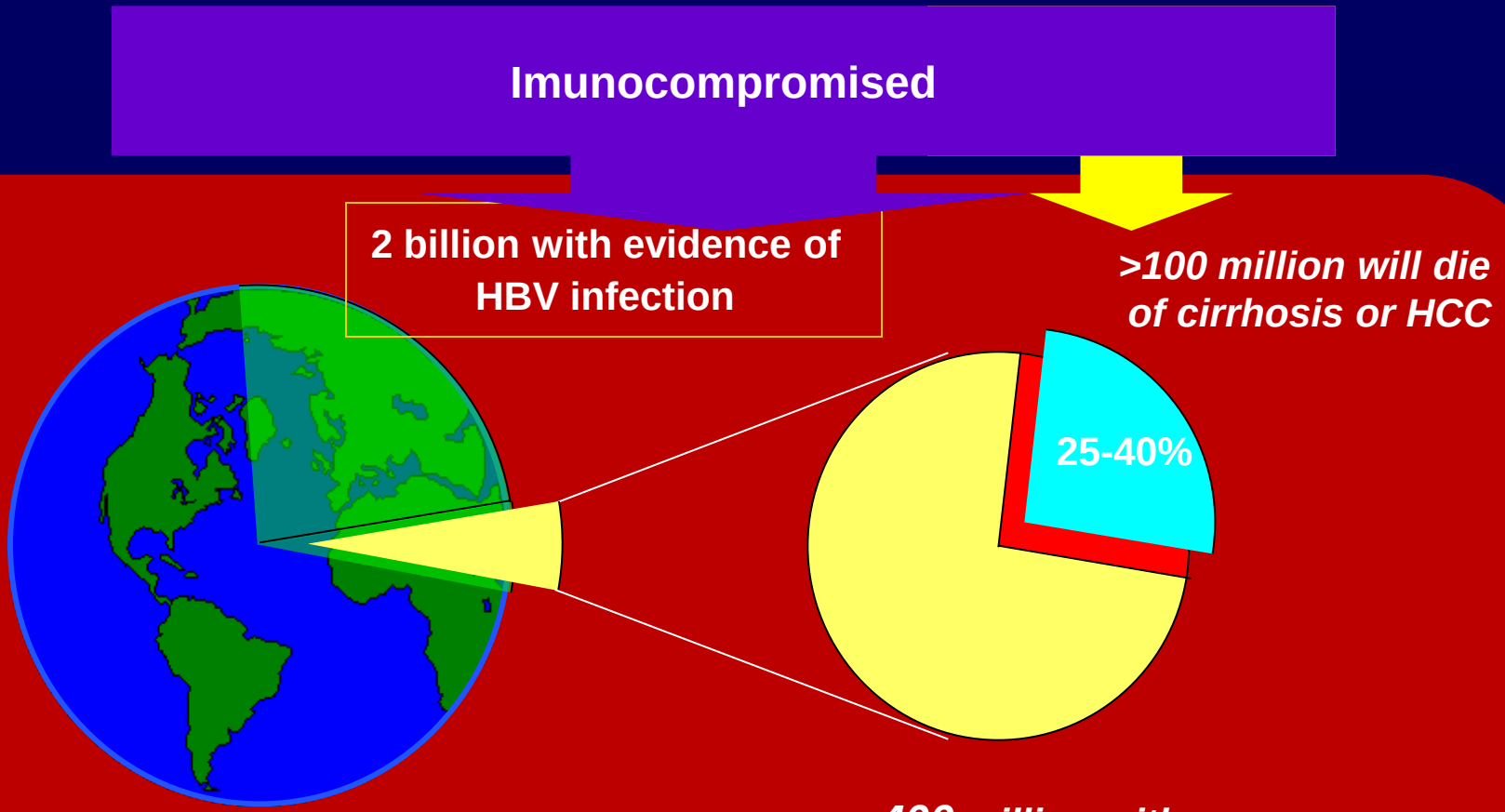
Vietri sul mare 16-17 marzo 2016

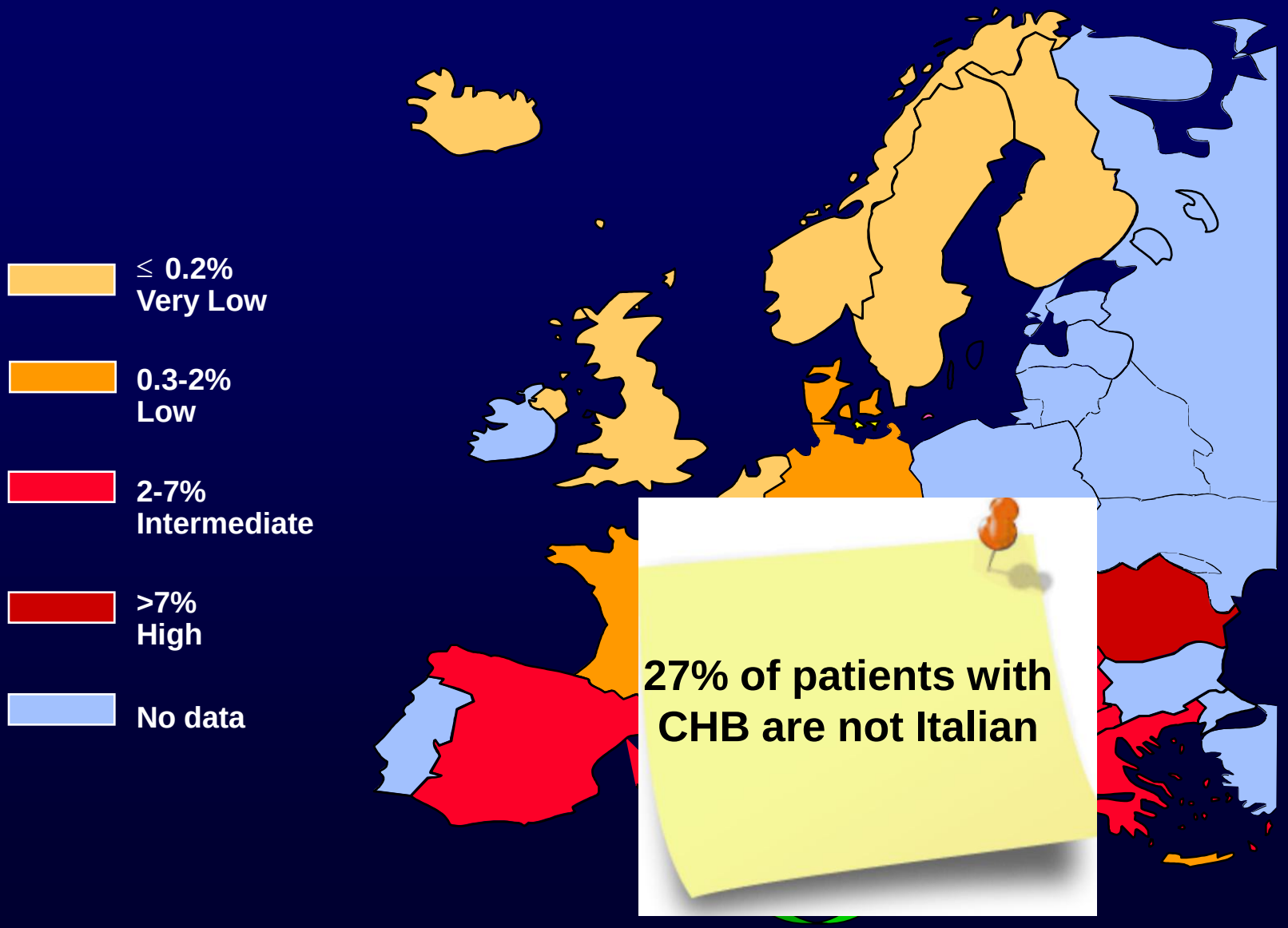
Patogenesi e storia naturale dell'epatite B

