



HBeAg-positive chronic hepatitis B

Why do I treat my patient with a nucleos(t)ide analogue ?

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WHY NOT!!

- **Efficacious!**
- **Safe!**
- **Cost effective!**

Landmarks for Prevention and Treatment

HBV Vaccine

Universal vaccination for newborns +/- HBIG



α-Interferon

Lamivudine

Adefovir

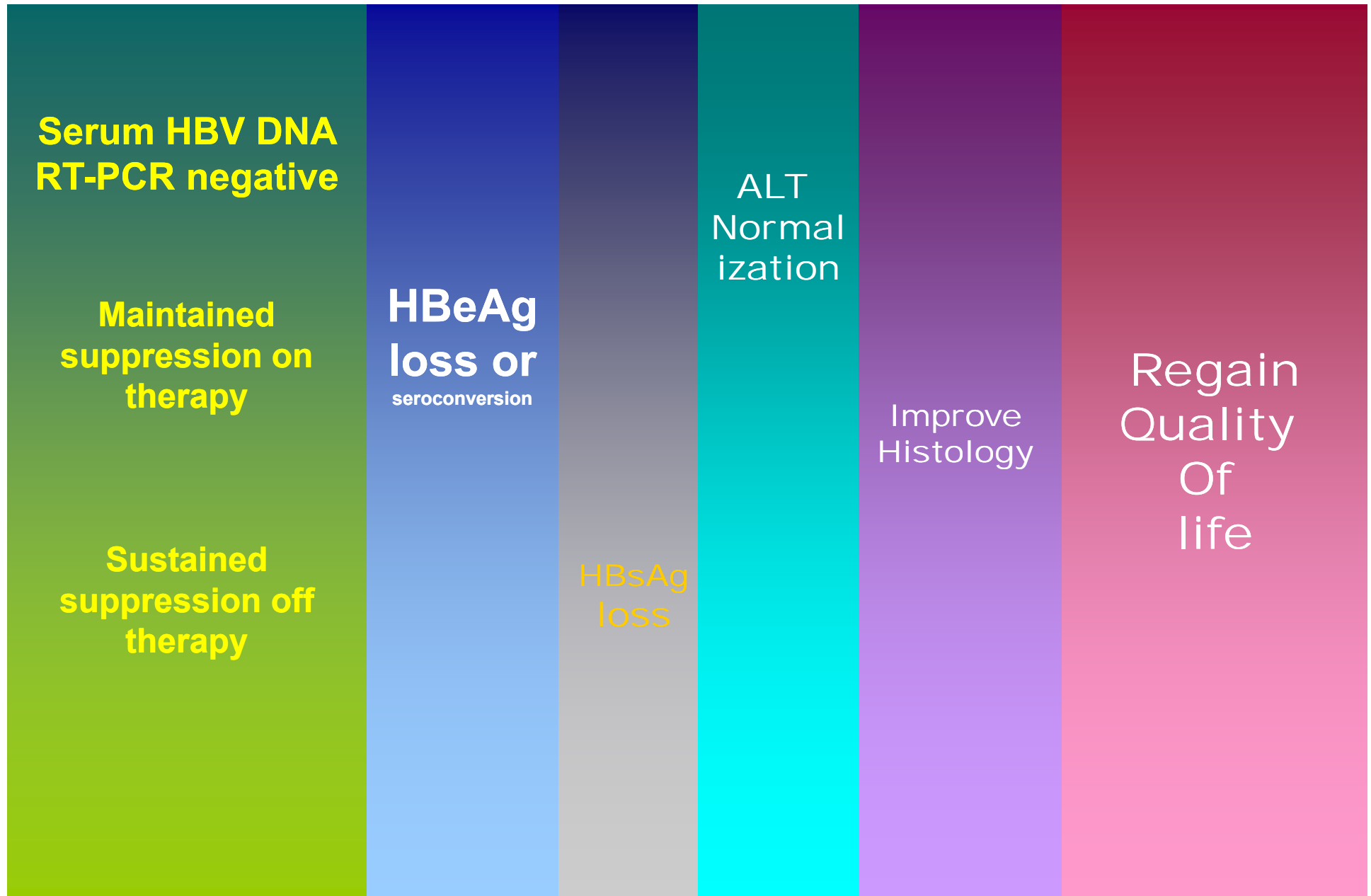
Pegylated Interferon α-2a

Entecavir

Telbivudine

Tenofovir

Milestones and Goals for Therapy



Serum HBV DNA
RT-PCR negative

Maintained
suppression on
therapy

Sustained
suppression off
therapy

HBeAg
loss or
seroconversion

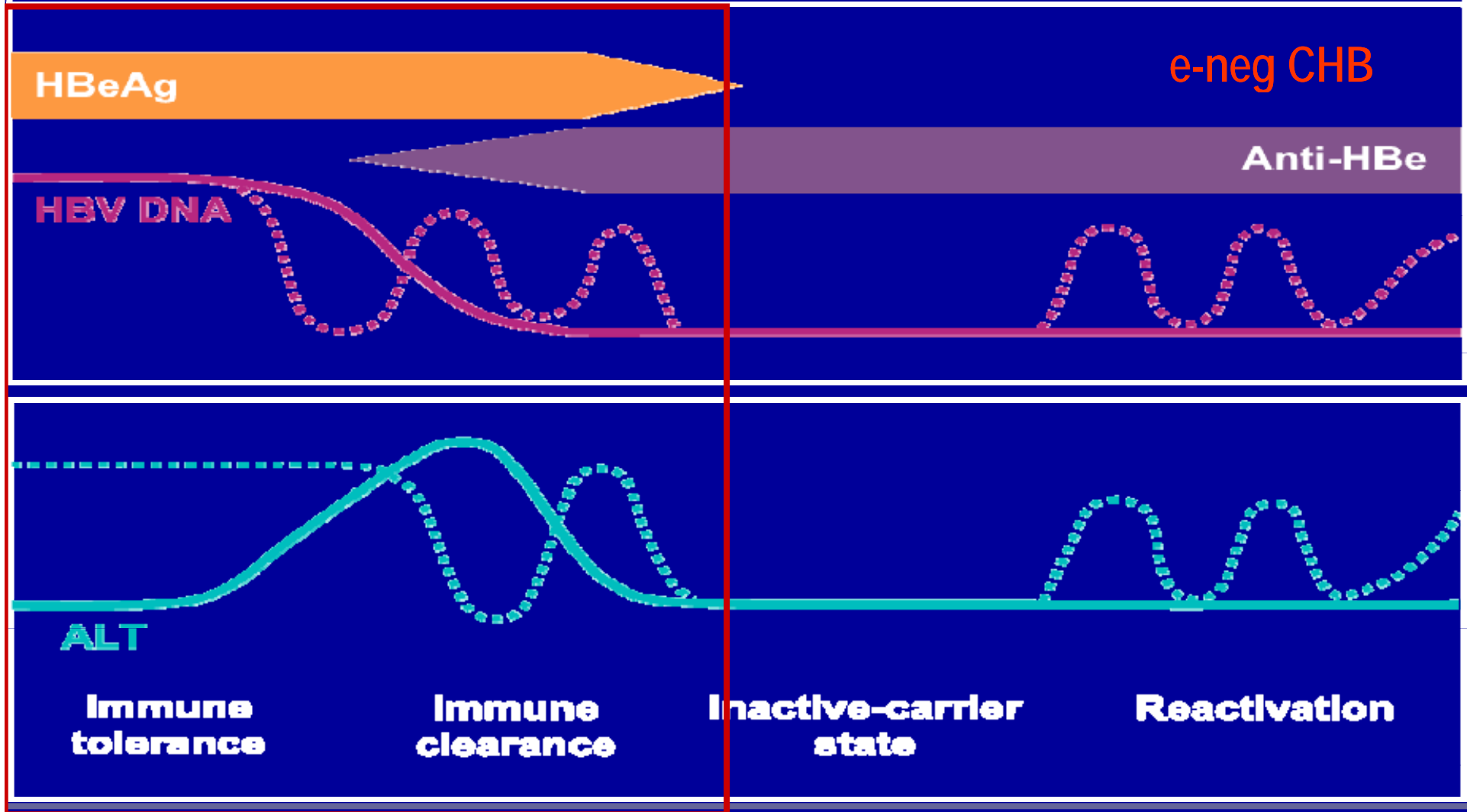
HBsAg
loss

ALT
Normal
ization

Improve
Histology

Regain
Quality
Of
life

Natural Course of Chronic HBV Infection



Natural Course of

HBeAg

Increasing age, persistent HBeAg positivity
⇒ higher incidence of cirrhosis and HCC (3.5%/ yr)
even in asymptomatic subjects

