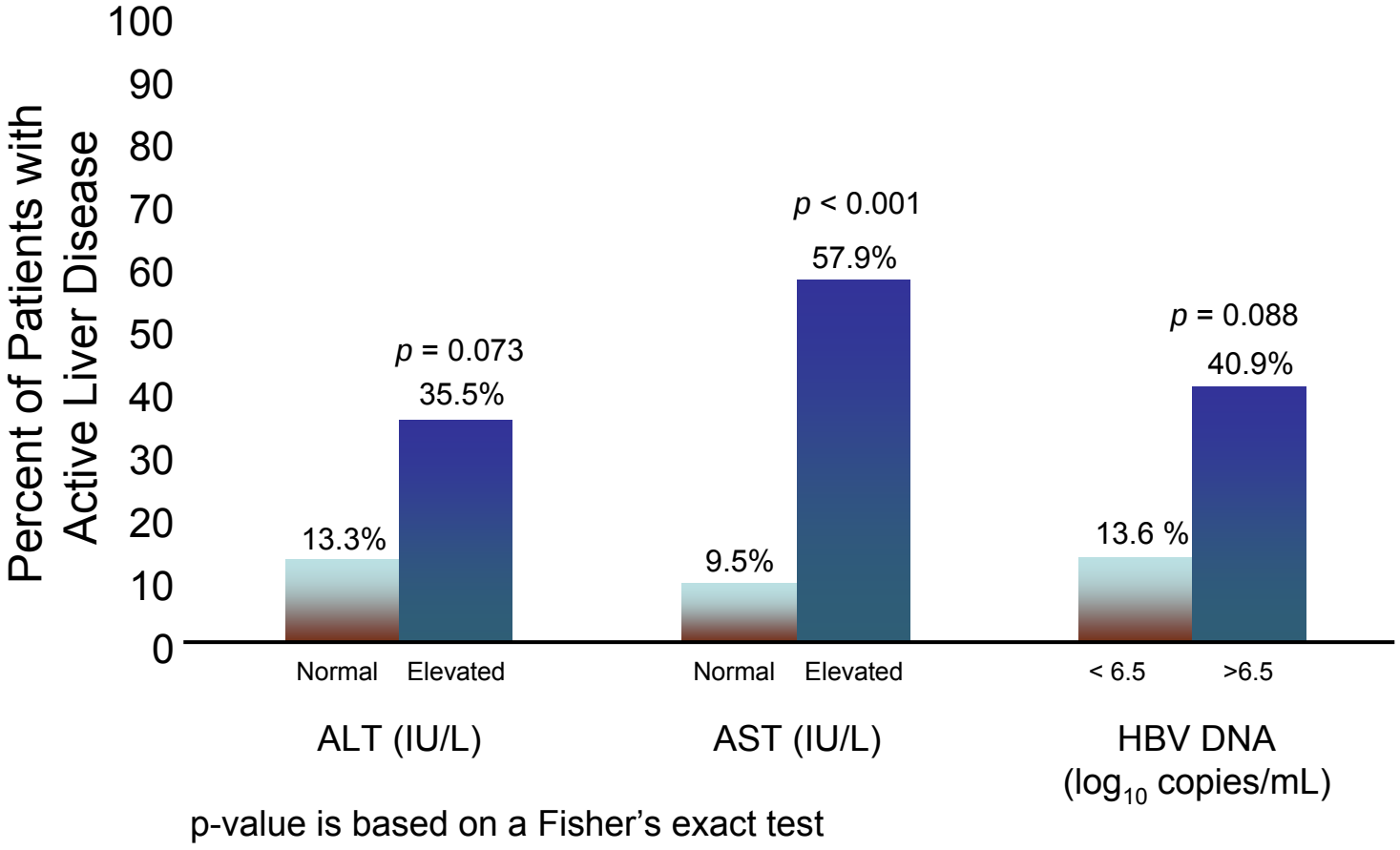
- **250.000 portatori tra cittadini immigrati**

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



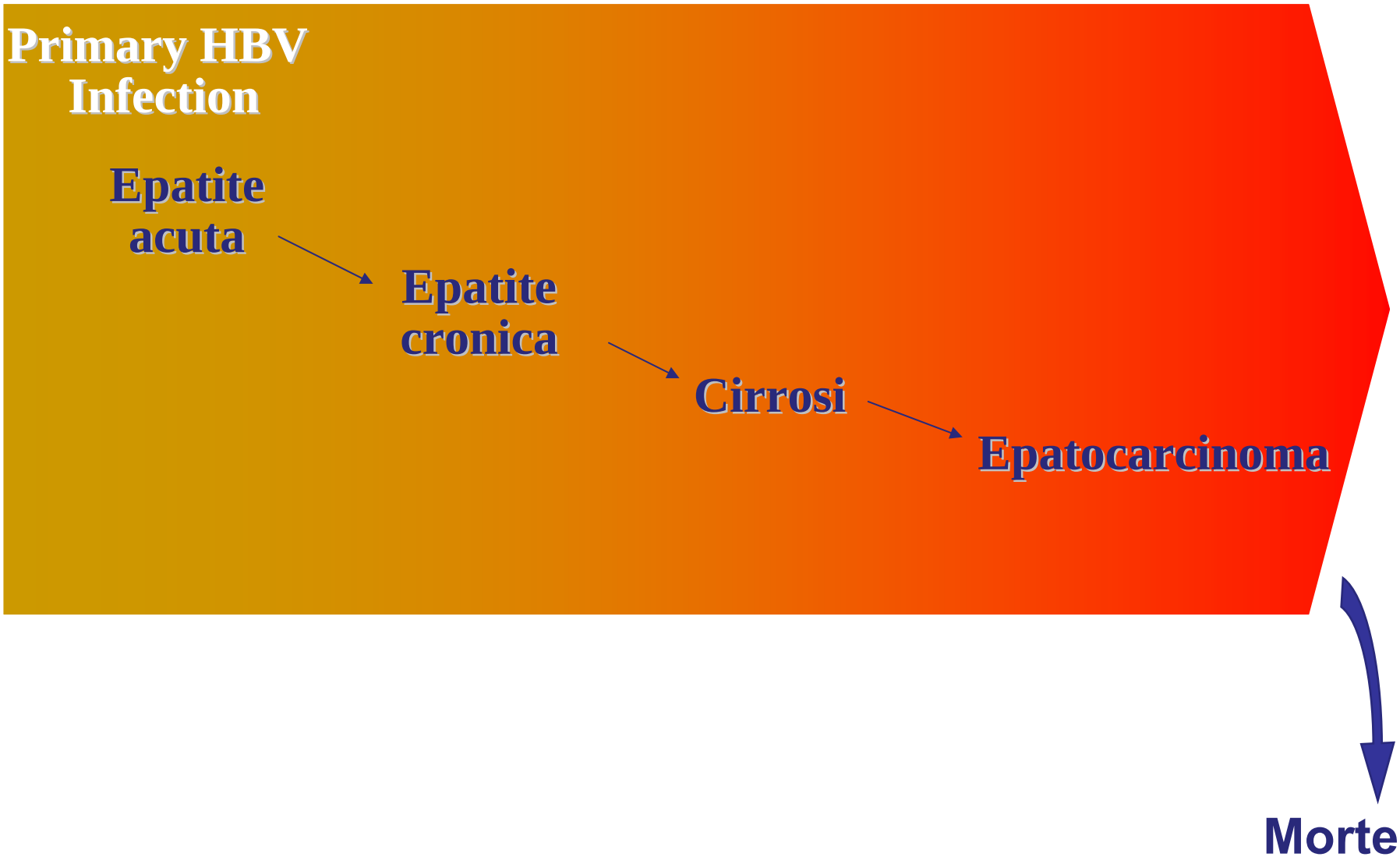
Association of Liver Disease with Virological/Biochemical Parameters



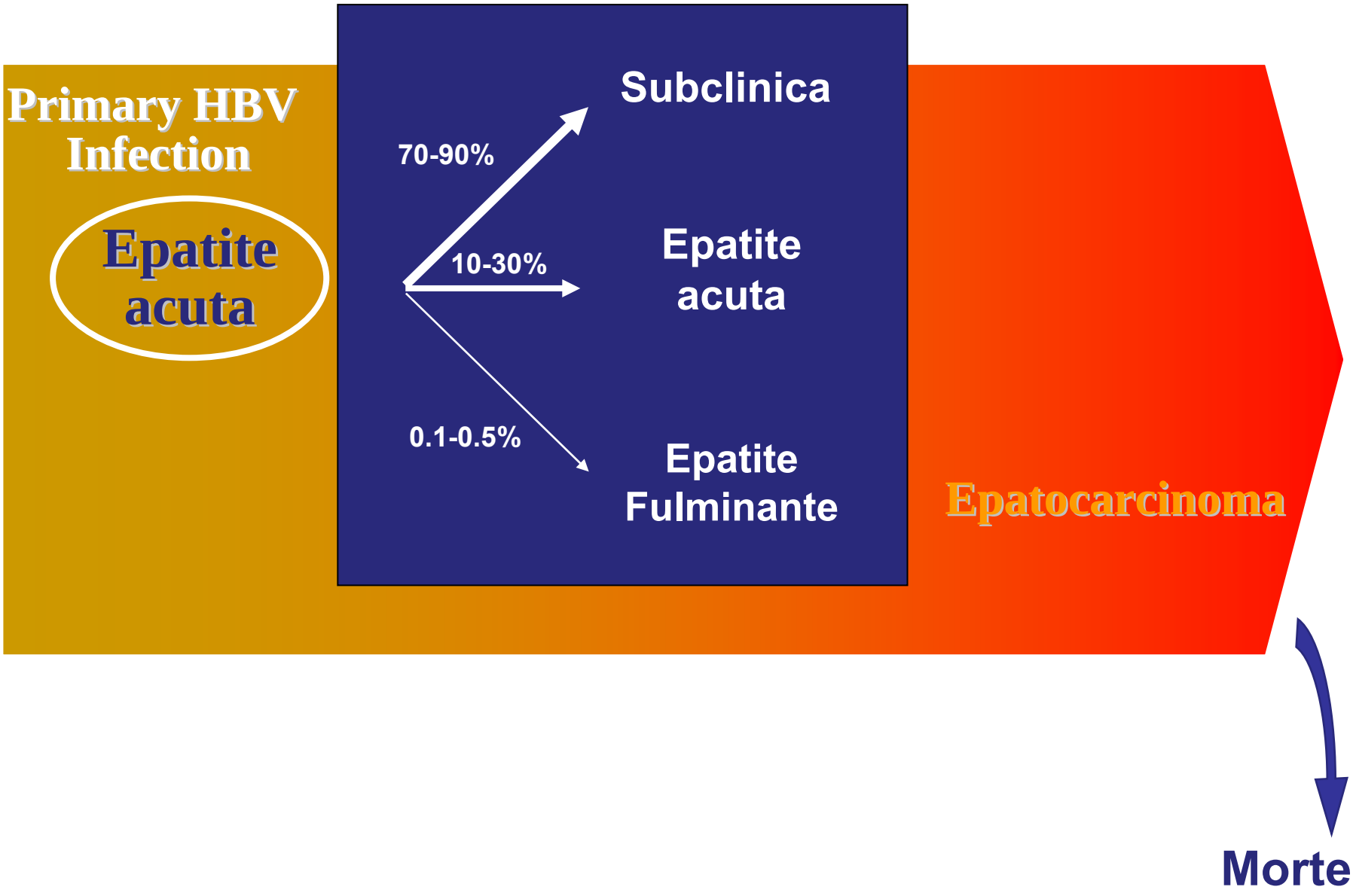
p-value is based on a Fisher's exact test

Hu KQ, et al. 43rd EASL; Milan, Italy; April 23-27, 2008. Abstract 653.

