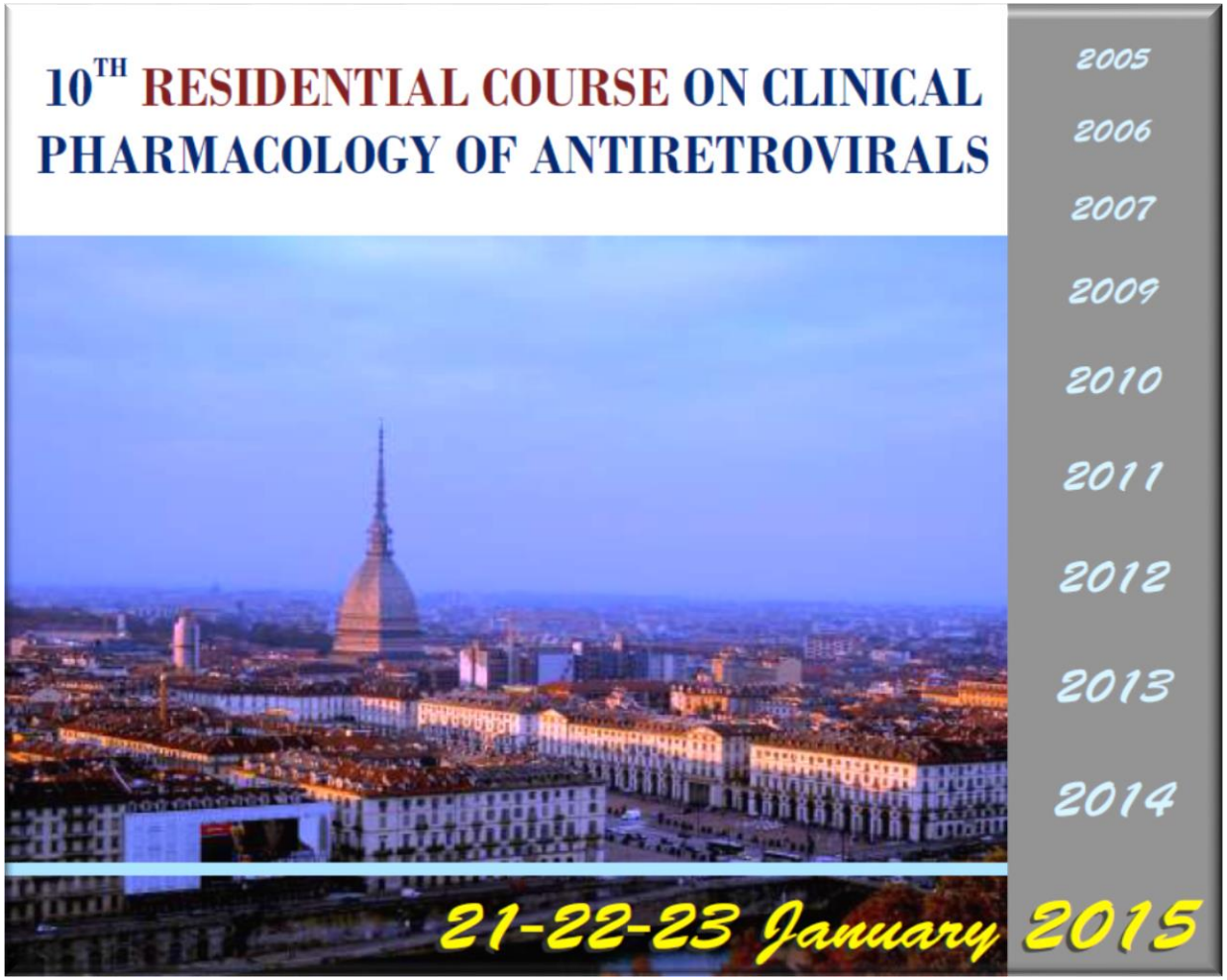


Advances in treatment of HBV

Alfredo Marzano
San Giovanni Battista Hospital
University of Turin
Italy

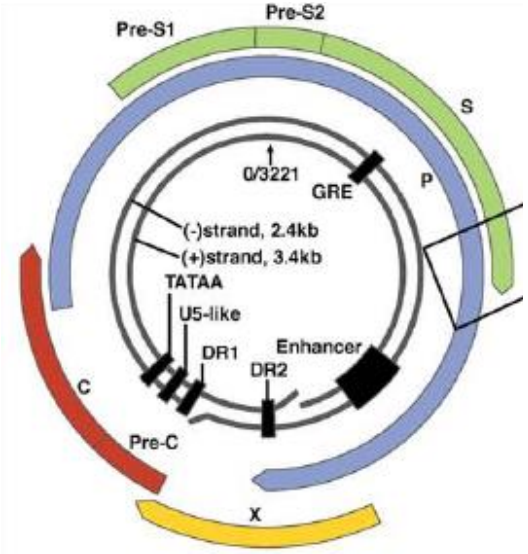
Outline

- General background
- Therapy
  - Aims
  - Strategies
  - Efficacy
  - Drugs and virus
  - Clinical results
  - Summary


10TH RESIDENTIAL COURSE ON CLINICAL
PHARMACOLOGY OF ANTIRETROVIRALS
2005
2006
2007
2009
2010
2011
2012
2013
2014
21-22-23 January 2015

Background

HBV



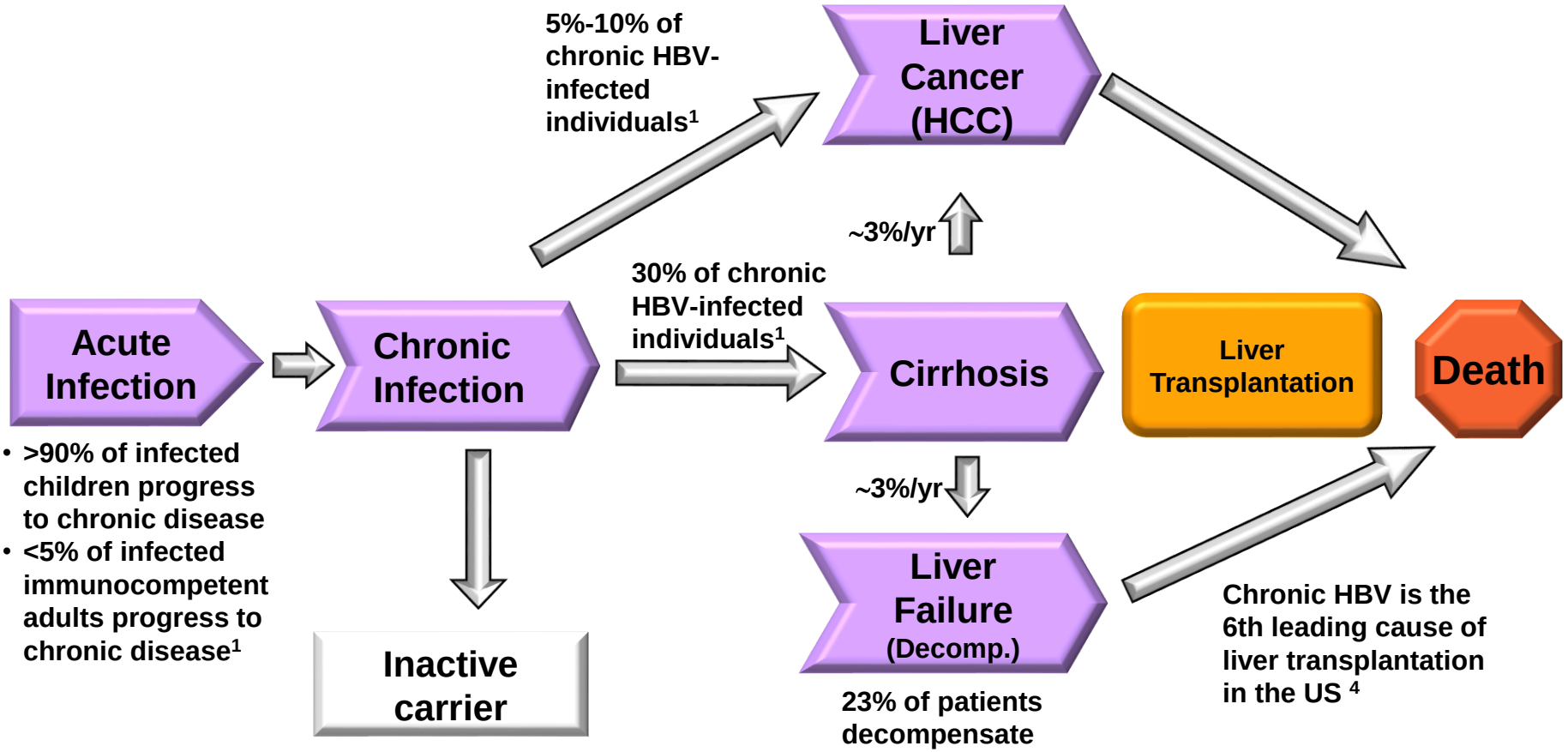
HBsAg+ > 400 millions
antiHBc+ > 2 billions
8 different genotypes.

High replicative activity : $10^{11\text{-}12}$ virions/daily
High Mutations rate: *1 every 100,000*

Fig. 3. World map showing distribution of HBV genotypes. The predominant genotypes of regions of the world are shown in larger font sizes.

Natural History of CHB

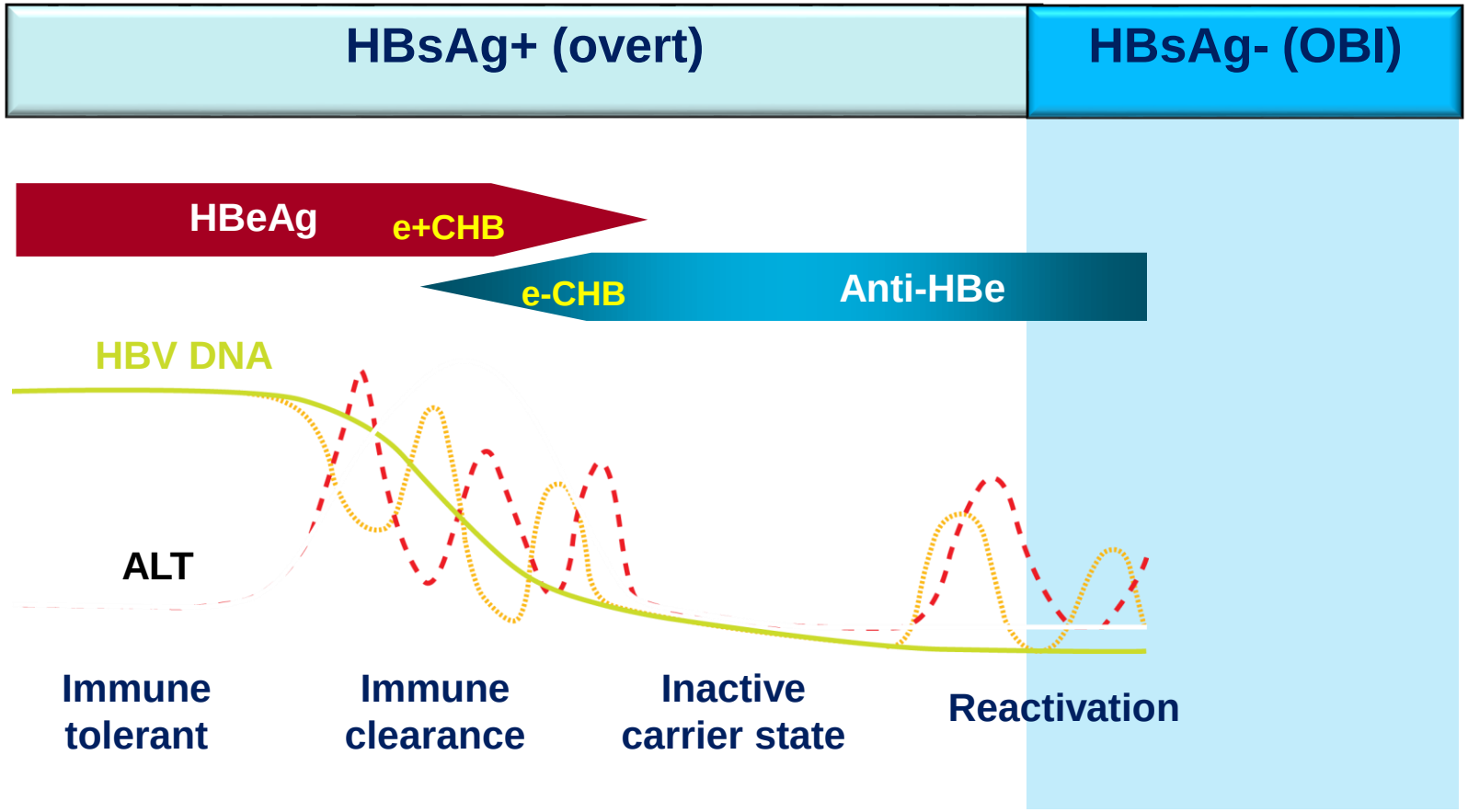
Disease



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.