Mauro Viganò
Unità Epatologia
Ospedale San Giuseppe
Università di Milano

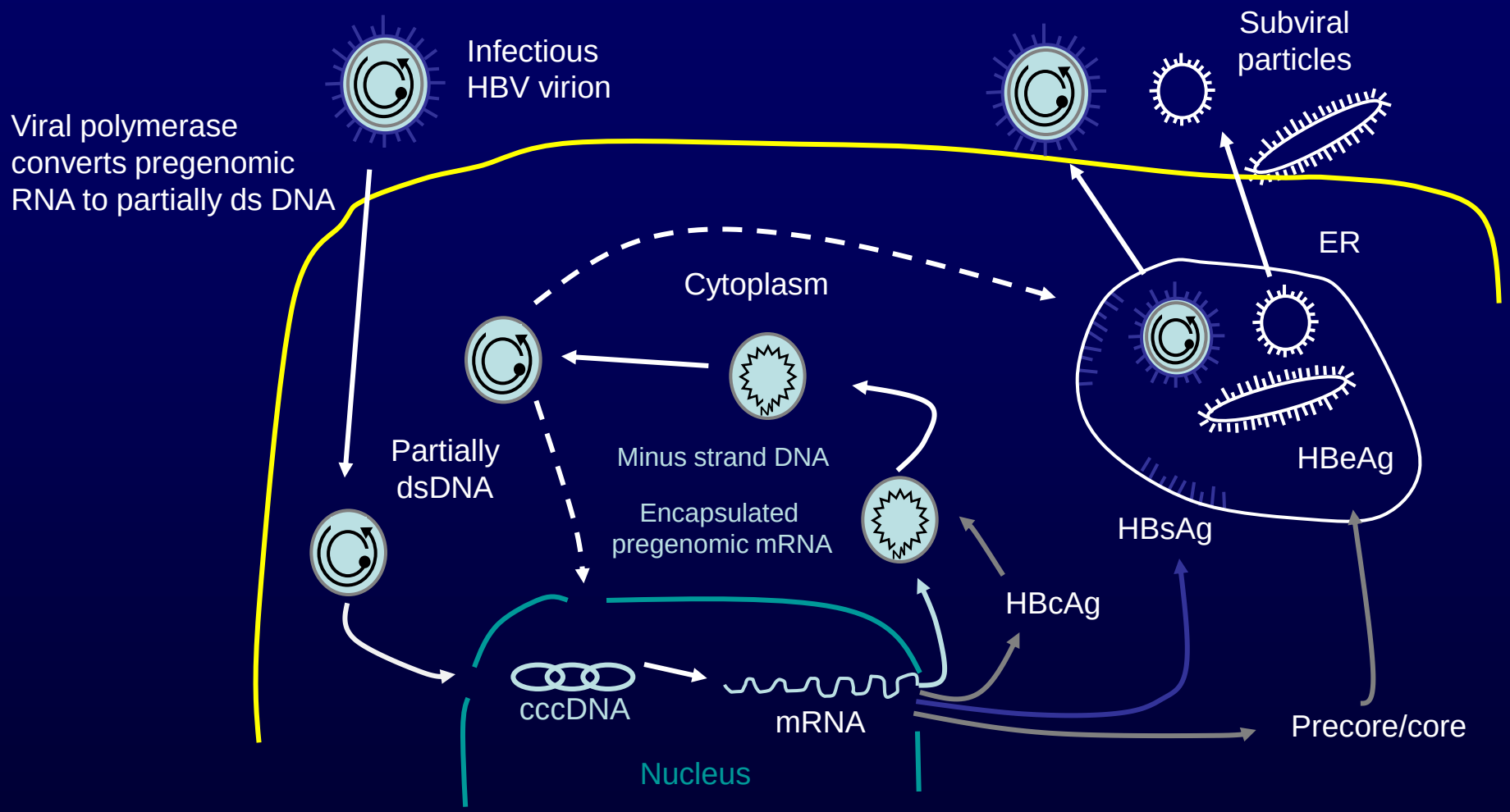
Global Impact of HBV Infection



Prevalence of HBsAg positivity in Europe



Life Cycle of HBV in the Hepatocyte

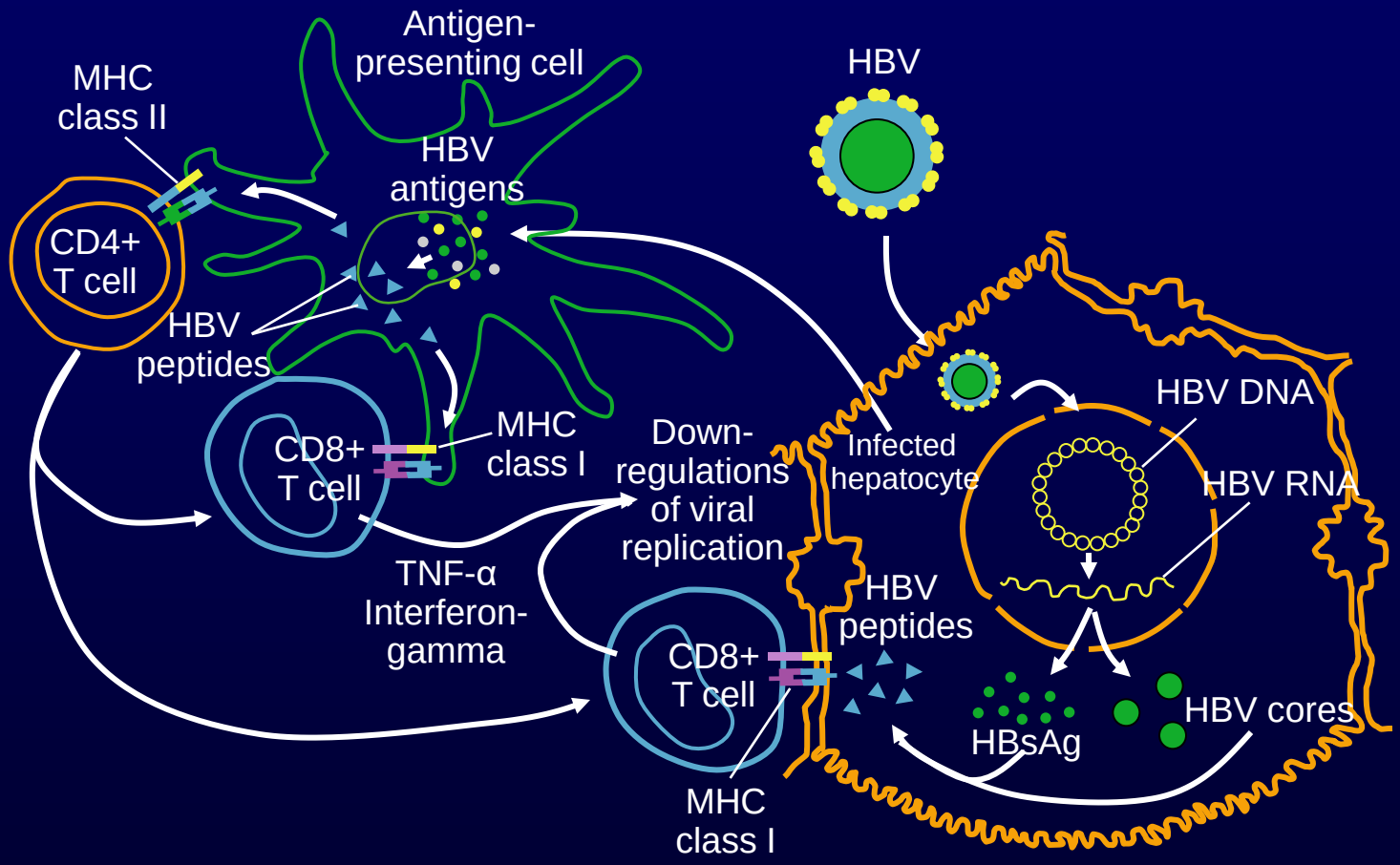


Viral DNA is integrated into host cell genome

(hepatocarcinogenesis)

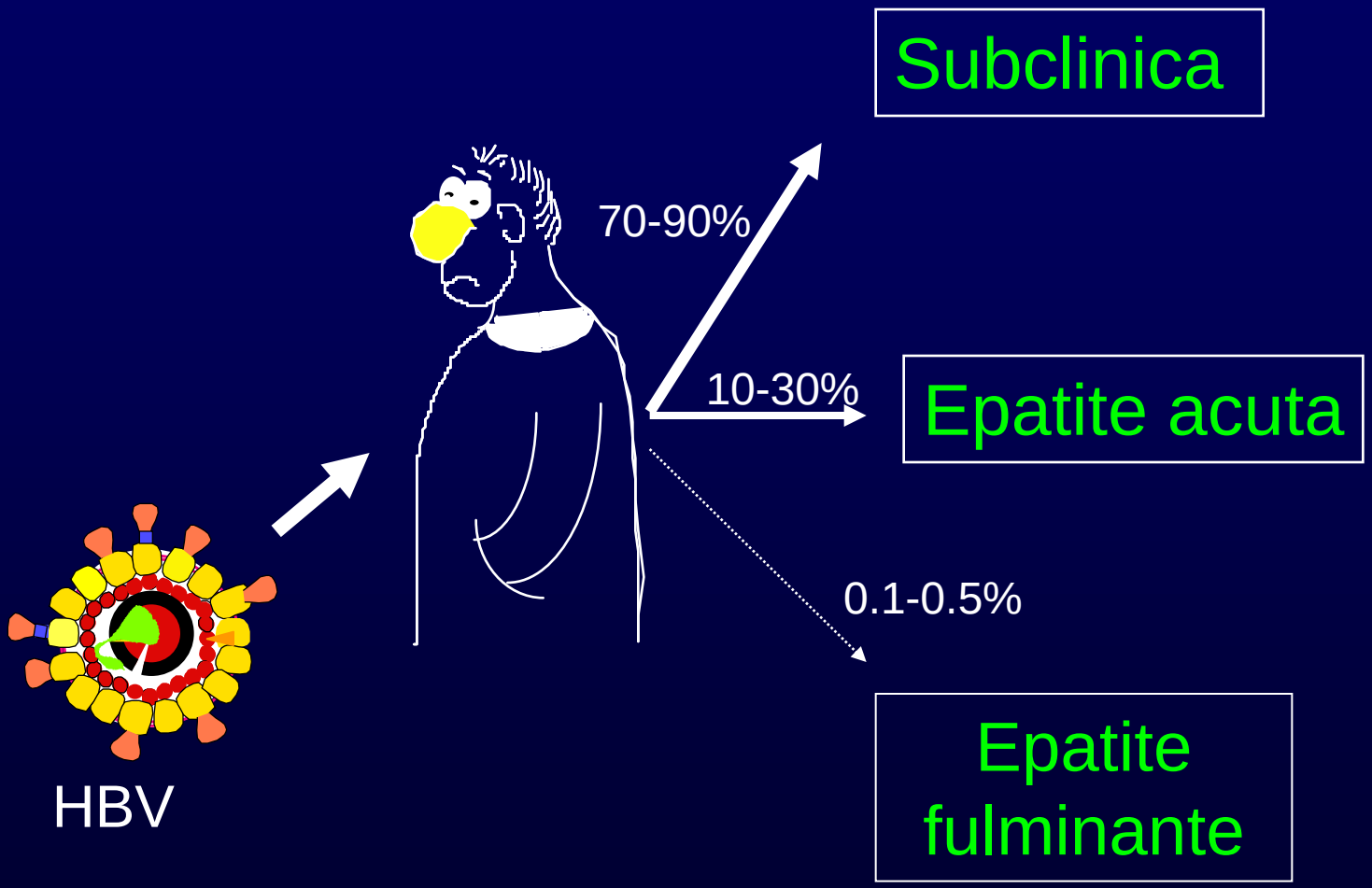
Lai CL, et al. J Med Virol. 2000;61:367-373.

HBV-Triggered Immune Response

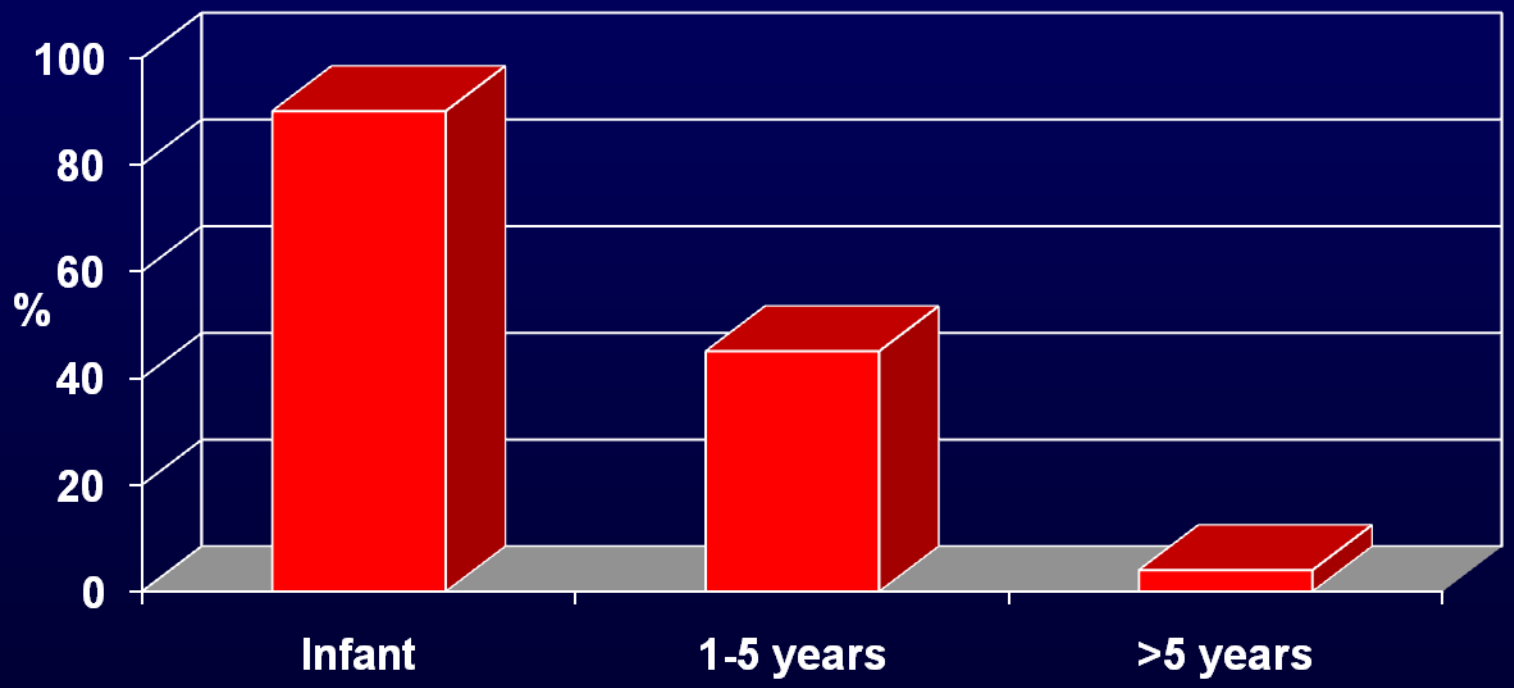


Ganem D, et al. N Engl J Med. 2004;350:1118-1129.