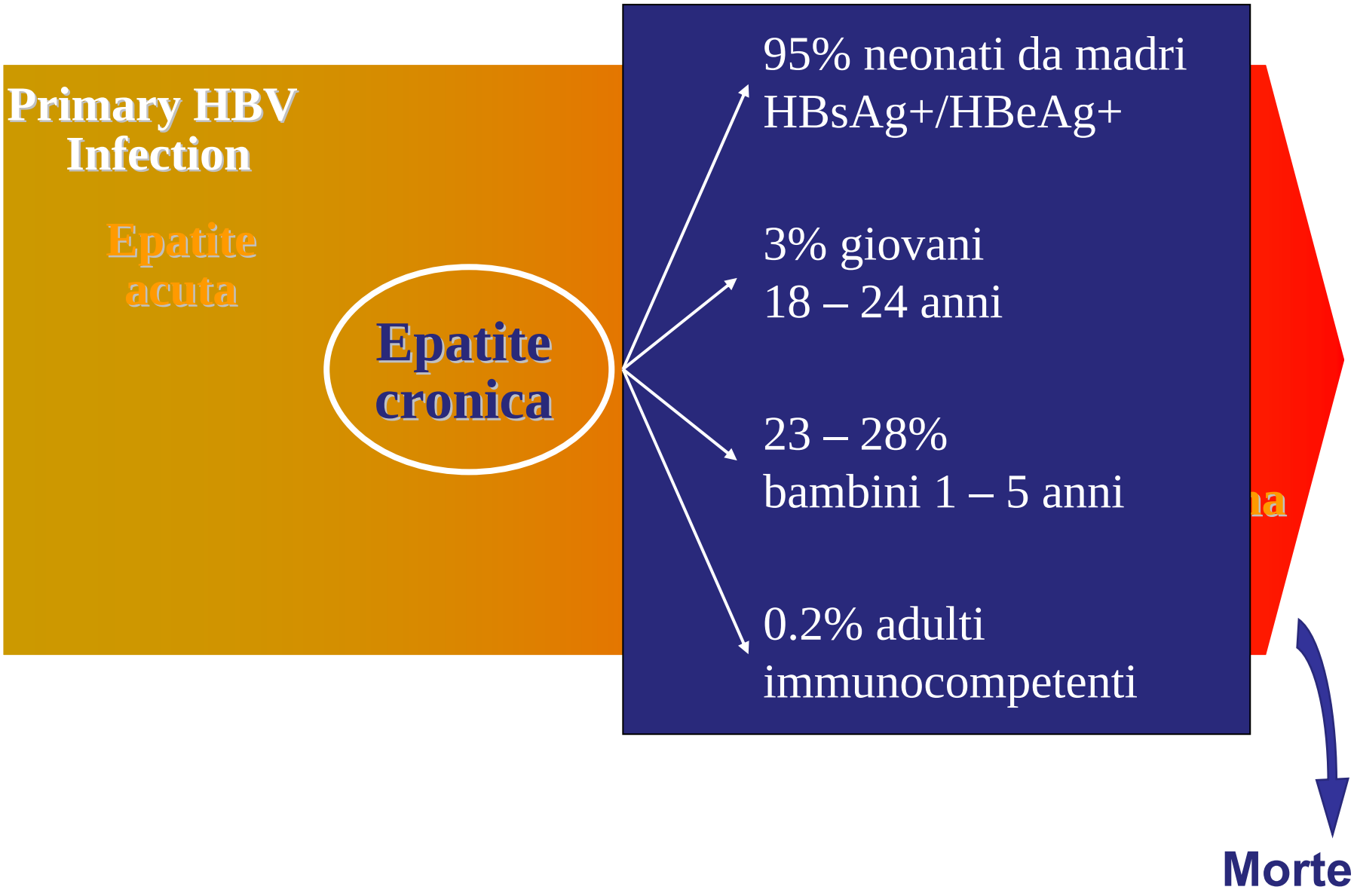
STORIA NATURALE



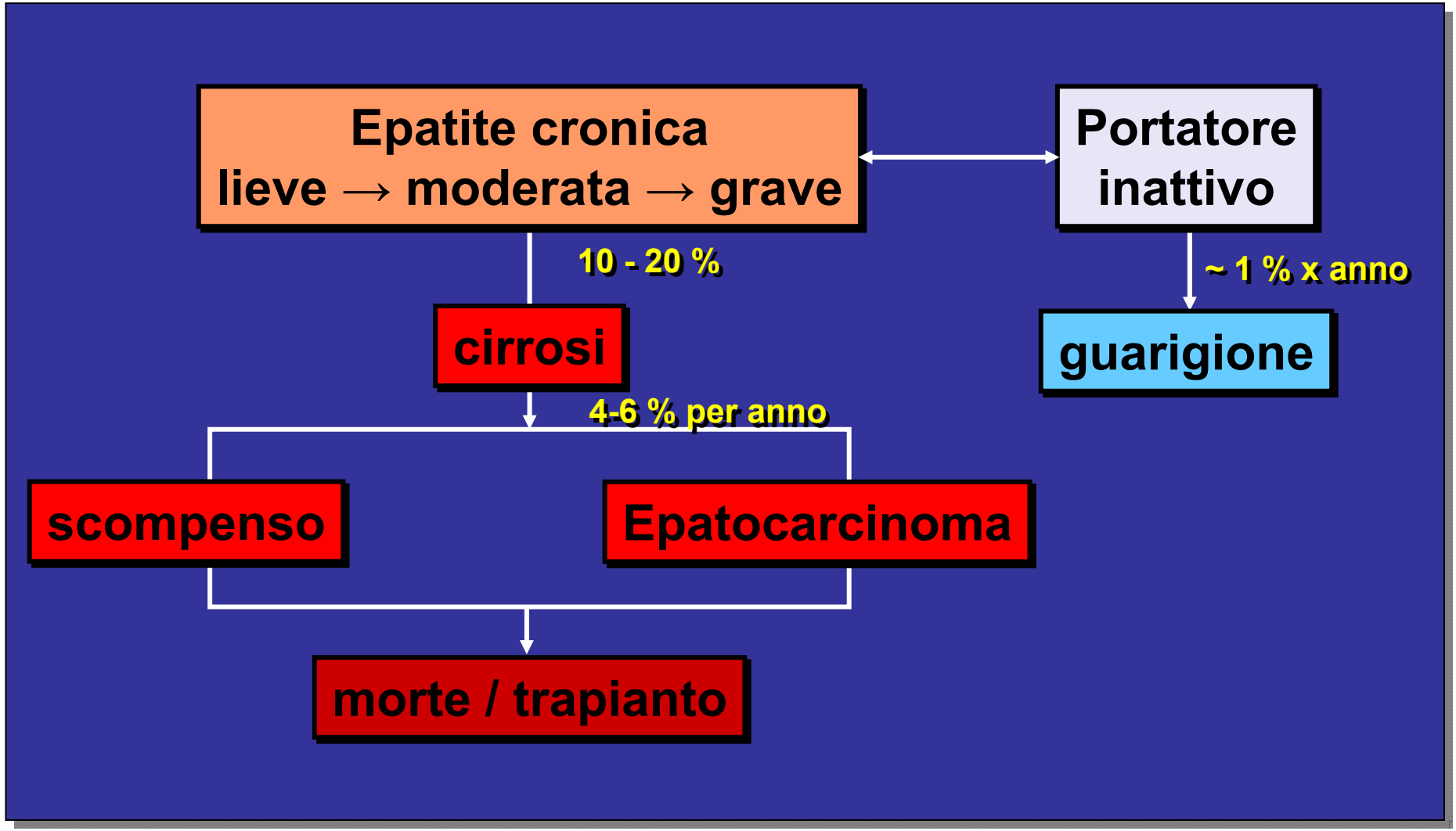
STORIA NATURALE



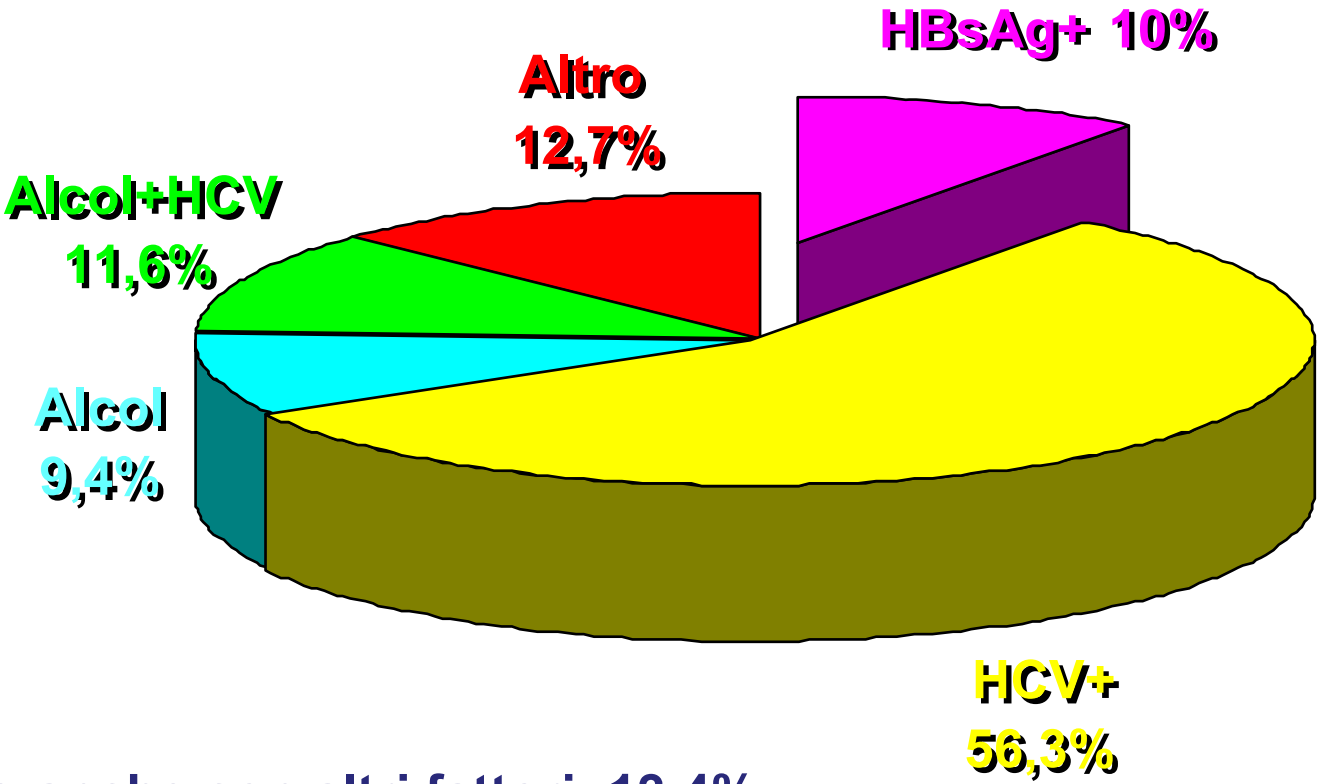
STORIA NATURALE



STORIA NATURALE



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



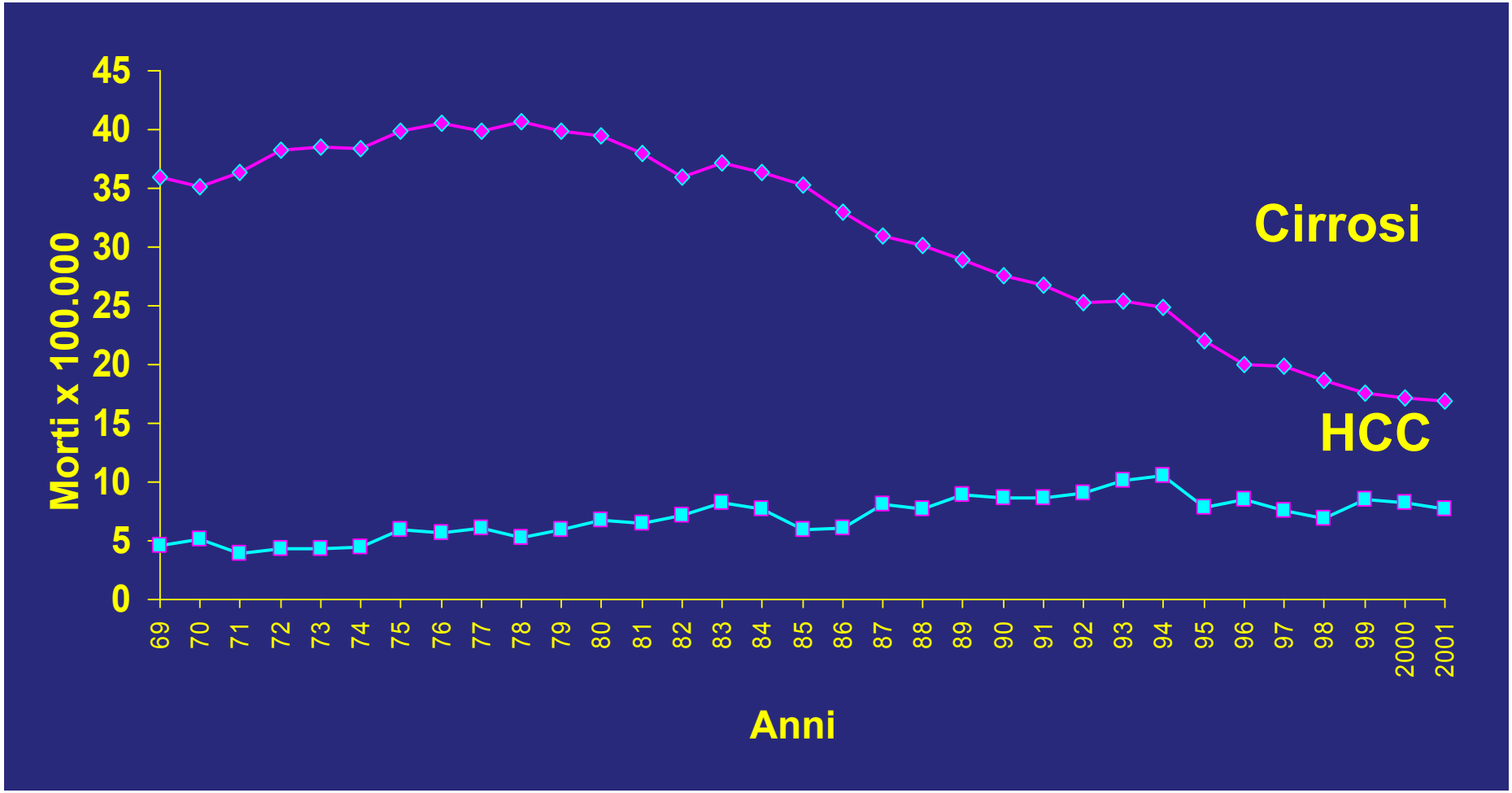
HBsAg anche con altri fattori=13,4%

HCV anche con altri fattori=69,9%

Alcol anche con altri fattori=23,0%

Sagnelli et al. J. Med. Virol. 2005

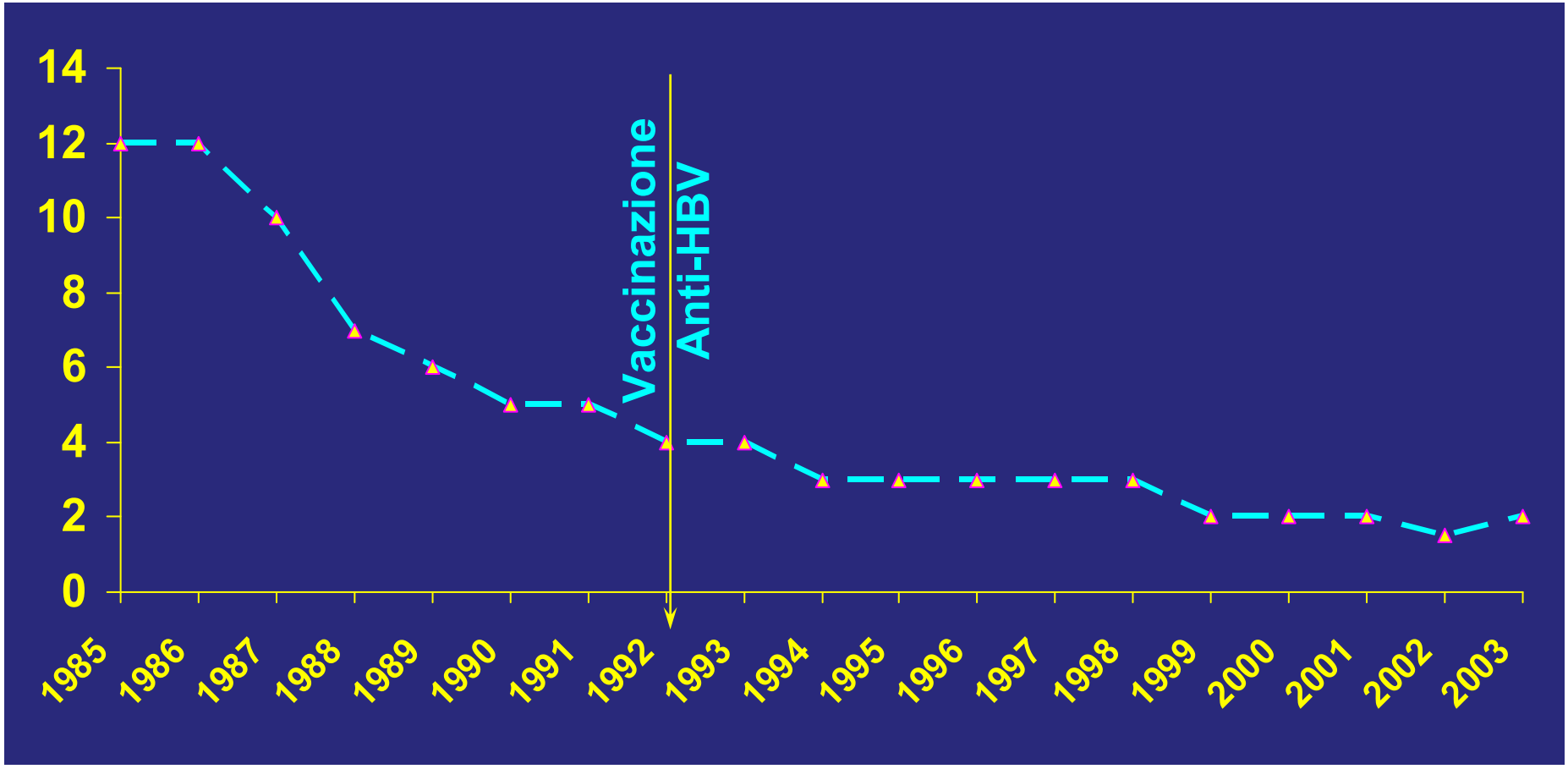
Tasso di mortalità (decessi per 100.000 abitanti) per Cirrosi ed HCC in Italia 1969-2001