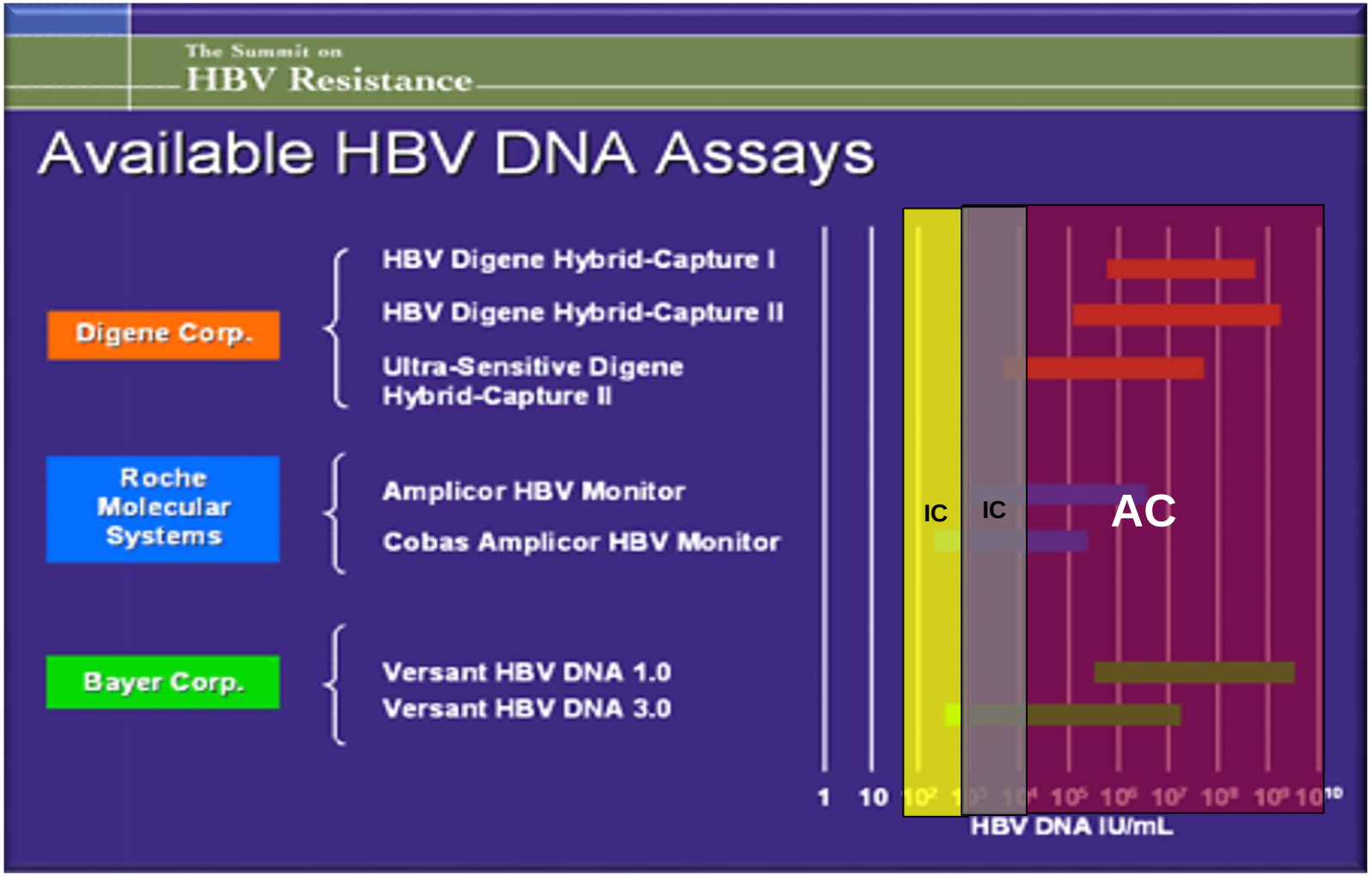
Natural history of CHB

Virological aspects (infection)

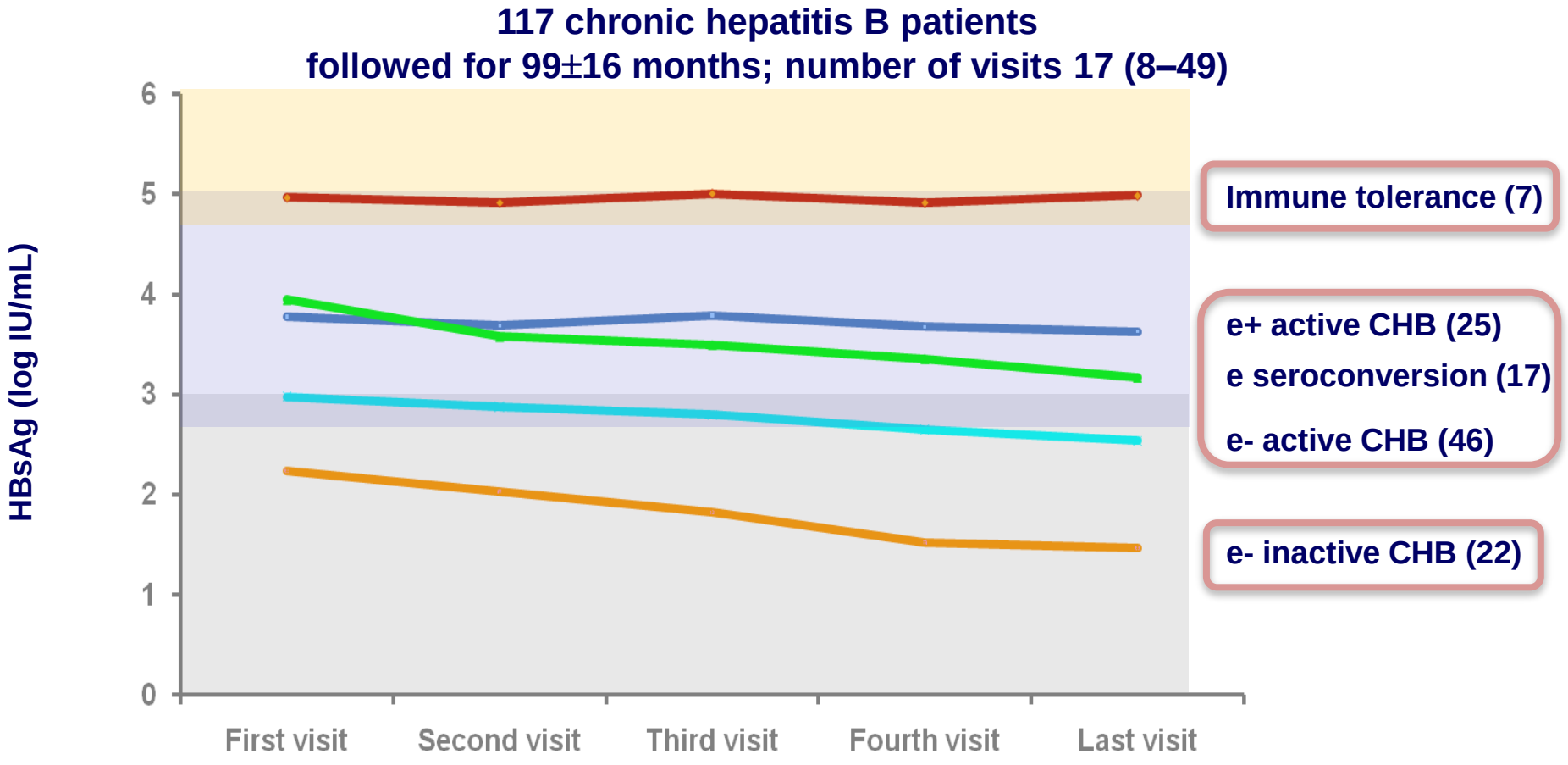


Adapted by Kim HJ & Lok ASF. Hepatology 2006

HBV DNA

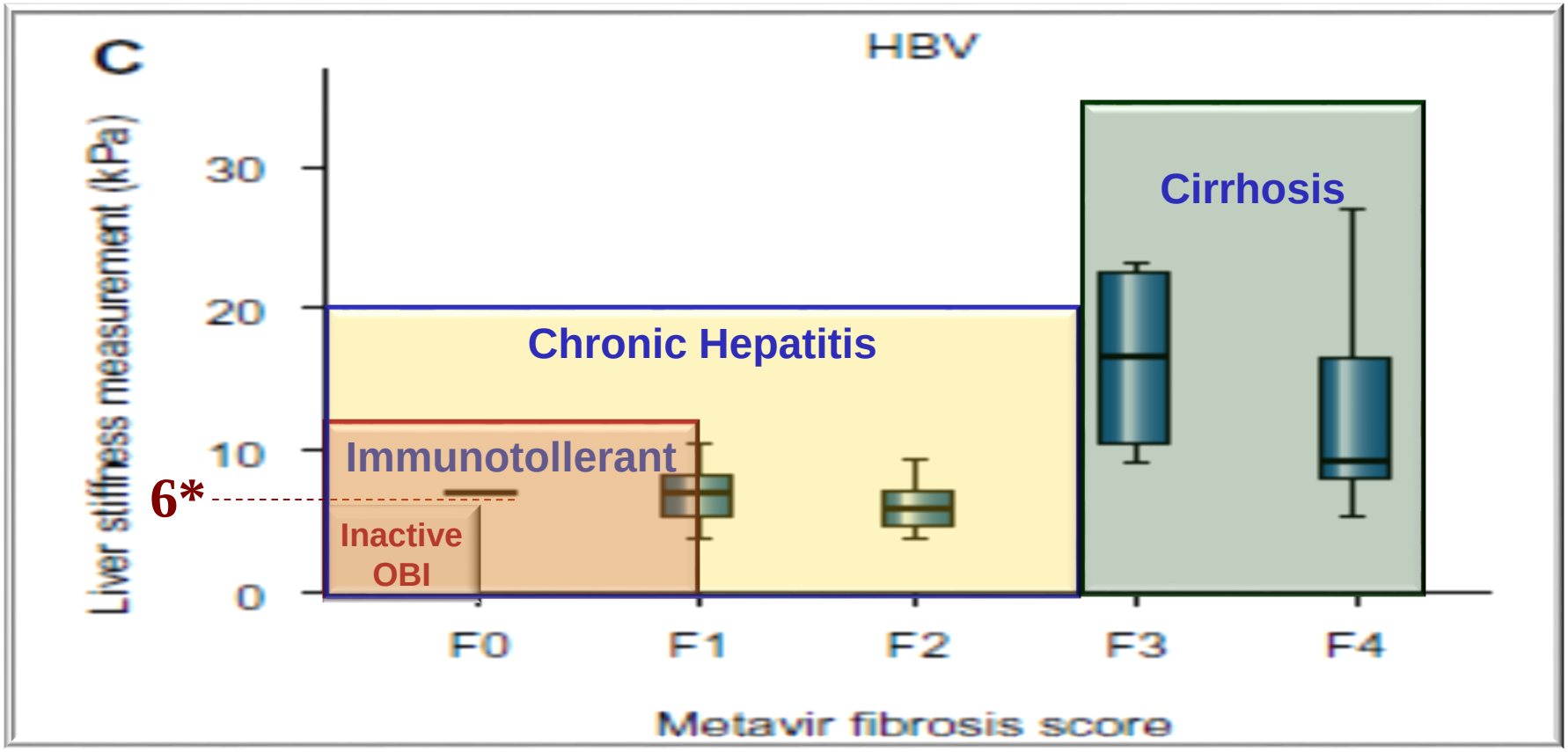

The Summit on
HBV Resistance
Available HBV DNA Assays
Digene Corp.
HBV Digene Hybrid-Capture I
HBV Digene Hybrid-Capture II
Ultra-Sensitive Digene Hybrid-Capture II
Roche Molecular Systems
Amplicor HBV Monitor
Cobas Amplicor HBV Monitor
Bayer Corp.
Versant HBV DNA 1.0
Versant HBV DNA 3.0
IC
IC
AC
1
10
HBV DNA IU/mL

qHBsAg



Chan HL et al. Hepatology 2010

Staging
Liver biopsy and Fibroscan



Gaia, J Hepatol 2011
** Oliveri, WJG 2008*

Therapy

aims

Antiviral Therapy in HBV Goals

		HBV DNA IU	qHBsAg IU	HBeAg
AC		> 2000	> 1000	Pos/neg
IC		< 2000	<1000	neg
		neg	<100	neg
OBI		neg	neg	neg

