

HEP DART 2005

frontiers in drug development for viral hepatitis

State of the Art Lecture

When to start, when to stop
and when to change

Yves Benhamou
Hôpital Pitié-Salpêtrière, France

Chronic Hepatitis B: When to start, When to stop and When to Change

**Yves Benhamou
Paris**

When to Start

Treatment Objectives of HBV

■ Long-term clinical goal

- Prevent or reverse cirrhosis, hepatic decompensation and HCC (improve event free survival)

■ Short-term goals

- Reduction in HBV DNA levels
 - Degree of viral load reduction to achieve 'cure' not yet clear
- Immune system activation
 - HBeAg seroconversion
- Reduction of liver damage
 - Normalisation of ALT
 - Improvement in liver histology
 - Event free survival in cirrhosis

Population of HBsAg+ Patients

	CHB	Immune tolerant	Inactive carrier
DNA			
e+	< 5 log	< 5 log	>3-4 log
e-	< 4 log	< 4 log	>3-4 log
ALT	< 2x ULN	≥ 1x ULN	N
Liver	Inflammation Fibrosis	N	N
Outcome	Cirrhosis HCC	CHB Inactive HCC?	CHB HCC?

Treatment Recommendations

HBV DNA	ALT	Recommendations	
HBeAg+			
< 5 logs	≤2 xULN	Monitor ^{1, 2, 3}	Intermittent ALT elev Treat if disease ¹
> 5 logs	>2 xULN	Monitor 3-6 mo; treat if no seroconv, high bilirubin/decomp	
HBeAg-			
< 5 logs	≤2 xULN	Monitor	4< DNA < 5 log Treat if disease ¹
> 5 logs	>2 x ULN	Treat ^{1, 2, 3}	