Dati ISTAT

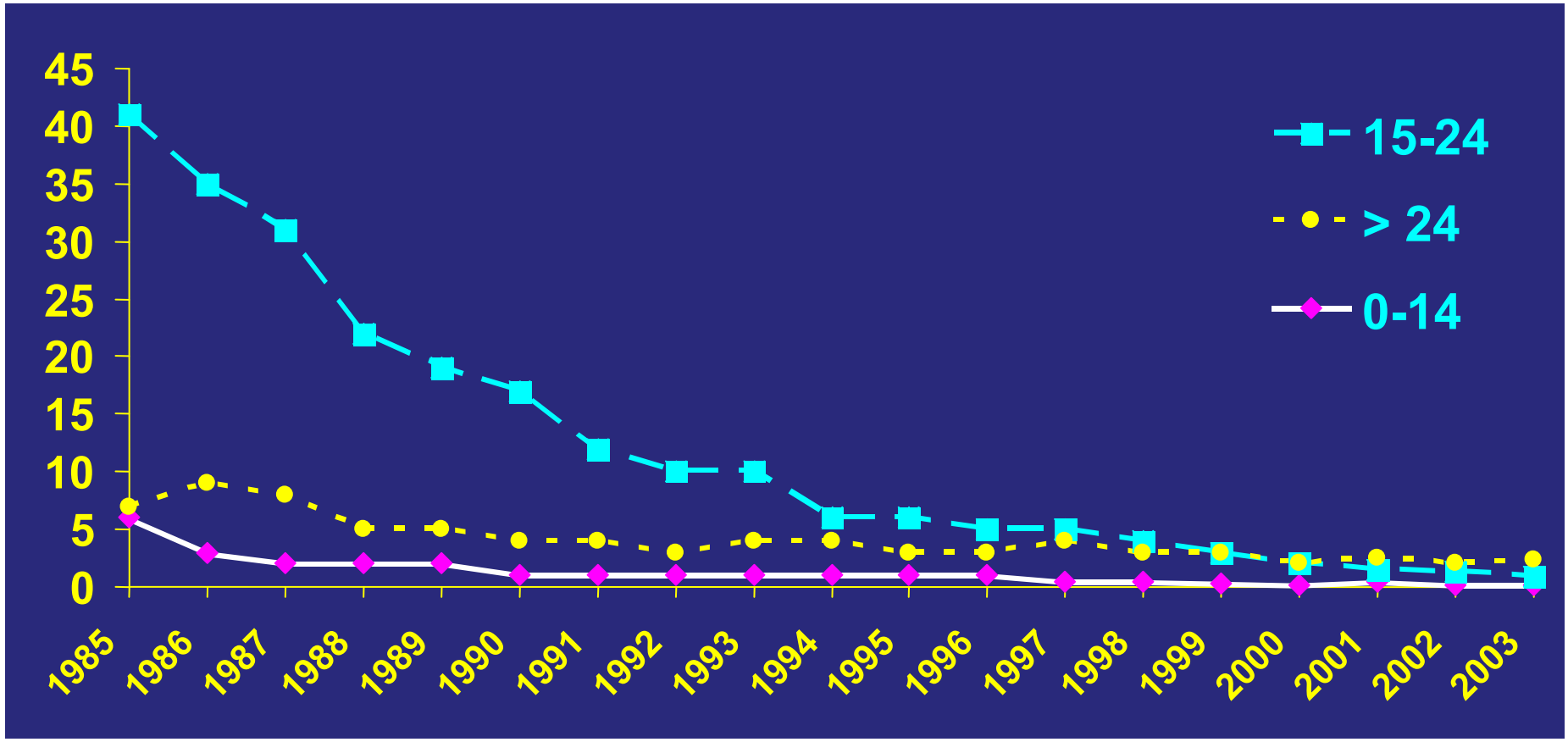
Perchè vaccinare?

Incidenza di epatite B in Italia. SEIEVA 1985-2003



Stroffoni Hepatol 2000

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



Stroffoni Hepatol 2000

Perchè sottoporre a screening?

Screening per epatite B: motivazioni

- **precoce identificazione e cura dei soggettti 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 screenig per epatite B

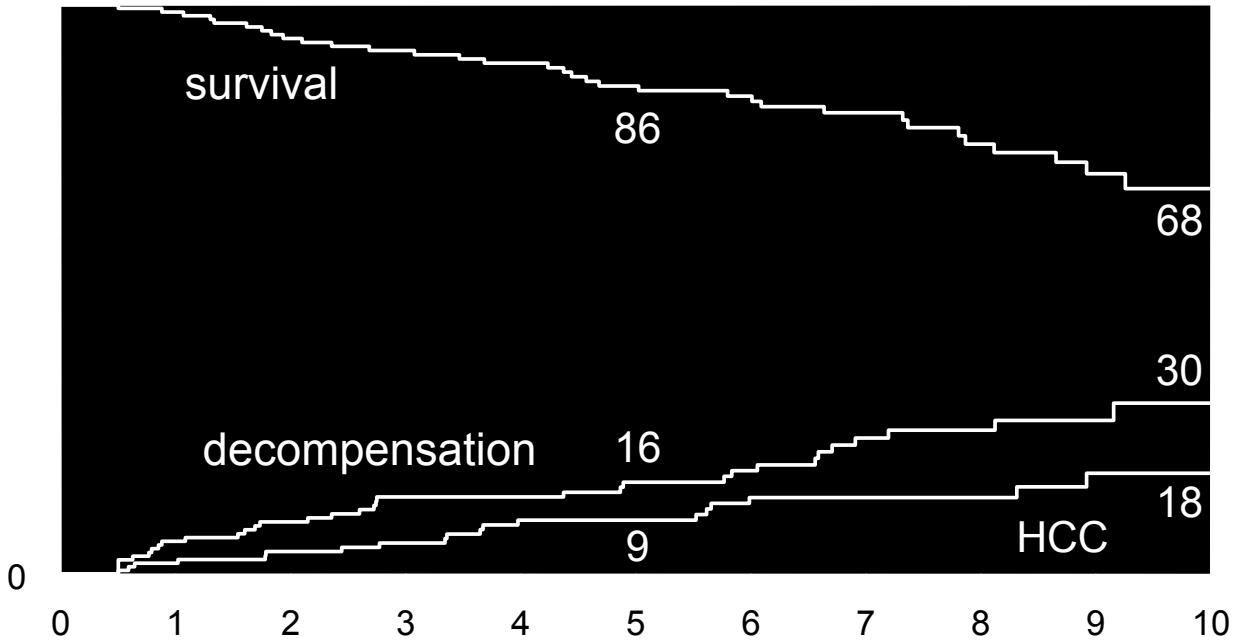
- Carceri
- Strutture sanitarie ed in particolare:
  - Centri per malattie sessualmente trasmissibili
  - Centri per il trattamento della dipendenza da sostanze d'abuso
  - Centri trasfusionali
  - Centri per la terapia dell'HIV

- Centri per immigrati
- Agenzie internazionali per l'adozione

Perchè trattare?

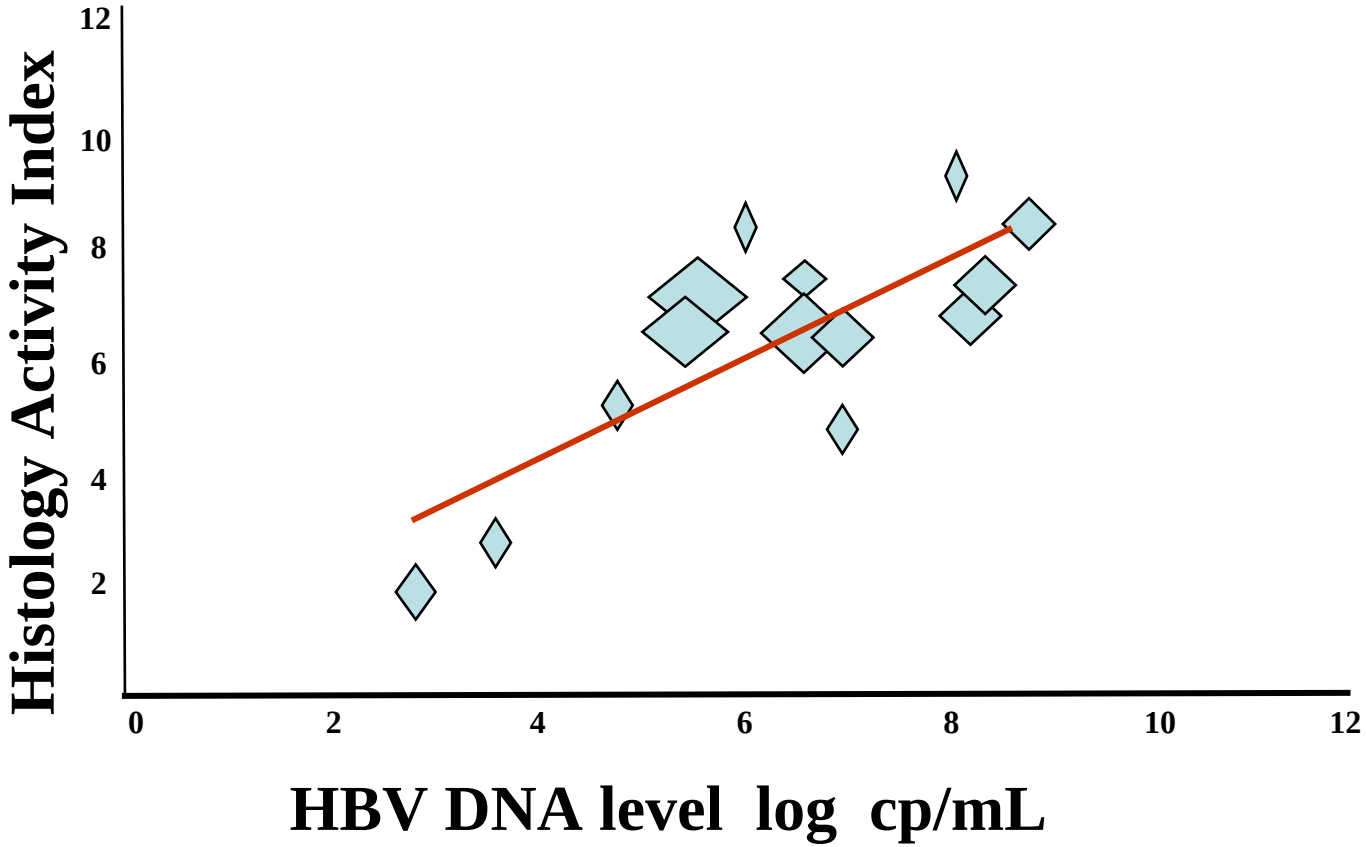
Survival in compensated cirrhosis B

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)



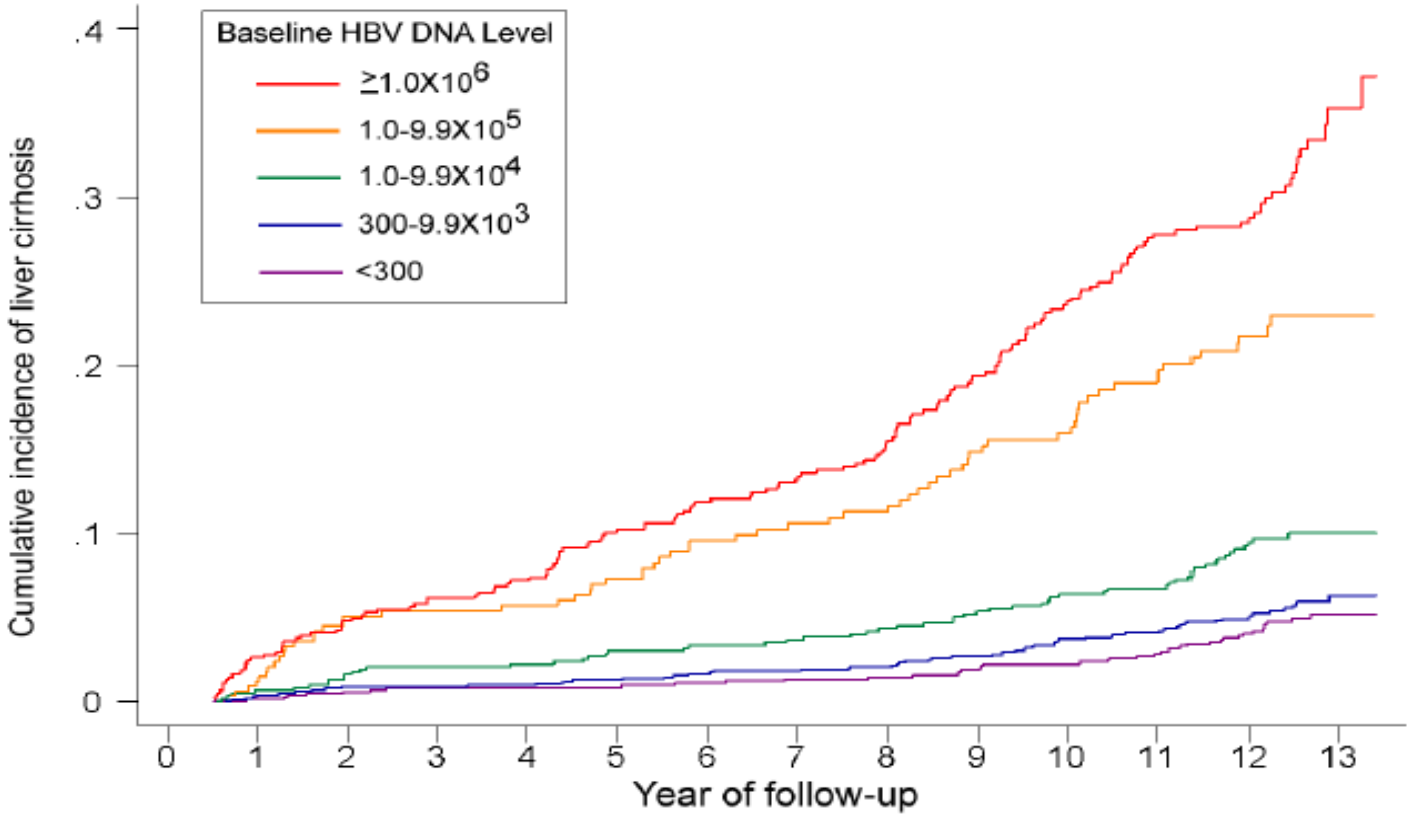
Fattovich, Am J Gastroenterol 2002; 97: 2886-95

Relazione tra livelli di HBV DNA e indice di attività istologica. Una review di 26 studi prospettici



From: Mommeja-Marin H, Hepatology. 2003.