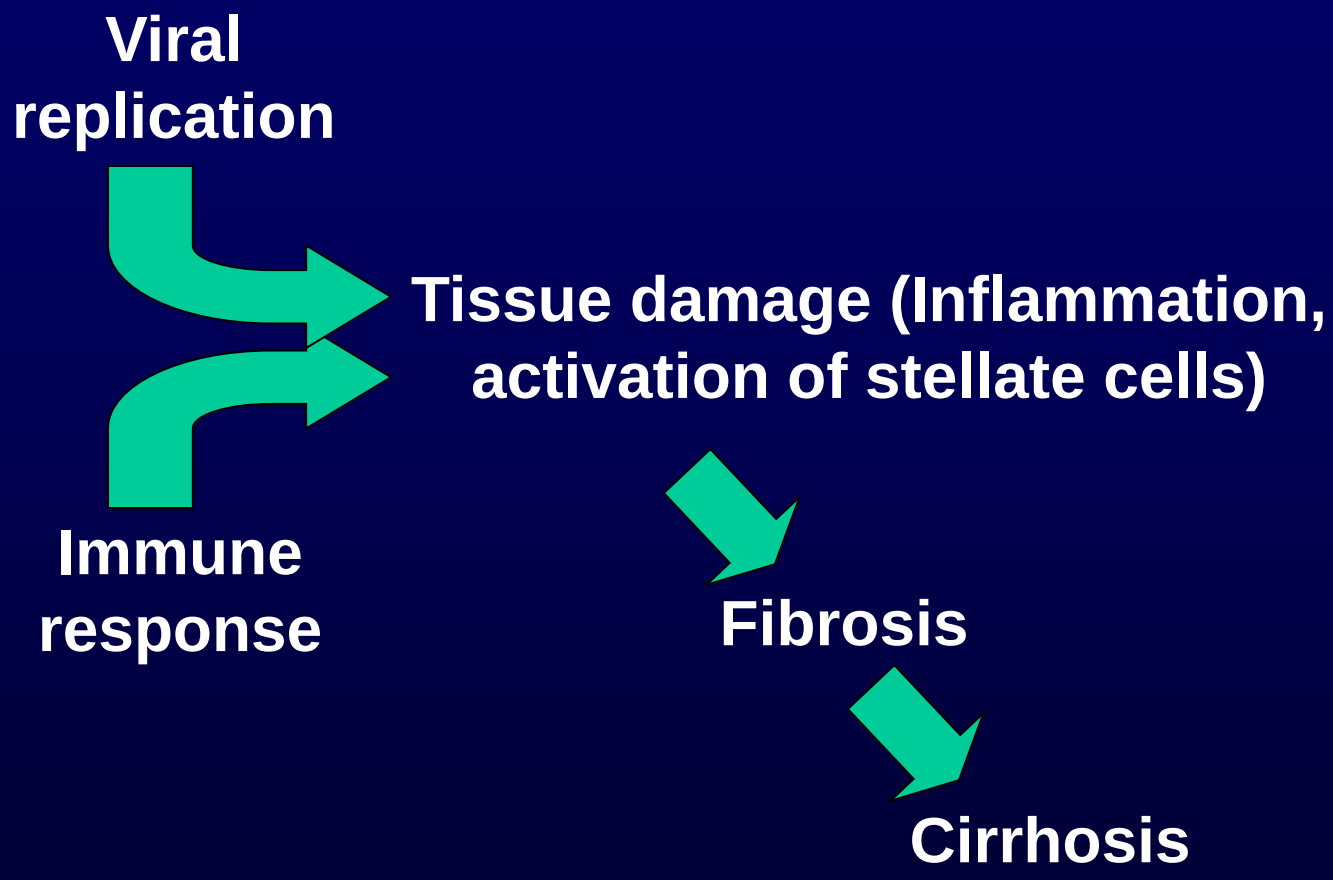
Infezione primaria da HBV



Risk of Developing Chronic Hepatitis B by Age at Infection

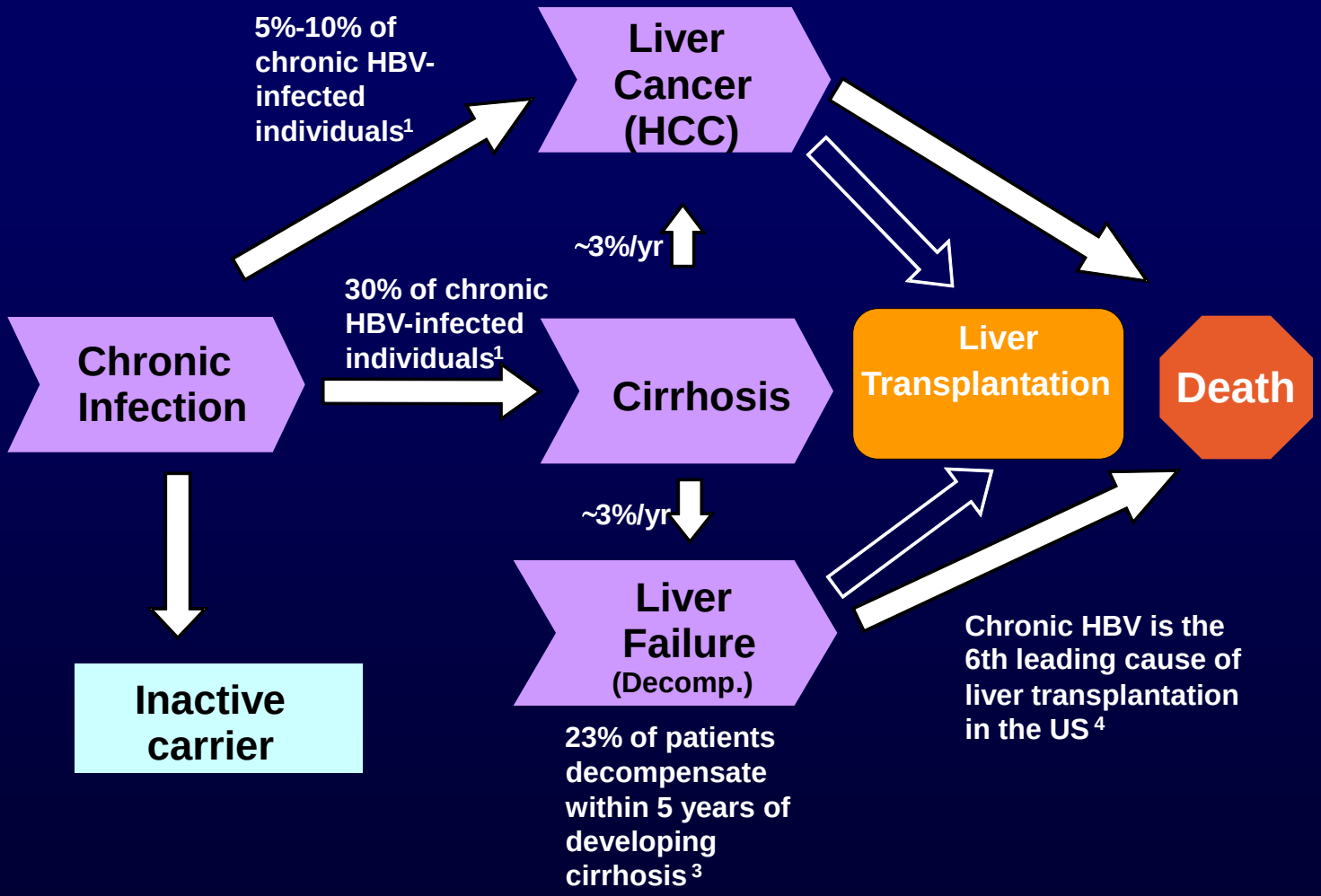


Chronic viral hepatitis B: pathogenesis



Bataller R & Brenner DA. J Clin Invest. 2005;115:209-18. Iredale JP. J Clin Invest. 2007;117:539-48. Hepatitis B Virus (2nd edition), 2008; pp10.9-10.15. Edited by Lai CL & Locarnini S. London: International Medical Press

Natural history of HBV Infection



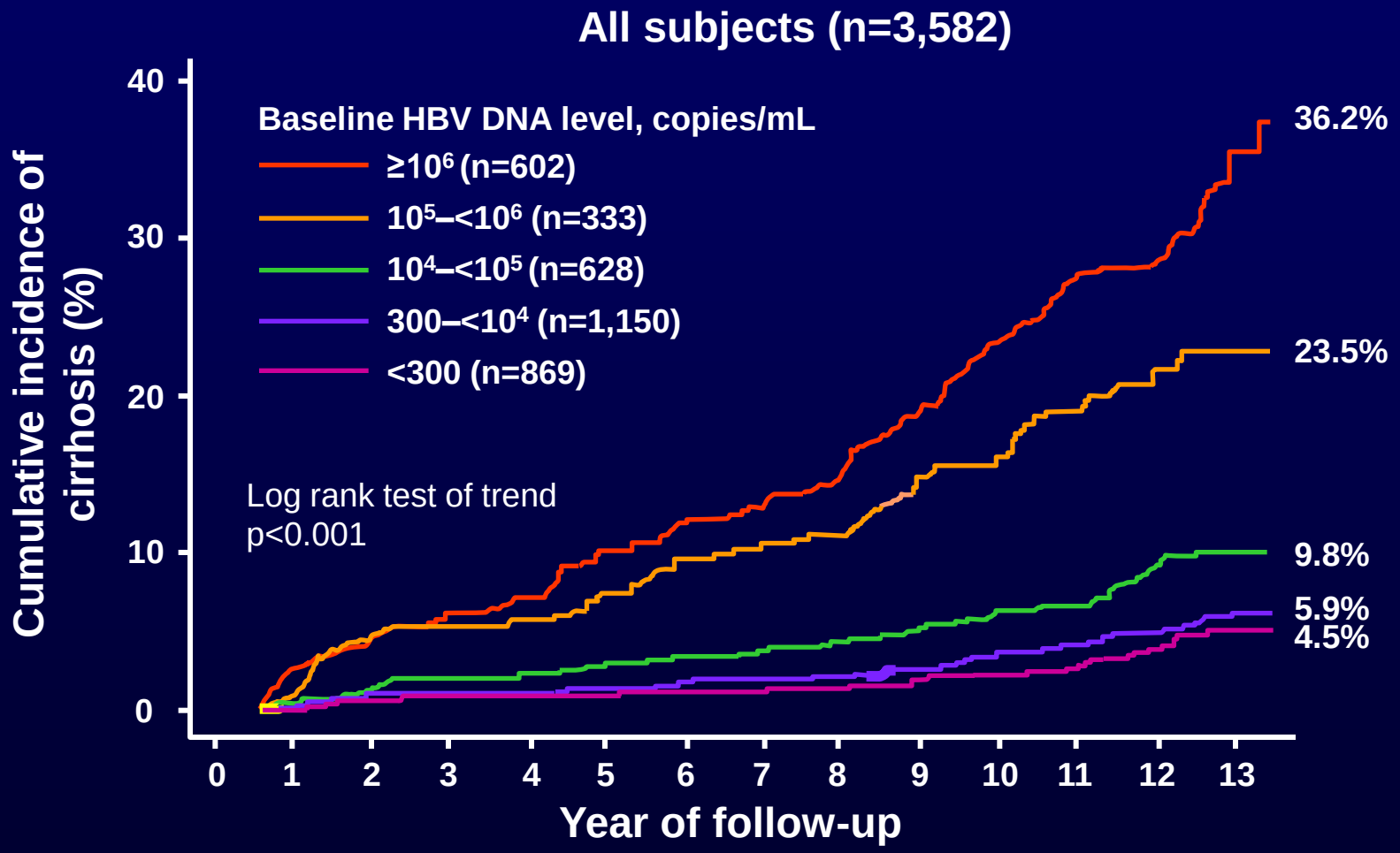
1. Torresi, J, Locarnini, S. Gastroenterology. 2000
2. Fattovich, G, Giustina, G, Schalm, SW, et al. Hepatology. 1995
3. Moyer, LA, Mast, EE. Am J Prev Med. 1994
4. Perrillo, R, et al. Hepatology. 2001