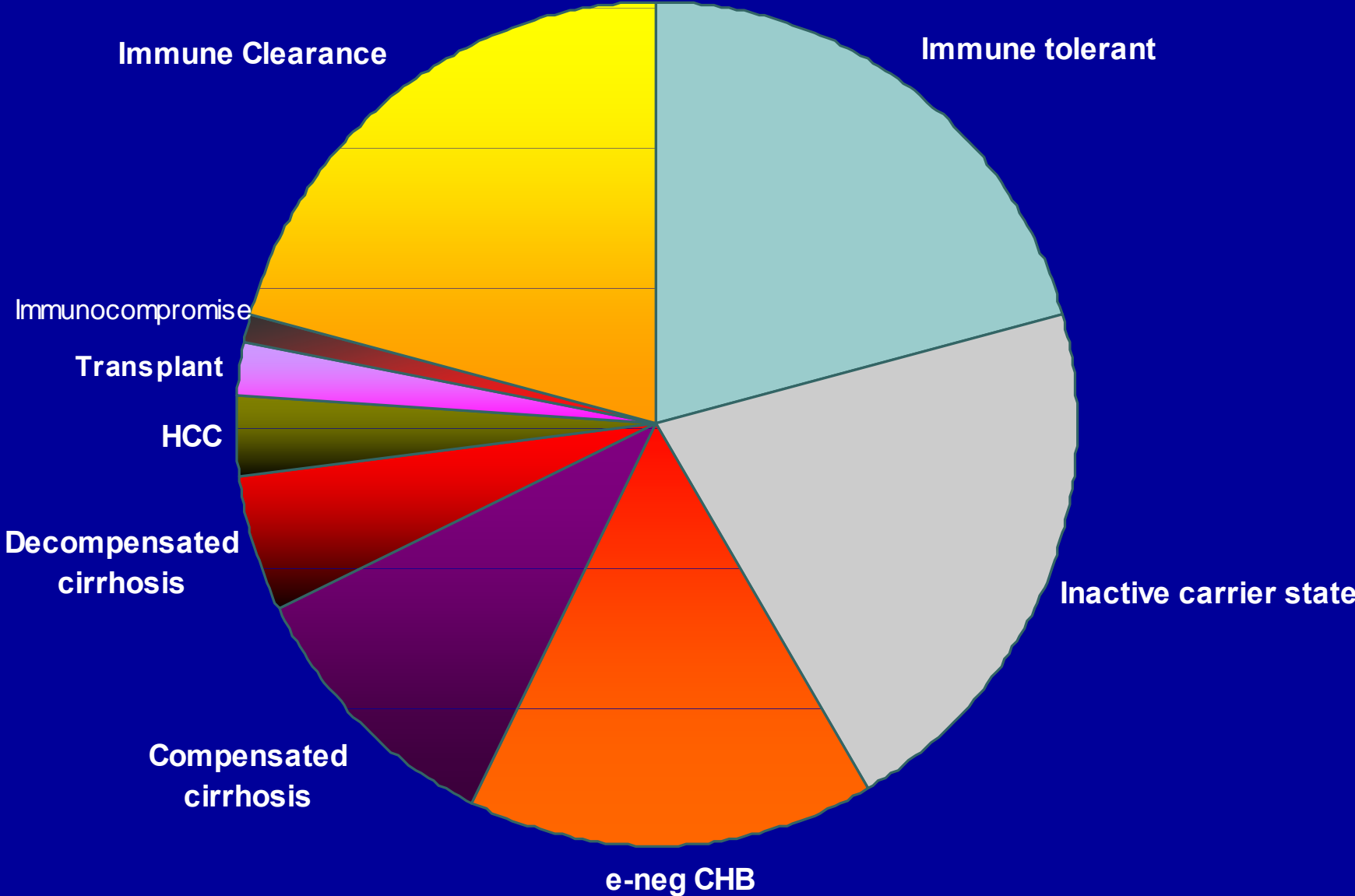
HBV DNA

ALT

**Immune
tolerance**

**Immune
clearance**

Spectrum of HBV Disease in Clinical Practices



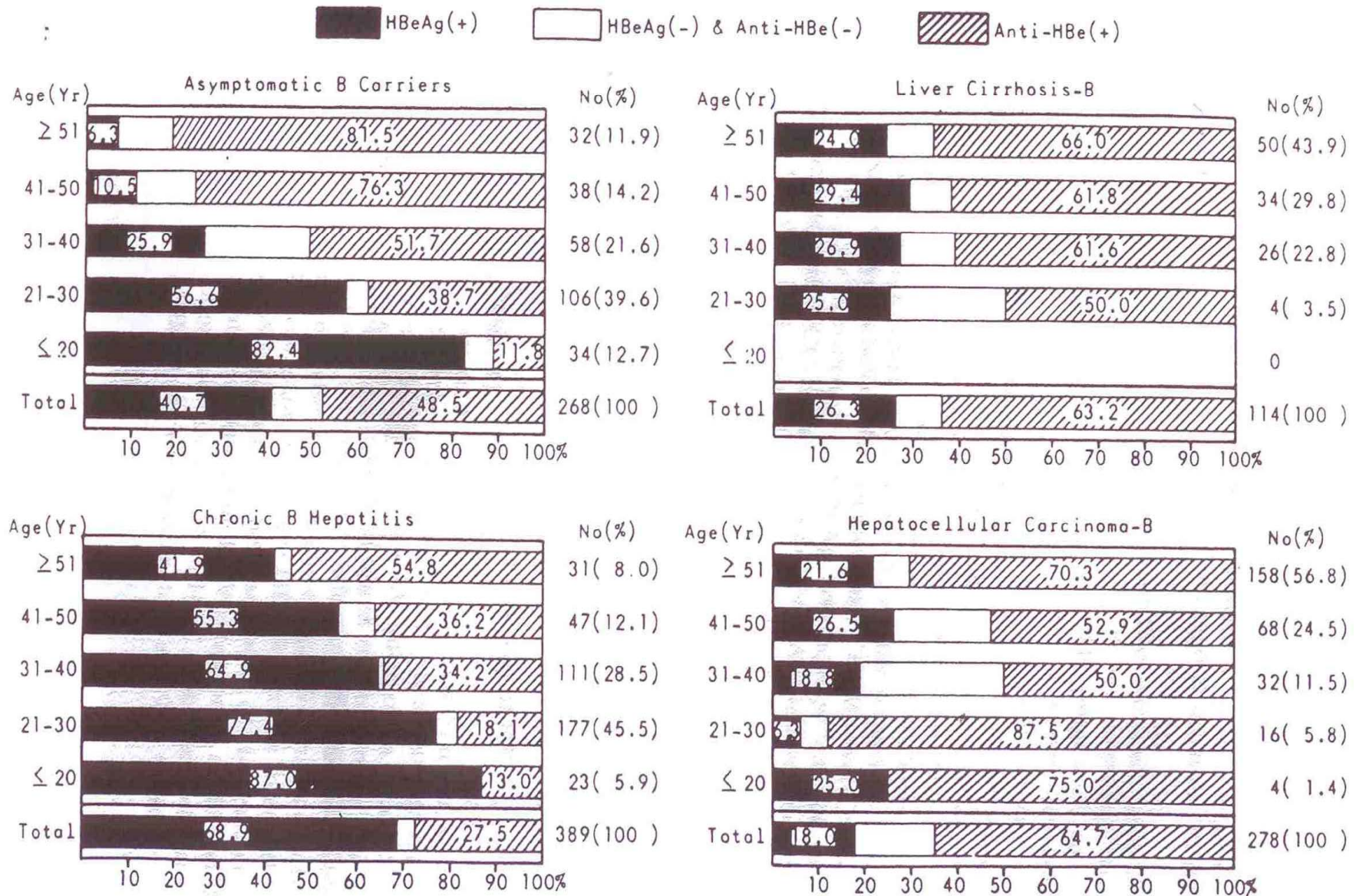


Fig. 1. The age-specific prevalence of HBeAg and anti-HBe in asymptomatic HBsAg carriers, patients with HBsAg positive chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The figures inside the bars represent percentage of respective markers.

More natural history data:

Delayed HBeAg seroconversion >Age 40

→ Significantly Higher Risk of e-neg CHB, Cirrhosis, and HCC

- N= 483, no evidence of cirrhosis or HCC at time of HBeAg seroconversion
- 15-year cumulative incidences

	HBeAg-negative hepatitis	Cirrhosis	HCC
(A) e-sero before 30	31.2%,	3.7%,	2.1%,
(C) e-sero after 40	66.7%	42.9%	7.7%
	(<i>P</i> < 0.0001)	(<i>P</i> < 0.0001)	(<i>P</i> = 0.29)
Hazard ratio (C) vs (A)	2.95	17.6	5.22

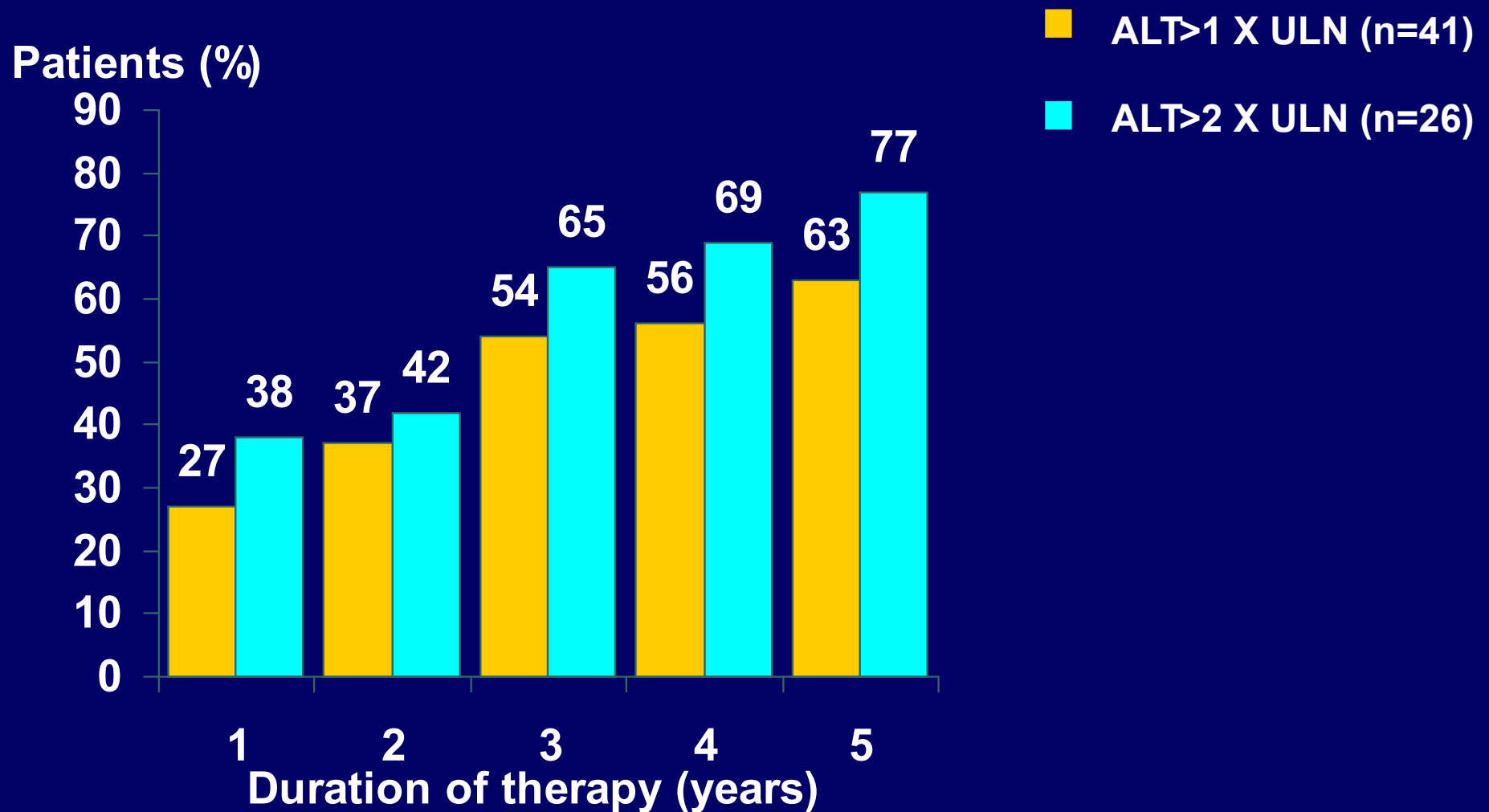


WHICH NA ?