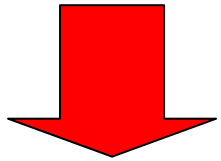
Relazione tra livelli di HBV DNA e sviluppo di cirrosi



Iloeje, Gastroenterology 2006

Clinical benefits of HBeAg and HBsAg clearance

HBeAg clearance



HBsAg clearance

Disease remission

HBsAg seroconversion

Prevention of HCC

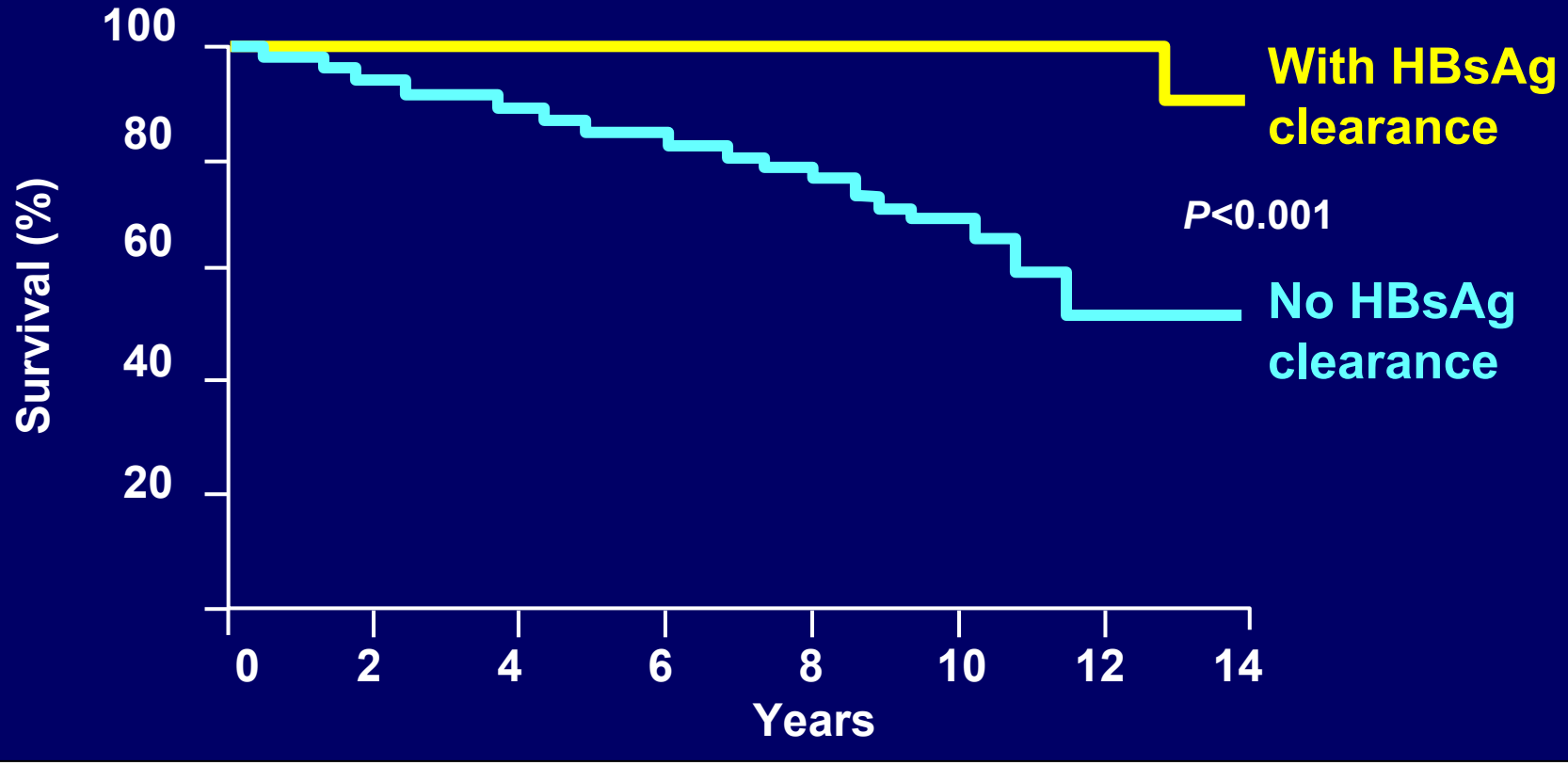
Increased survival

Hoofnagle *Ann Intern Med* 1981; Fattovich *Hepatology* 1986;Di Bisceglie *Gastroenterology* 1987;
Niederau *NEJM* 1996; Chu *Gastroenterology* 2002; van Zonneveld *Hepatology* 2004

HBsAg clearance improves survival rates

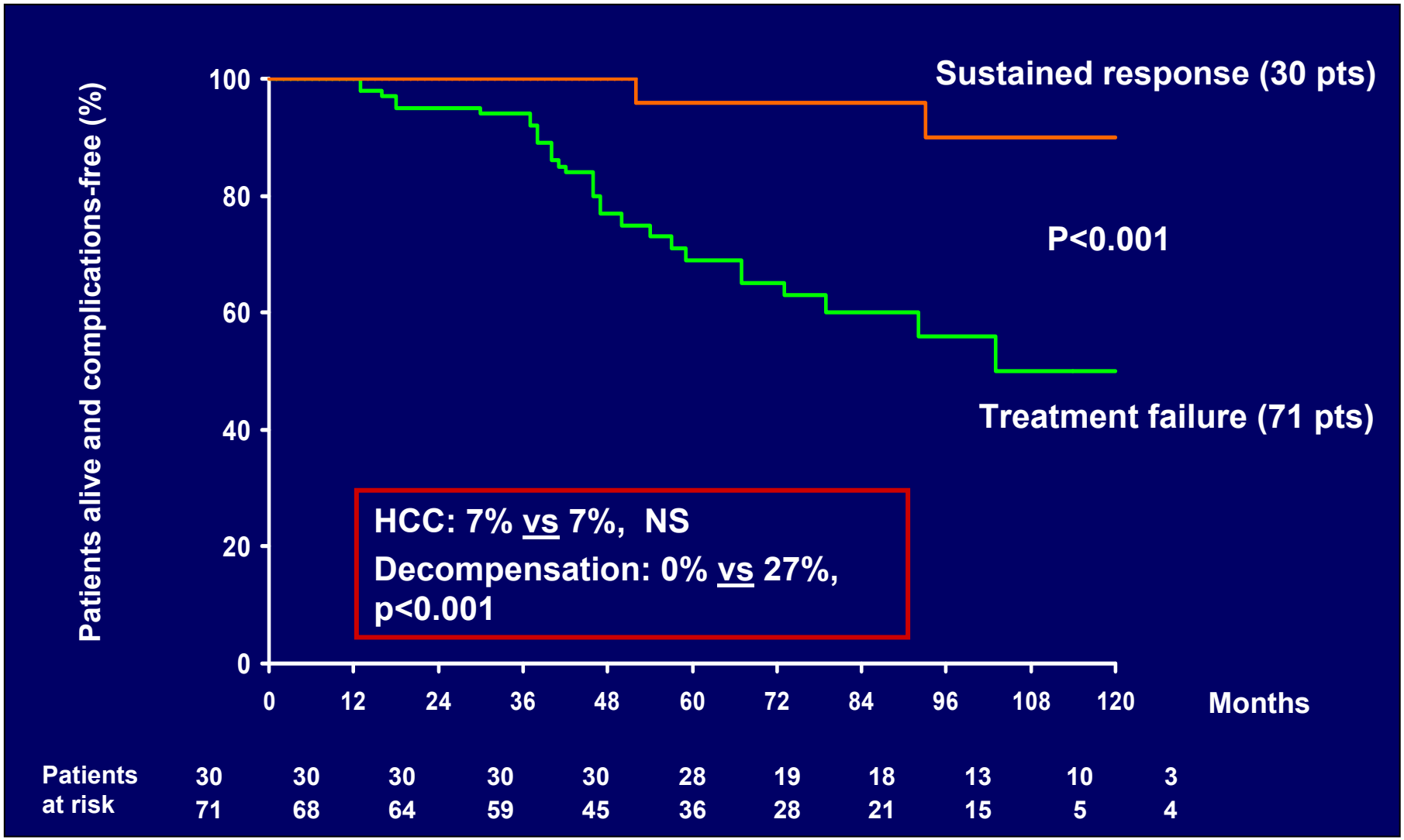
Probability of survival in patients with and without HBsAg clearance

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



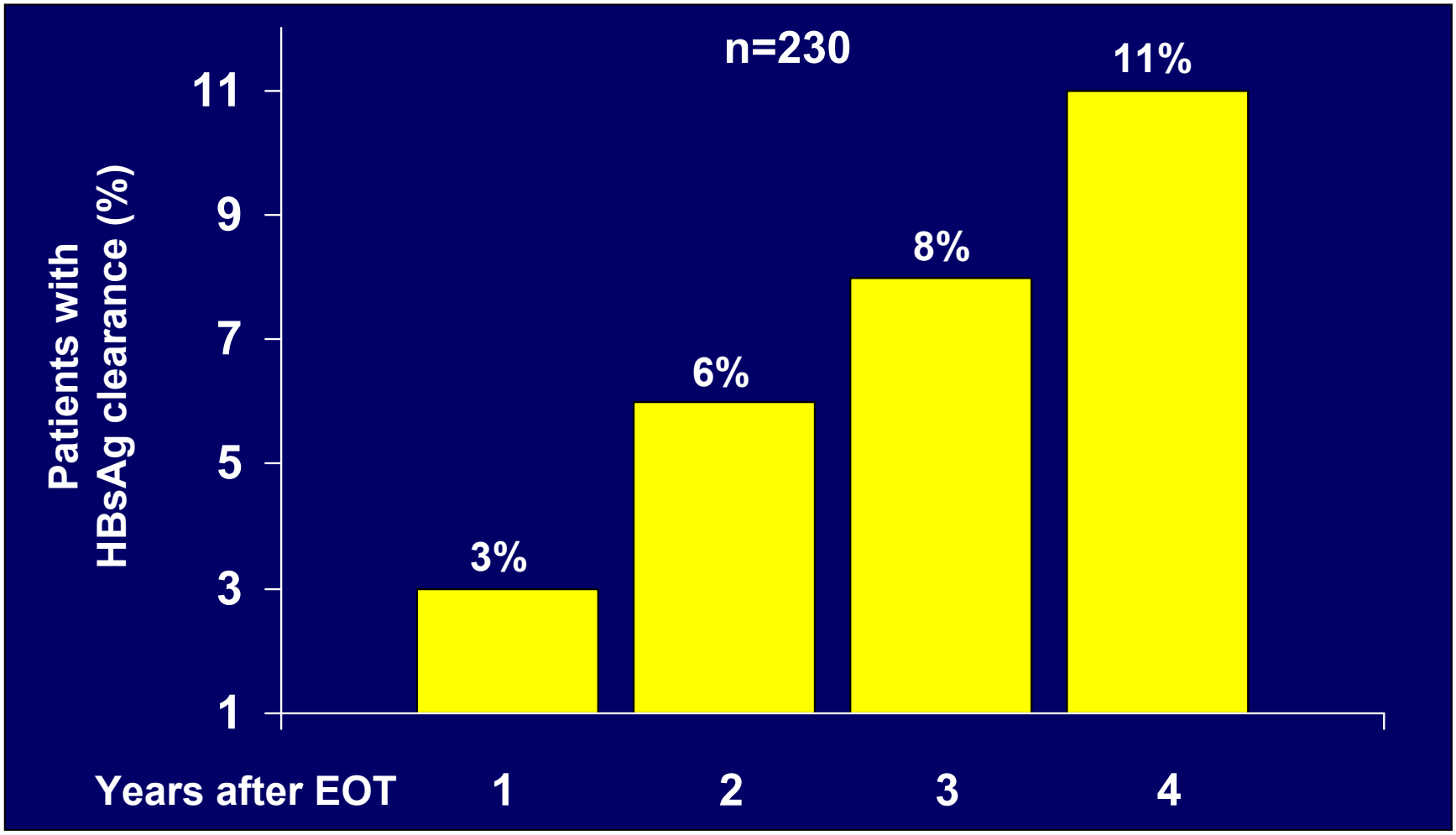
Fattovich et al. Am J Gastroenterol 1998

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



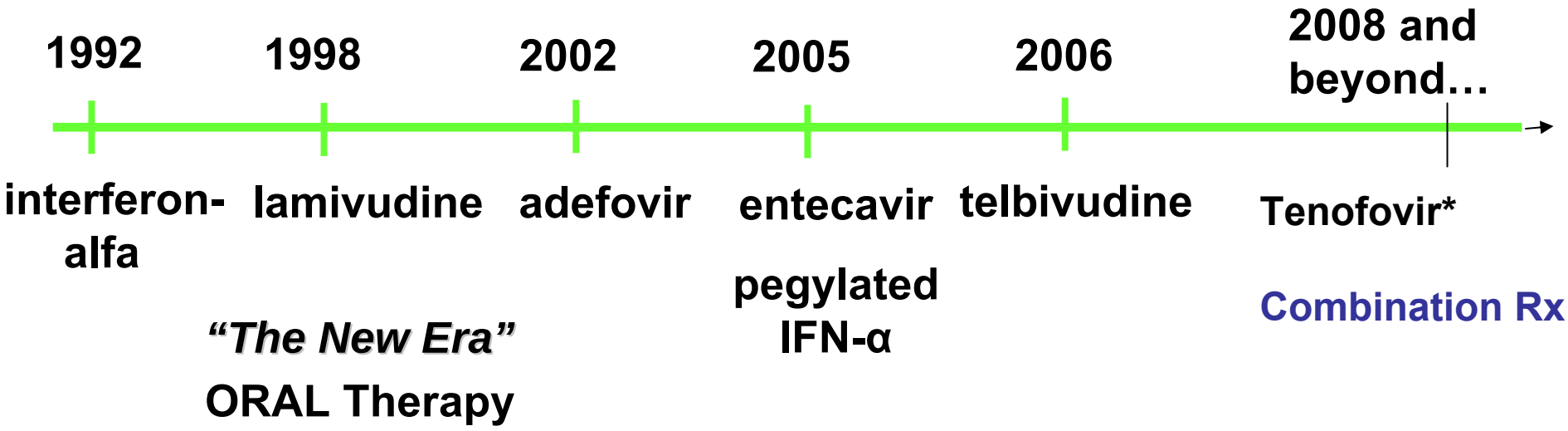
Lampertico, Hepatol 2003

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



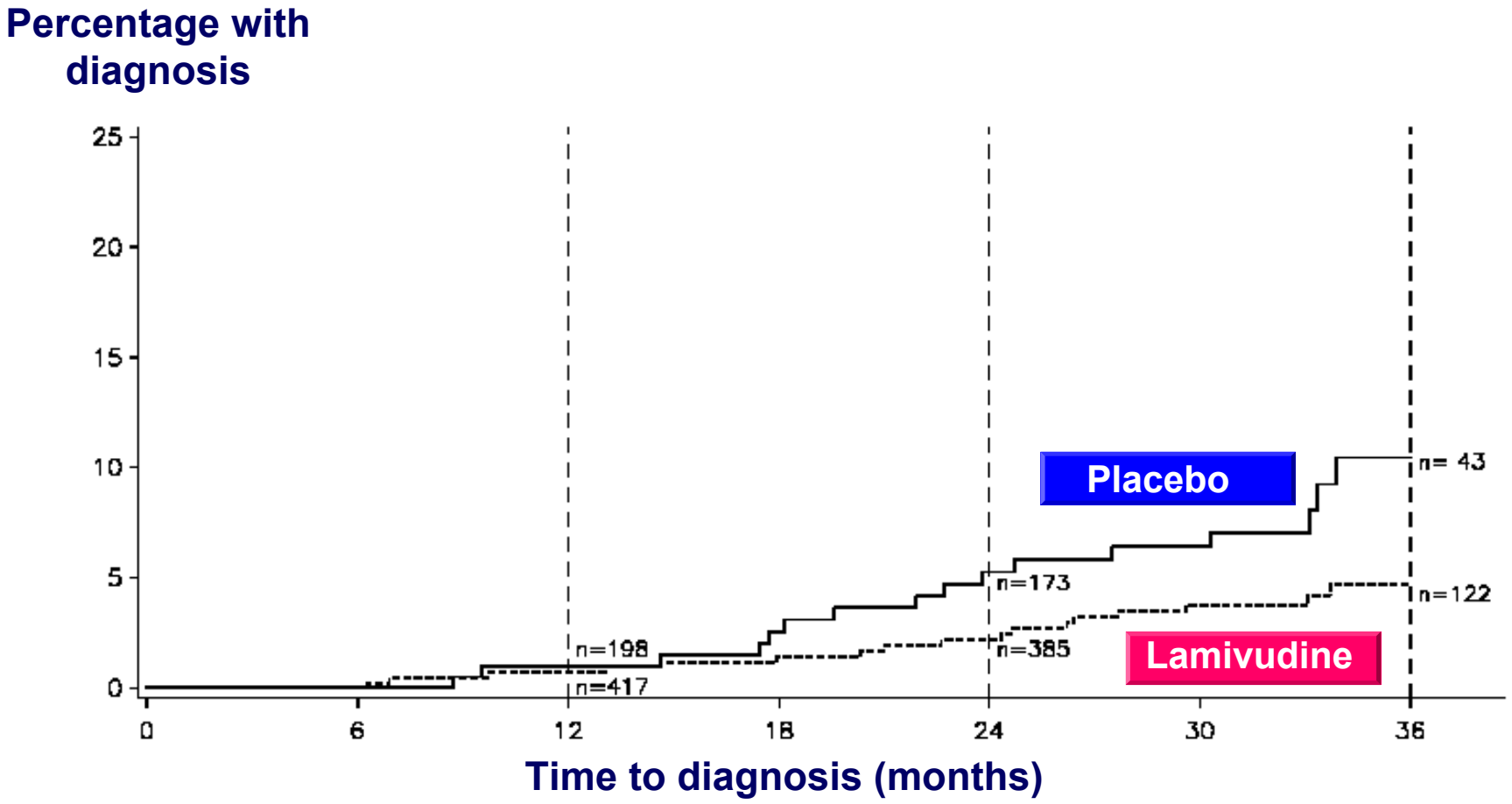
Marcellin et al. EASL 2008

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



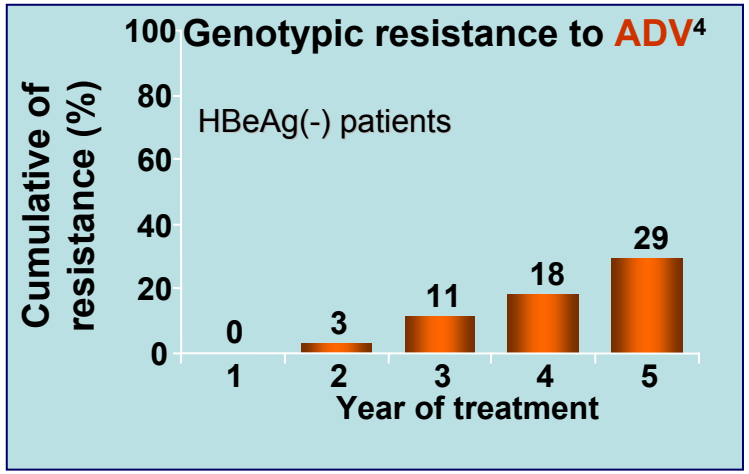
Excluding 5 cases in yr1: HR=0.47; P=0.052