Risk Factors for progression to cirrhosis or HCC in HBsAg-Positive Individuals

- Older age (>40 years)
- Male gender
- Severity of fibrosis stage at presentation (F3)
- Recurrent flares of hepatitis
- Genetic diversity
- Co-infection (HCV, HDV)
- Family history of HCC
- Race (Asian, African)
- Genotype B, C
- Precore mutation and basal core promoter mutation
- Alcohol
- Obesity, diabetes

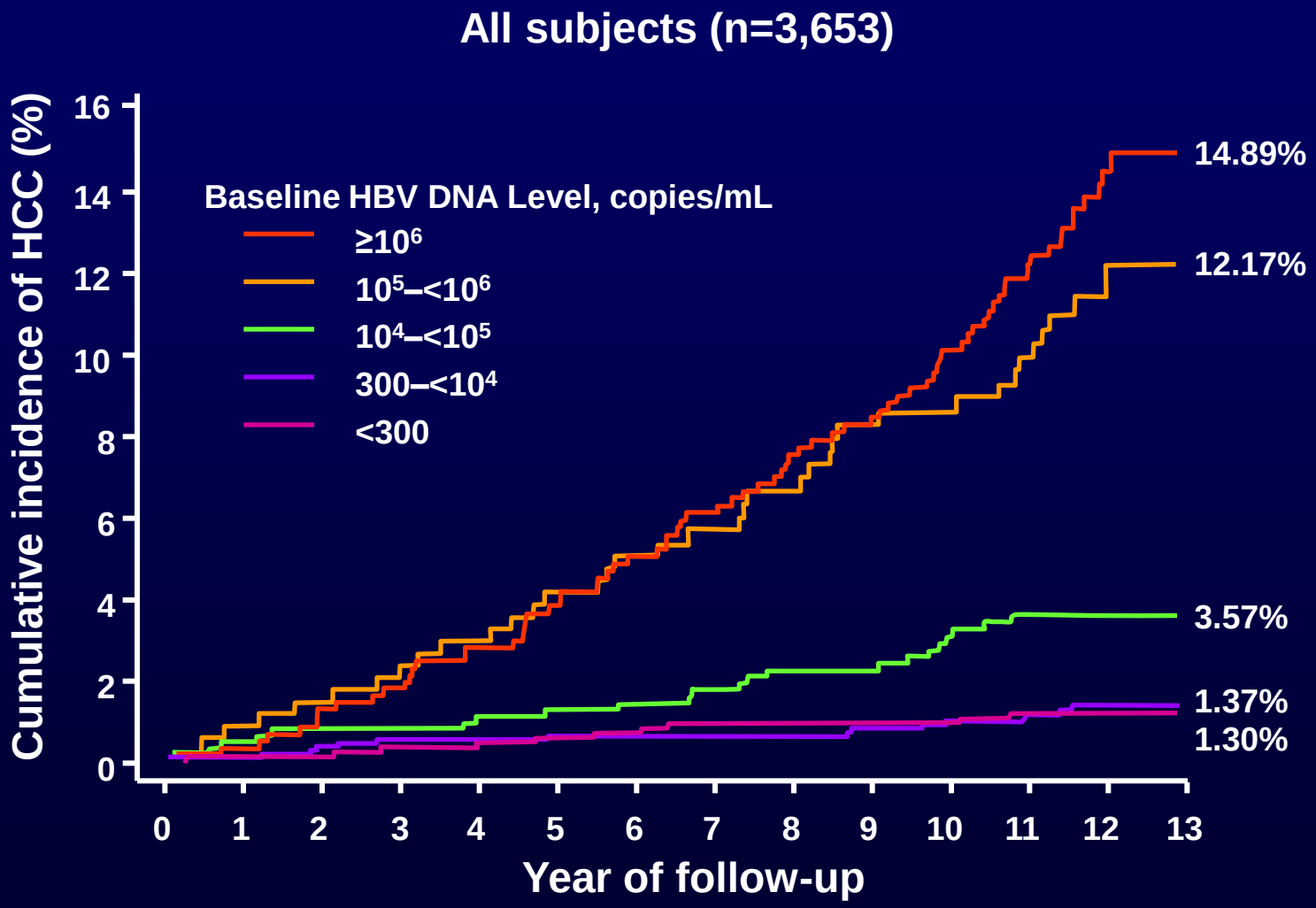
McClune AC, et al. Clin Liver Dis. 2010;14:461-476
Fattovich G., et al. J of Hepatology 2008; 48: 335-352

High viral load is associated with increased incidence of cirrhosis



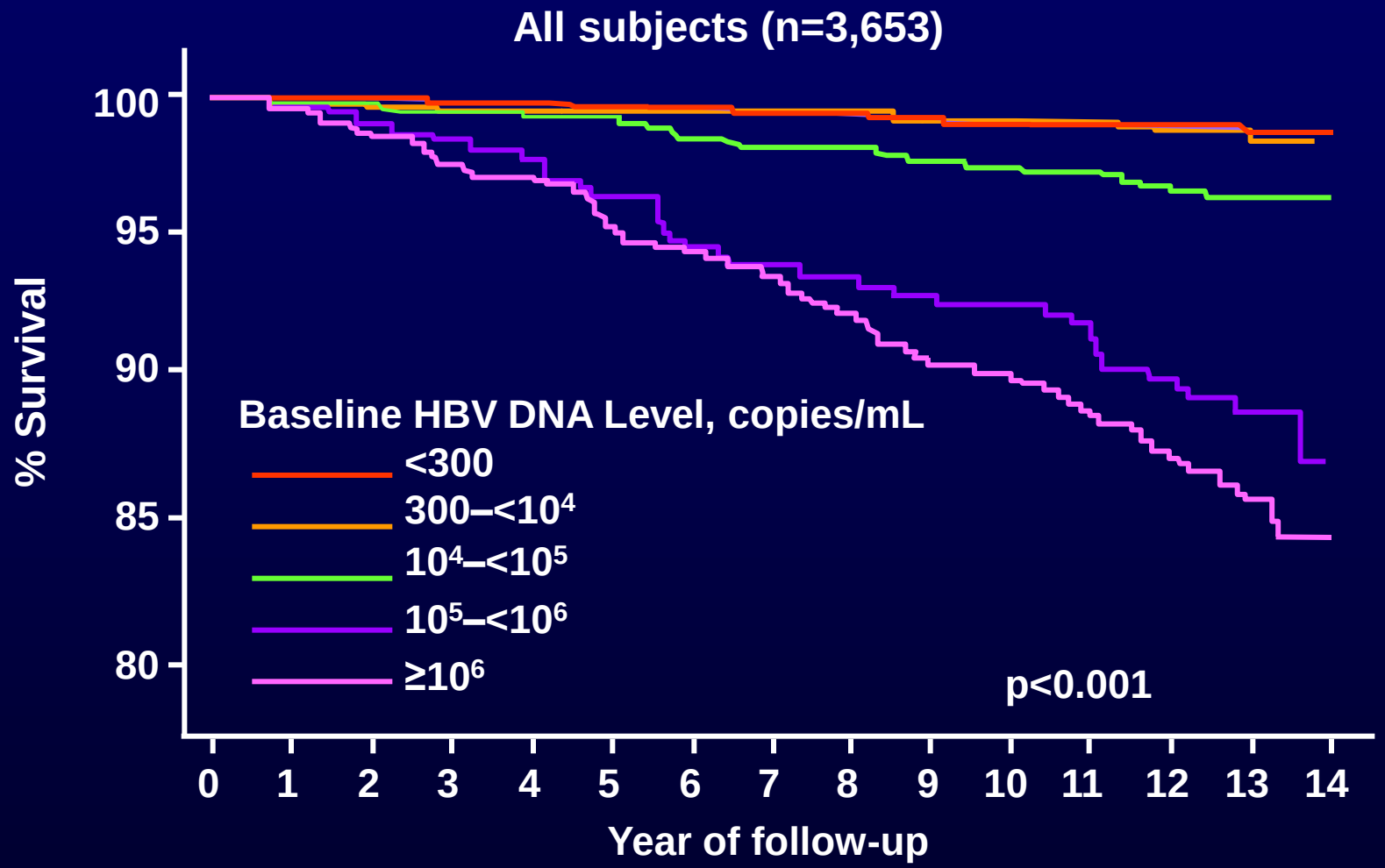
Iloeje UH, et al. Gastroenterology. 2006;130;678-86