- **Efficacious!**
- **Safe!**
- **Cost effective!**

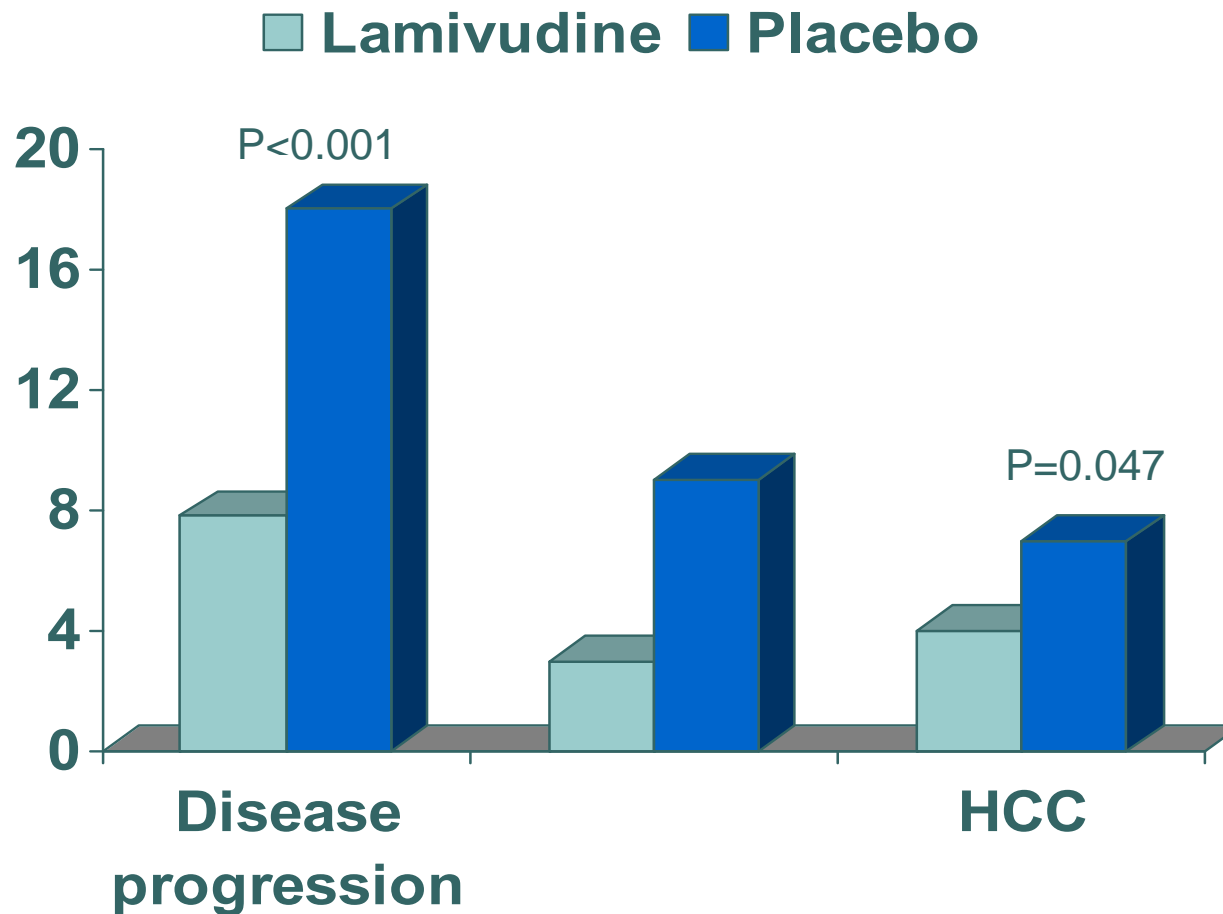
Lamivudine HBeAg seroconversion over 5 years of treatment in patients with elevated ALT

Seroconversion = HBeAg-ve and HBeAb+ve



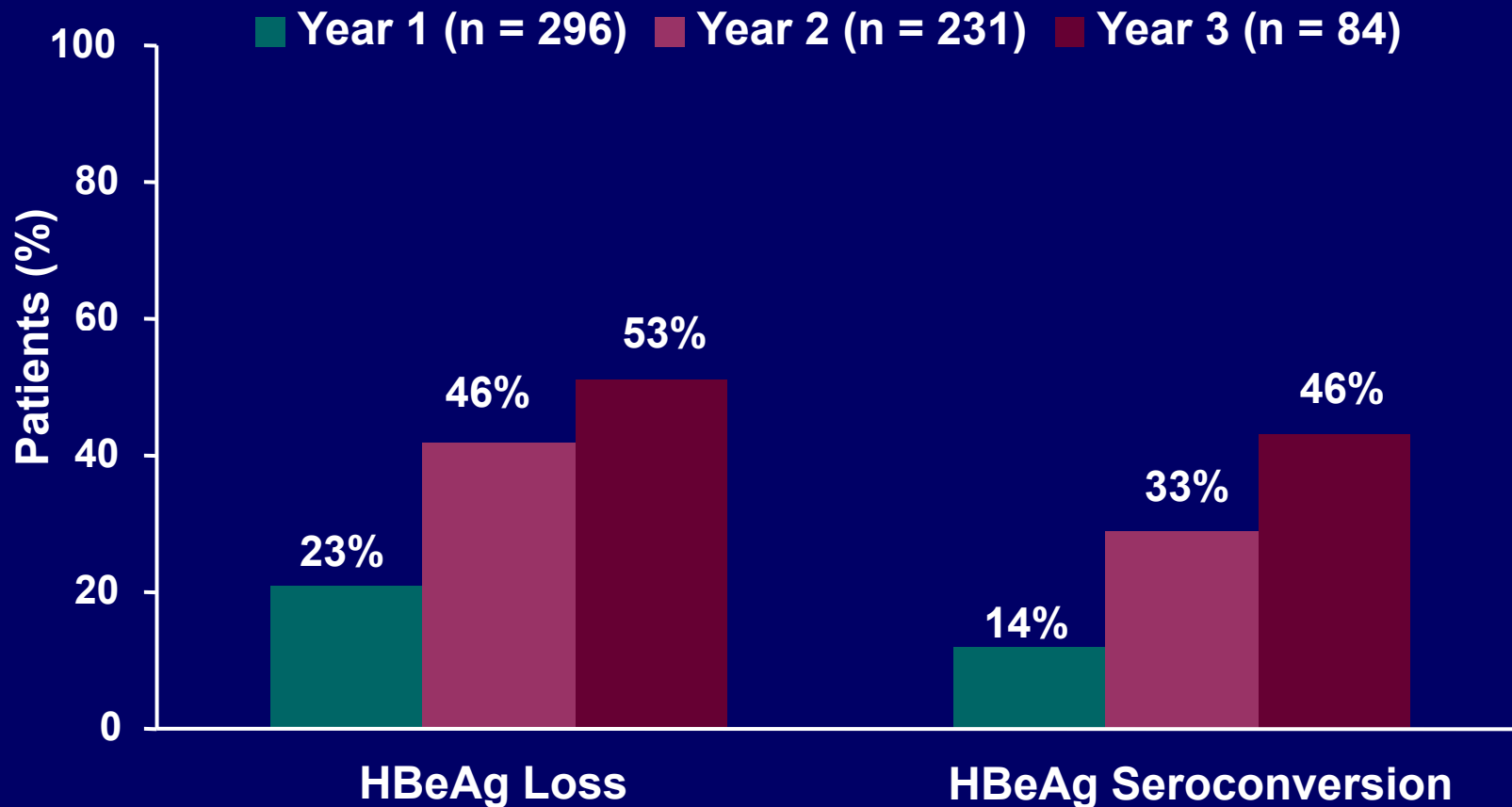
Effect of Lamivudine on Disease Progression and Development of Liver Cancer in Advanced CHB:

N=651 Randomized double blind placebo control trial
Study terminated at second interim analysis



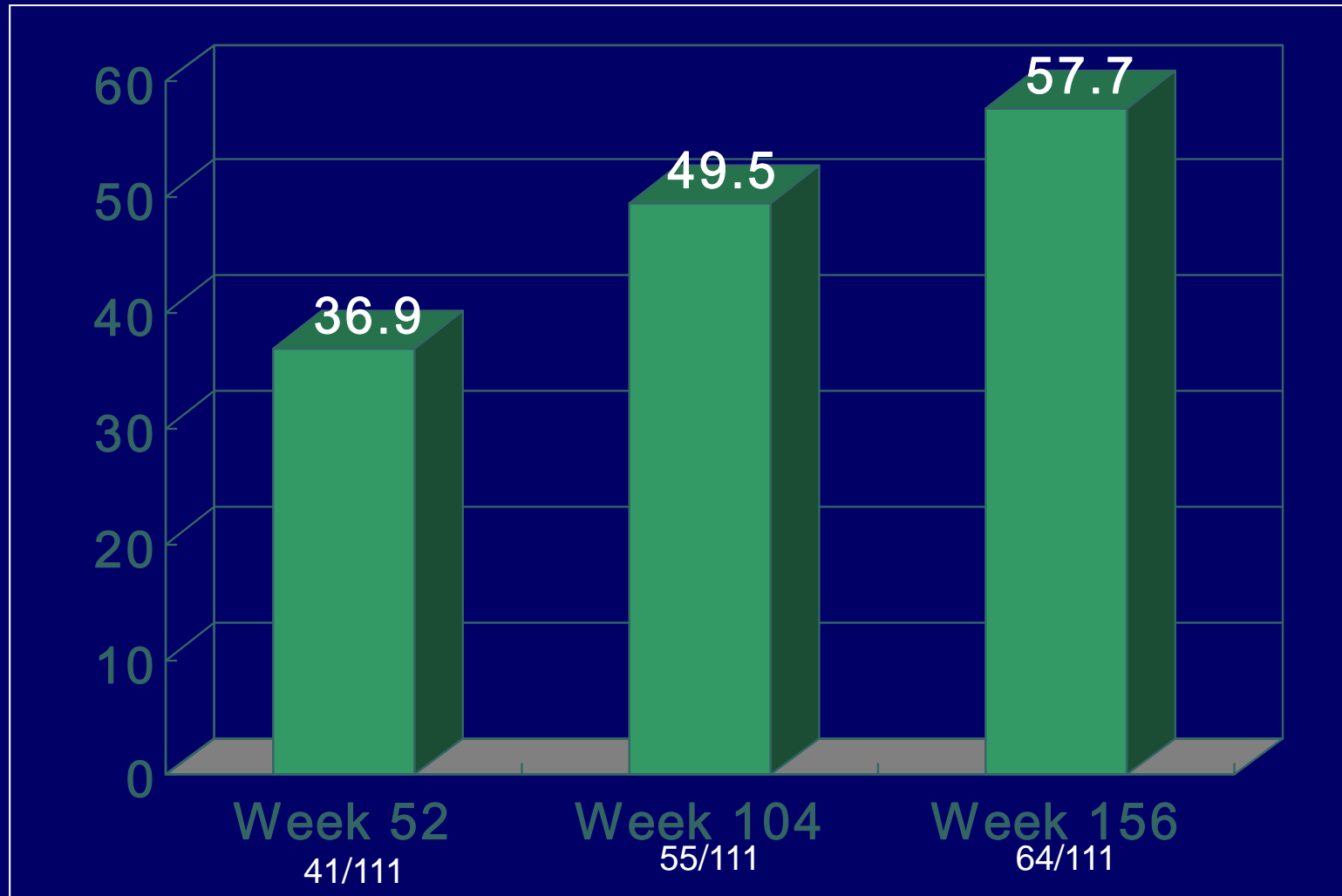
Adefovir dipivoxil: Increasing HBeAg Serological Response with Prolonged Treatment*