¹AASLD, ²EASL, ³APASL

HBV DNA and Short Term Histologic Activity Index

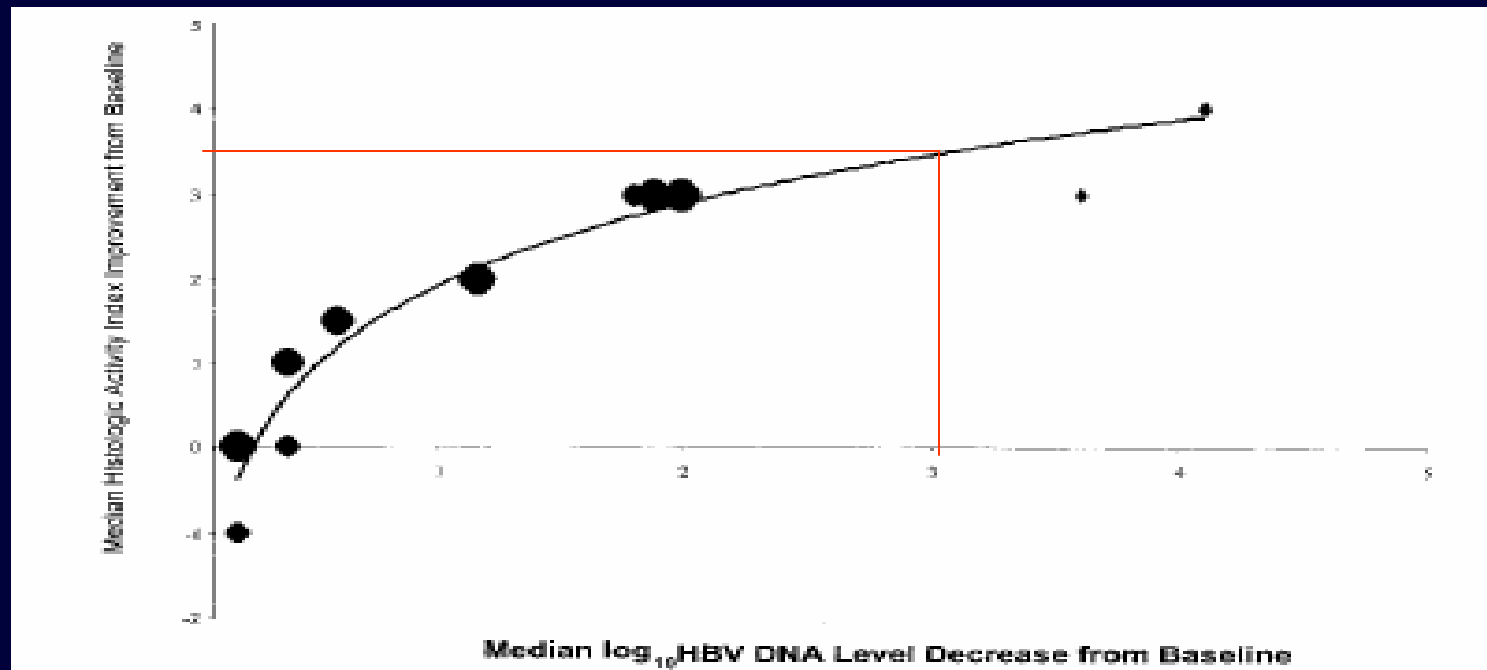


Fig. 3. Correlation between change in median viral load level and change in median histologic activity index from beginning to end of the treatment ($r = 0.96$; $P < 3 \times 10^{-6}$). Prospective studies are reported as one point per arm; the size of the point is proportional to the arm size.