High viral load is associated with increased incidence of HCC



Chen C-J, et al. JAMA. 2006;295:65-73

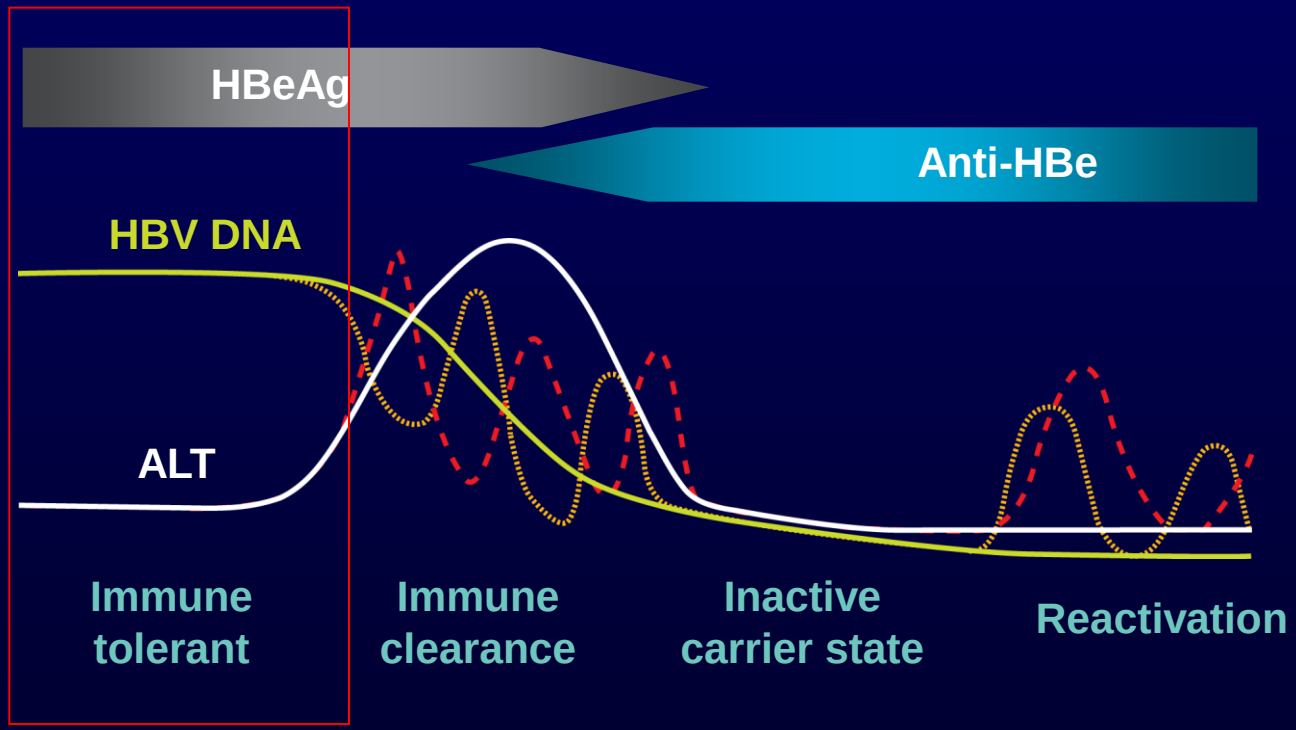
Liver-related mortality according to baseline HBV DNA levels



Iloeje UH, et al. 57th Annual AASLD meeting, October 27–31, 2006, Boston, USA. Poster 949

Natural History of CHB

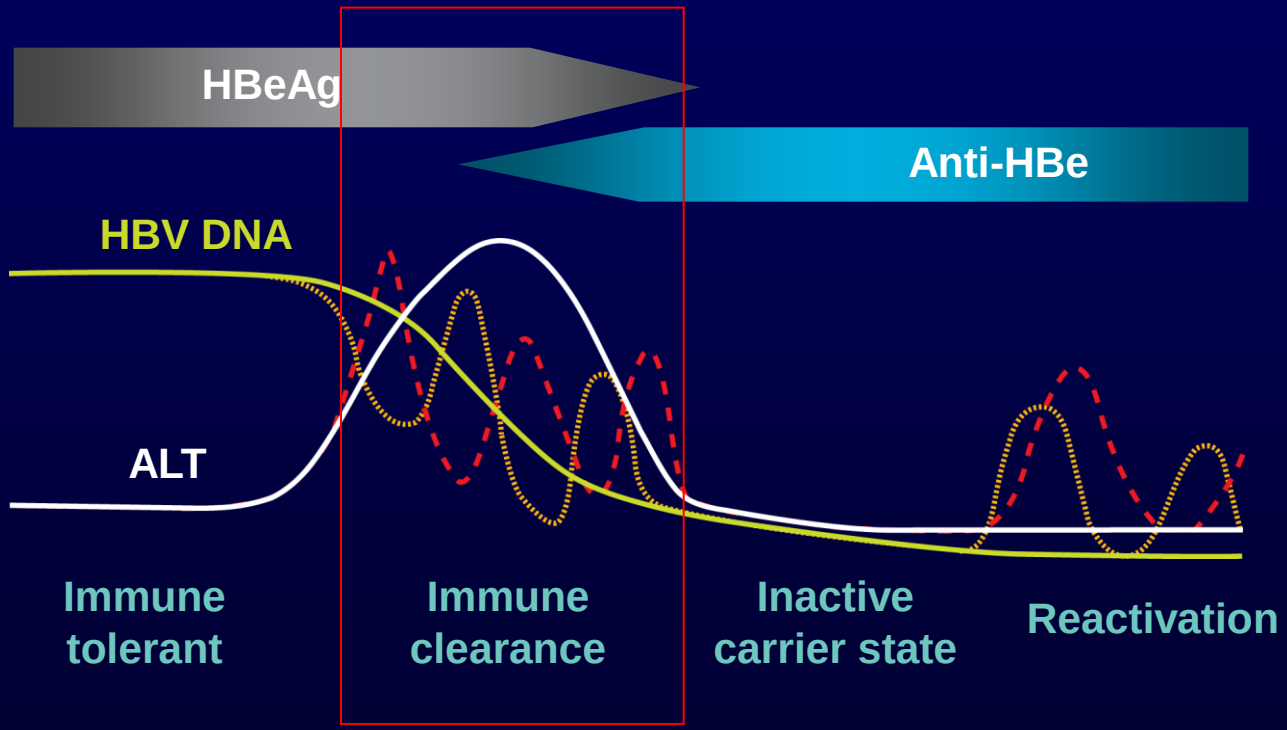
- Immune tolerance
  - HBeAg(+), high HBV DNA, normal ALT, minimal or no necroinflammation



Kim HJ & Lok ASF. Hepatology. 2006;43:S173-81.

Natural History of CHB

- HBeAg(+) CHB/immune clearance
  - HBeAg(+), high or fluctuating HBV DNA, elevated ALT, active necroinflammation



Kim HJ & Lok ASF. Hepatology. 2006;43:S173-81.

Annual Incidence of Cirrhosis and HCC in Patients with CHB

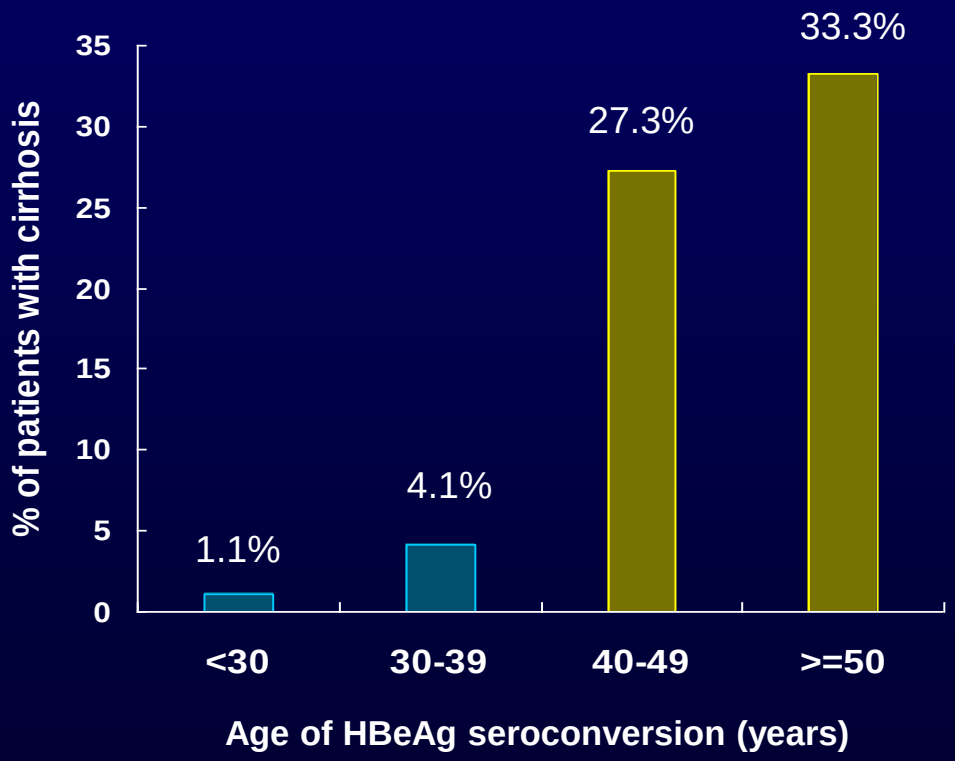
HBV status at entry	Pts, n	Age, yrs*	F-up, yrs*	Cirrhosis, %	HCC, %	Ref.
HBeAg (+)	509	31	2.8#	2.4	NA	Liaw
(+) → (+)	134	31	6.8 #	3.5	1.3	Lin
(+) → (-)	74	31	6.8 #	1.5	0.3	"
HBeAg seroconversion	269	32	8.6**	0.9	0.2	Hsu

* Mean; # including 64 IFN-treated patients; ** after spontaneous HBeAg seroconversion score; § after spontaneous HBsAg loss

Factors for cirrhosis development

Cirrhosis is more likely if spontaneous HBeAg clearance occurs at age >40 yr

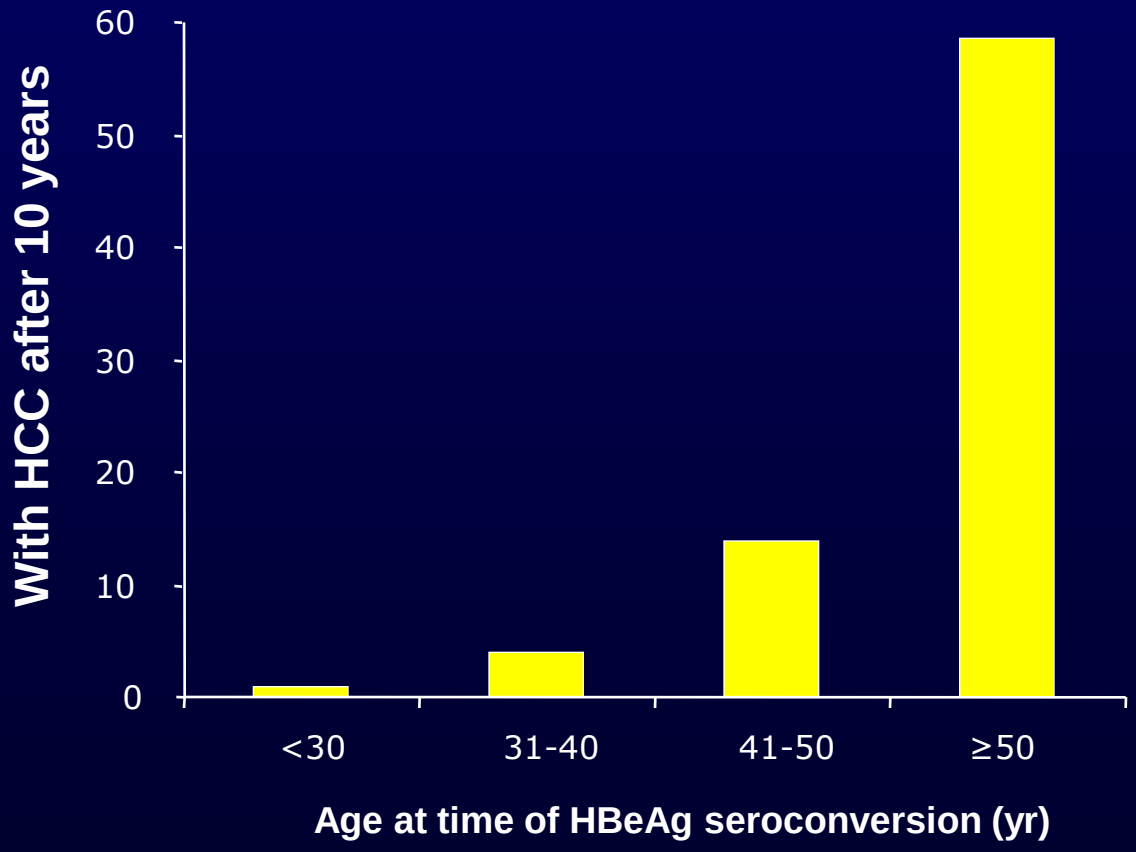
* Age: entry and seroconversion
* Male gender
* Genotype (C > B)
* **Prolonged immune clearance/ reactivation**
* **Severity, extent, frequency, duration of hepatitis or flare**
* HCV/HDV/HIV co-infection