- 20-50% of patients failed to achieve 2log₁₀ reduction in serum HBV DNA



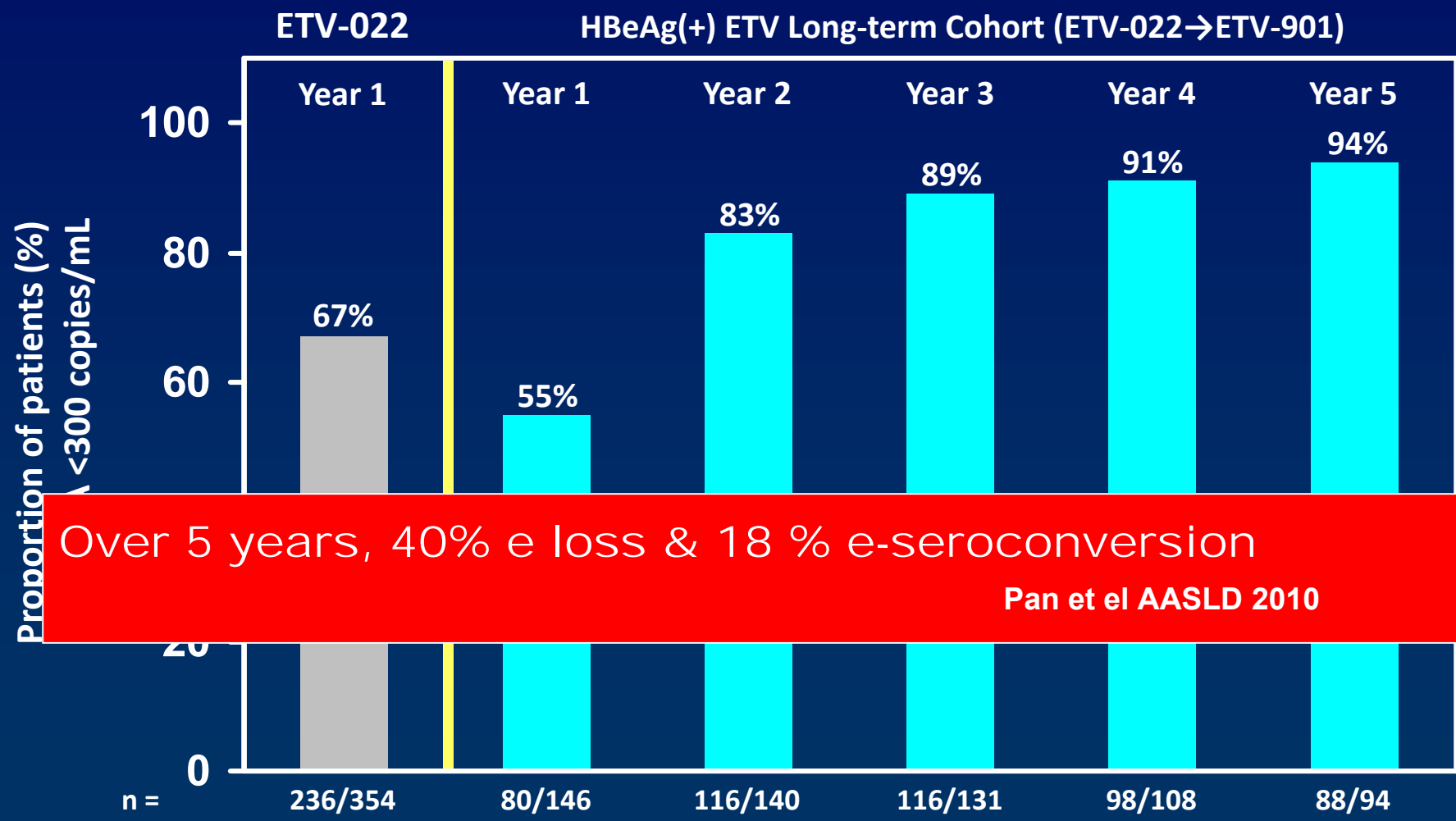
*Kaplan Meier estimates

Cumulative HBeAg Seroconversion over 3 Years **GLOBE** Telbivudine **Study** Among CHB Patients Achieving HBV DNA <300 cpm by Week 24



52 patients stopped therapy 24 weeks after HBeAg seroconversion + HBV DNA <300cpm. 84% sustained response in one year.

Entecavir - % of Patients Achieving HBV DNA < 300 copies/mL through 5 Years



Over 5 years, 40% e loss & 18 % e-seroconversion
Pan et al AASLD 2010

Chang TT, Lai CL et al (in preparation)

Entecavir - HBeAg & HBsAg Seroconversion

Week 96

31% (110 / 354) HBeAg seroconversion

5% (18 / 354) HBsAg seroconversion

Week 96 – Year 5

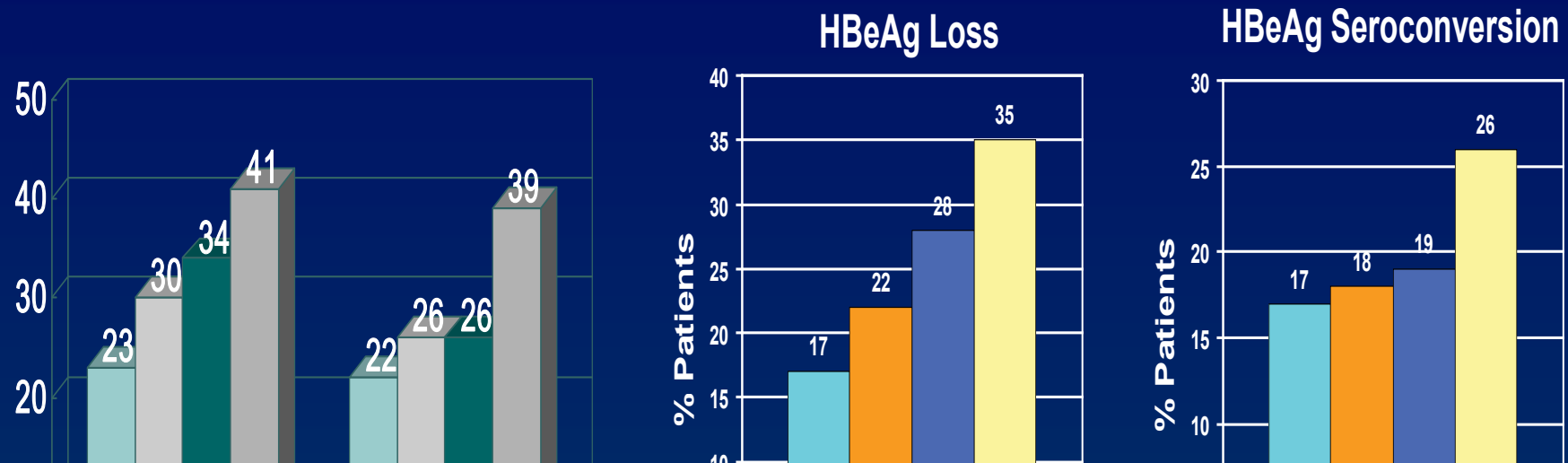
23% (33 / 141) additional HBeAg seroconversion

1.4% (2 / 145) additional HBsAg seroconversion

4 Years Tenofovir Therapy for HBeAg Positive CHB: Increasing Serological Response*

*Kaplan Meier estimates

GS-US-174-0103 (HBeAg+)



S loss at year 3 was 8%, increased to 15.2% at year 4

Gordon SC et al AASLD 2010

S loss 10% S seroconversion 7.5%

Heathcote J et al AASLD 2010

- No resistance detected
- Stable creatinine levels
- Good tolerability.

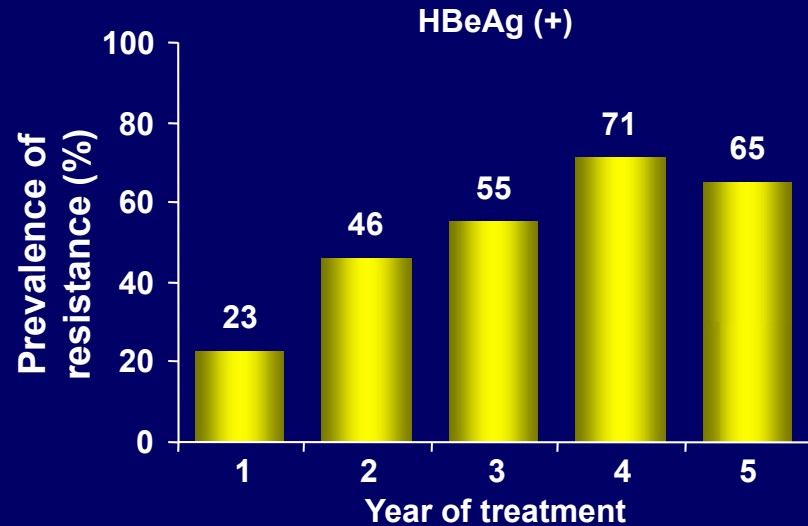
Gane E et al AASLD 2010 Poster # 481

Viral response usually followed by biochemical, histologic improvement, even regression of fibrosis

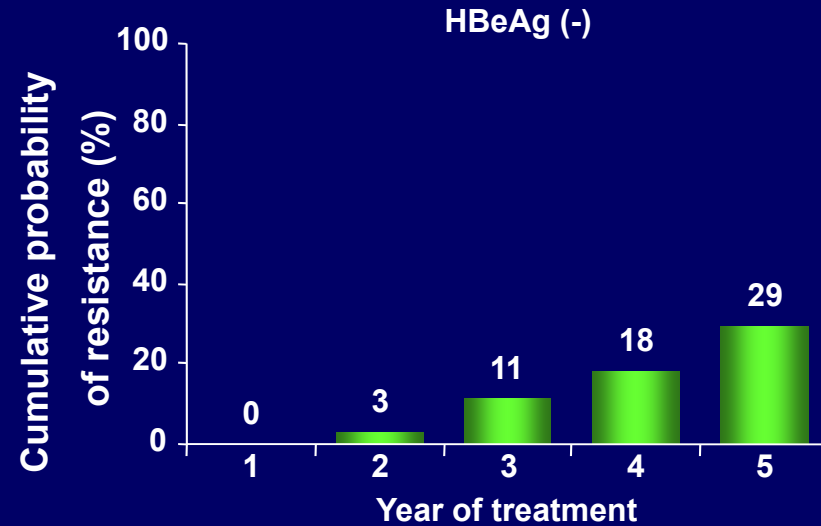
Main Issue with NAs..... Drug Resistance