HBV DNA and ALT

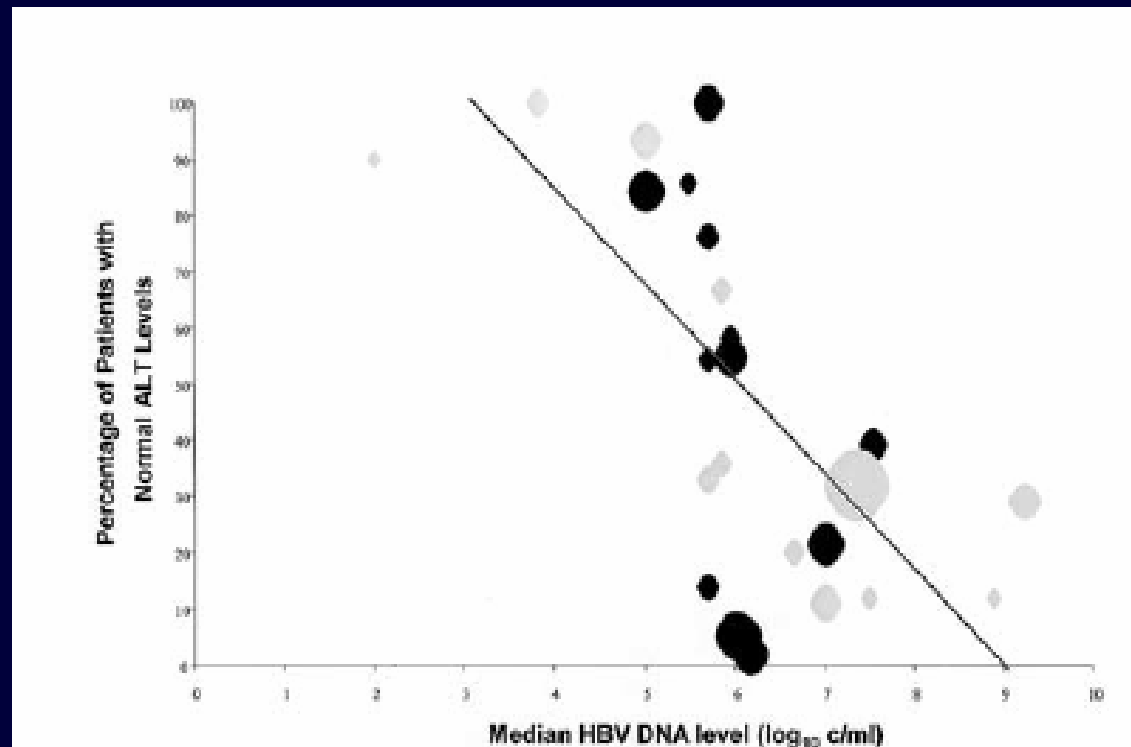
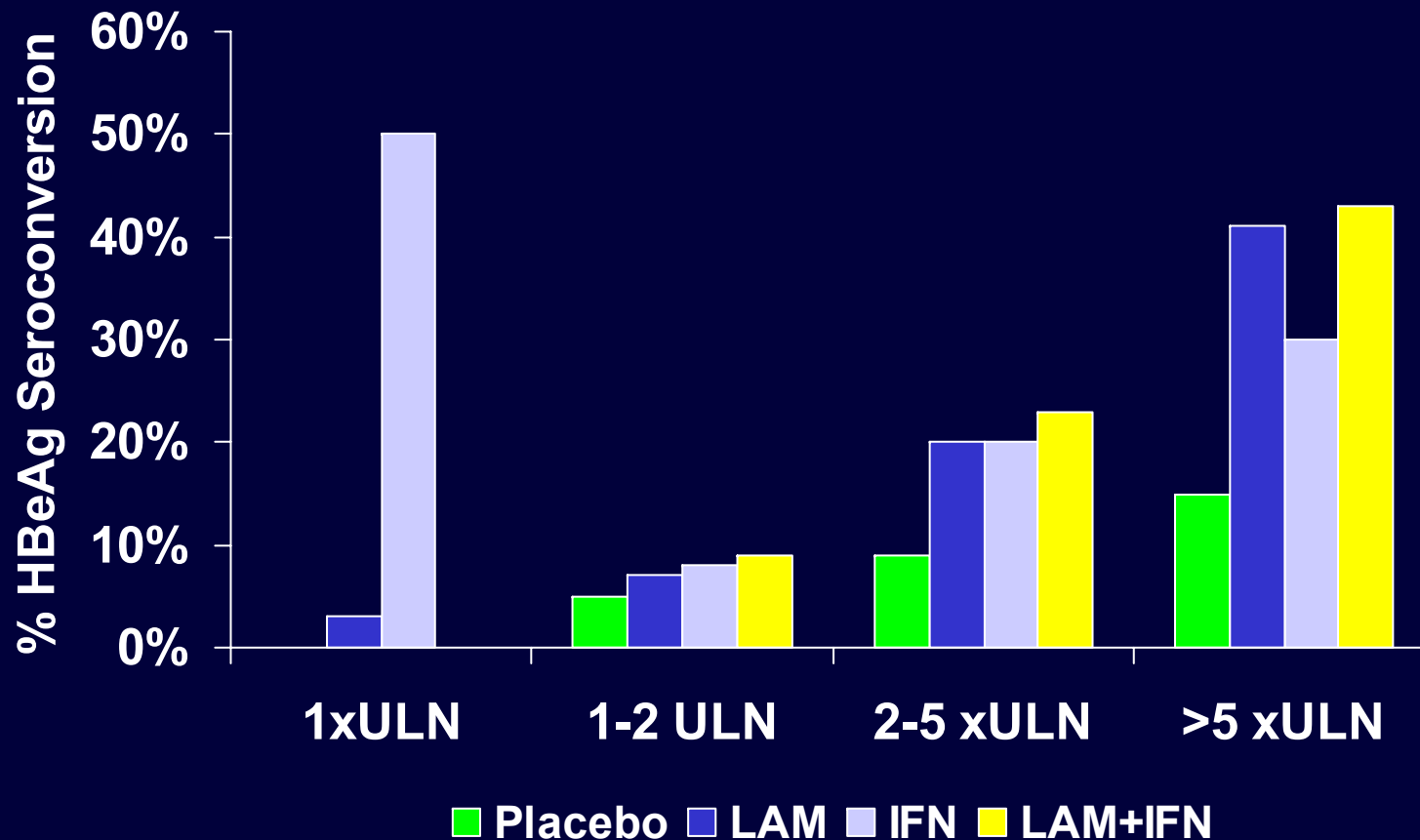


Fig. 4. Correlation between viral load level (\log_{10} HBV DNA) and percentage \pm 95% confidence interval of patients with normal ALT levels ($r = 0.62$; $P = .0004$). Prospective studies are represented as one point per arm, studies without interferon (grey), and studies with interferon (black).

Mommeja-Marin H et al. Hepatology 2003

Baseline ALT and Response to Therapy in HBe+ Patients



Perrillo et al. Hepatology. 2002.