Chu, Liaw J Viral Hepati 2007

Timing is important: earlier seroconversion is associated with reduced risk of HCC

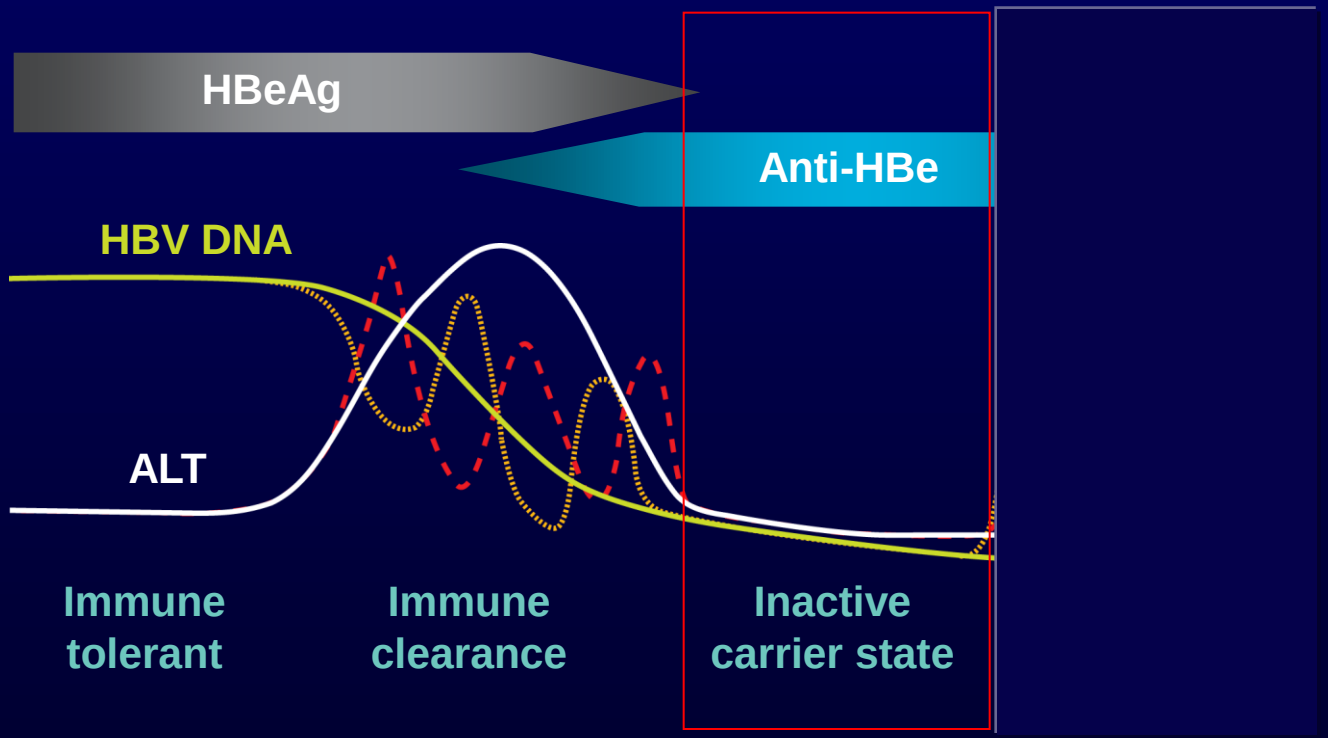
HCC is more likely if spontaneous HBeAg clearance occurs at age >40 yr



Fung et al. EASL 2007

Natural History of CHB

- Inactive carrier state
  - HBeAg(-), anti-HBe(+), low or undetectable HBV DNA, persistently normal ALT, minimal fibrosis on biopsy



Kim HJ & Lok ASF. Hepatology. 2006;43:S173-81.

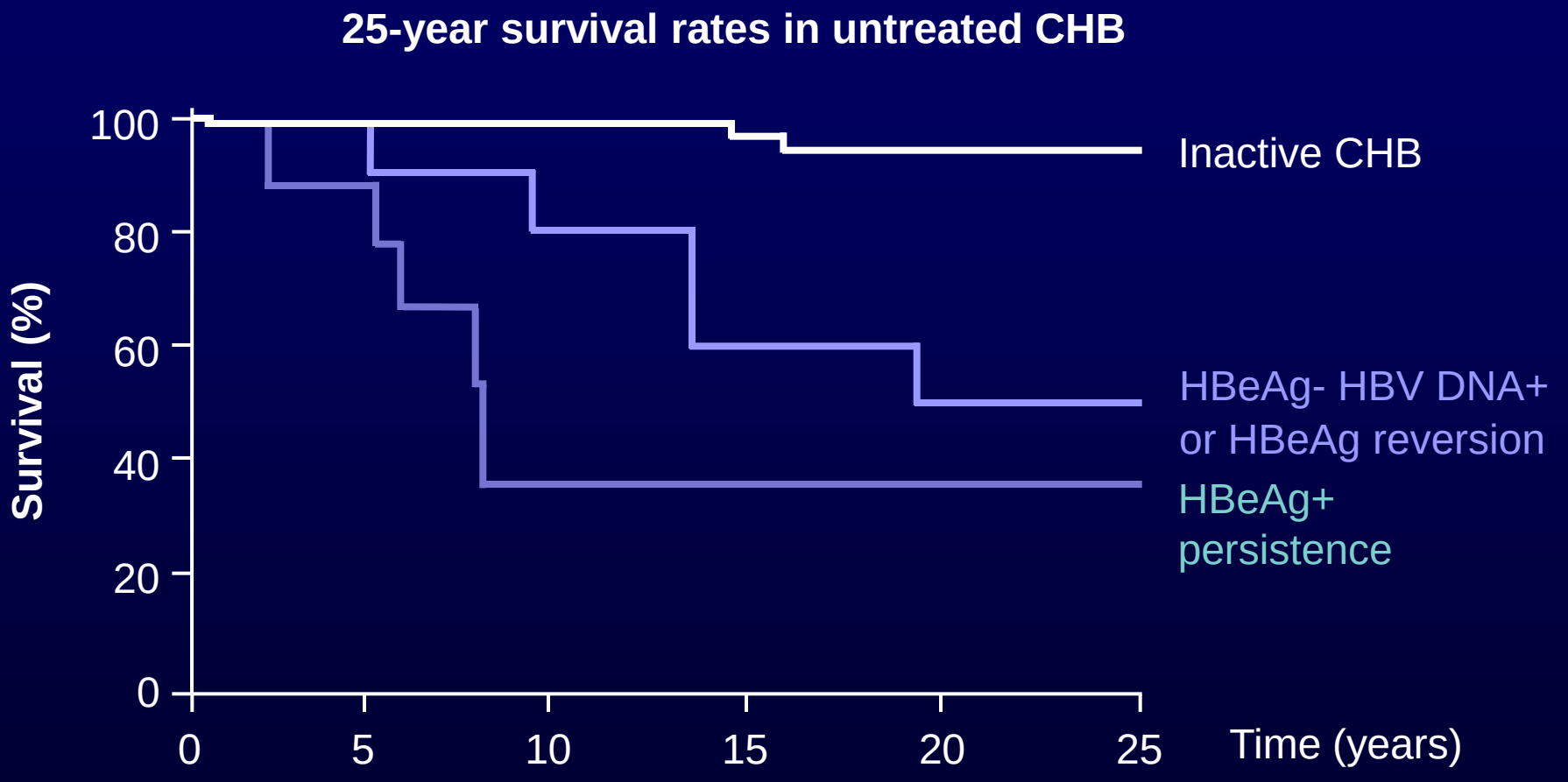
Portatore inattivo di HBsAg

Criteri diagnostici

- positività HBsAg
- positività anti-HBe
- HBV DNA <2.000 UI/mL (< 10,000 copie/mL)
- IgM anti-HBc < 0.10
- livelli di ALT/AST persistentemente normali