STOP
Evolution
Cirrhosis (regression)
Portal hypertension
Liver transplantation
HCC
Mortality

Therapy

Strategies

Therapeutic strategies

PEG
NUC (e+)

Curative (defined time)

Suppressive (NUC) (undefined time)

This topic falls outside my time

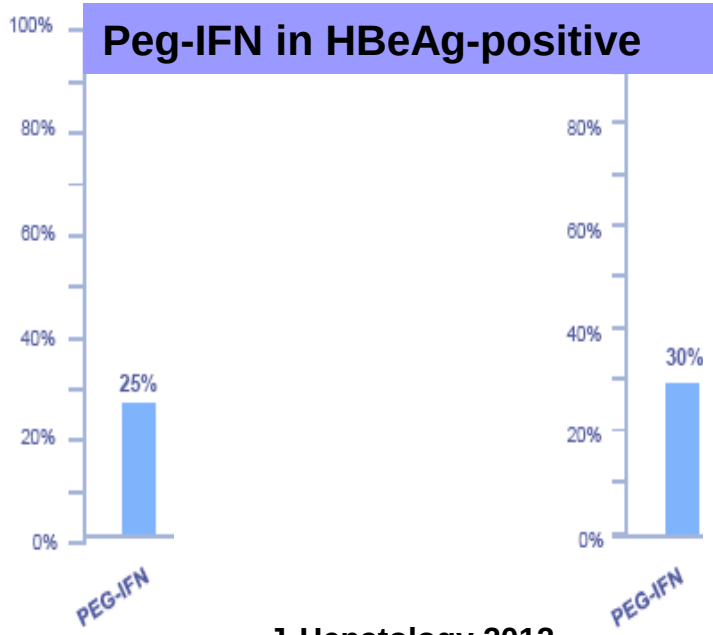
Therapy

Efficacy

PEG-IFN

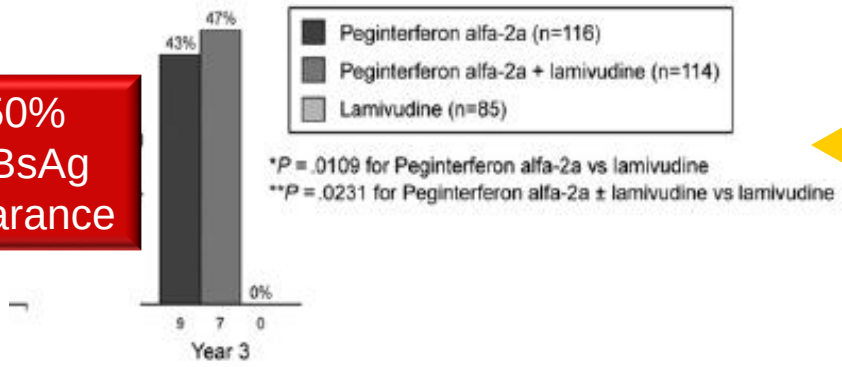
e+

Peg-IFN in HBeAg-positive



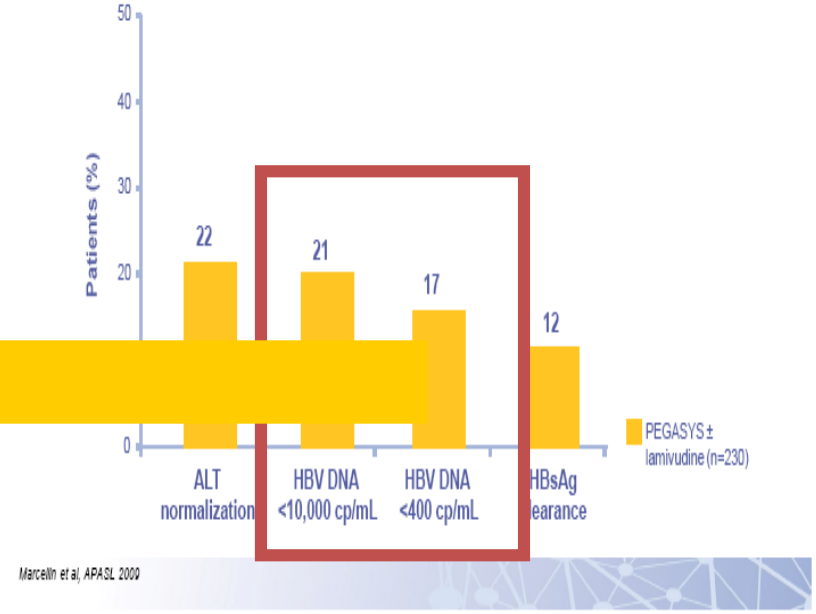
J Hepatology 2012

50% HBsAg clearance



e-

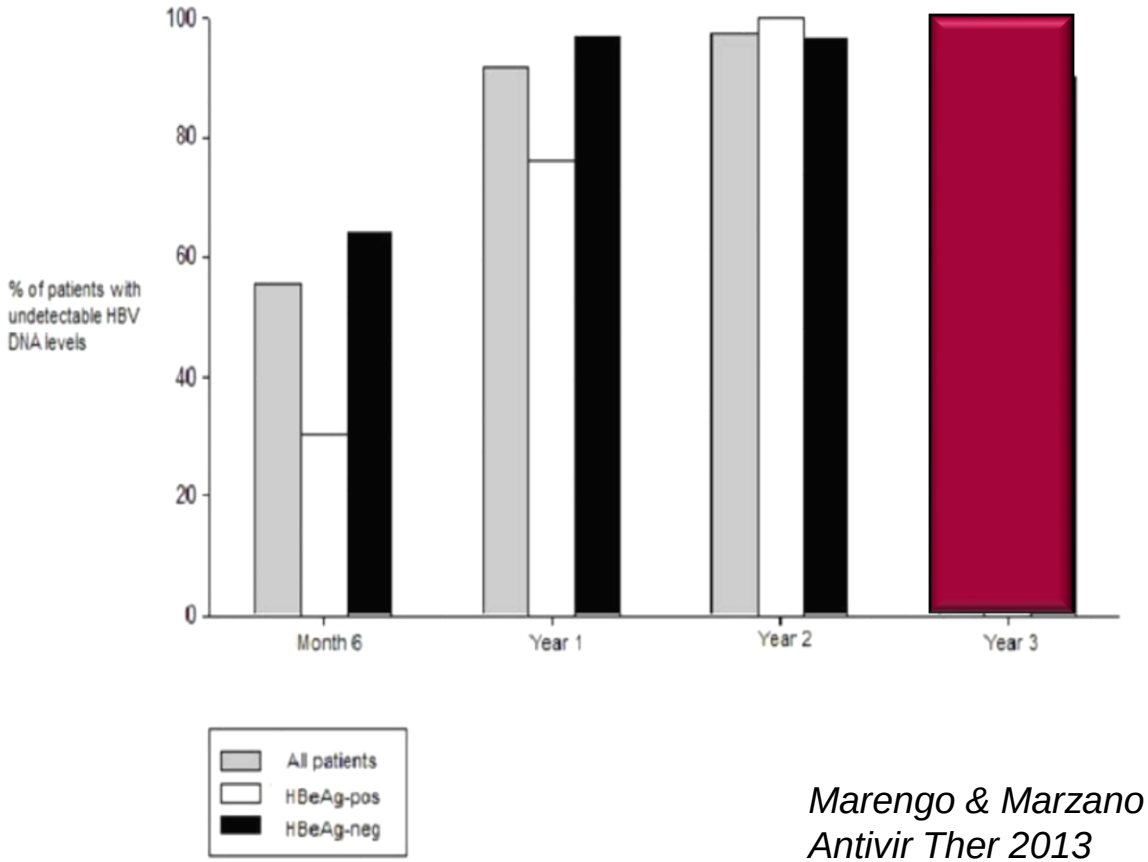
Peg-IFN alpha-2a in HBeAg-negative CHB. Sustained response (5 yr)



Better response in genotype non-D/E

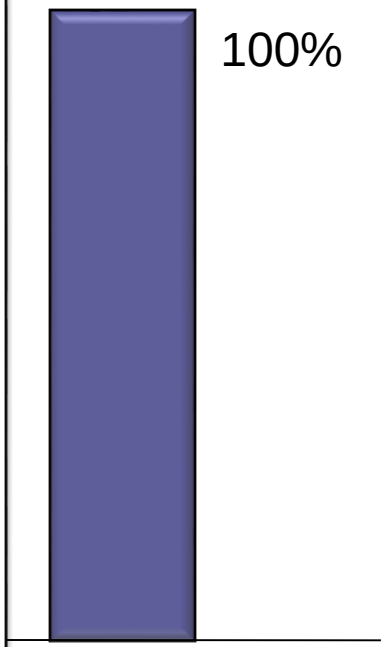
Marcellin, Gastroenterology 2009

ETV



Marengo & Marzano
Antivir Ther 2013

TDF



Marengo & Marzano
APT 2014

Pangenotypic

Therapy

Drugs and Virus

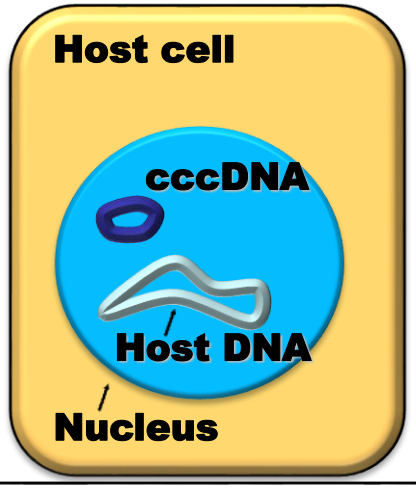
Why the mono-therapy is effective?

Virus and Drugs characteristics

Suppression vs. cure: viral biology is the basis

HBV

10 genotypes
(Latent Reservoir)

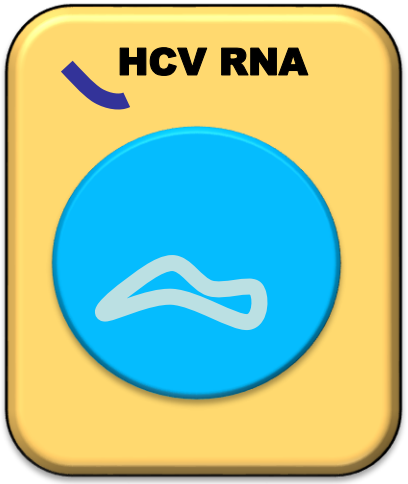


Long-time cccDNA
"Low " replicative space

Suppression

HCV

6 genotypes
(No Latent Reservoir)