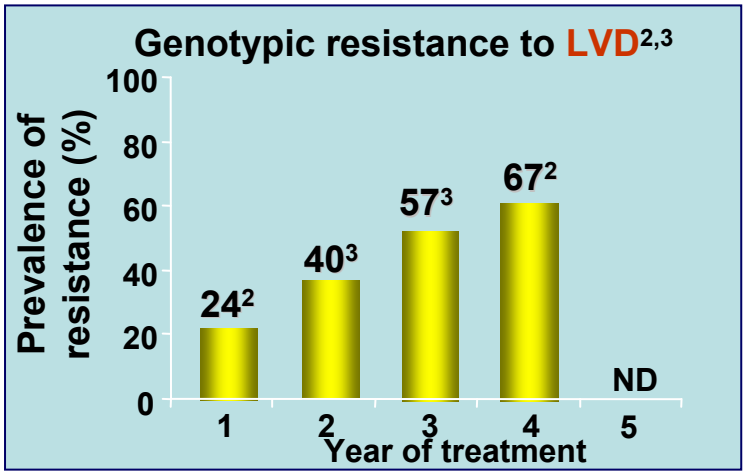
——— **Placebo (n=215)**

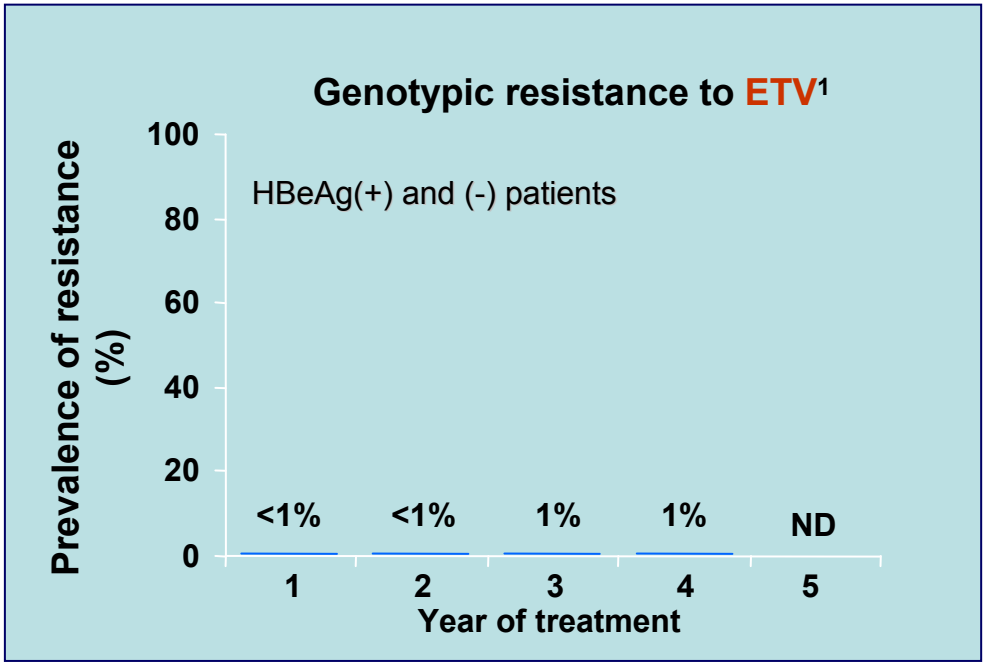
····· **Lamivudine (n=436)**

Liaw et al, NEJM 2004

Resistance Rates in Naïve Patients

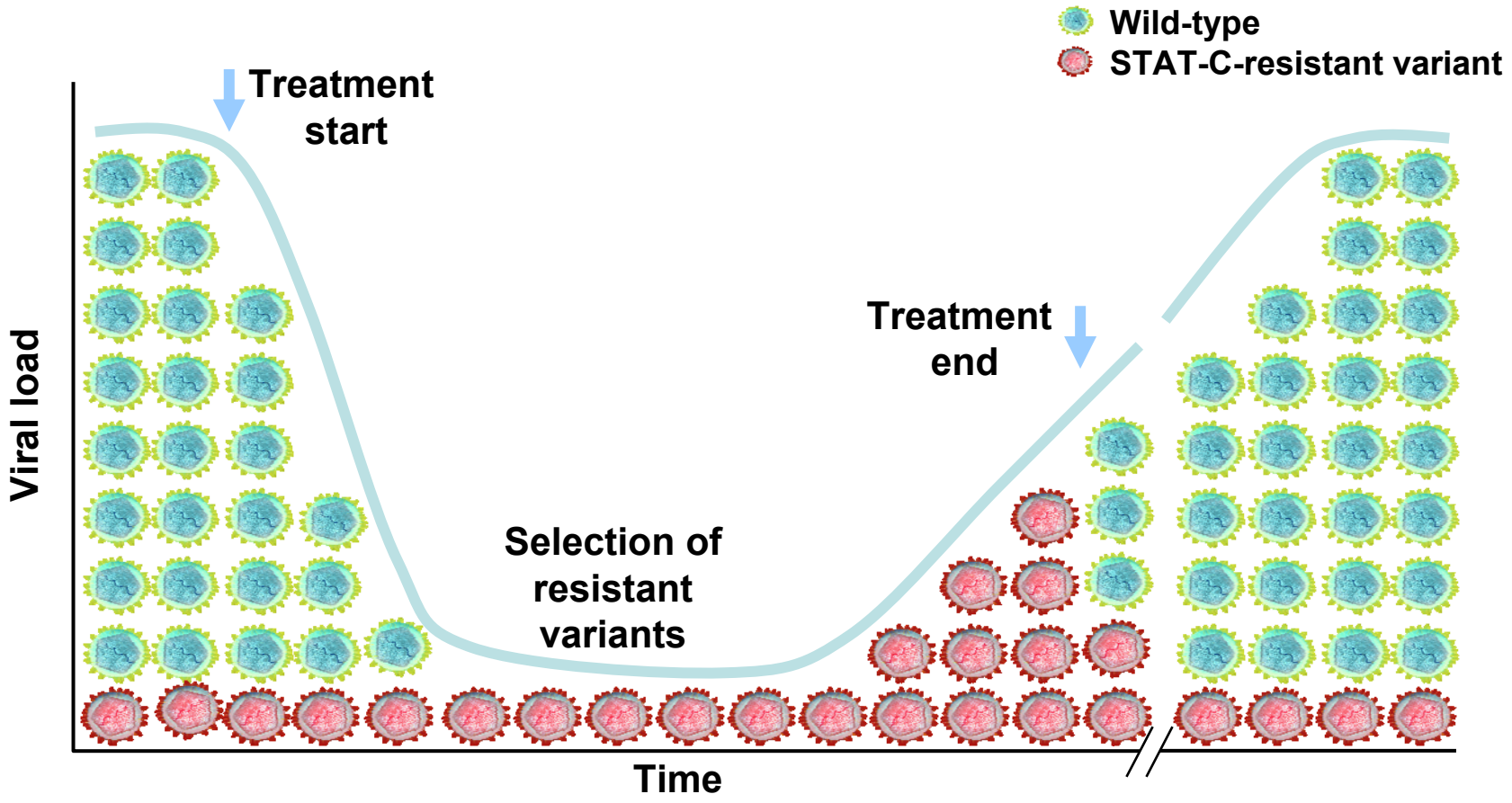






Colonno RJ, Hepatology. 2006; Zefix® (lamivudine) (August 2006) . Chang TT. *J Gastroenterol Hepatol* 2004; Hepsera® (August 2006) Standrigg DN, J Hepatol. 2006; Lai CL, Hepatology. 2006

Monotherapy exerts pressure on replicating virus



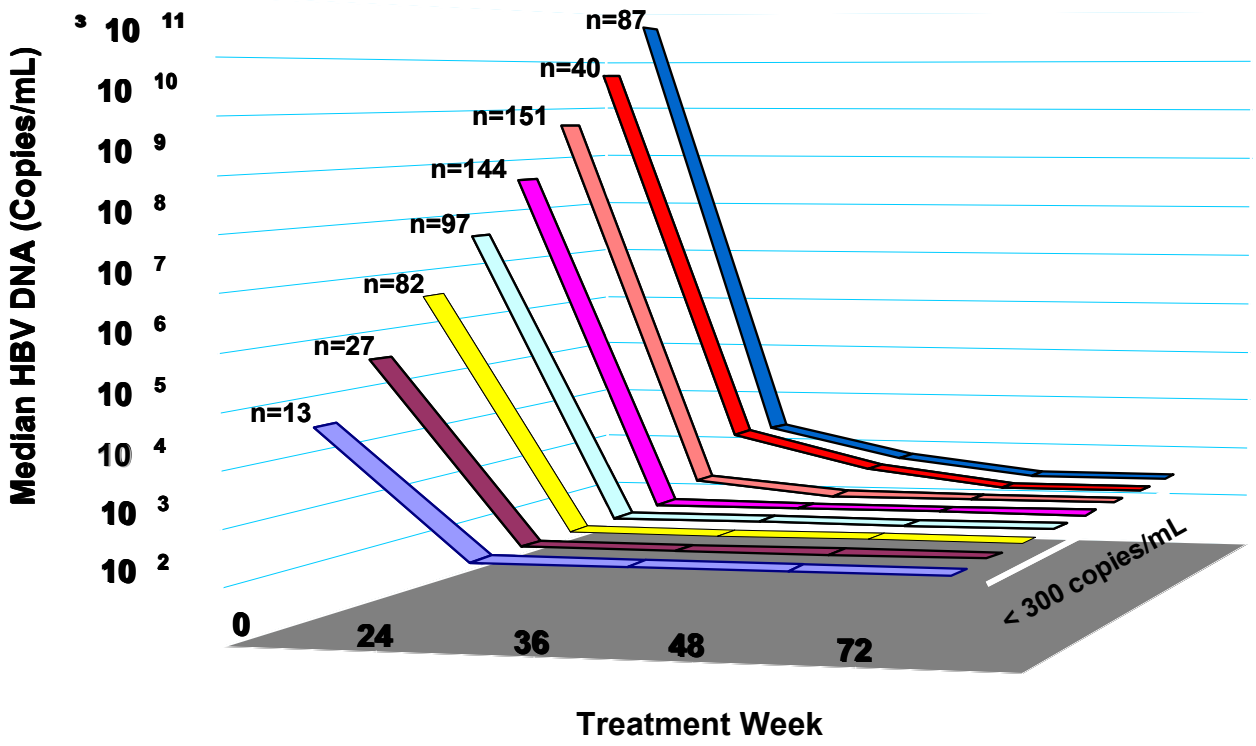
Hypothetical representation based on information from Sarrazin C, et al. *Gastroenterology* 2007;132:1767-1777; Hinrichsen H, et al. *Gastroenterology* 2004;127:1347-1355

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[1]

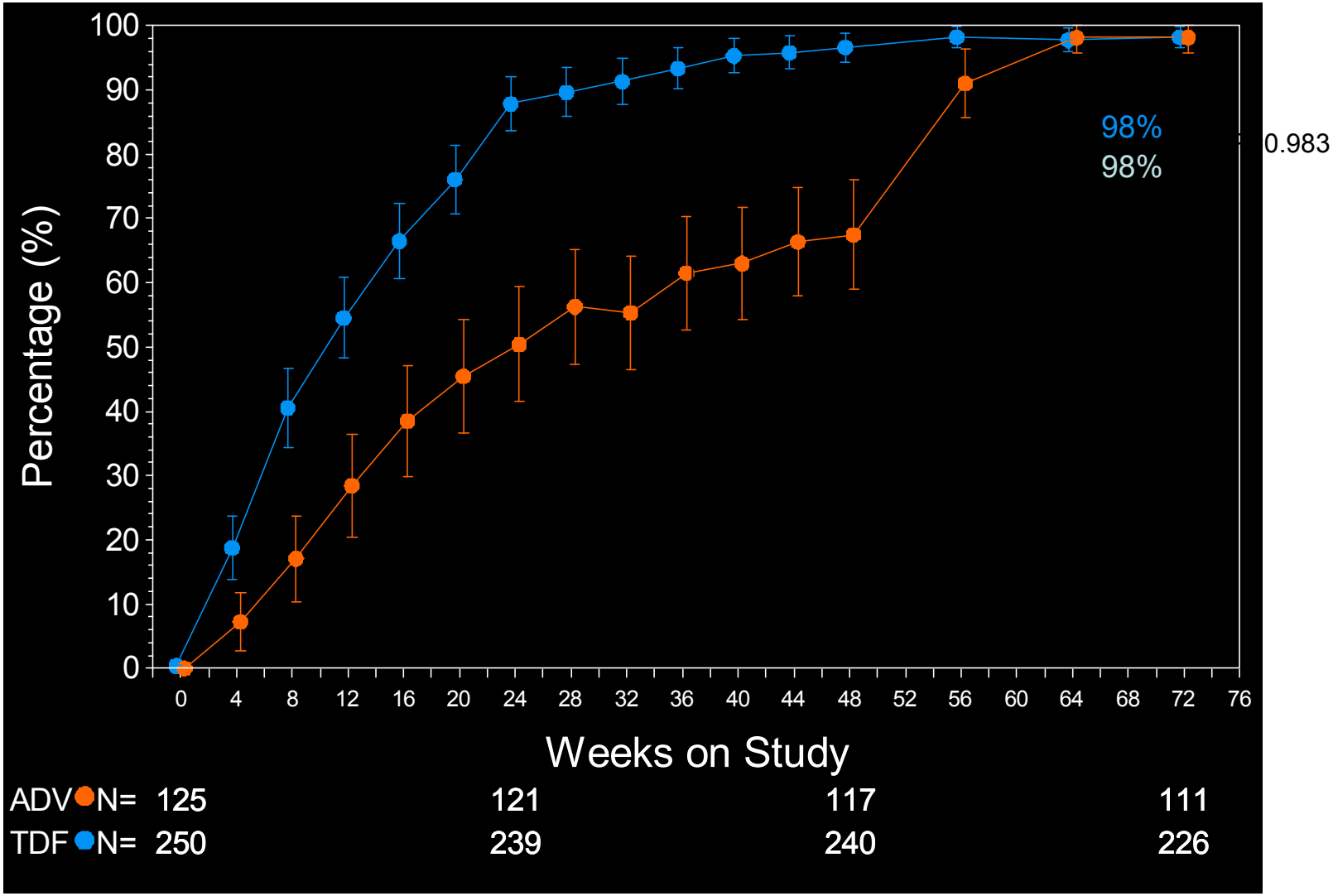
HBV DNA reductions by baseline DNA level[2]