Scarsa o assente attività necro-infiammatoria alla biopsia epatica

Inactive carrier is associated with good prognosis



Fattovich et al. Gut 2008

Natural history of inactive HBsAg carriers

incidence per 100 person years of major events

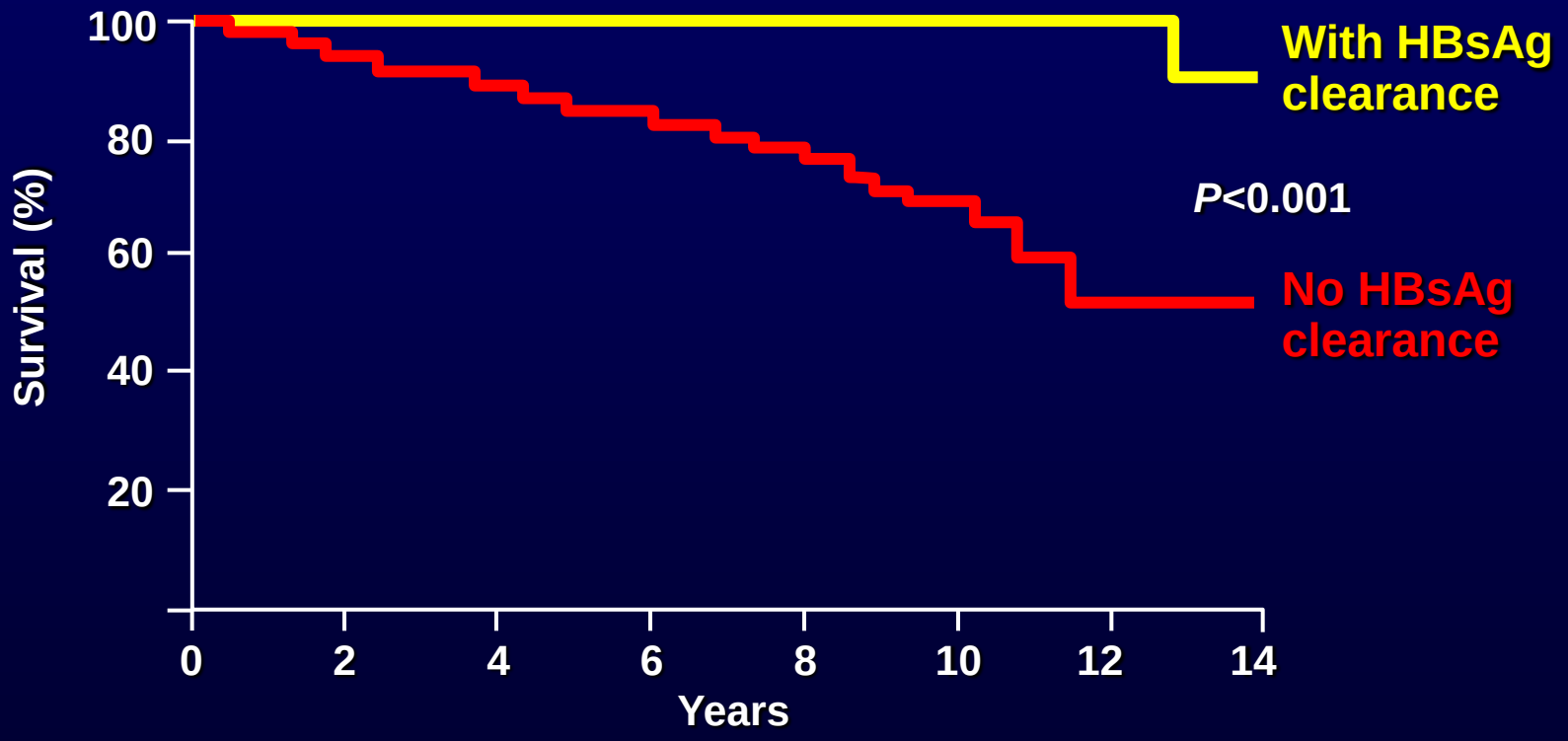
	De Franchis 1993	Bellentani 2002	Villa 2004	Hsu 2002
• area	Europe	Europe	Europe	Asia
• N° patients	68	46	296	189
• Median follow-up (yrs)	10	9	29	8
• Histologic deterioration	0.15	NR	NR	0.06
• HCC	0	0	0.02	0.19
• Liver-related death	0	0	0.01	0
• HBsAg loss	1.0	0.9	1.0	0.6

NR = not reported

HBsAg clearance improves survival rates

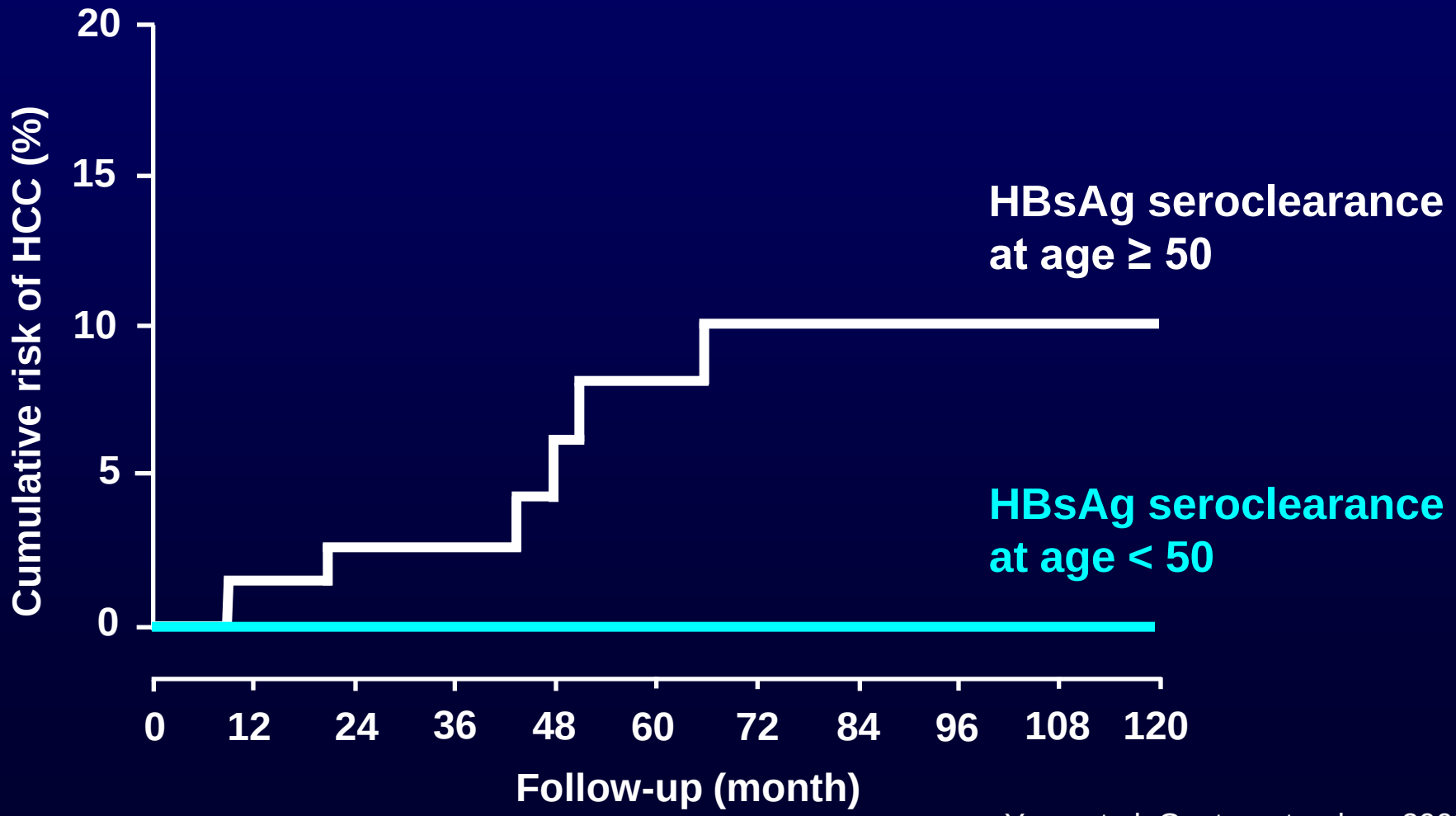
Probability of survival in patients with and without HBsAg clearance

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



Fattovich et al. Am J Gastroenterology 1998;93: 896-900

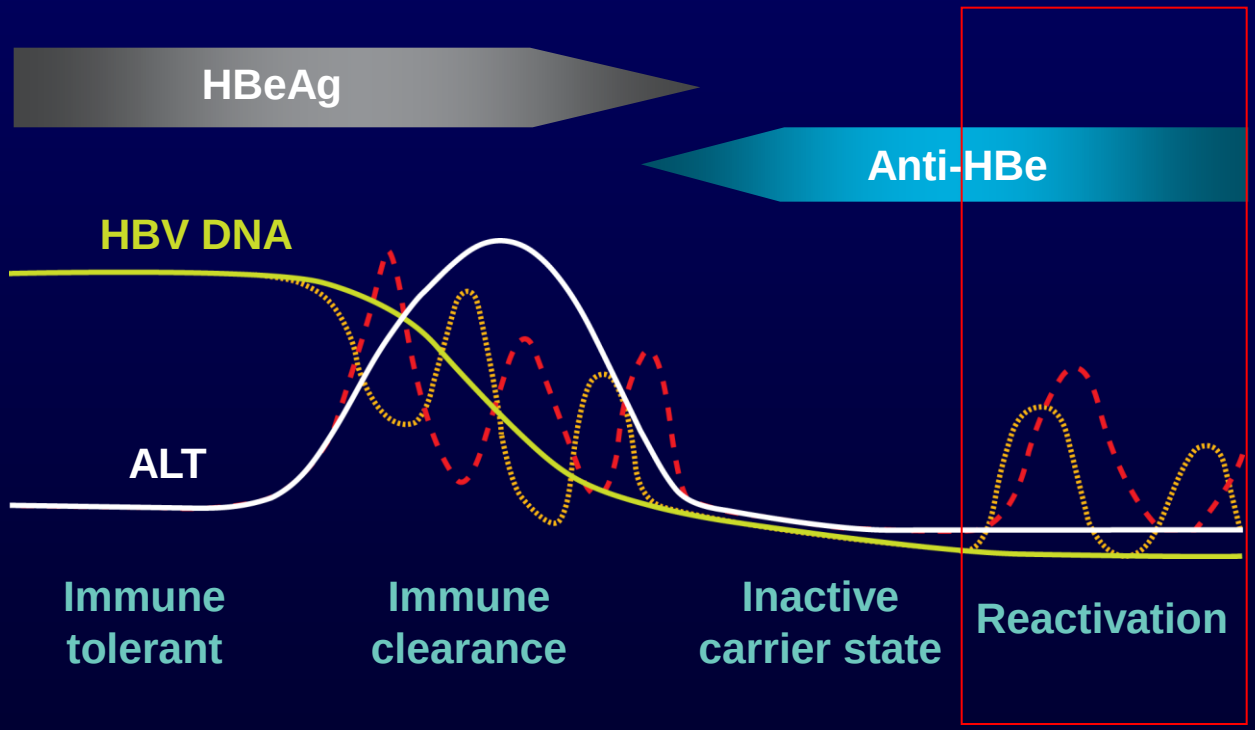
Risk of HCC is lower if HBsAg clearance occurs before 50 years



Yuen et al. Gastroenterology 2009

Natural History of CHB

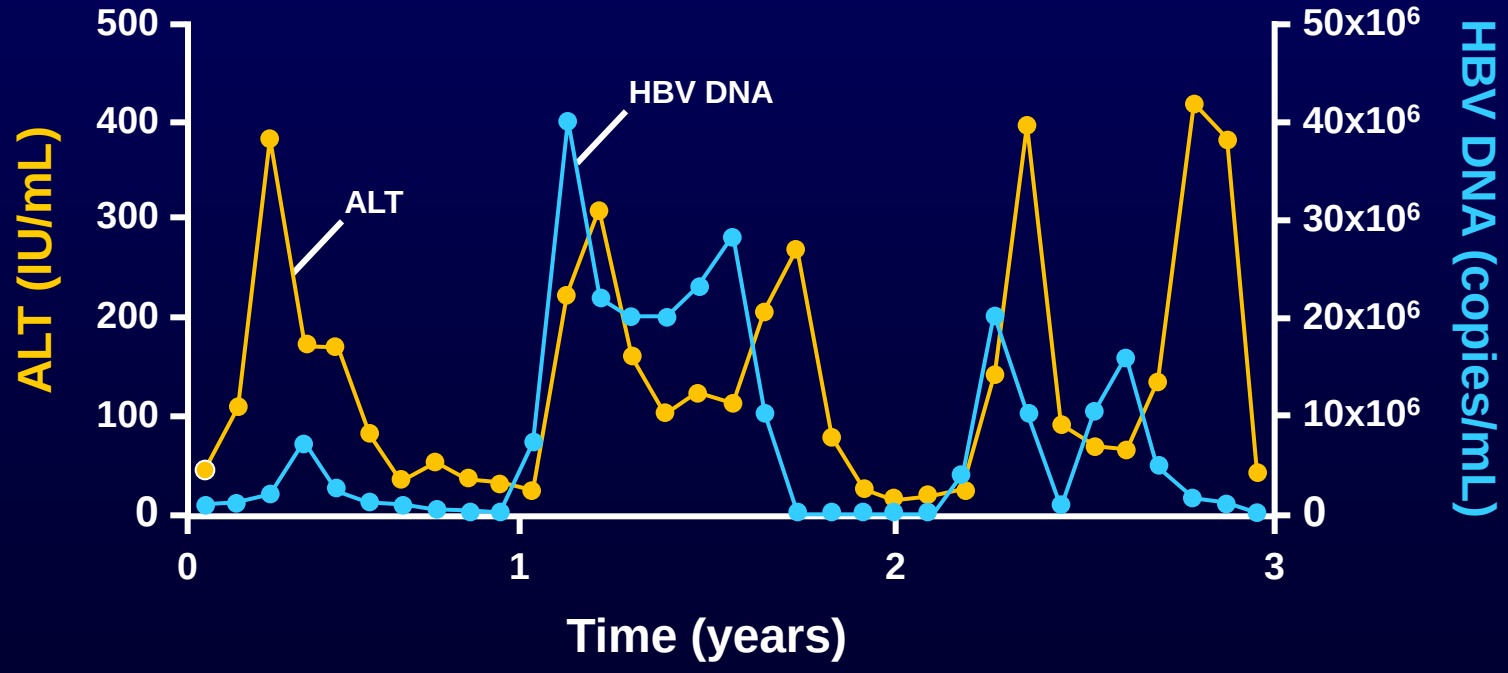
- HBeAg(-) CHB/reactivation
  - HBeAg(-), anti-HBe(+), detectable HBV DNA, elevated ALT, active necroinflammation