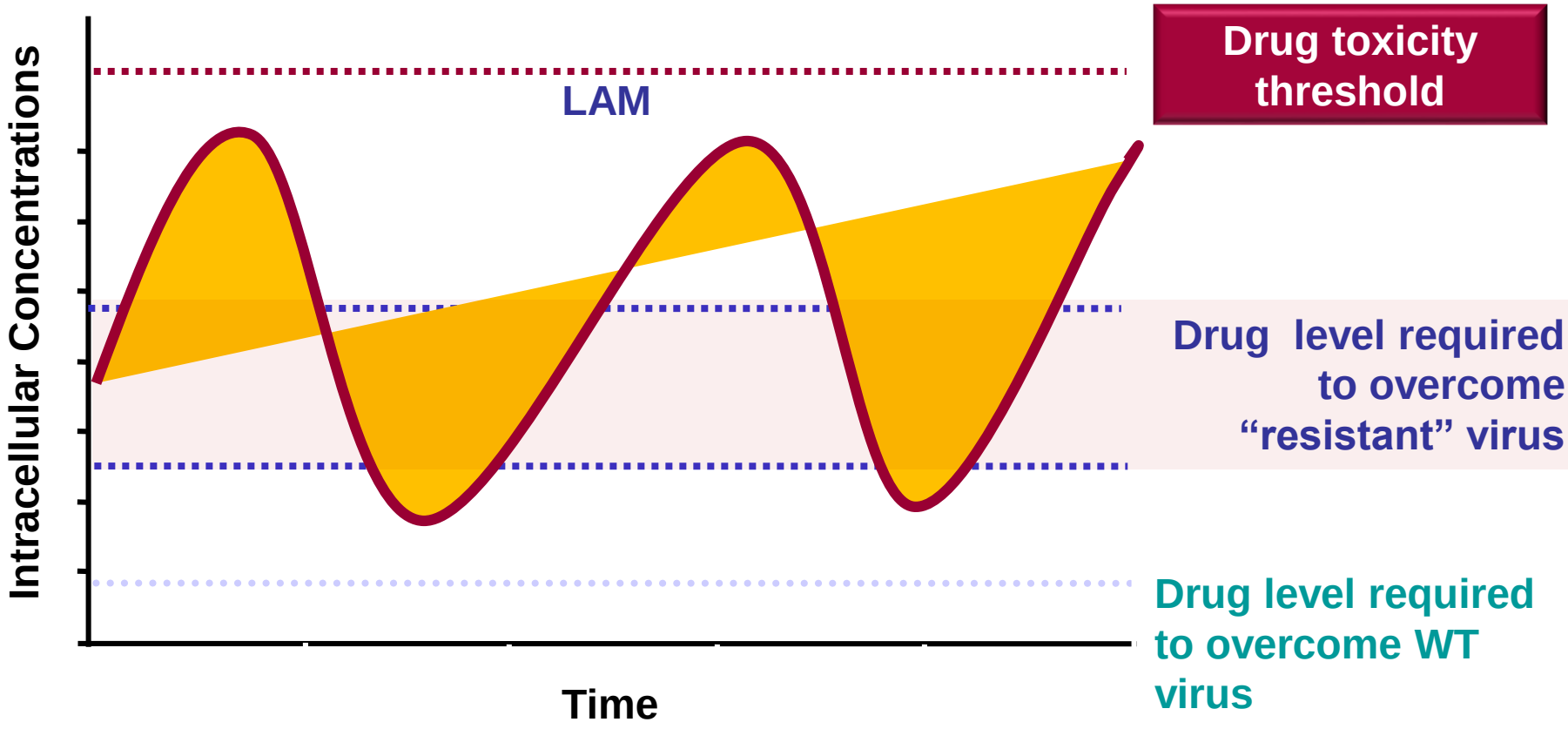
Definitive Viral Clearance

Cure

cccDNA = covalently closed circular DNA.

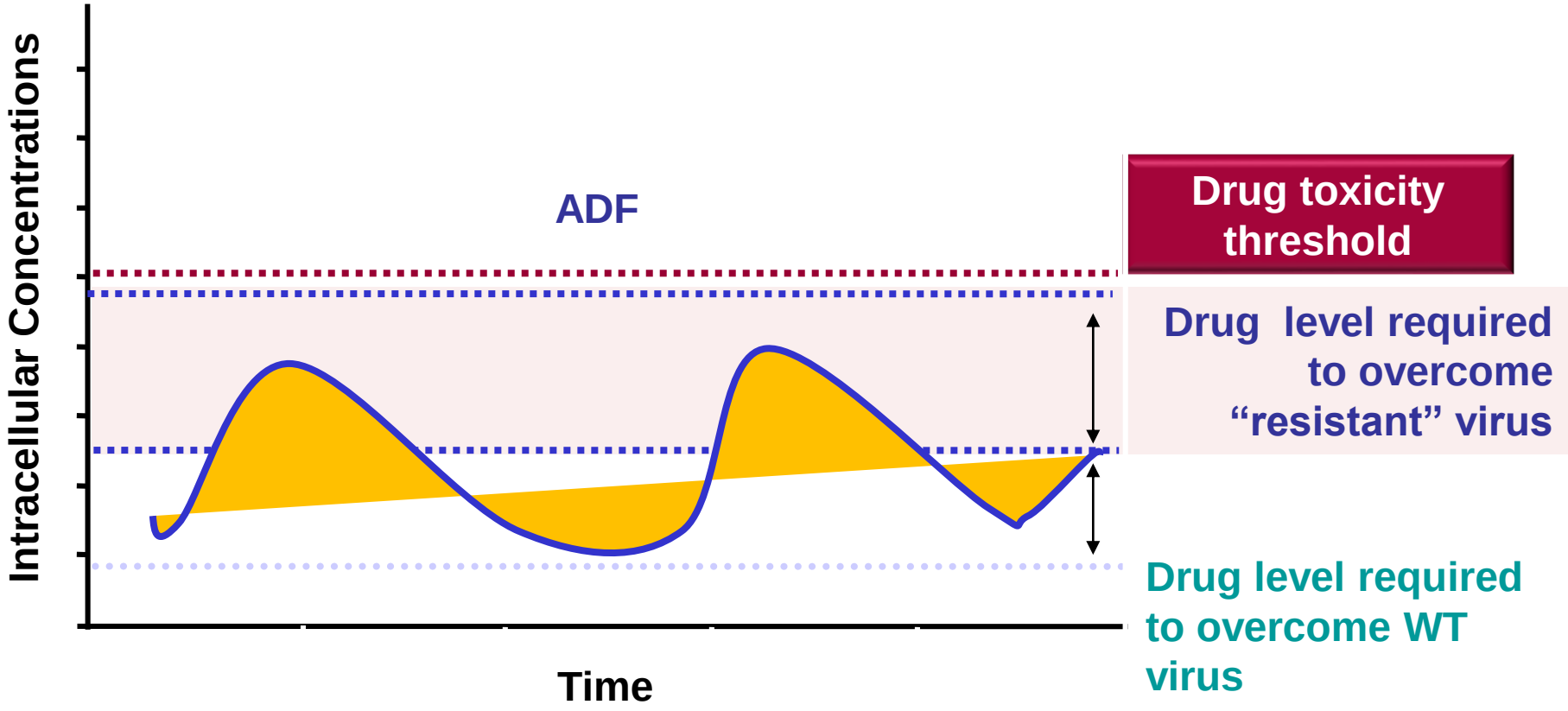
Kieffer TL, et al. *J Antimicrob Chemother*. 2010;65:202-212.

Drugs
Pharmacologic barrier
Intracellular drugs levels and resistance
I generation (high drug levels)
Low toxicity, medium potency



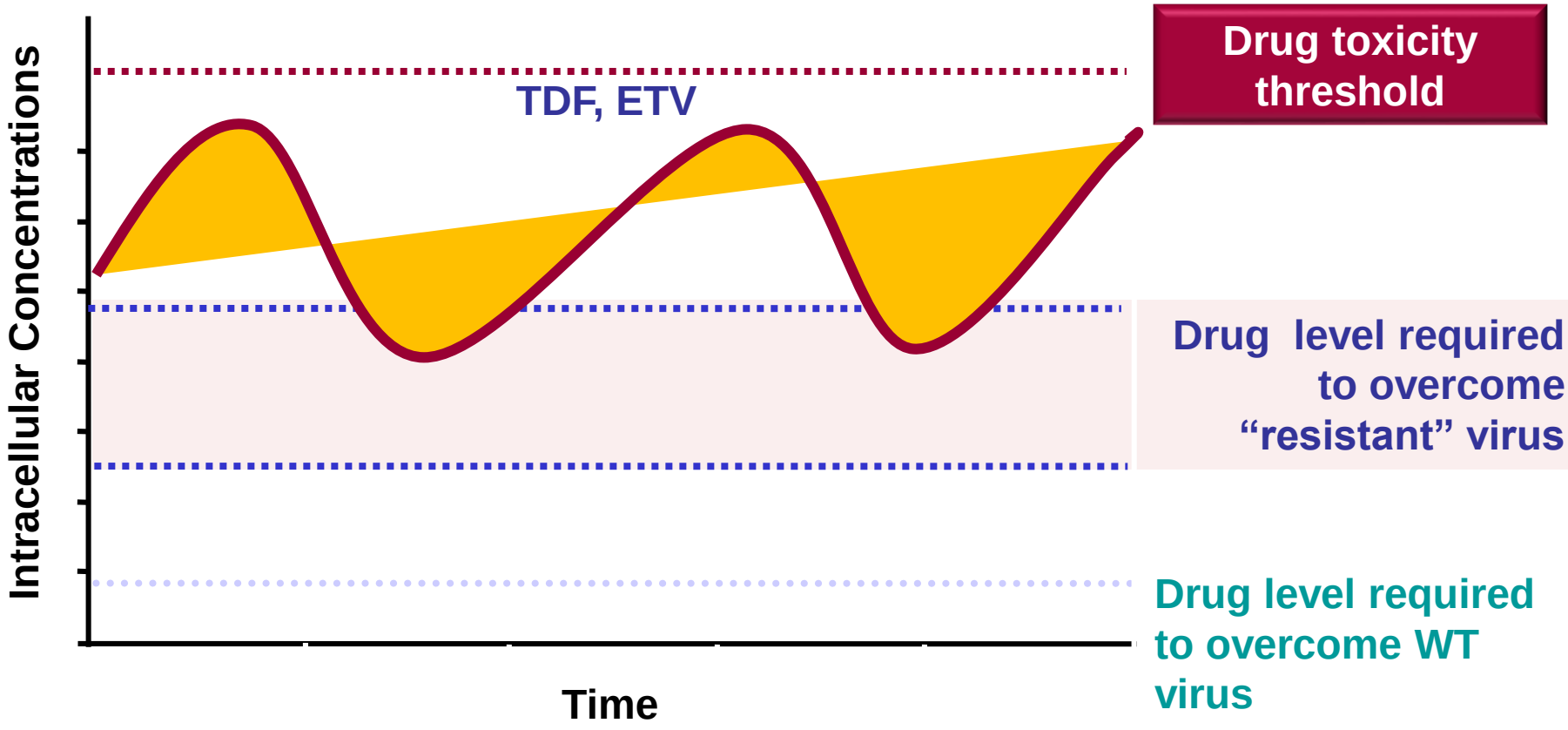
Modified from Moyle G, et al. Drugs. 1996

Drugs
Pharmacologic barrier
Intracellular drugs levels and resistance
II generation (low drug levels)
High toxicity, medium potency



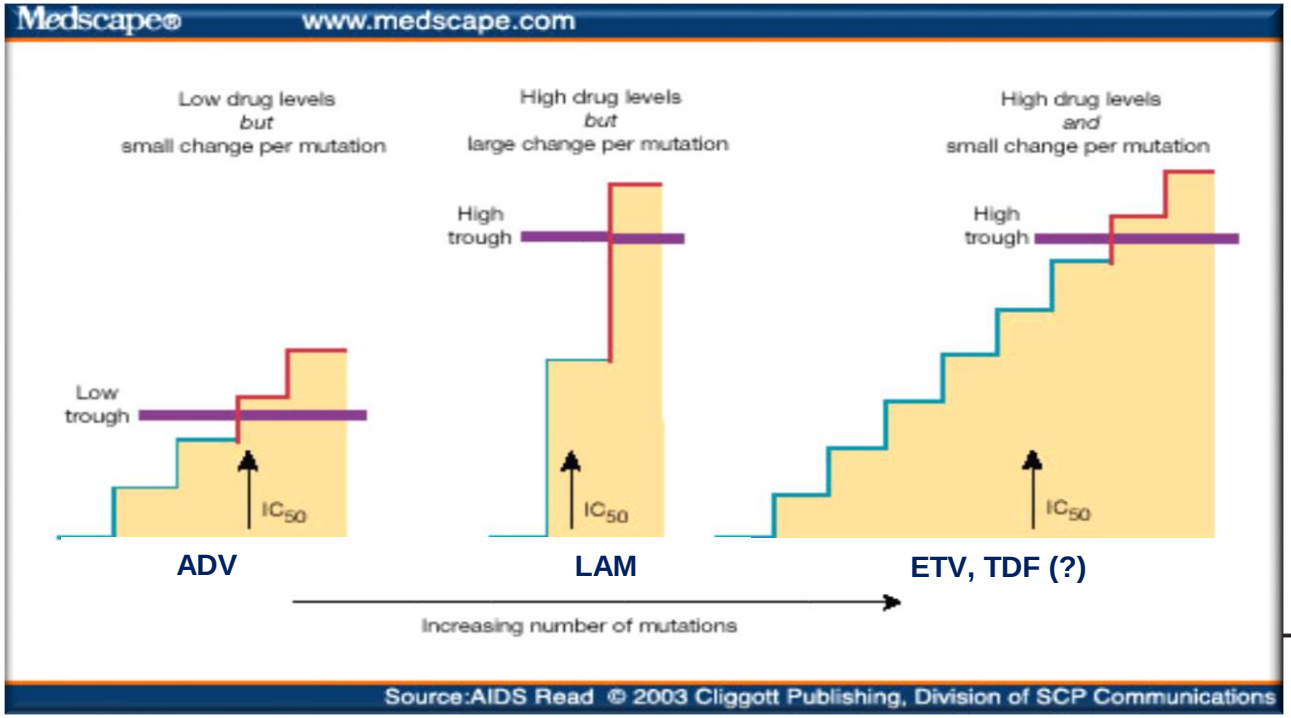
Modified from Moyle G, et al. Drugs. 1996