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



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

Patients with HBV DNA <400 c/mL

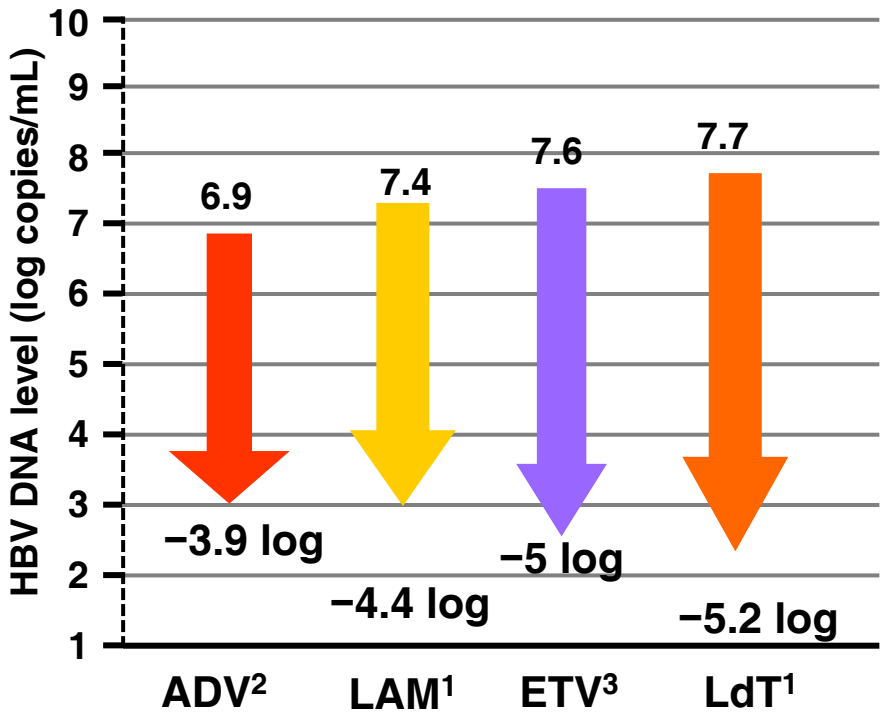


Observed Data

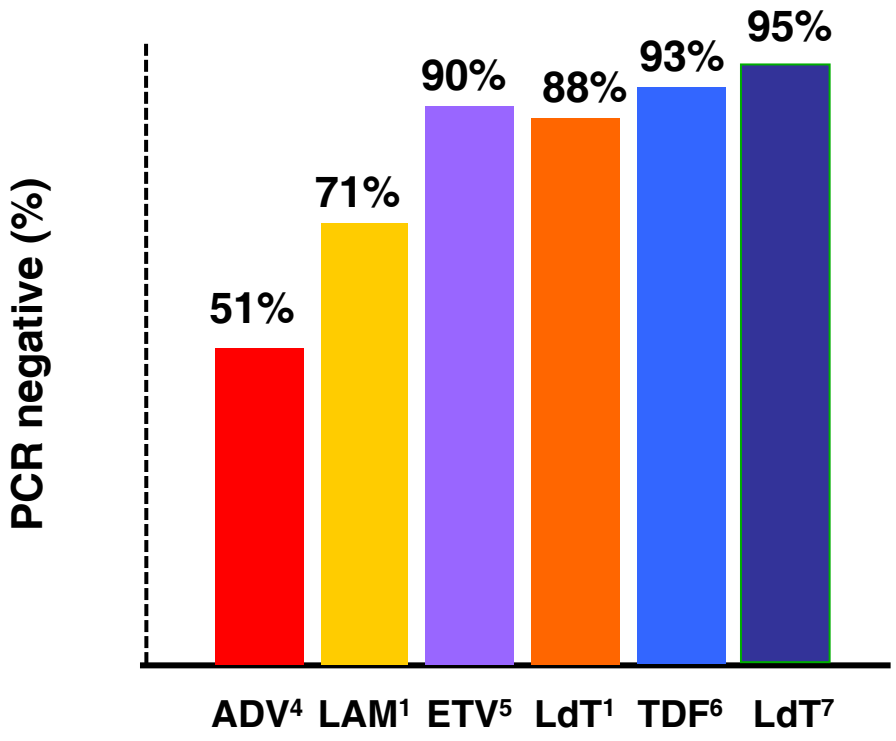
Marcellin P, et al. 43rd EASL; Milan, Italy; April 23-27, 2008. Abstract 57.

Efficacy Varies among Nucleos(t)ide Analogs

HBV DNA mean reduction at 1 year
HBeAg-negative patients



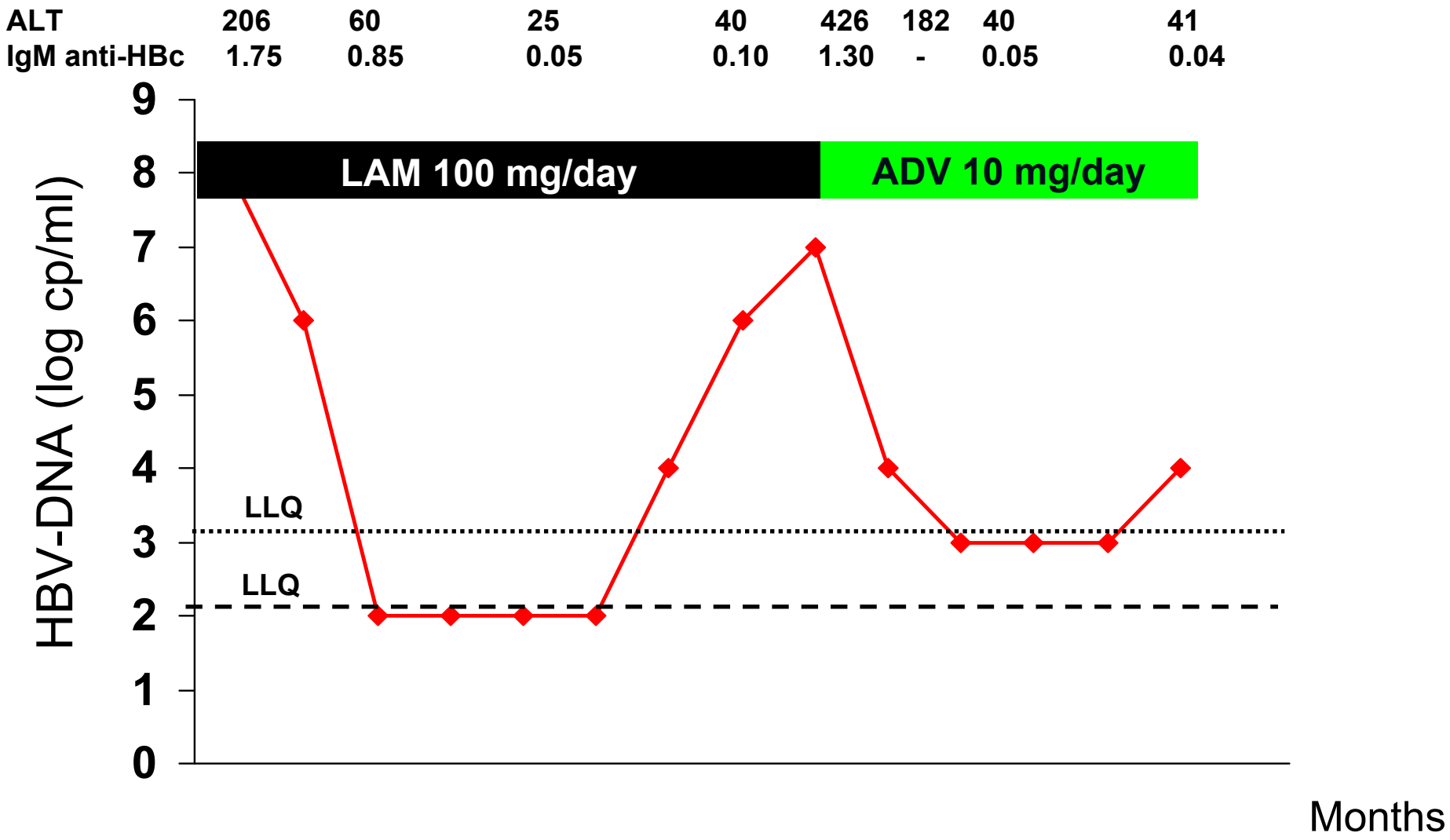
HBV DNA PCR negativity at 1 year
HBeAg-negative patients



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

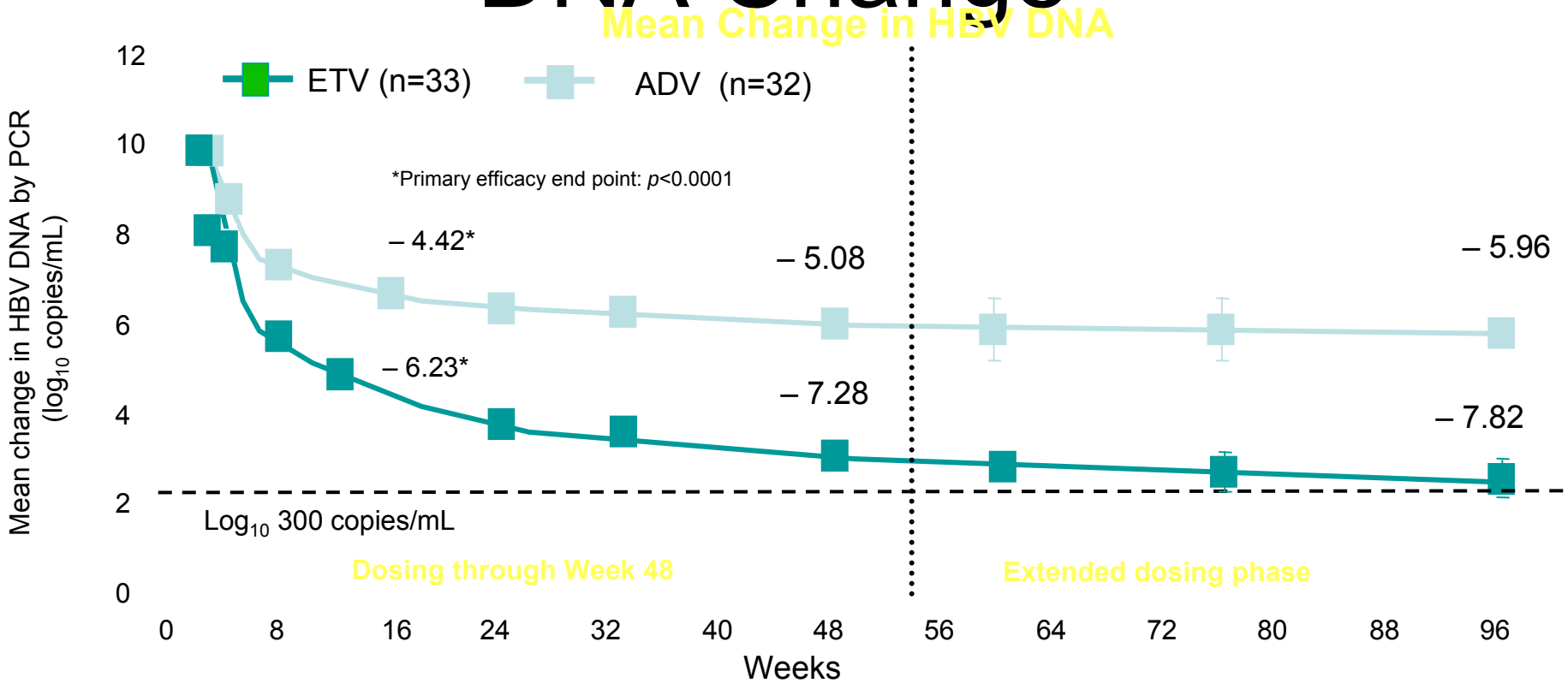



SOGNI D'ORO, E CERCA
DI NON FARTI
PRENDERE
DAL PANICO.
AUTAN.