Drug Resistance

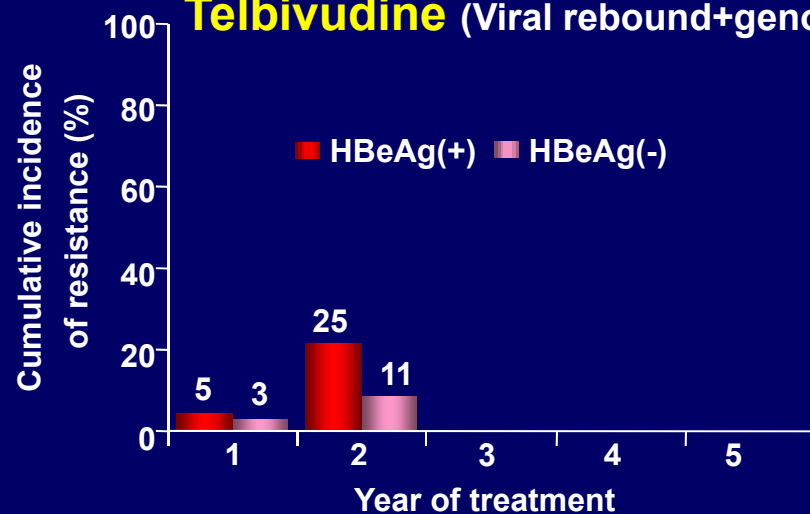
Lamivudine (Genotypic)



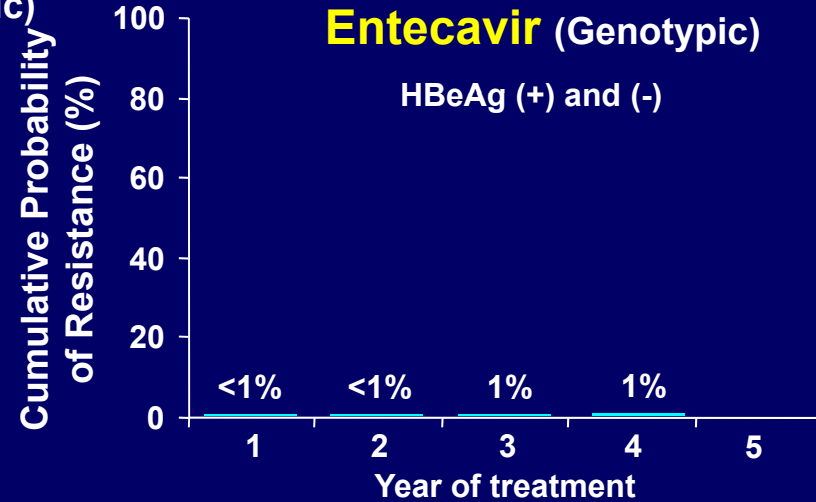
Adefovir (Genotypic)



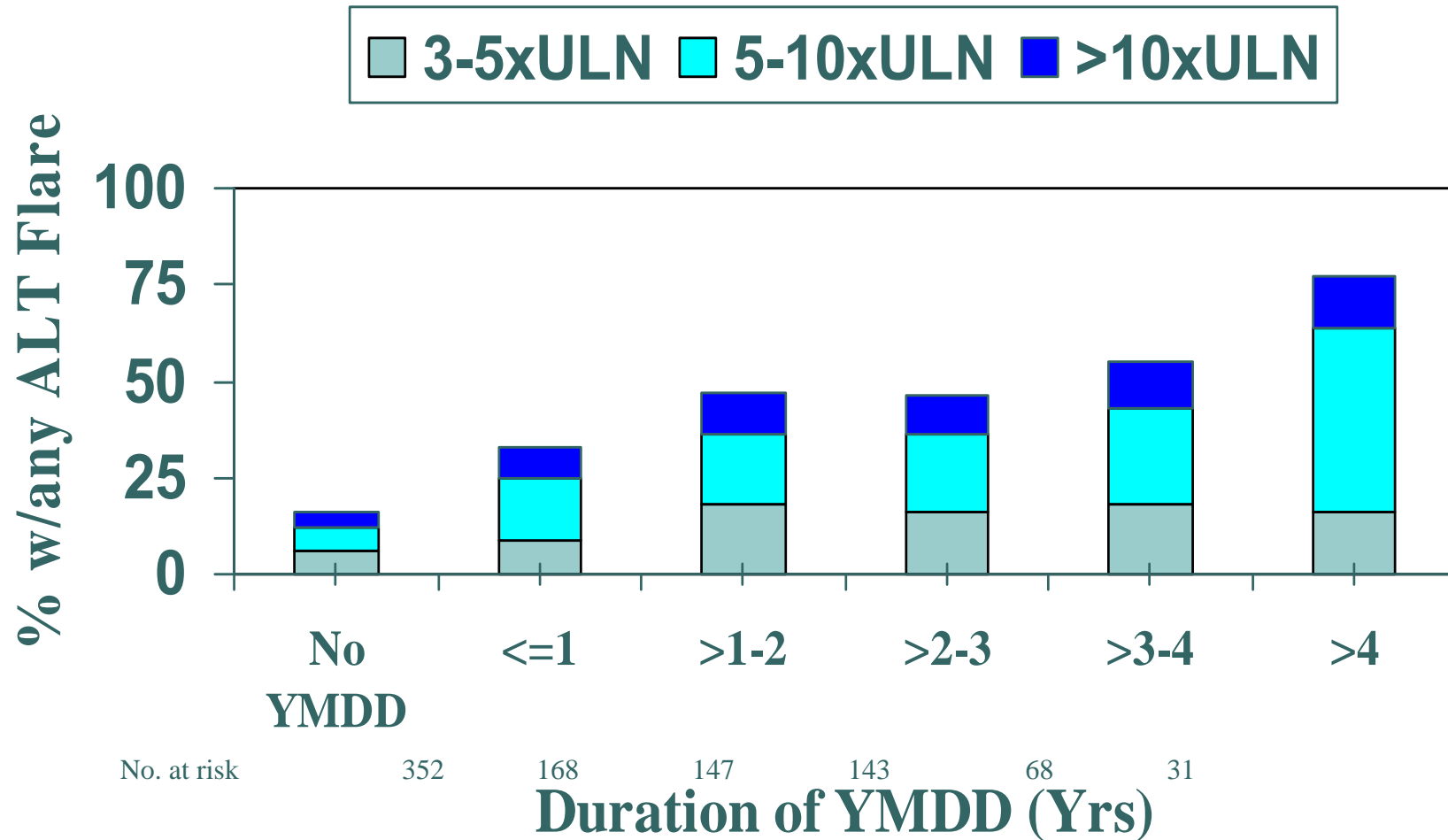
Telbivudine (Viral rebound+genotypic)



Entecavir (Genotypic)



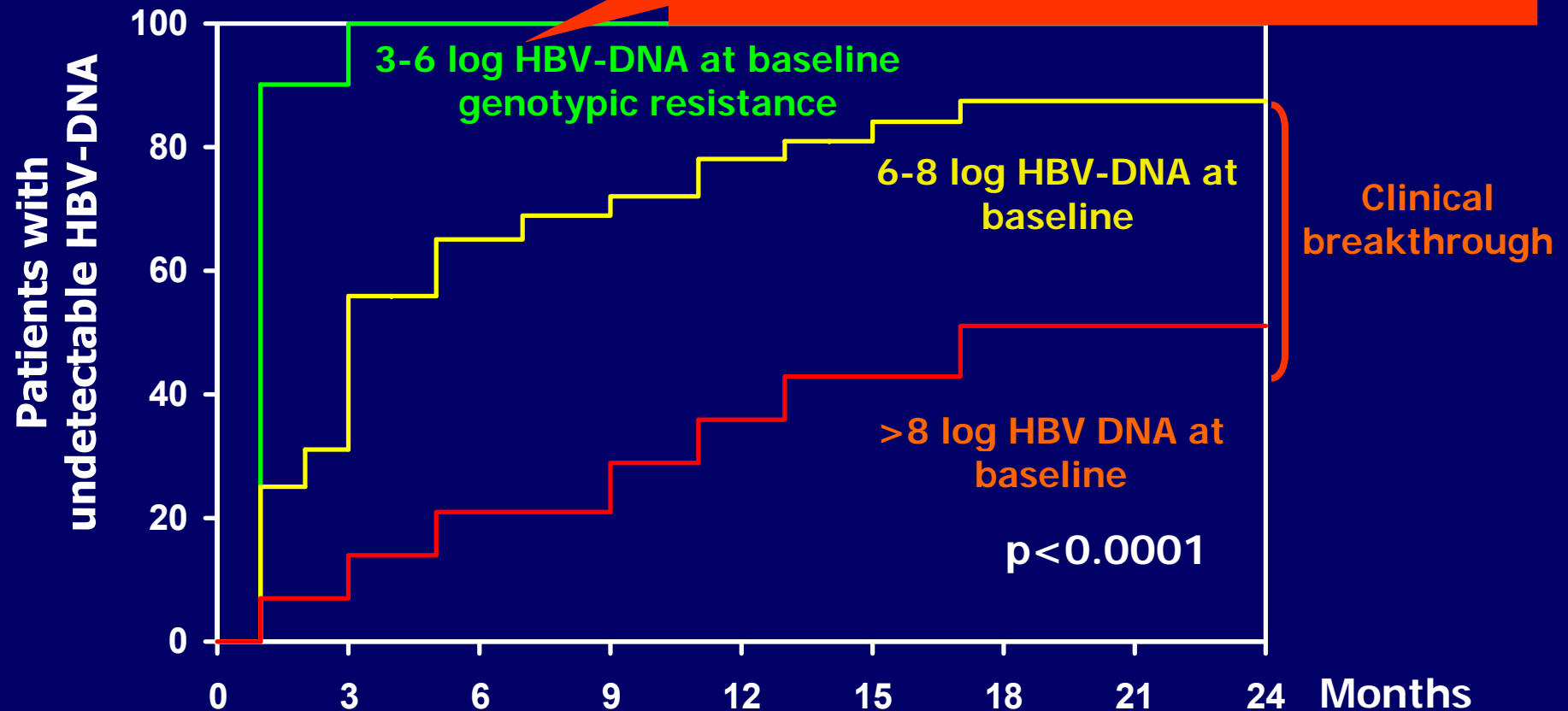
Hepatitis Flare Among Patients with Lamivudine Resistant Mutants for <1 to >4 Years vs Those Without