Drugs
Pharmacologic barrier
Intracellular drugs levels and resistance
III generation (high drug levels)
Low toxicity, high potency

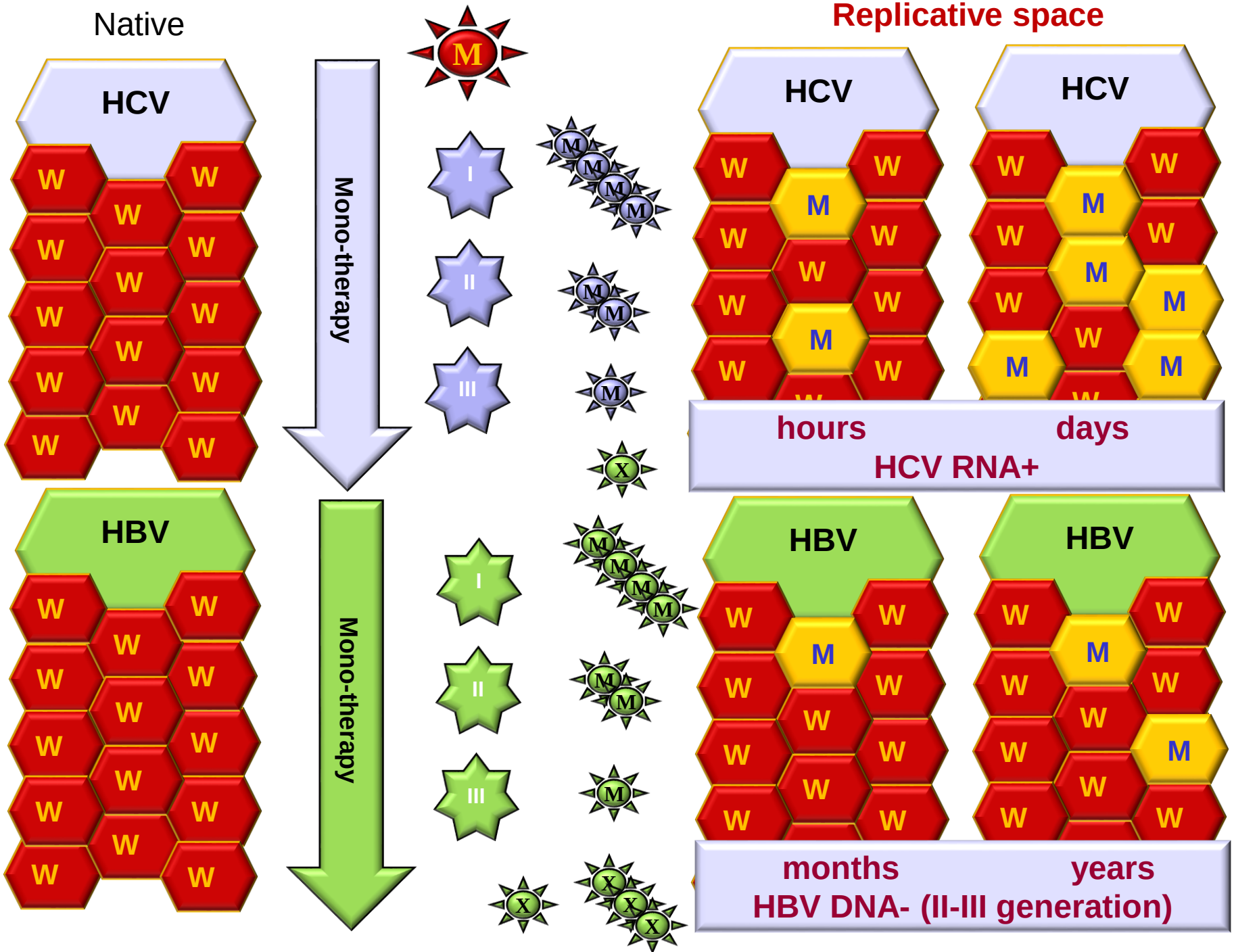


Modified from Moyle G, et al. Drugs. 1996

Drug levels, Genetic barrier and the virus

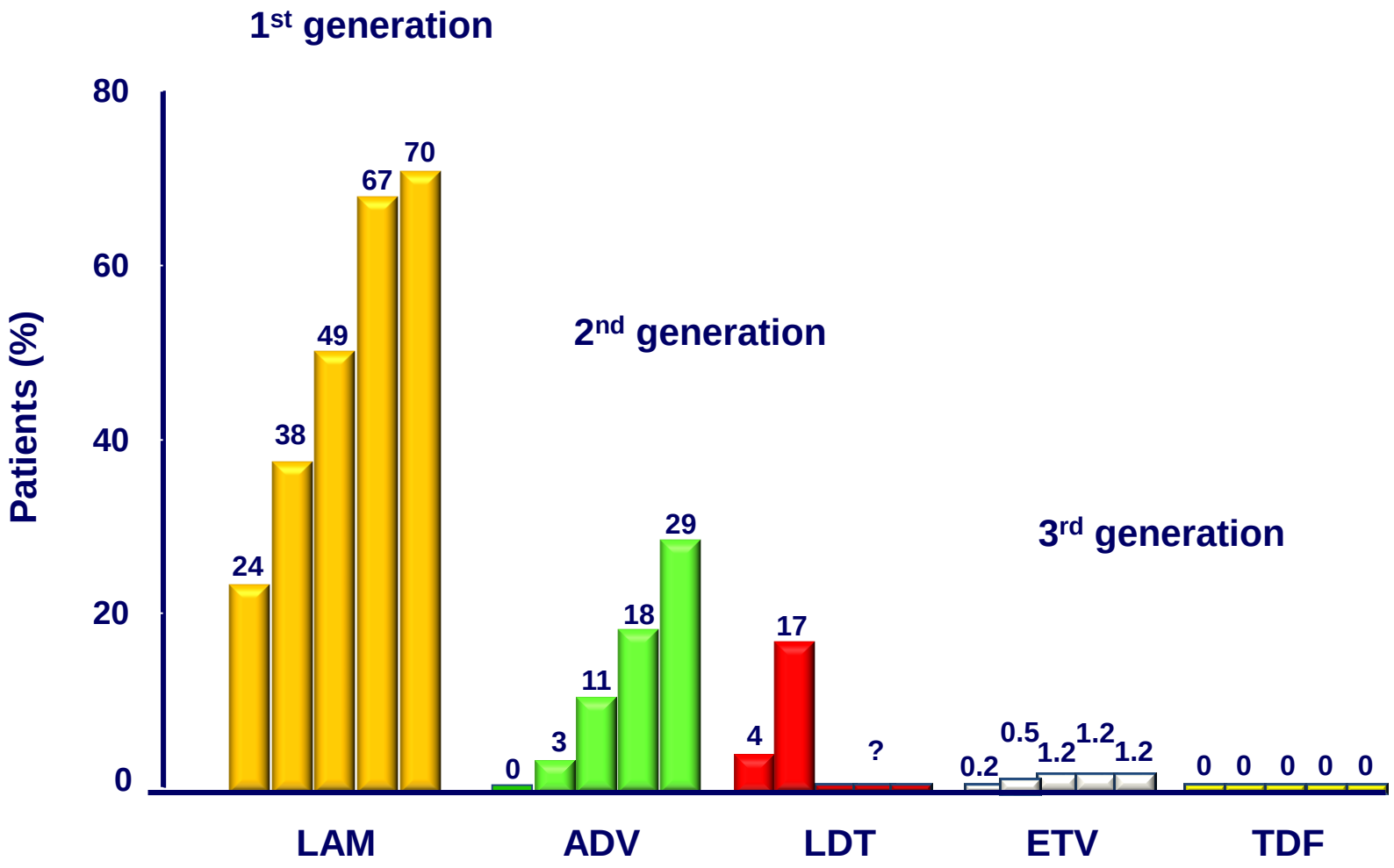


		HBV	HCV
Virus			
daily production of virions per day		10^{12}–10^{13}	10^{12}
half-life of free virions (h)		3–24	2–3
half-life of intracellular virions		months (dependent on infected cells $t_{1/2}$)	hours (not dependent on infected cells $t_{1/2}$)
mutation rate		high	very high
constraints due to ORFs in targeted viral enzymes		high	none
immune-mediated escape mutants		infrequent	frequent
Target cells			
half-life of infected cells		months	weeks
size of susceptible cells compartment		small	probably large
intracellular viral reservoir	yes (integrated cDNA)	yes (cccDNA)	no


Native
Replicative space
HCV
HBV
W
M
X
I
II
III
Mono-therapy
Mono-therapy
hours
days
HCV RNA+
months
years
HBV DNA- (II-III generation)

Genetic Barrier

Incidence of Resistance in NUC-naïve Patients



Therapy

Clinical Results

Can we reach clinical results with the NUCs?