Association with past viral load with current liver disease

1681 patients - 10 years prospective cohort period

	Baseline Serum HBV DNA		P
	Low vs Undetected AOR (95% CI)	High vs Undetected AOR (95% CI)	
Mild/Moderate	1.3 (0.7 – 2.4)	1.7 (0.9 – 3.2)	0.015
Severe/HCC	1.3 (0.8 – 2.2)	2.8 (1.7 – 4.6)	<0.001

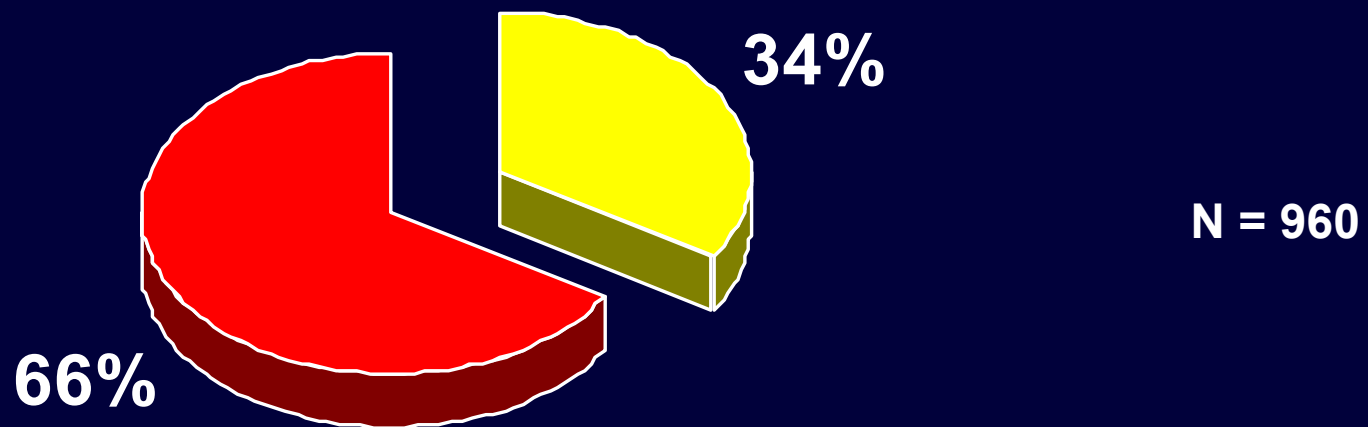
Undetected: < 1.6 10³ log copies/mL

Low : > 1.6 10³ – 9.9 10⁴ copies/mL

High: ≥ 10⁵ copies/mL

Chen et al. Hepatology. 2004.

Low and undetectable HBV DNA and liver disease after 10 years



■ No liver disease ■ Liver disease

Undetectable: $< 1.6 \times 10^3$ log copies/mL

Low : $> 1.6 \times 10^3 - 9.9 \times 10^4$ copies/mL

Chen et al. Hepatology. 2004.

Treatment Recommendations

	HBV DNA	ALT	Treatment
HBeAg +	< 5 log copies/mL	Normal	Monitor. Consider treatment if disease
	≥ 5 log copies/mL	Normal	Consider biopsy: Treat if disease
		Elevated	Treat
HBeAg-	< 4 log copies/mL	Normal	No – F. up
	≥ 4 log copies/mL	Normal	Consider biopsy; Treat if disease
		Elevated	Treat

Keefe et al. Clinical Gastroenterology and Hepatology 2004.

Treatment Recommendations

Cirrhosis

	HBV DNA	ALT	Treatment
HBeAg +/-	> 5 logs	Elevated	Compensated: Treat ^{1, 2} Decompensated: Treat + LT ^{1, 2}
	< 5 logs	—	Compensated: Monitor ^{1, 2} Decompensated: LT ^{1, 2}
HBeAg-	< 5 logs	N	Monitor ²
HBeAg +/-	< 4 log	—	Compensated : Monitor or Treat ³
	≥4 log	—	Compensated : Treat ³
	—	—	Decompensated : Treat + LT ³

ALT and HBe Ag and Risk of HCC

Study of HBV progression and HCC in 11,893 men in Taiwan

HBsAg	HBeAg	ALT	RR
-	-	N	1
-	-	Elevated	5.4
+	-	Normal	10.3
+	-	Elevated	29.3
+	+	Normal	61.3
+	+	Elevated	109

Yang et al. NEJM 2002.