O.DONNELL

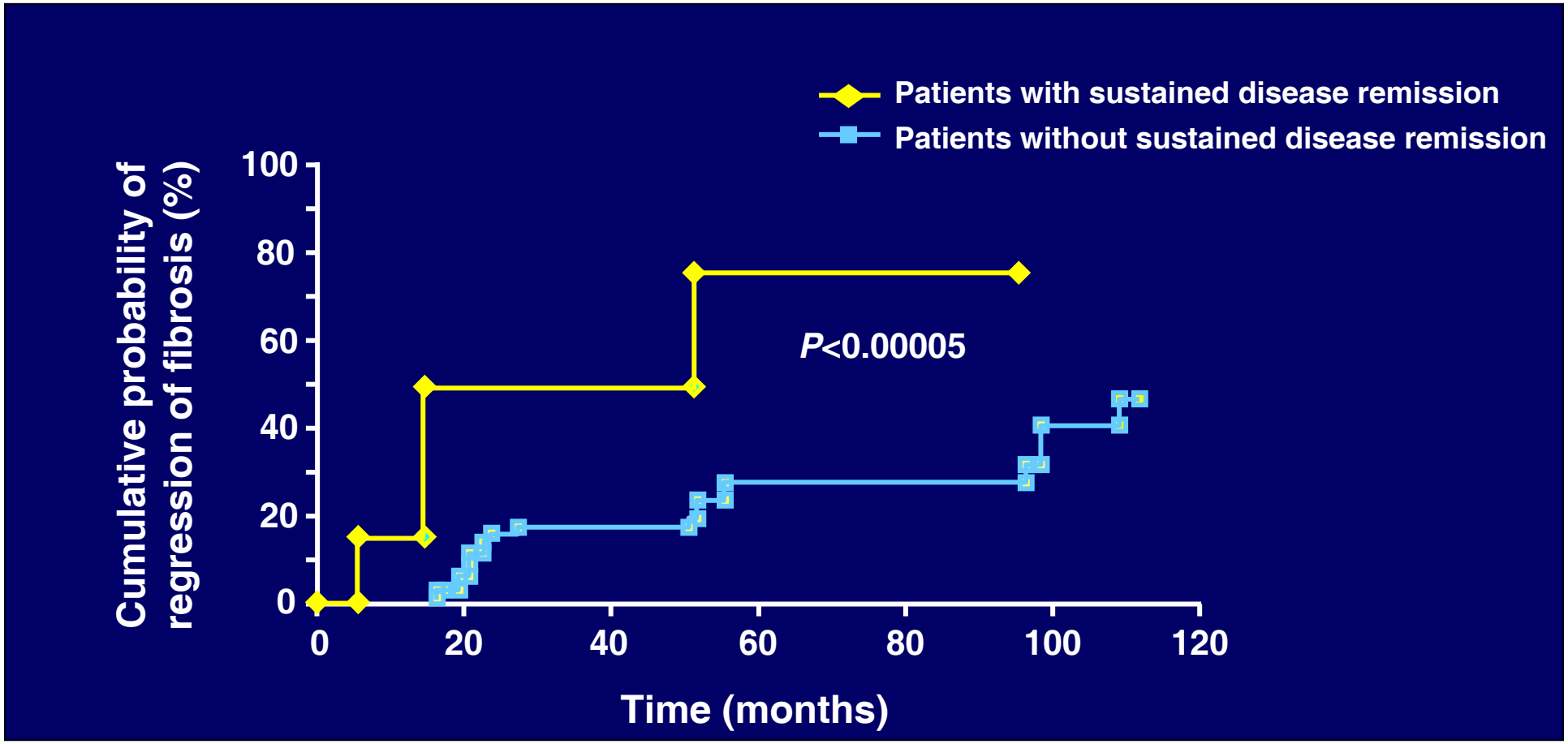
E.A.R.L.Y. Study: Mean HBV DNA Change



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

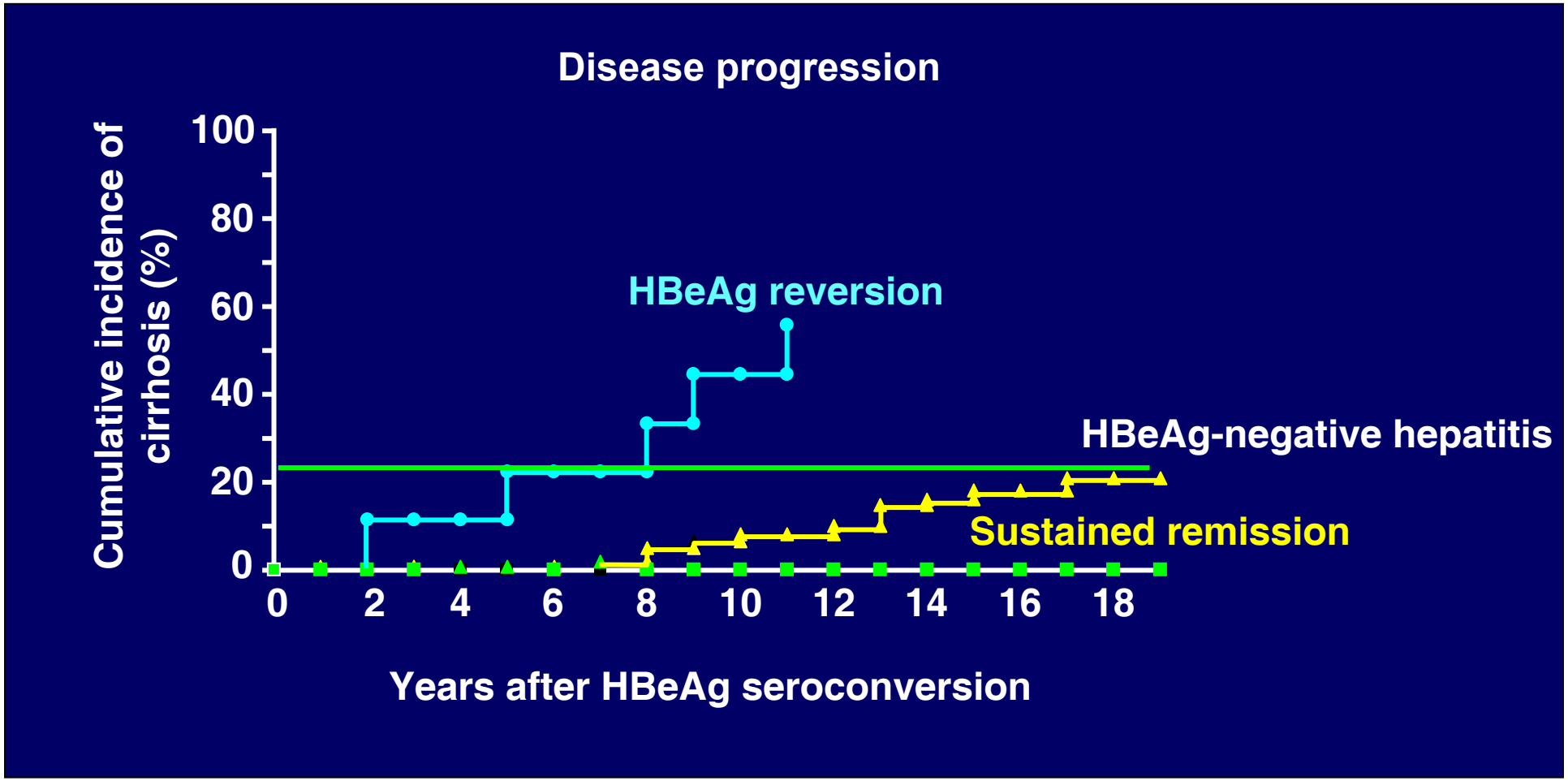
Leung N, et al. 43rd EASL; Milan, Italy; April 23-27, 2008. Abstract 998.