Regression of histological cirrhosis with TDF

***Marcellin P; The Lancet* 2013**

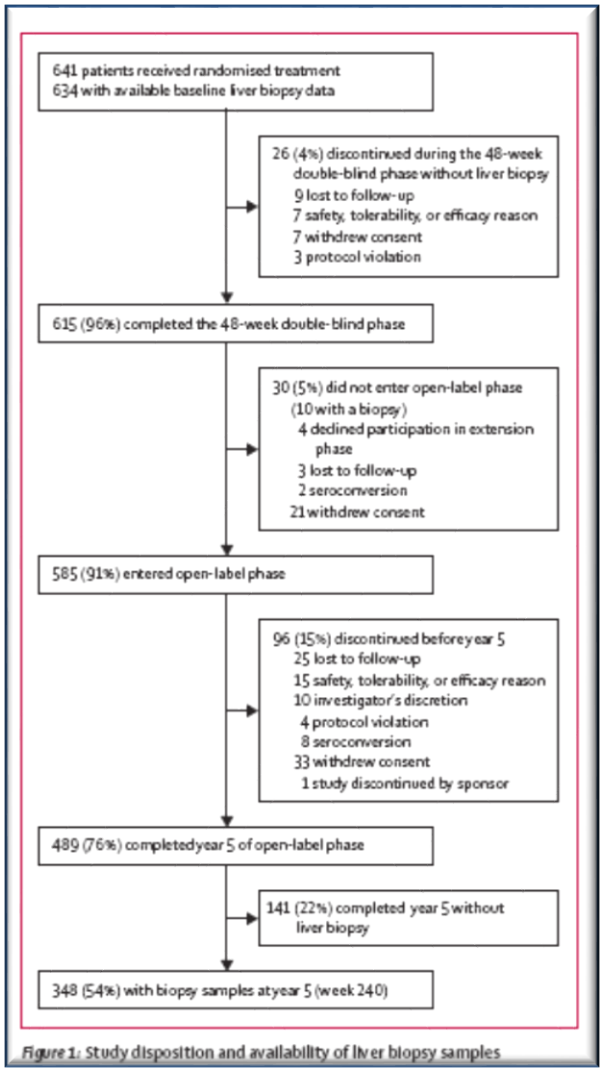


Figure 1: Study disposition and availability of liver biopsy samples

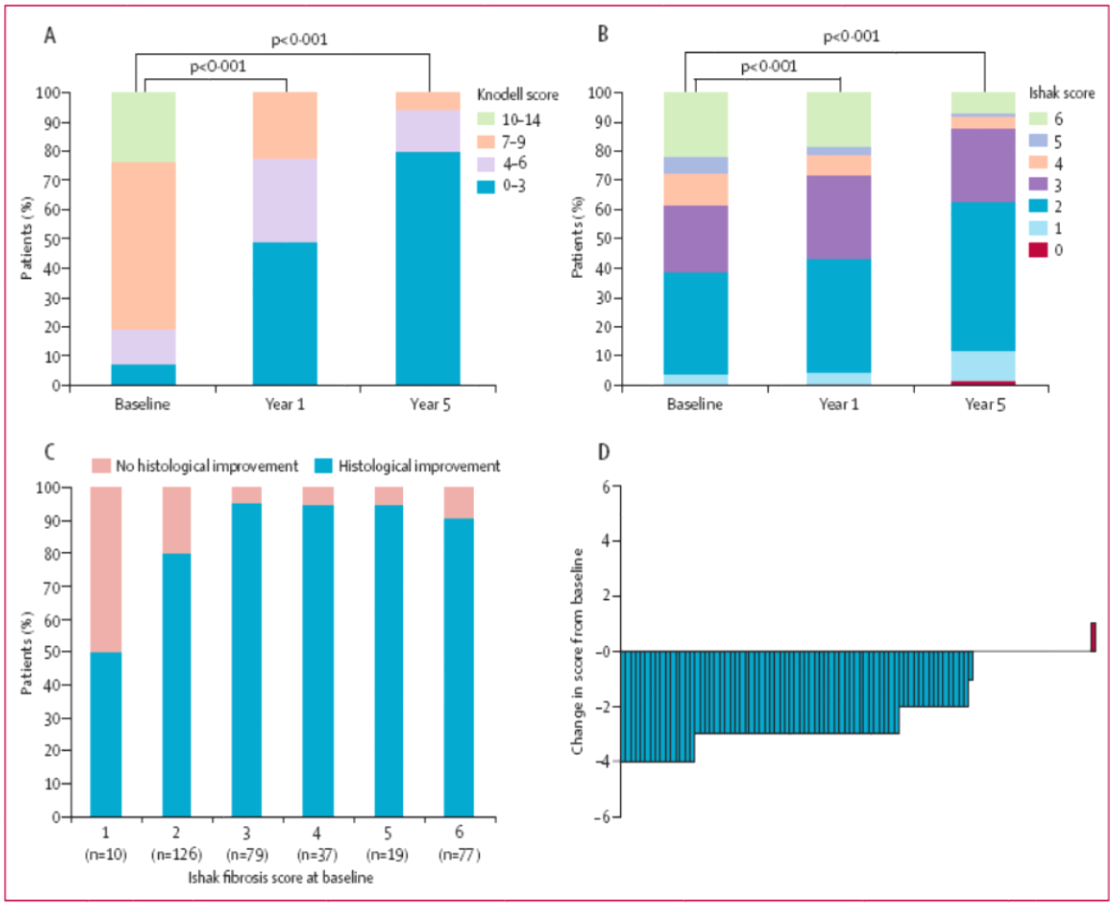
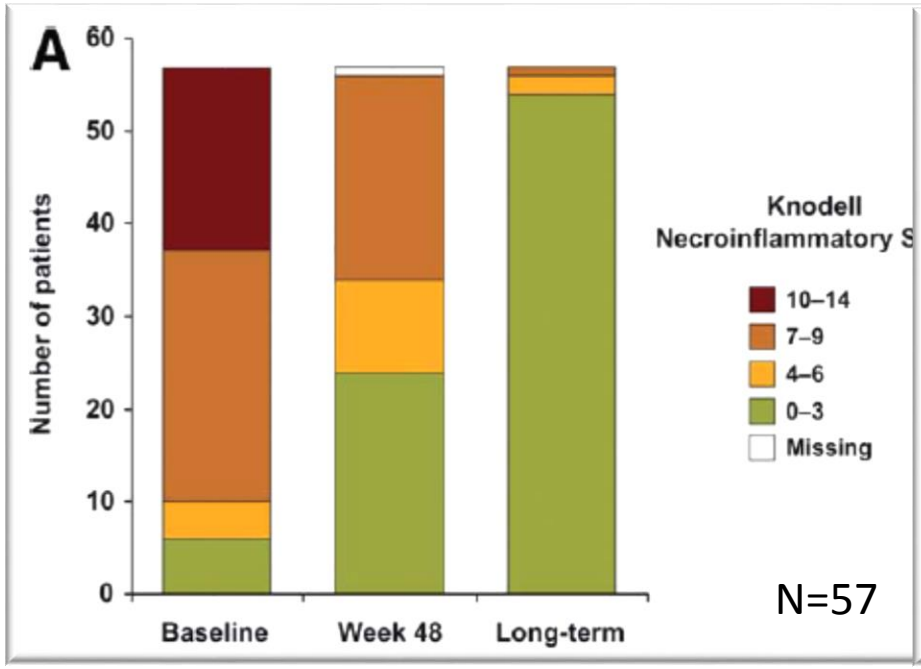
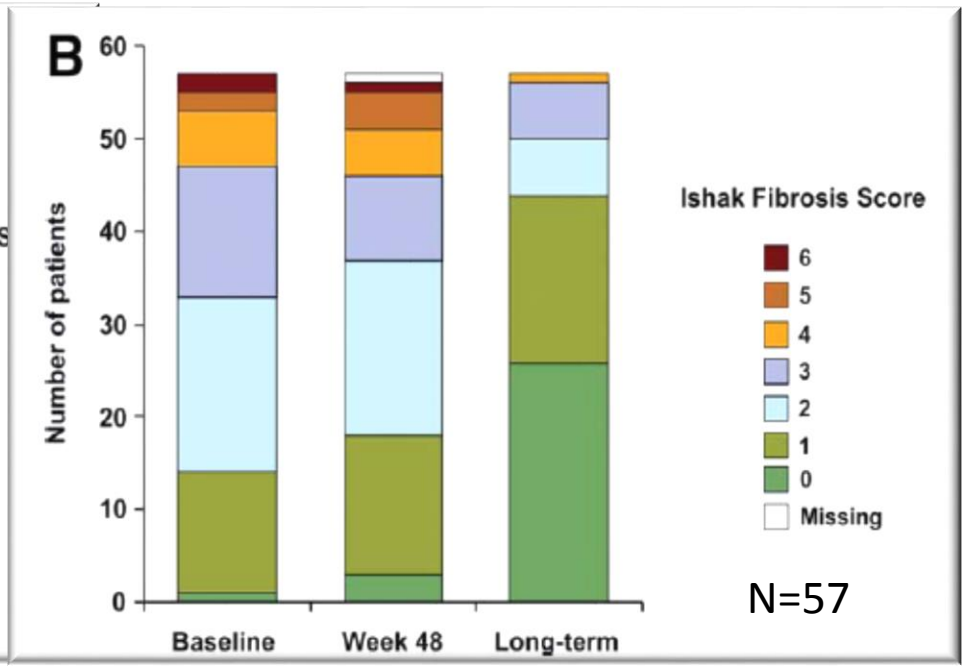


Figure 2: Histology results over 5-year treatment phase

(A) Distribution of Knodell necroinflammatory scores in 348 patients with results available at each time point. (B) Distribution of Ishak fibrosis scores in 348 patients with baseline and year 5 data, and 344 with data for all three time points. (C) Histological response at year 5 according to baseline Ishak fibrosis scores for 348 patients with data available at baseline and year 5. (D) Change from baseline to year 5 in Ishak fibrosis scores for the subset of 96 patients with cirrhosis (Ishak score ≥5) at baseline; each cell represents an individual patient's response. For 24 of 96 patients no changes were noted in Ishak score from baseline.

Reversal of fibrosis/cirrhosis with ETV





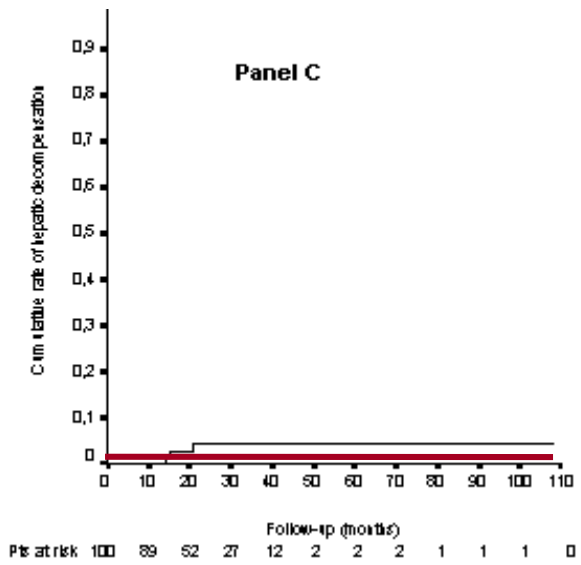
* Median time of long-term biopsy: 6 years (range: 3–7 years)

Chang TT, Hepatology 2010

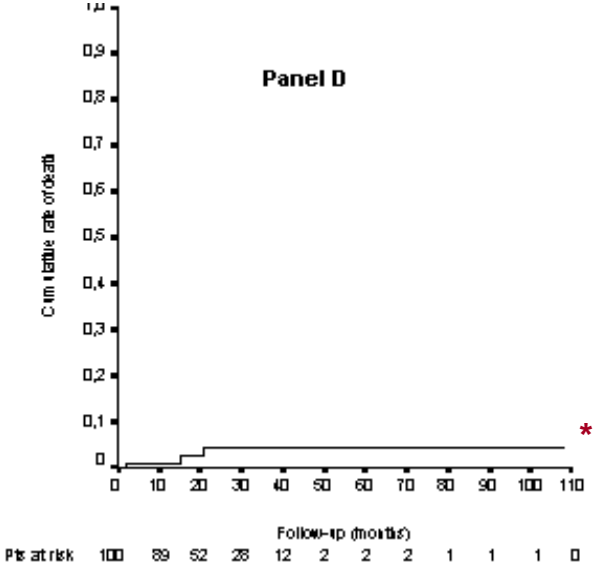
Clinical experience with III gen NUCs:

Entecavir 100 pts (55 compensated cirrhosis)

Decompensation



Death



*** 2 CH**

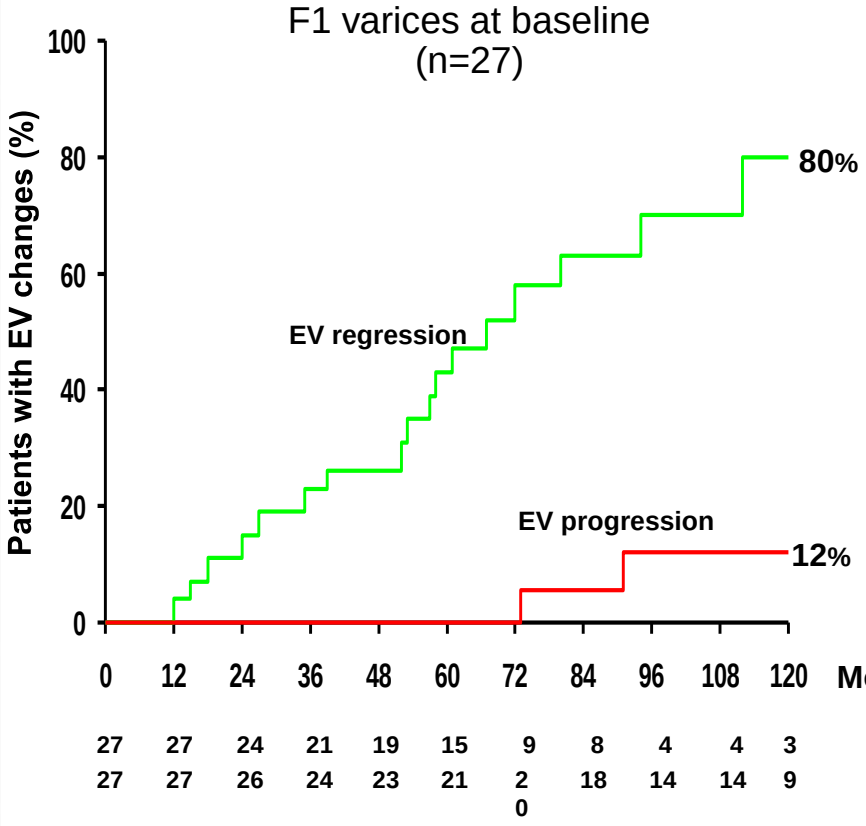
Cirrhosis

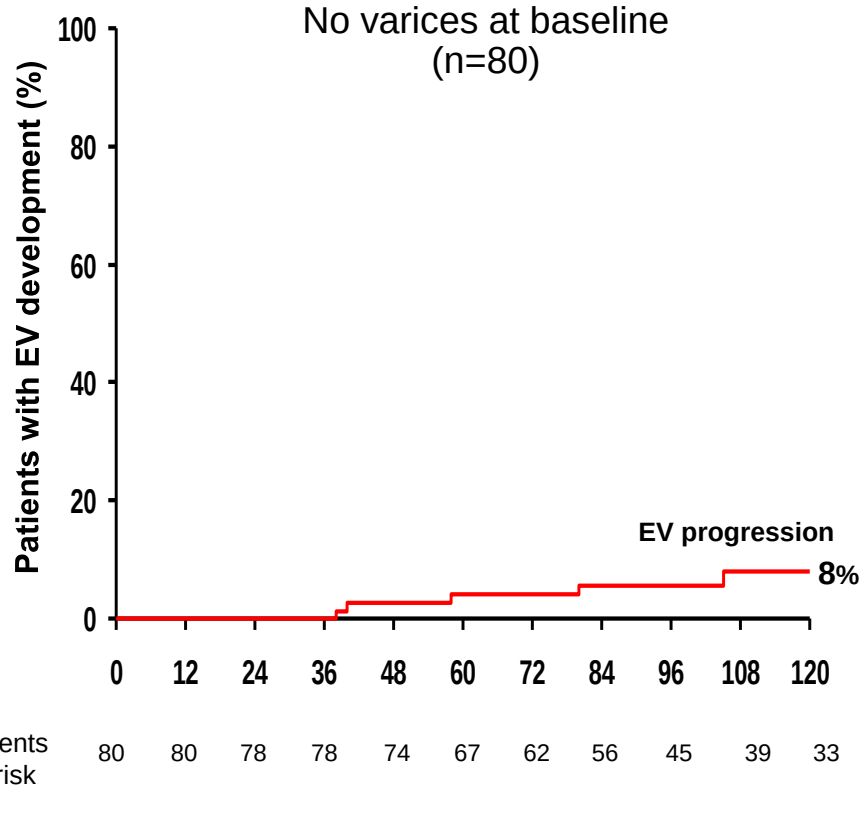
CH

Marengo, & Marzano Antiviral Therapy 2013

Changes of esophageal varices (EV) in compensated cirrhotics treated with LAM±TDF for 10 years