HBV DNA and Risk of HCC

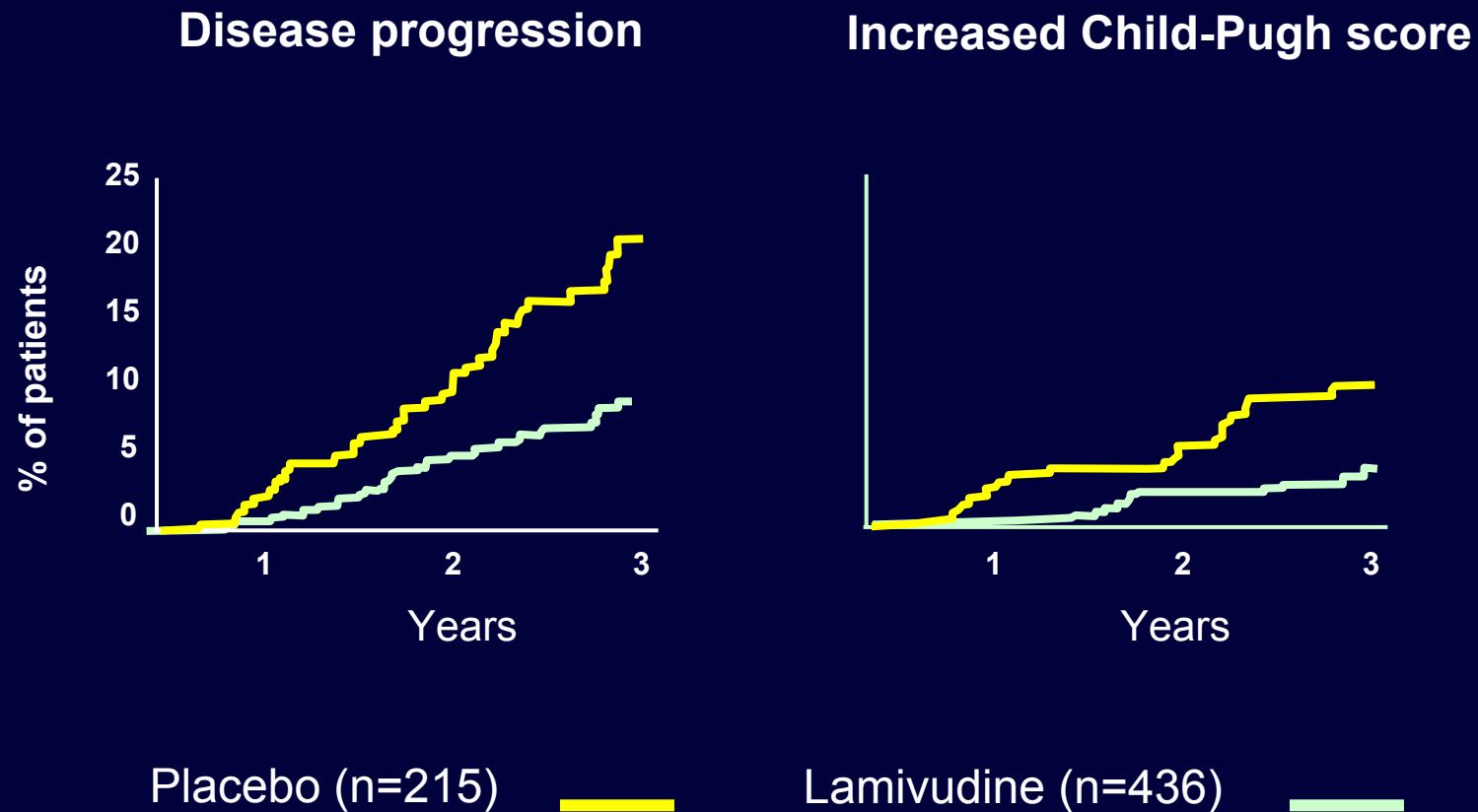
Baseline HBV DNA (logs copies/mL)	≤4.22	4.23-5.9	≥5.91
No of Case /No of controls	11/15	18/13	42/16
Adjusted OR (95% CI)	6.55 (2.23-19.27)	13.00 (4.65-36.31)	26.49 (10.41-67.42)

- Risk of HCC is 3.9 times more in patients with detectable DNA vs those with undetectable DNA

Yu et al. J Natl Cancer Inst. 2005.