ADV Added to LAM in LAM-r Patients

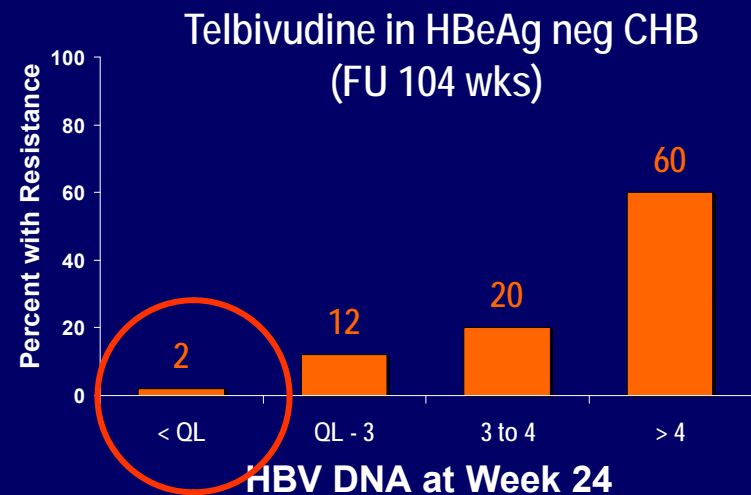
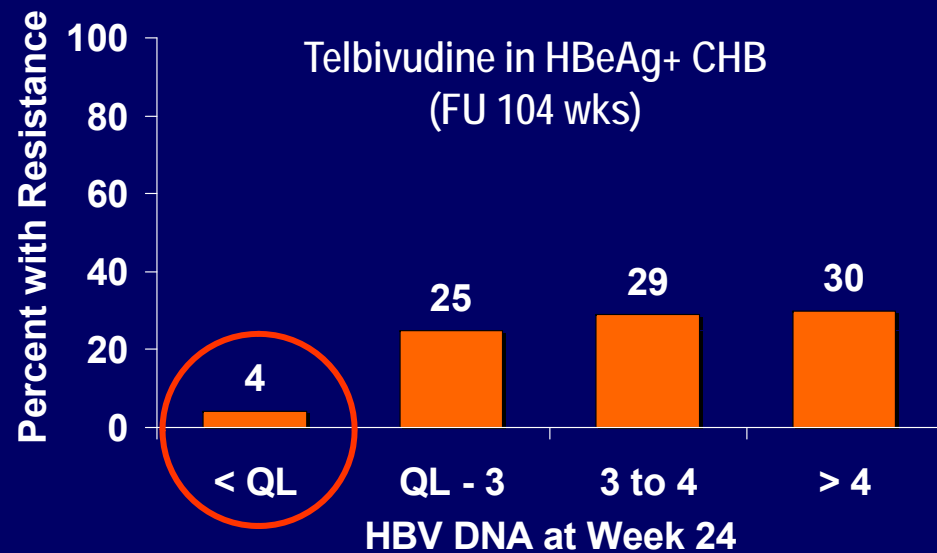
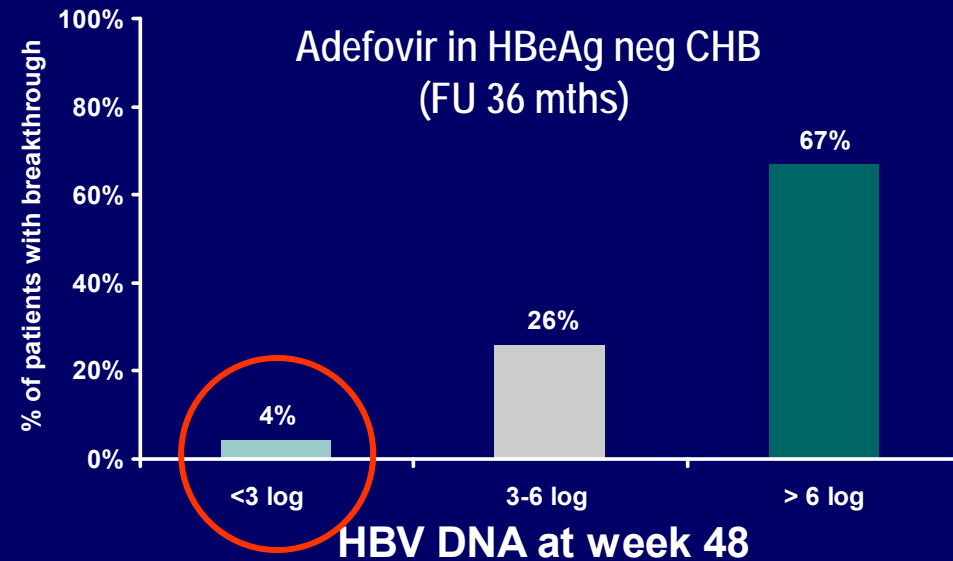
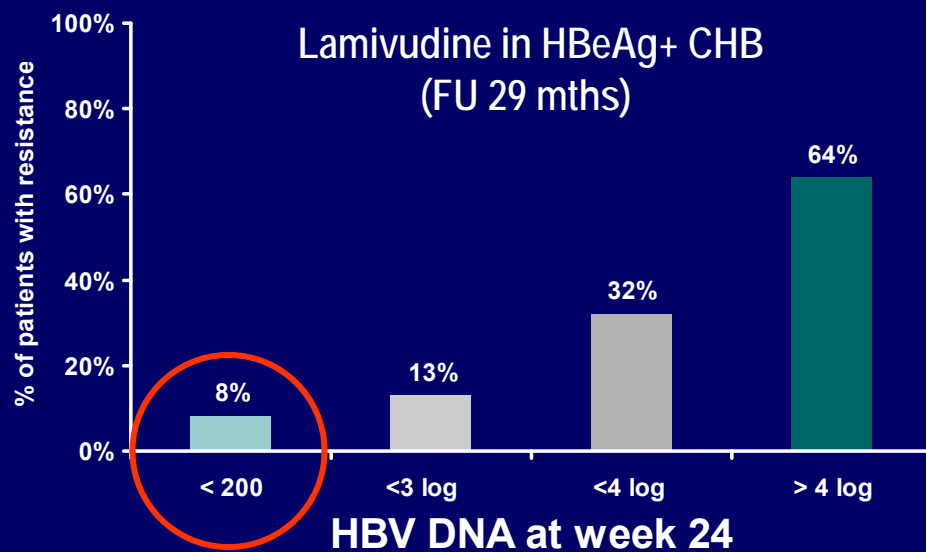
Genotypic resistance vs Virological Breakthrough

3-6 monthly HBV DNA monitor during antiviral therapy to detect 1log₁₀ cpm rise from nadir

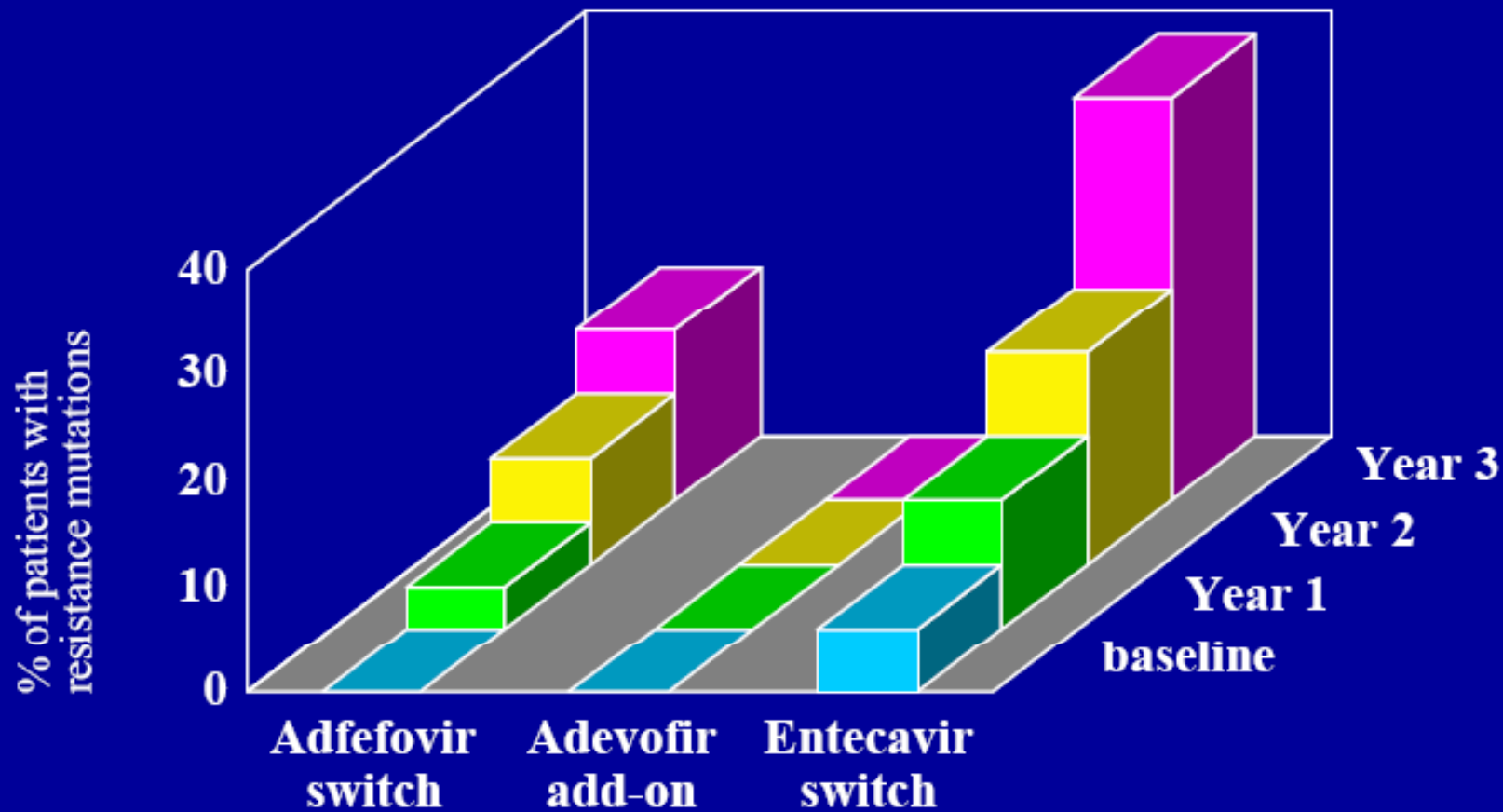


Patients	28	3	1	0	0	0	0	0	0
still at risk	32	22	14	10	9	6	5	4	2
	14	13	12	11	10	9	6	4	3