Overall, EV worsening rate per year: 0.9%*





* 6 of 7 progressors (86%) had either LMV-R and/or HCC

Lampertico et al, submitted 2013

Decompensated cirrhosis

Table 1 Studies of nucleos/tide analogues in patients with HBV-induced decompensated cirrhosis

Study(reference)	Fontana[26]	Schiff[27]	Liaw* [30]			Liaw[28]		Shim[29]
No. of patients treated	154	226	45	45	22	100	91	70
Drug(s) used	LAM	ADV+LAM	TDF	TDF+FTC	ETV	ETV	ADV	ETV
Baseline characteristics								
Lamivudine experienced	0%	100%	42%	38%	36%	36%	33%	0%
HBV DNA (log10 c/ml)	~7	7	5.7	6.3	5.9	7.5	8.2	7.2
CP score	9	60% B/C	7	7	7	8.8	8.4	8.4
MELD score	NR	NR	11.0	13.0	10.5	17.1	15.3	11.5
1-year efficacy and safety data								
Undetectable HBV DNA	NR	59%	71%	88%	73%	57%	20%	89%
CP ≥2 point decrease	NR	~50%	26%	48%	42%	35%	27%	49%
Decrease in MELD score	NR	2	2	2	2	2.6	1.7	2.3
Mortality	16%	14%	4%	4%	9%	12%†	12%†	12.9%§
HCC	NR	NR	NR	NR	NR	12%‡	20%‡	6.9%
Cr ≥0.5 mg/dl increase	NR	6%	9%	2%	5%	17%‡	24%‡	NR
Phosphorus <2.0 mg/dl	NR	NR	2%	4%	3%	NR	NR	NR
Drug resistance	27%	0	0%	0%	0%	0%	0%	NR

*Patients with 2 log decrease in HBV DNA at week 8 can switch to open label TDF+FTC.
†Mortality at 24 weeks, cumulative rates of mortality were 23% and 33% and of LT 11% and 3%, respectively, for ETV and ADV.
‡Cumulative rates.
§Mortality or liver transplant.
ADV, adefovir dipivoxil; CP, Child–Pugh score; ETV, entecavir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LAM, lamivudine; TDF, tenofovir disoproxil fumarate. FTC, emtricitabine; MELD, model for end-stage liver disease; NR, not recorded; MELD; model for end-stage liver disease.

Mutimer DJ, Gut 2012

Prophylaxis of hepatitis B recurrence after LT

2429 pts

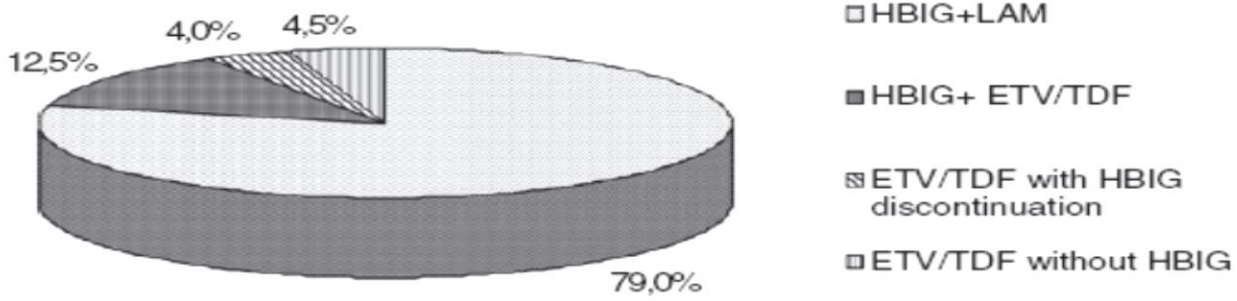


Figure 1: Subgroups of patients under antiviral prophylaxis against HBV recurrence after liver transplantation: 1910 (79%) patients received HBIG and LAM, 304 (12.5%) HBIG and ETV/TDF, 103 (4%) ETV/TDF after HBIG discontinuation and 112 (4.5%) ETV/TDF without any HBIG. HBIG= hepatitis B immunoglobulin; LAM= lamivudine; ETV= entecavir; TDF= tenofovir.

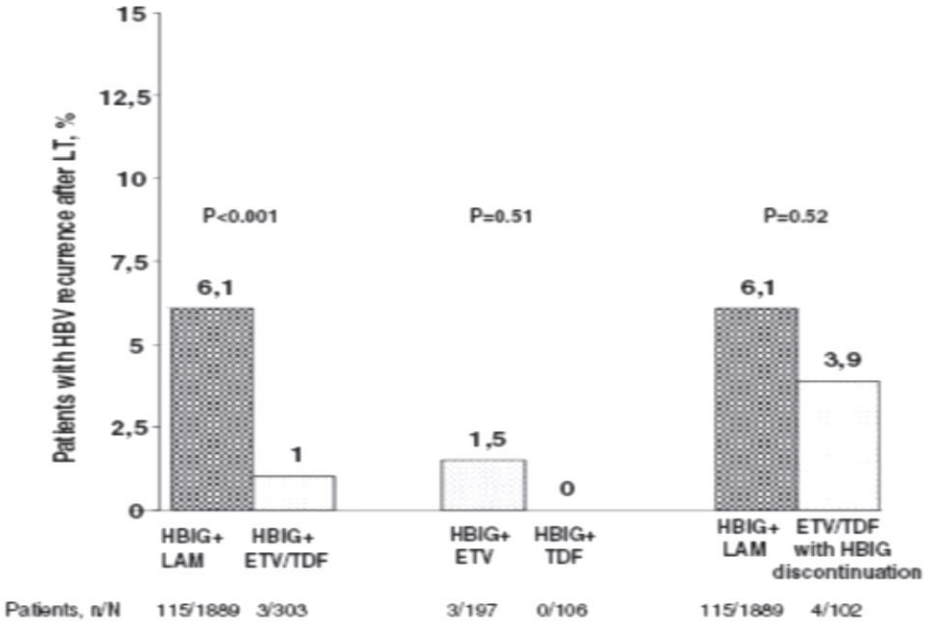
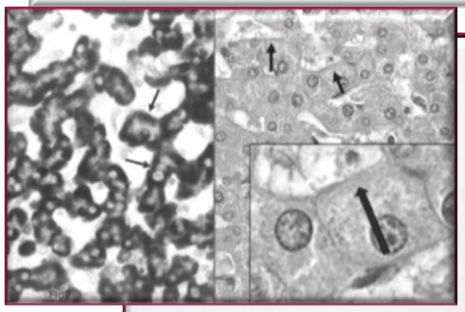


Figure 2: Risk of recurrence hepatitis B virus (HBV) infection after liver transplantation (LT) in relation to the type of posttransplant HBV prophylaxis. HBIG = hepatitis B immunoglobulin; LAM = lamivudine; ETV = entecavir; TDF = tenofovir.

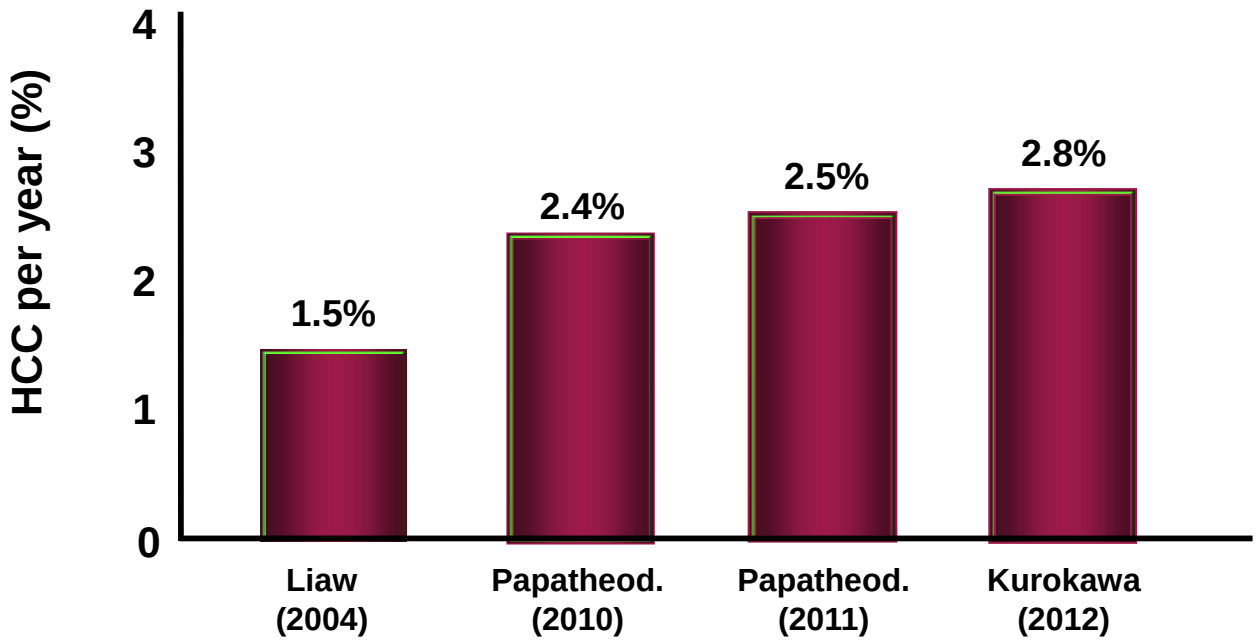
Excellent results but……

HCC remains the residual problem



Expected annual risk in Europe (untreated) 0.2% (CH) -2% (Cirrhosis)