Lamivudine Maintenance Therapy in Patients with Cirrhosis

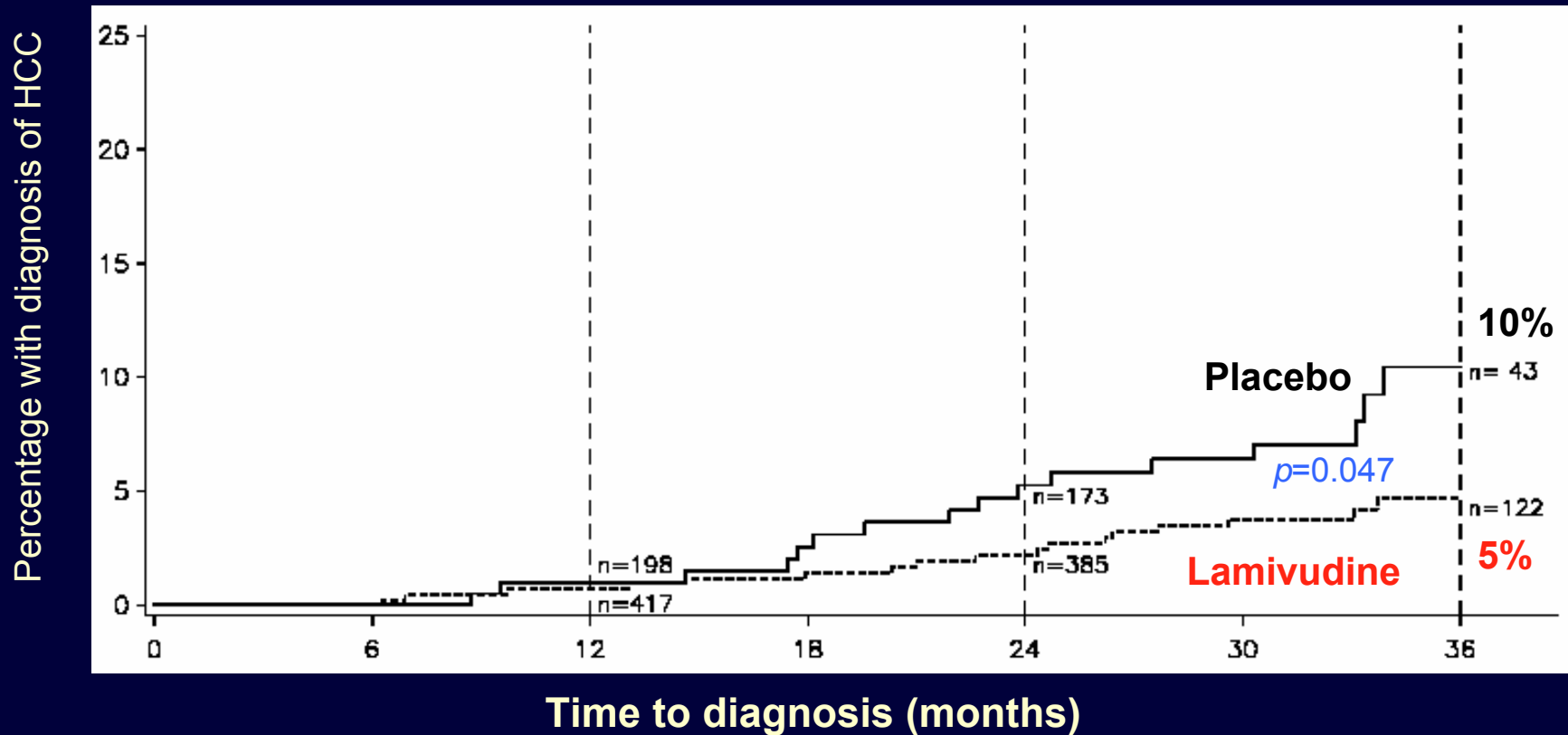
Control of HBV replication reduces the disease progression



Liaw et al. N Engl J Med 2004

Long-term Outcome in Lamivudine Treated Patients

Control of HBV replication (Lamivudine)
reduces the risk of HCC



Liaw et al, NEJM 2004

Immune Tolerant Patients

Reasons to don't start	Reasons to start
Long term benefit ? Usually limited response to therapy ? Treatment related AE and resistance ?	Prevention of HCC ? Missed flares (biopsy) ? Reduction of infectivity ?

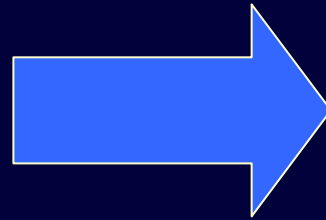
When to Start ?