Early Viral Suppression Predicts Low Risk of Resistance



Incidence of Resistance in Lamivudine Refractory Patients



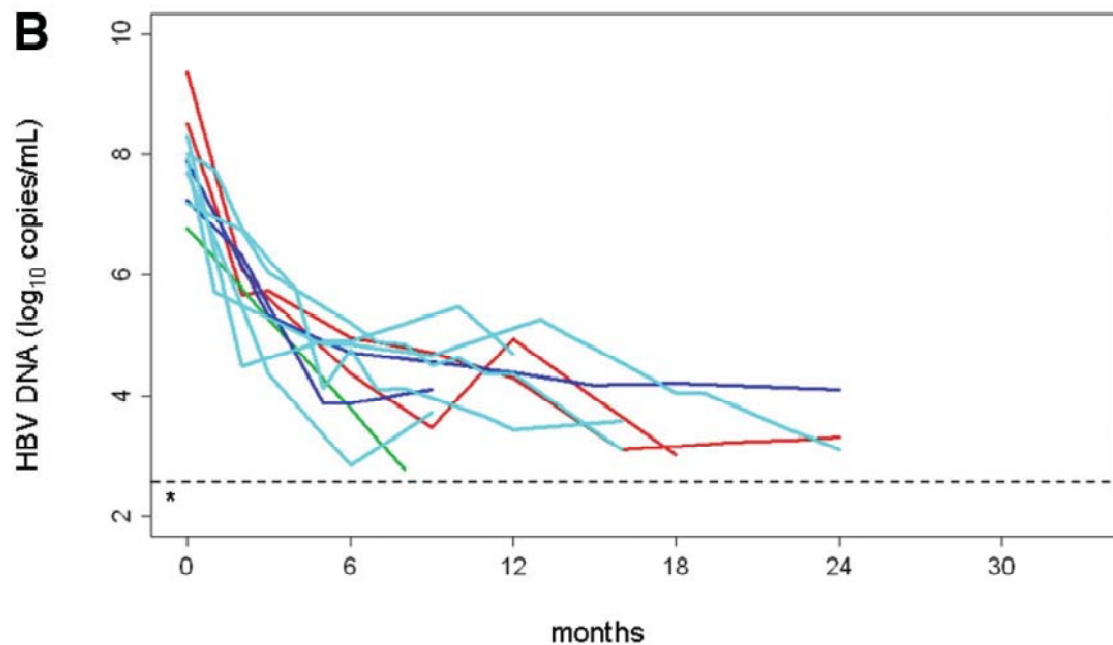
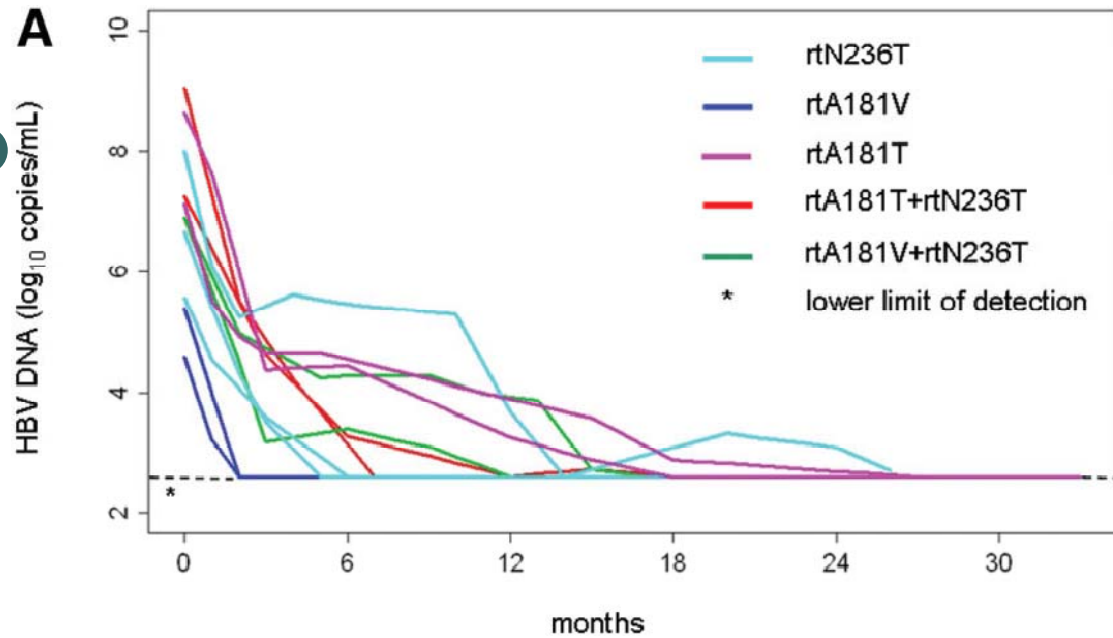
Lampertico et al AASLD 2006; Colonna et al AASLD 2006

No Resistance to Tenofovir Disoproxil Fumarate (TDF) Detected Following up to 192 Weeks of Treatment in Subjects Mono-Infected with Chronic Hepatitis B Virus

A Snow-Lampart¹, K Kitrinis¹, B Chappell¹, F Myrick¹,
J Schawalder¹, E J Heathcote², P Marcellin³, and
K Borroto-Esoda¹

¹Gilead Sciences, NC, USA; ²Toronto General
Hospital, Ontario, Canada; ³Hospital Beaujon, Clichy,
France

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for the Study of Liver Diseases
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Poster # 1365



Individual courses of HBV DNA levels of 21 CHB patients with genotypic resistance to ADV during TDF monotherapy.

(A) Courses of 10 patients who achieved HBV DNA levels 400 copies/mL

(B) Courses of 11 patients who had detectable HBV DNA during the observation period

At baseline, the mean HBV DNA level in group (A) was 6.9 ± 0.73 (4.6-9.0) and group (B) 7.9 (6.8-9.4) copies/mL (P 0.055)

Month 12 mean HBV DNA level was (A) 2.9 ± 0.5 (2.6-3.7) and (B) 4.4 ± 0.5 (3.4-4.9) at months 12 (P 0.0001), respectively.

The pattern of the mutations associated with ADV resistance had no influence on the response to TDF treatment.

WHY NOT!! **Safe!**

SAFETY IN LONGTERM NOT PROVEN

- Telbivudine – myopathy, neuropathy
- Adefovir – renal tubular acidosis with hypophosphatemia; 3% of experienced increase creatinine after 4 to 5 years
- Tenofovir – renal toxicity, ? Osteoporosis

Parameter	Asians* (n = 163)	Non-Asians* (n = 422)
Grade 3/4 AEs	17 (10.4%)	50 (11.8%)
AEs causing discontinuation	2 (1.2%)	5 (1.2%)
Serious AEs	10 (6.1%)	61 (14%)
Phosphorus < 2 mg/dL	1 (0.6%)	6 (1.4%)
Creatinine ≥ 0.5 mg/dL increase	1 (0.6%)	4 (0.9%)
CrCl < 50 ml/min	0 (0%)	1 (0.2%)

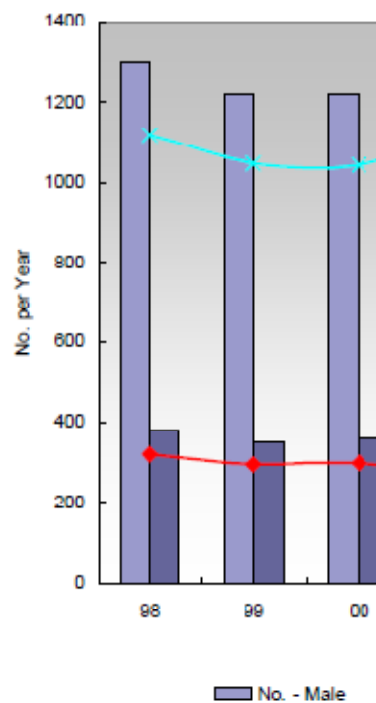


WHY NOT!!

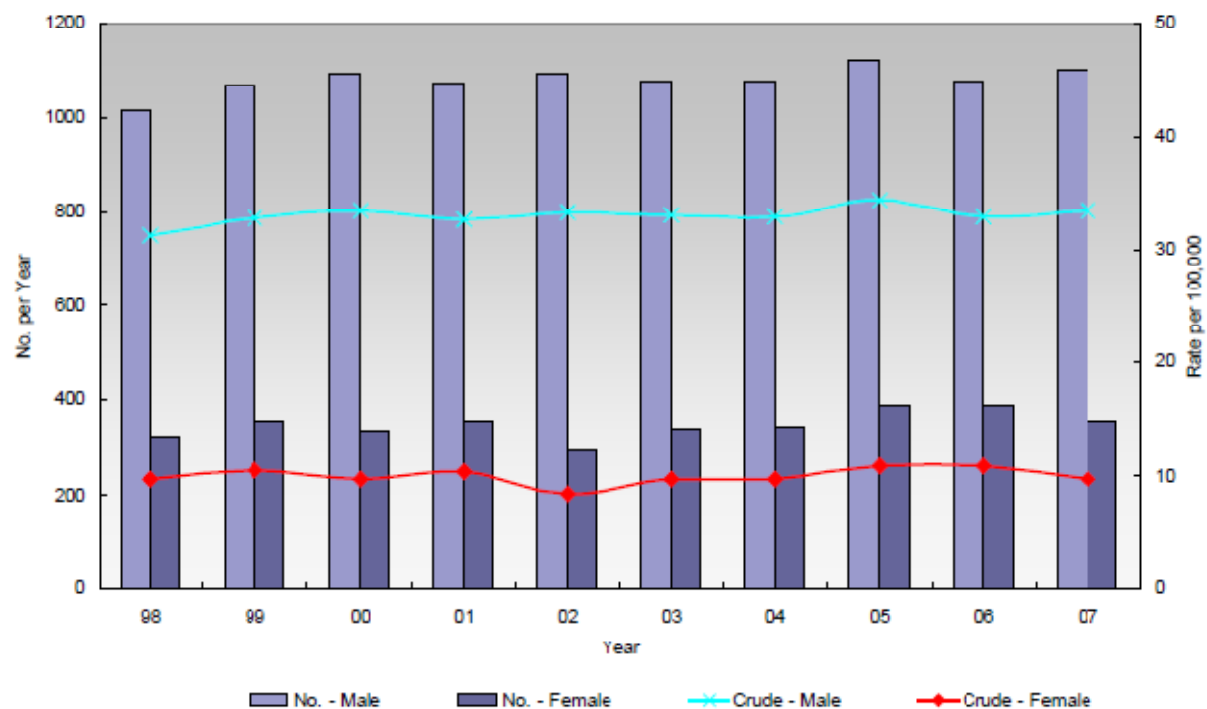
- **Efficacious!**
- **Safe!**
- **Cost effective!**
 - **Based on countries and regions**
 - Pricing of medication, lab tests, consultation
 - How available is management schedule for secondary and tertiary complication e.g. transplantation