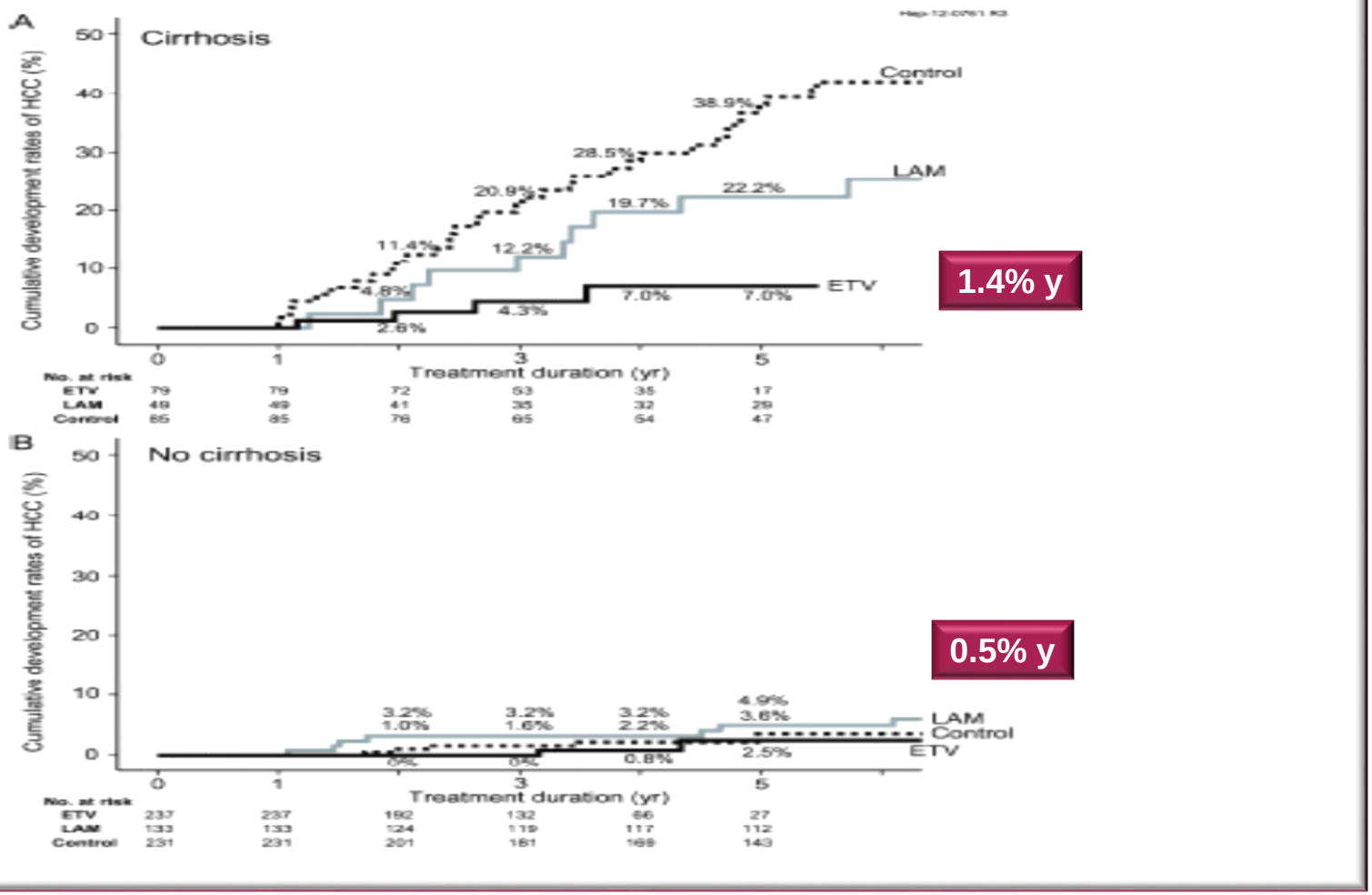
HCC rates in NUC-naïve cirrhotic patients long-term responding to NUC (LAM-exp)



Num. of pts:	211	81	62	42
Drug:	LAM	LAM	LAM	LAM
Study:	RCT	Review	Retrosp.	Retrosp.
Follow-up:	3 yrs	2 yrs	6 yrs	5 yrs

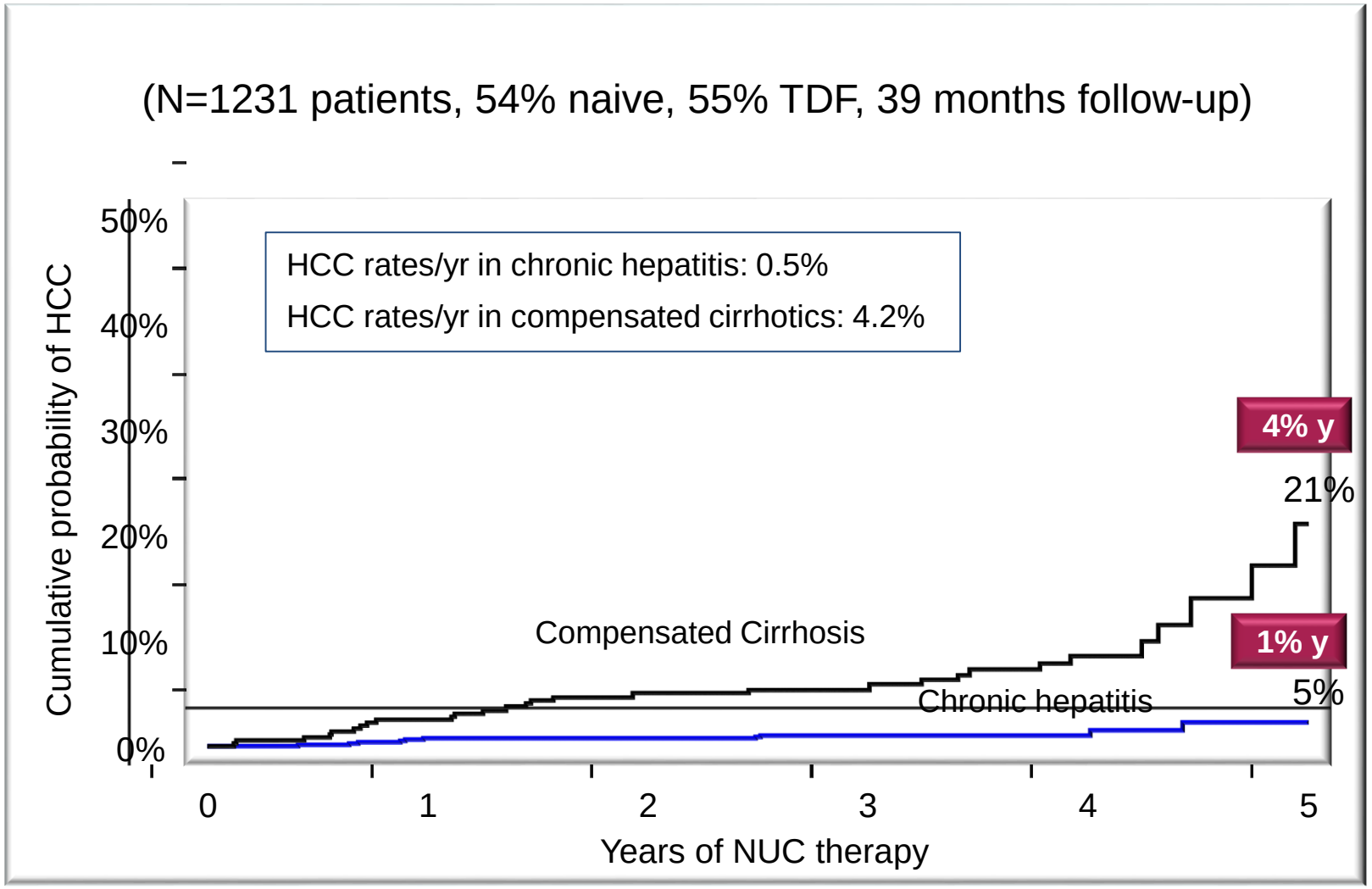
Aghemo A et al, J Hepatol 2012

Clinical experience with ETV: HCC in 472 (gen B-C) vs 1143 untreated patients



Hosaka, Hepatology 2012

HCC rates in ETV or TDF treated CHB pts
European multicenter study



Papatheodoridis G & Lampertico P et al, AASLD 2013

LT for HBV-related cirrhosis in US and Europe

Van Bommel, Liver Int 2013; Burra & Marzano, J Hepatol 2013

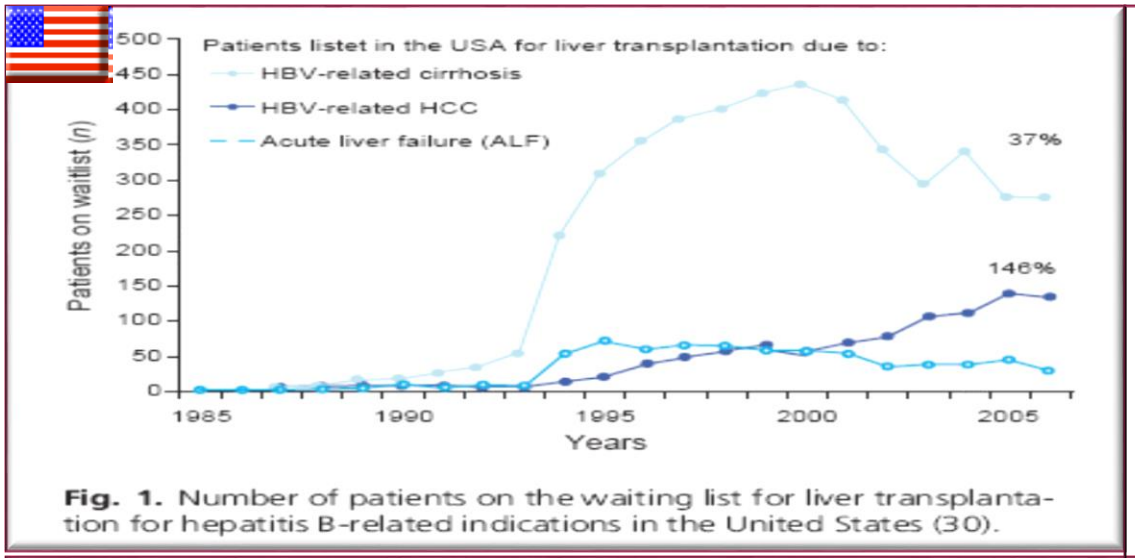
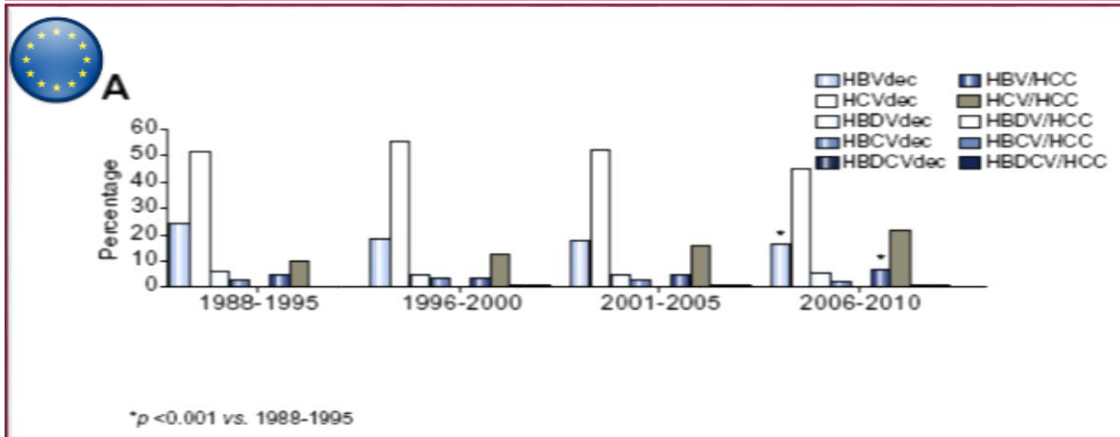


Fig. 1. Number of patients on the waiting list for liver transplantation for hepatitis B-related indications in the United States (30).

Decompens.
vs
HCC



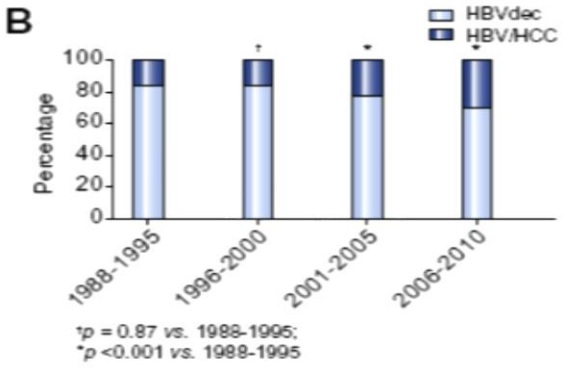
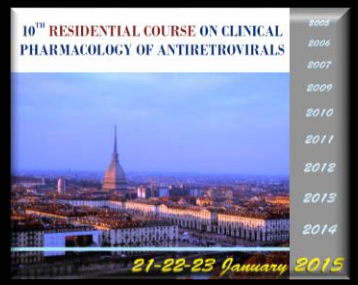


Fig. 1. Evolution of liver transplantation for virus-related chronic liver disease in Europe according to different time periods. (A) Evolution of liver transplantation for HBV-related liver disease considering the whole cohort of study. (B) Evolution of liver transplantation for HBV-related liver disease according to the indication for liver transplantation (HBVdec and HBV/HCC).

Summary



DE BEERS
A DIAMOND IS FOREVER

HBV …. too