Spontaneous HBeAg seroconversion: reduces fibrosis progression



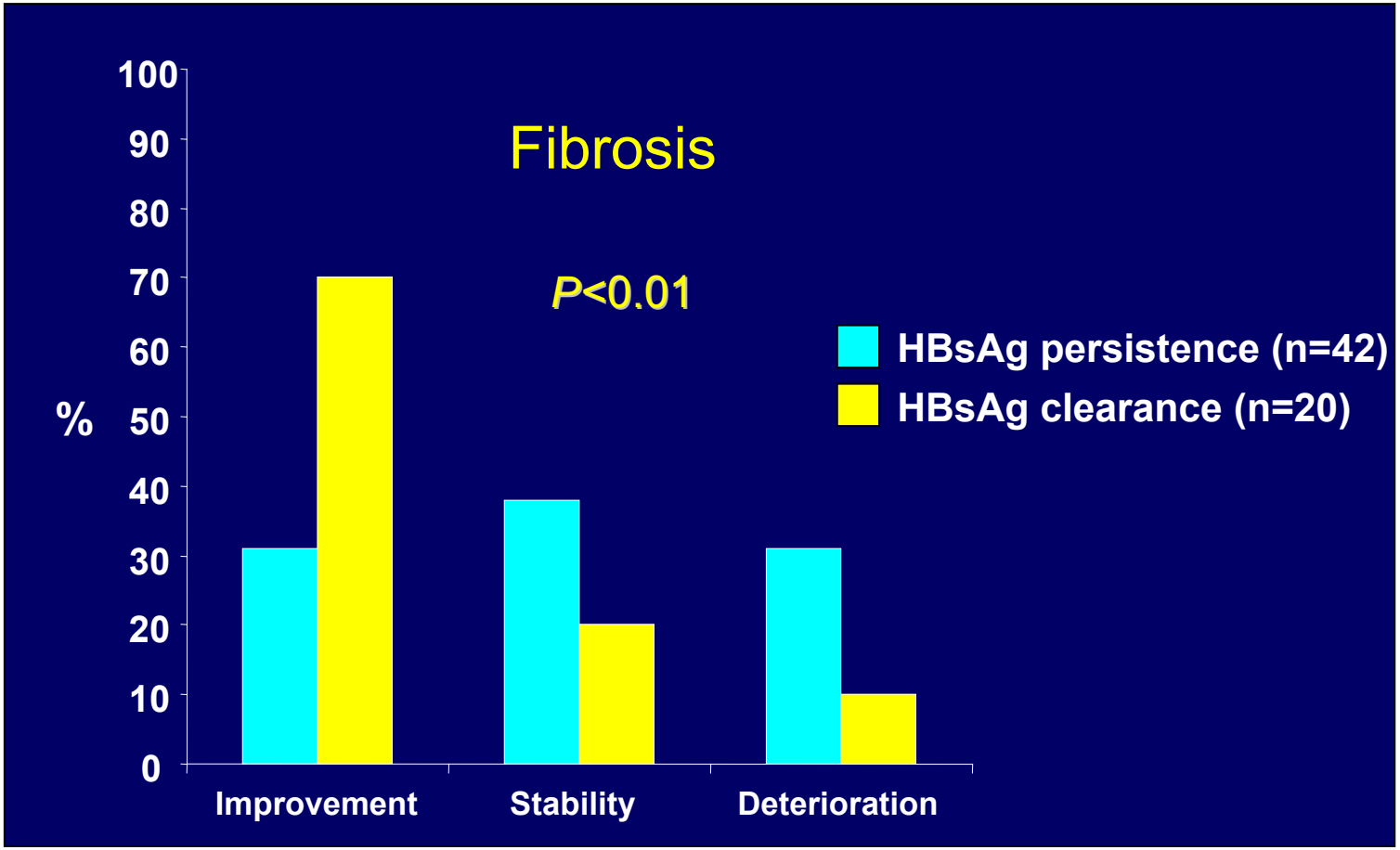
Hui et al. *Hepatology* 2007

Spontaneous HBeAg seroconversion: reduces incidence of cirrhosis



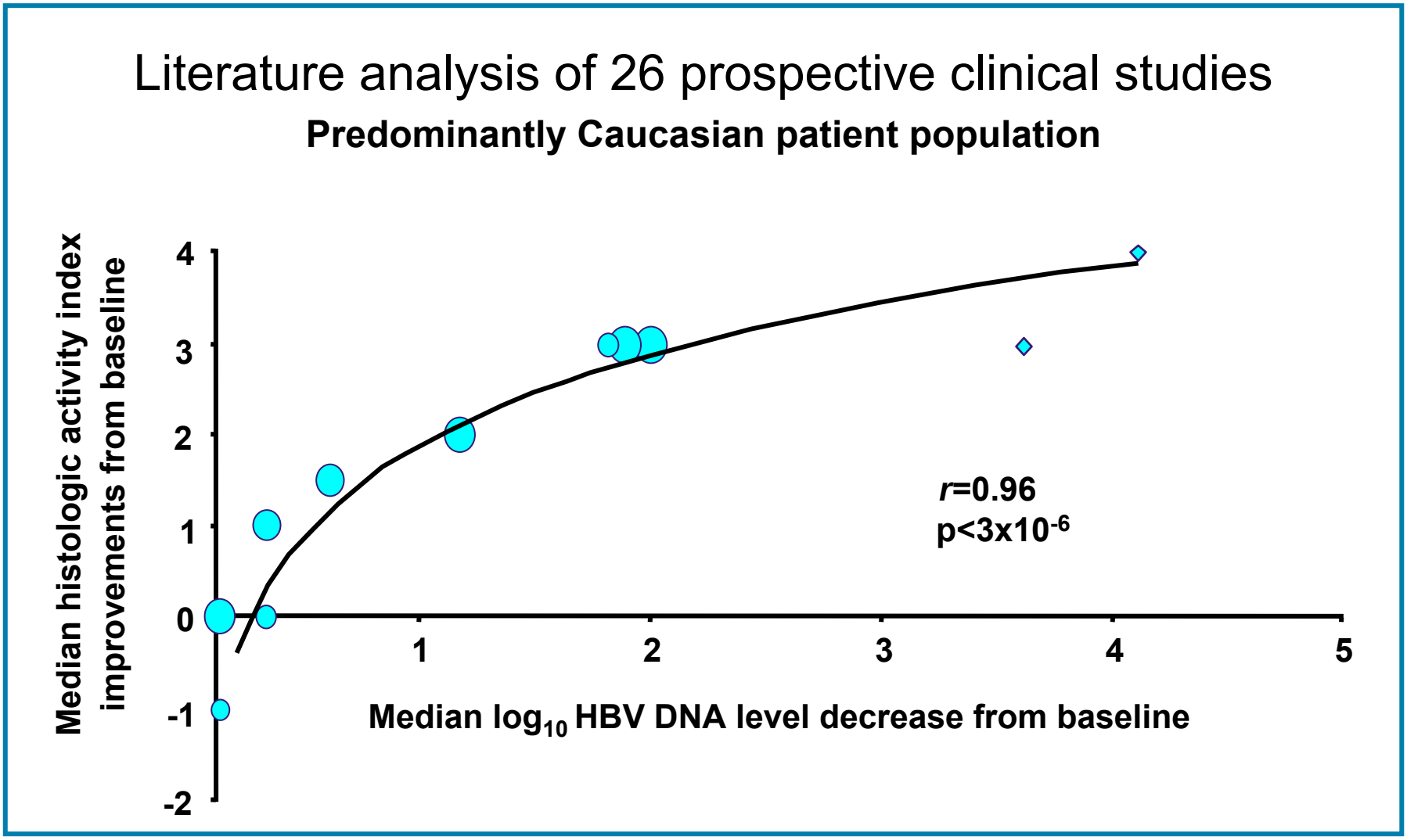
Hsu et al. *Hepatology* 2002

Histological outcome



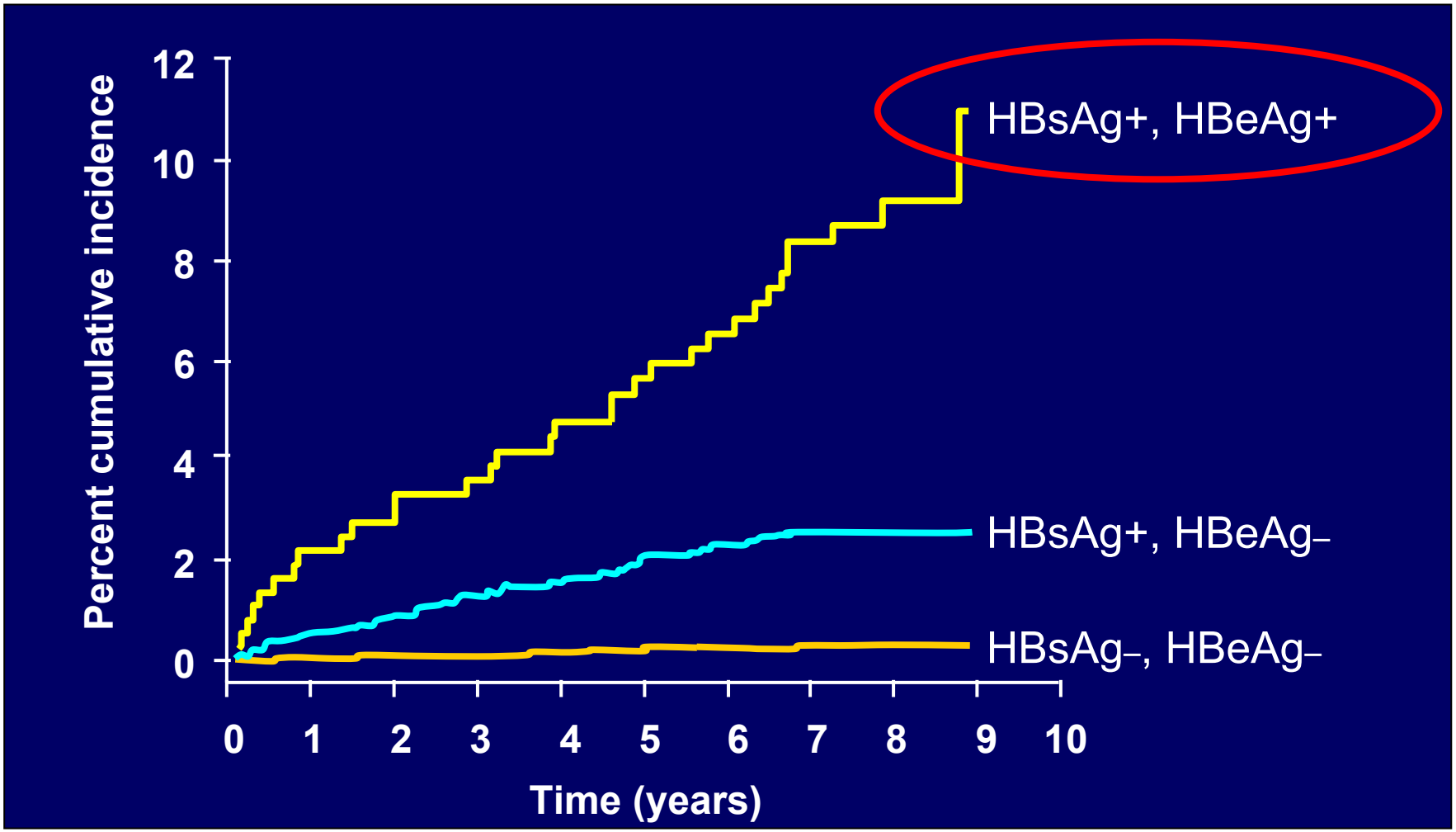
Korevaar et al. AASLD 2007

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



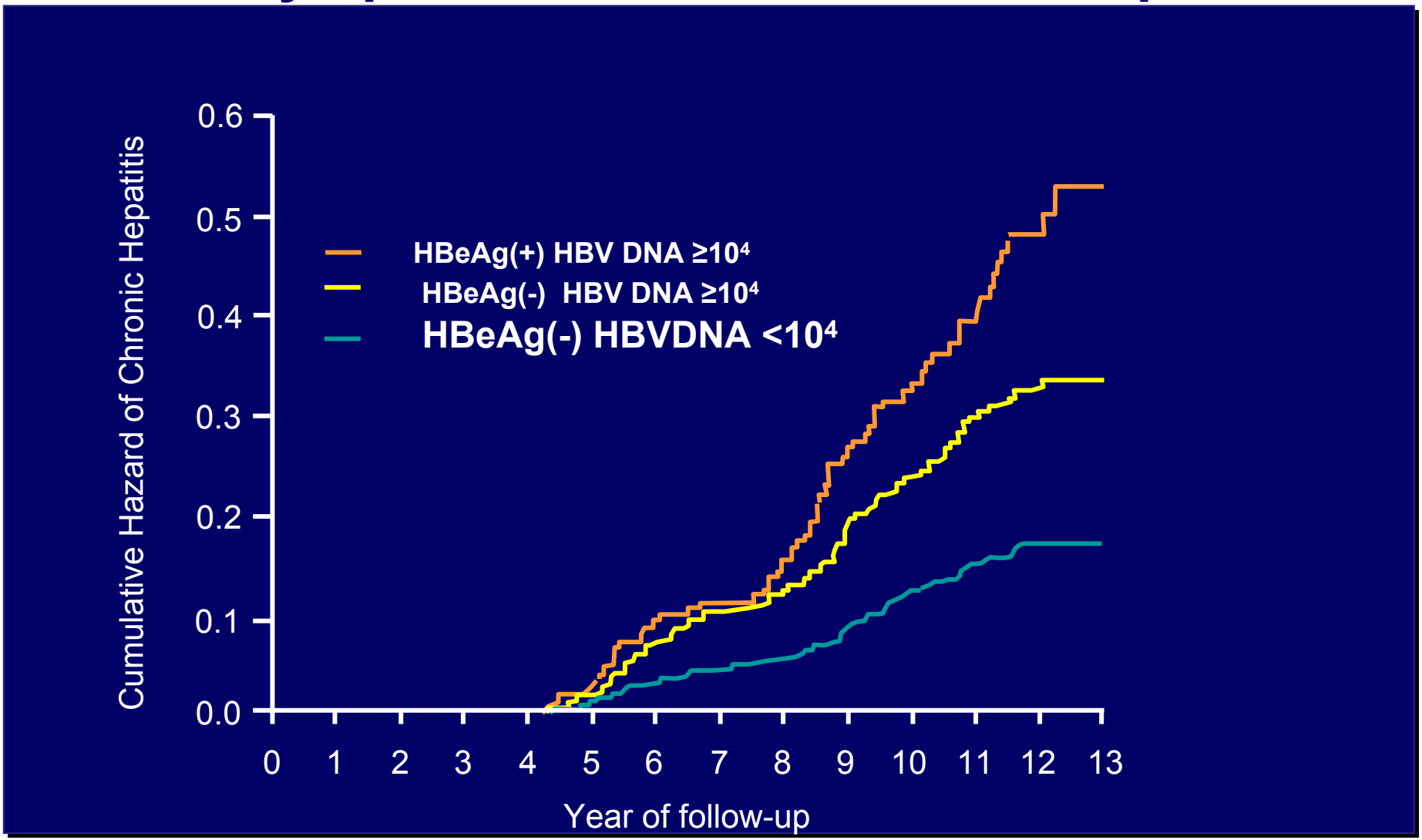
Mommeja-Marin H, Hepatol 2003

Hepatitis B and risk of HCC



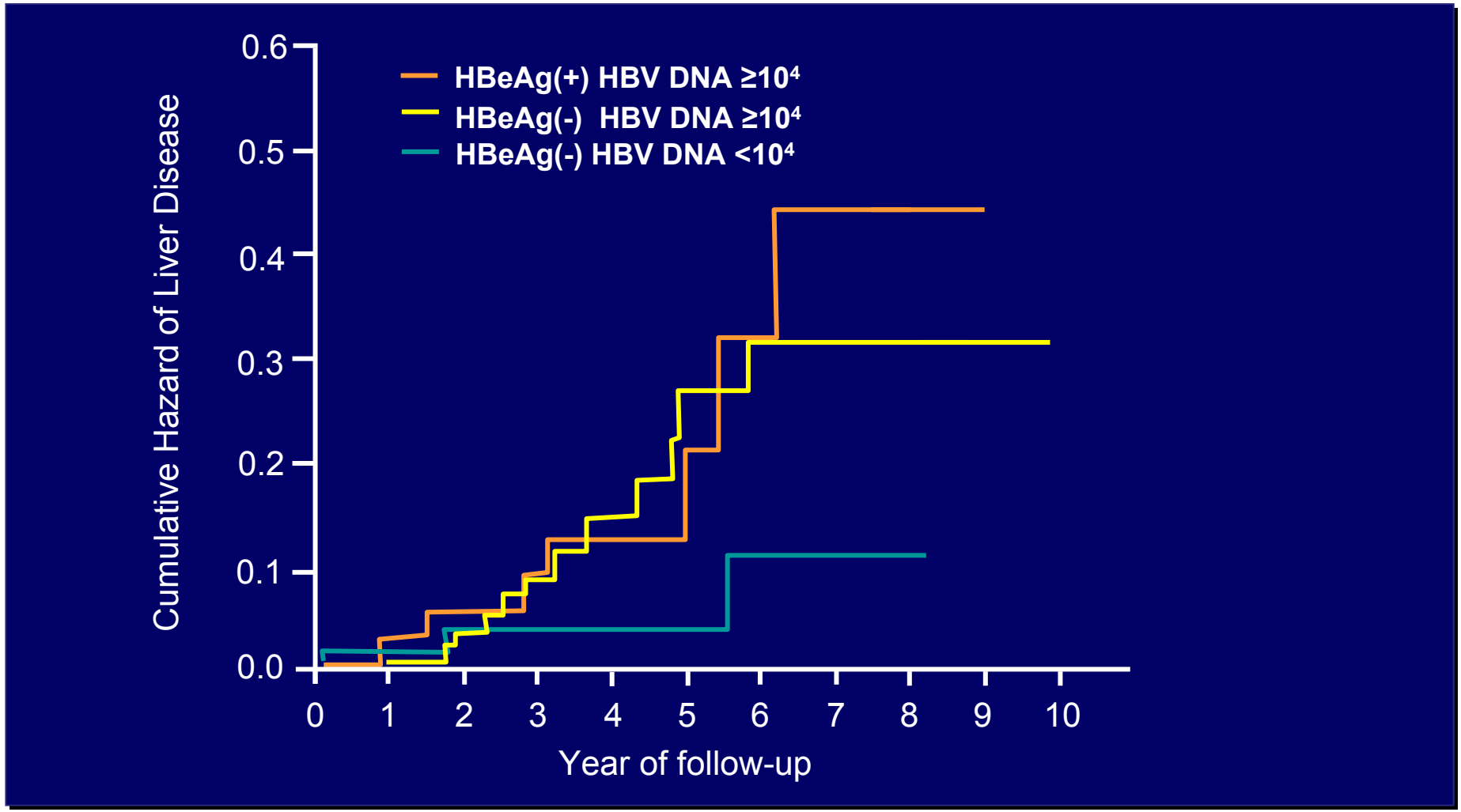
Yang *NEJM* 2002

Cumulative Hazards of Progression from Asymptomatic CHB to Chronic Hepatitis



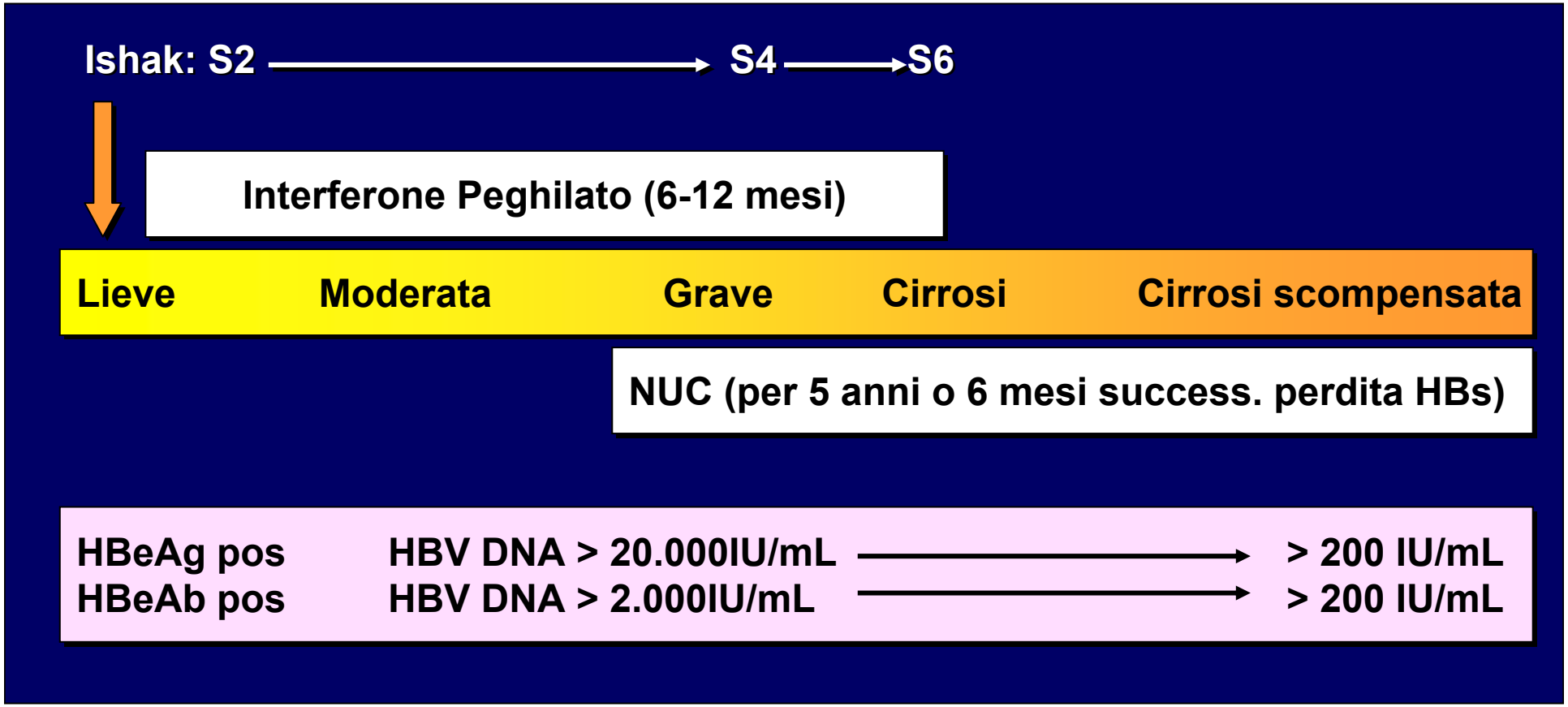
Chen JD, et al. 43rd EASL; Milan, Italy; April 23-27, 2008. Abstract 644.

Cumulative Hazards of Progression from Chronic Hepatitis to Cirrhosis



Chen JD, et al. 43rd EASL; Milan, Italy; April 23-27, 2008. Abstract 644.

Il trattamento dell'epatite cronica B
Stresa 2007



Treatment of chronic hepatitis B
Summary

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

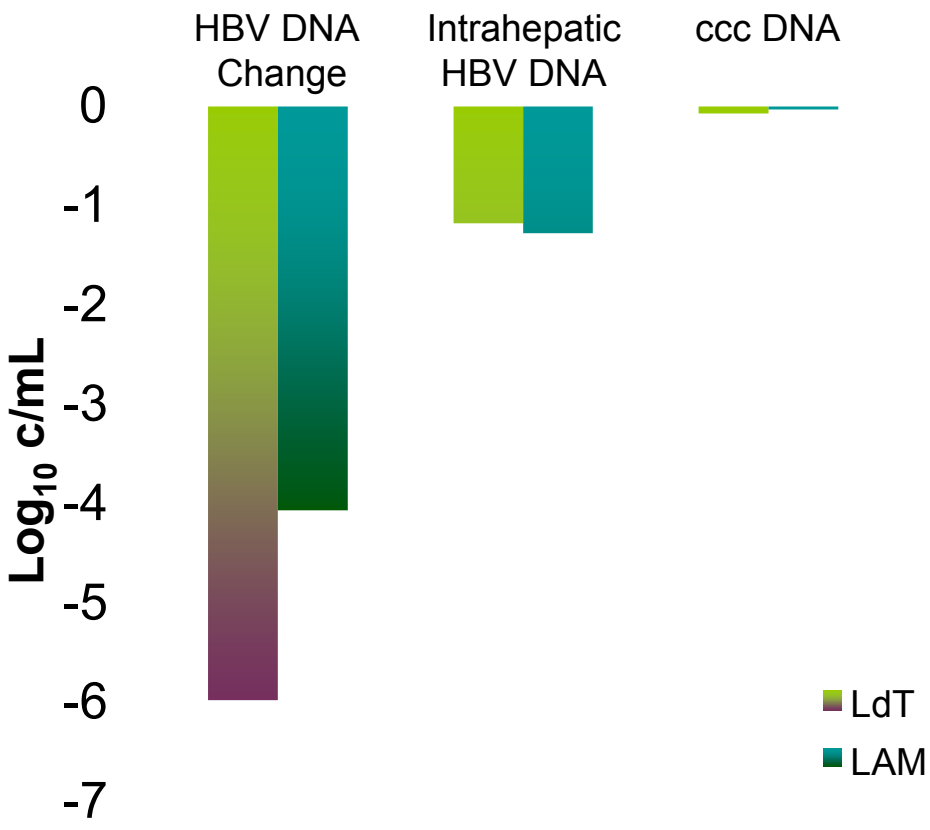
	PegInterferon	Lamivudine	Adefovir	Entecavir
Response in Yr 2				
HBe Ag+(**seroconversion**)		**12-14%***	**11%*****	
HBe Ag+ (HBV DNA neg[1])			**81%*****	
HBe Ag- (HBV DNA neg[1])	**34%°**	**71%****		
Response in Yr 5				
HBe Ag+(**seroconversion**)		**50%§**		
HBe Ag+ (HBV DNA neg[1])				
HBe Ag- (HBV DNA neg[1])			**67% §§**	

1 PCR assays

° Hepatol 2005
* NEJM 2003
** NEJM 2005
*** NEJM 2006
§ Gastroenterol 2003
§§ 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**



Wong DKH, et al. 43rd EASL; Milan, Italy; April 23-27, 2008. Abstract 1002.