Hong Kong Cancer Registry for Liver Cancer: 90% related to HBV

Incidence Trend 1998-2007



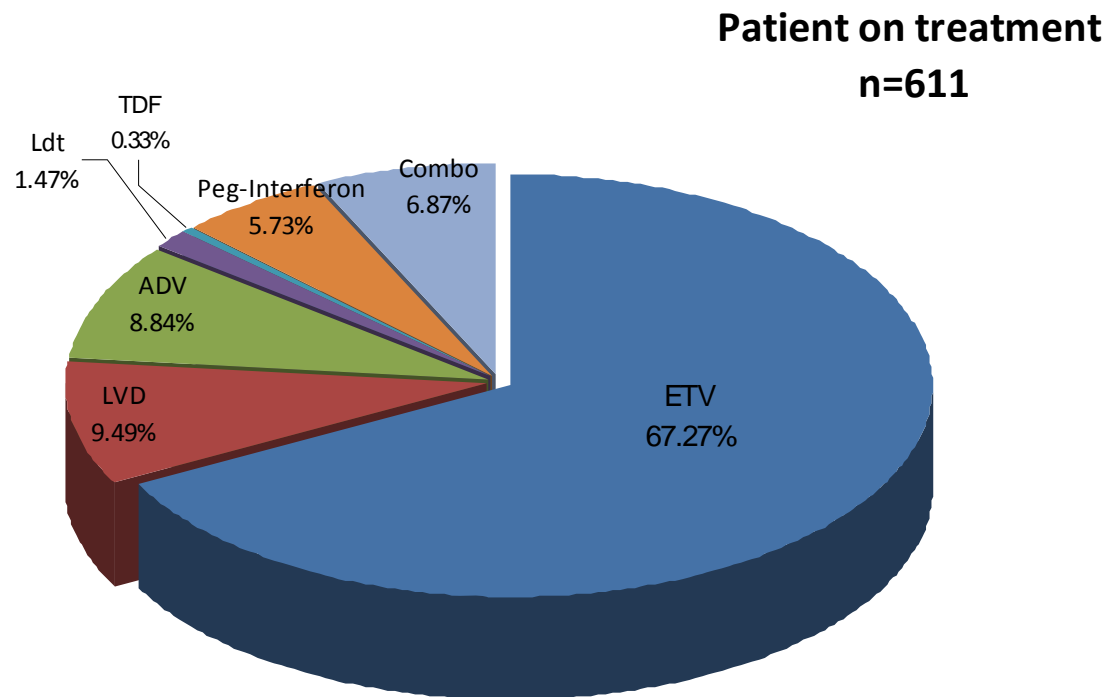
Mortality Trend 1998-2007



My Personal Experience in Hong Kong

611 (40.3%) of 1515 CHB patients had been or are on antiviral therapy

- 258 (42.2%) of the treated patients were treatment naïve and started entecavir
- 55 non responders to standard or pegylated interferon switched to entecavir therapy
- 98 participated in multicentre international clinical trials switched to entecavir after trial



Entecavir 411

Lamivudine 58

Adefovir 54

Telbivudine 9

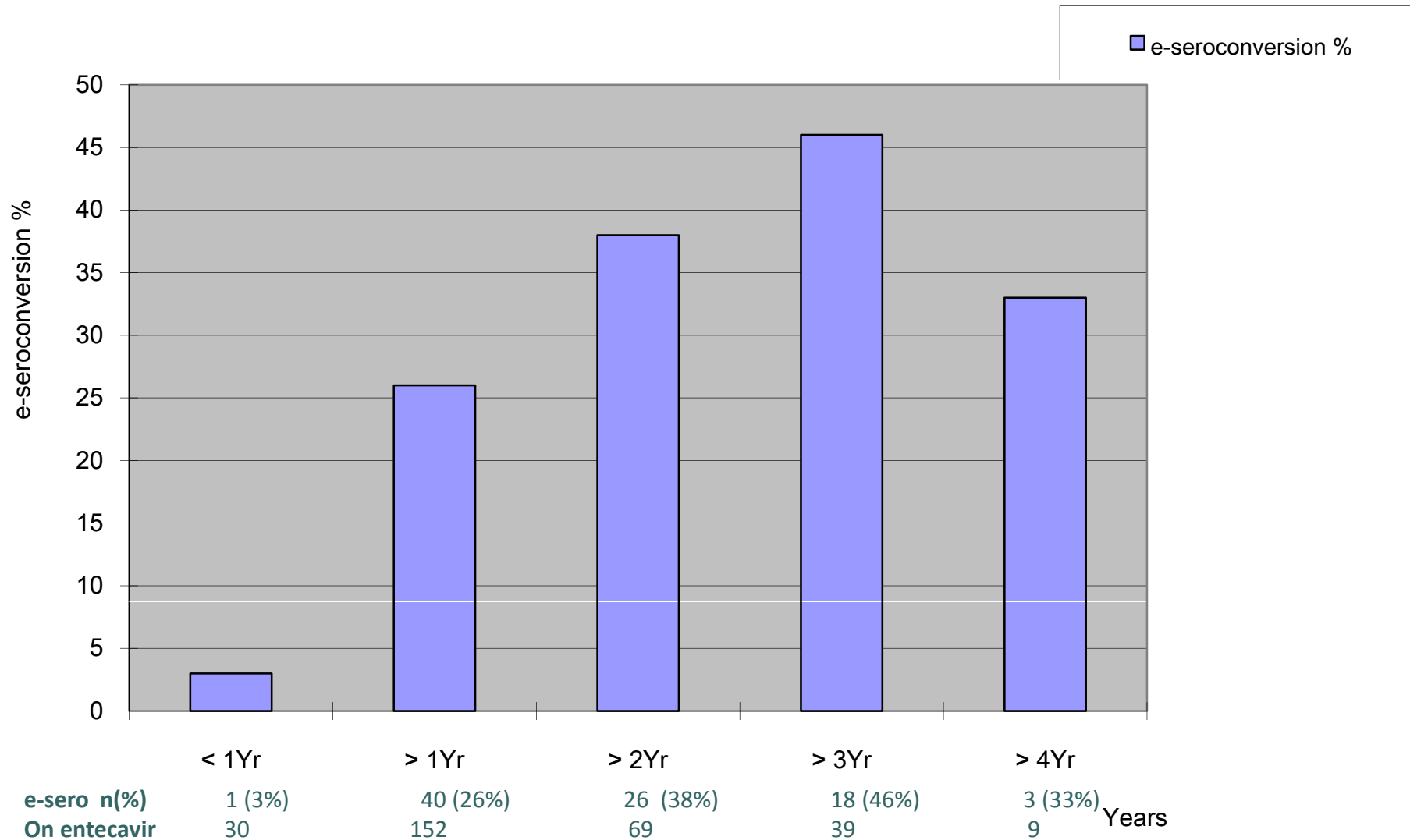
Tenofovir 2

Peg Interferon 35

Combo 42

My Personal Experience in Hong Kong

E-seroconversion % for HbeAg +ve patients on Entecavir



When to Stop Oral A

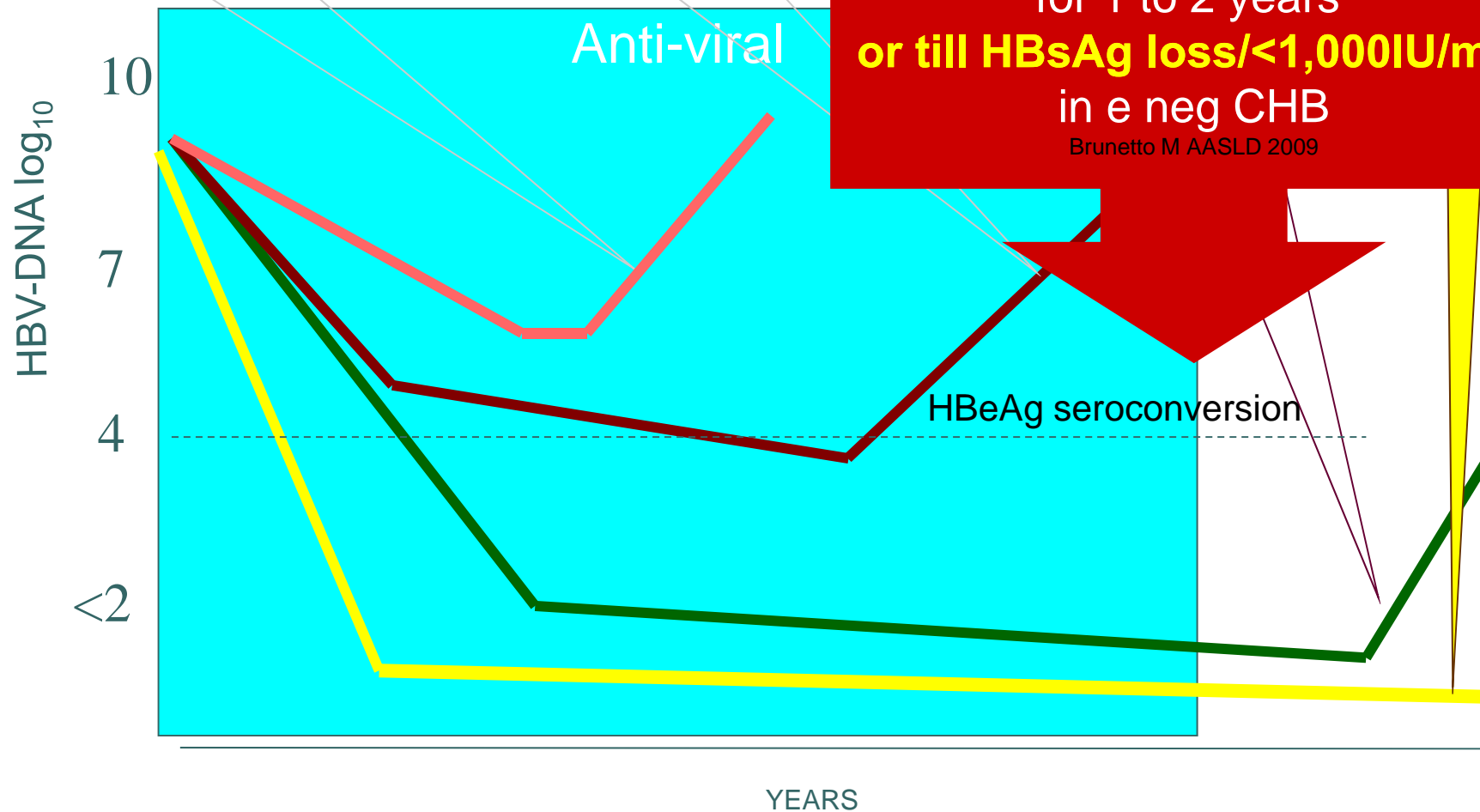
Poor response → early drug resistance

Inadequate response → drug resistance

STOP THERAPY
 6-12M after HBeAg loss/serocon
 + serum HBV DNA neg
or till HBsAg loss <1,000IU/mL

Serum HBV DNA neg
 for 1 to 2 years
or till HBsAg loss <1,000IU/mL
 in e neg CHB

Brunetto M AASLD 2009



Why I treat HBeAg positive CHB with NA?

Evidence based medicine

Efficacy

Maintained response

Sustained response

Safety

Tailored to individual patient

*Cost-effectiveness for
patient or healthcare system*

GOAL OF THERAPY



Thanks you!!