Kim HJ & Lok ASF. Hepatology. 2006;43:S173-81.

HBeAg(-) CHB may be misdiagnosed as inactive disease due to its fluctuating activity

- Monitoring ALT and HBV DNA levels at Years 1 and 2 would not reveal the fluctuating nature of these parameters in this patient



Adapted from Hadziyannis SJ & Vassilopoulos D. *Hepatology* 2001;34:617-24.

Natural history of Chronic Hepatitis B

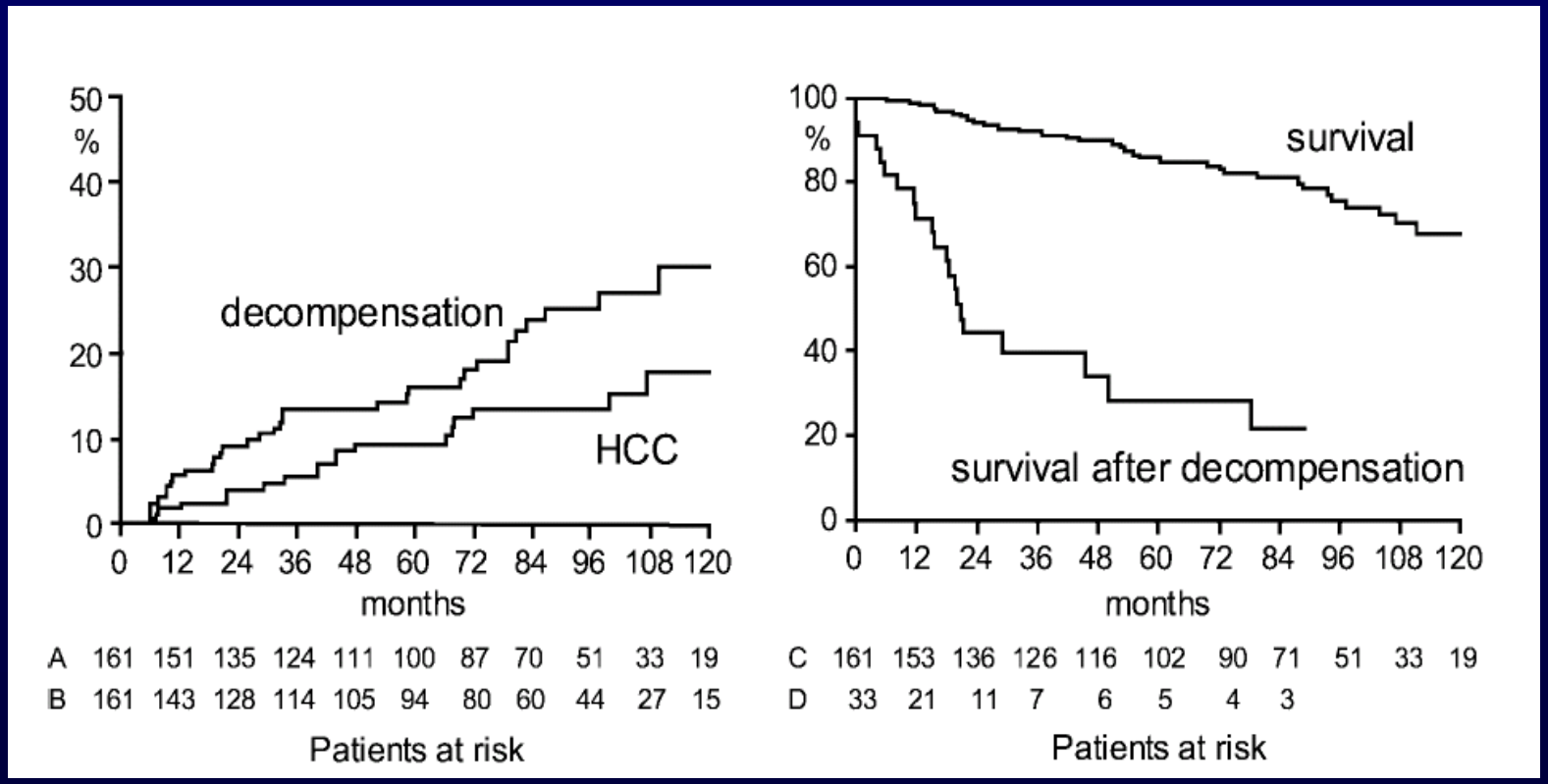
Outcomes	HBeAg pos	HBeAg neg
Cirrhosis x yr	2.4%-6.0%	1.3%-4.6%
Decompensation x yr*	3.8%	3.2%-6.6%
HCC x yr*	1.8%	1.5%-2.4%
Survival at 5-yr*	66.0%-83.0%	86.9%-97.0%

** patients with cirrhosis*

Liaw 1988, Fattovich 1991, 1995, 2000, De Jongh 1992, Weisberg 1984, Niederau 1996, Papatheodoridis 200, Brunetto 2002

Natural history of HBV cirrhosis

Cumulative incidence of HCC and decompensation in 161 untreated Italian patients with compensated HBV cirrhosis



Hepatocellular Carcinoma

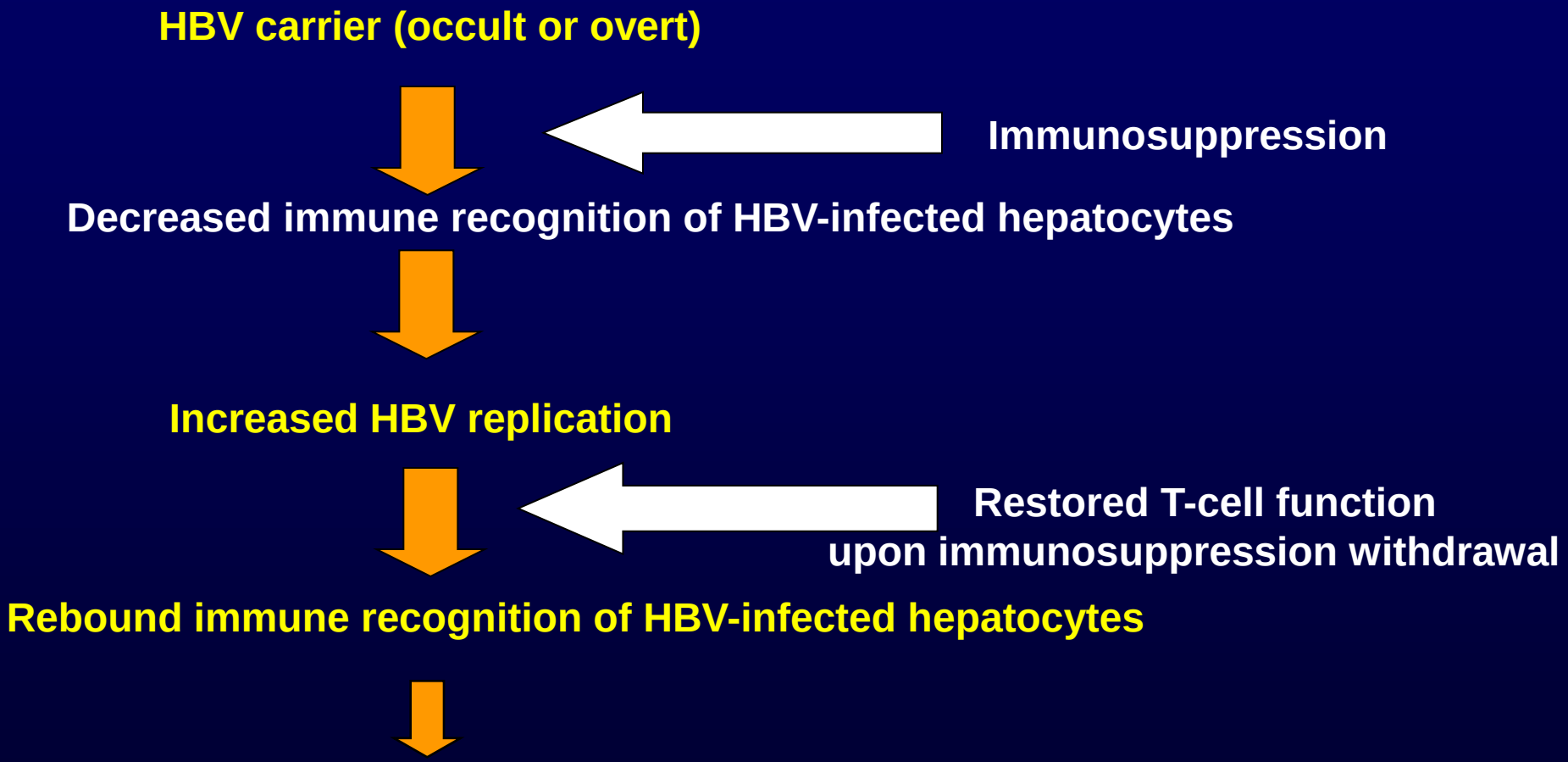
- HBeAg negative/HBV DNA negative: 8%
- HBeAg negative/HBV DNA positive: 14%
- HBeAg positive: 9%

Liver decompensation

- HBeAg negative/HBV DNA negative: 4%
- HBeAg negative/HBV DNA positive: 14%
- HBeAg positive: 16%

G. Fattovich, Seminars Liver Disease 2003

Prevention of HBV reactivation in the immunocompromised patient



HBV is a dynamic disease

- Status may change over time
- Individualize treatment decisions
- Long term monitoring

HBV DNA and immune response = engine
ALT/necroinflammatory activity = train speed
Fibrosis stage = distance from destination