Grey Zones

HBV DNA and ALT and the risk of disease progression and HCC ?

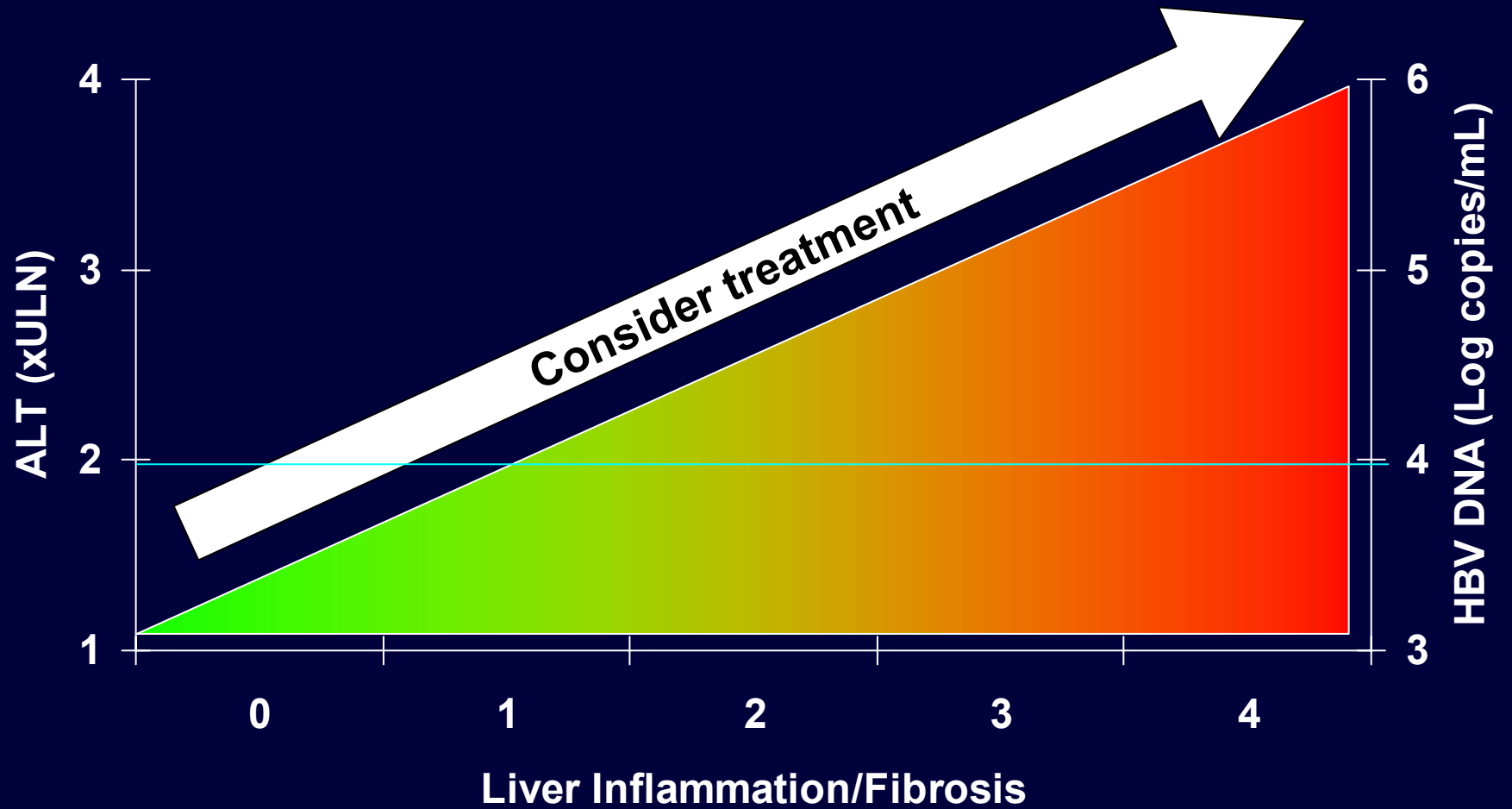
- HBV DNA
 - < 5 or 4 logs ?
 - DNA flares ?
- ALT
 - < 2 x ULN ?
 - ALT flares ?



LIVER EVALUATION

Role of genotype, Age, others?

When to Start ?

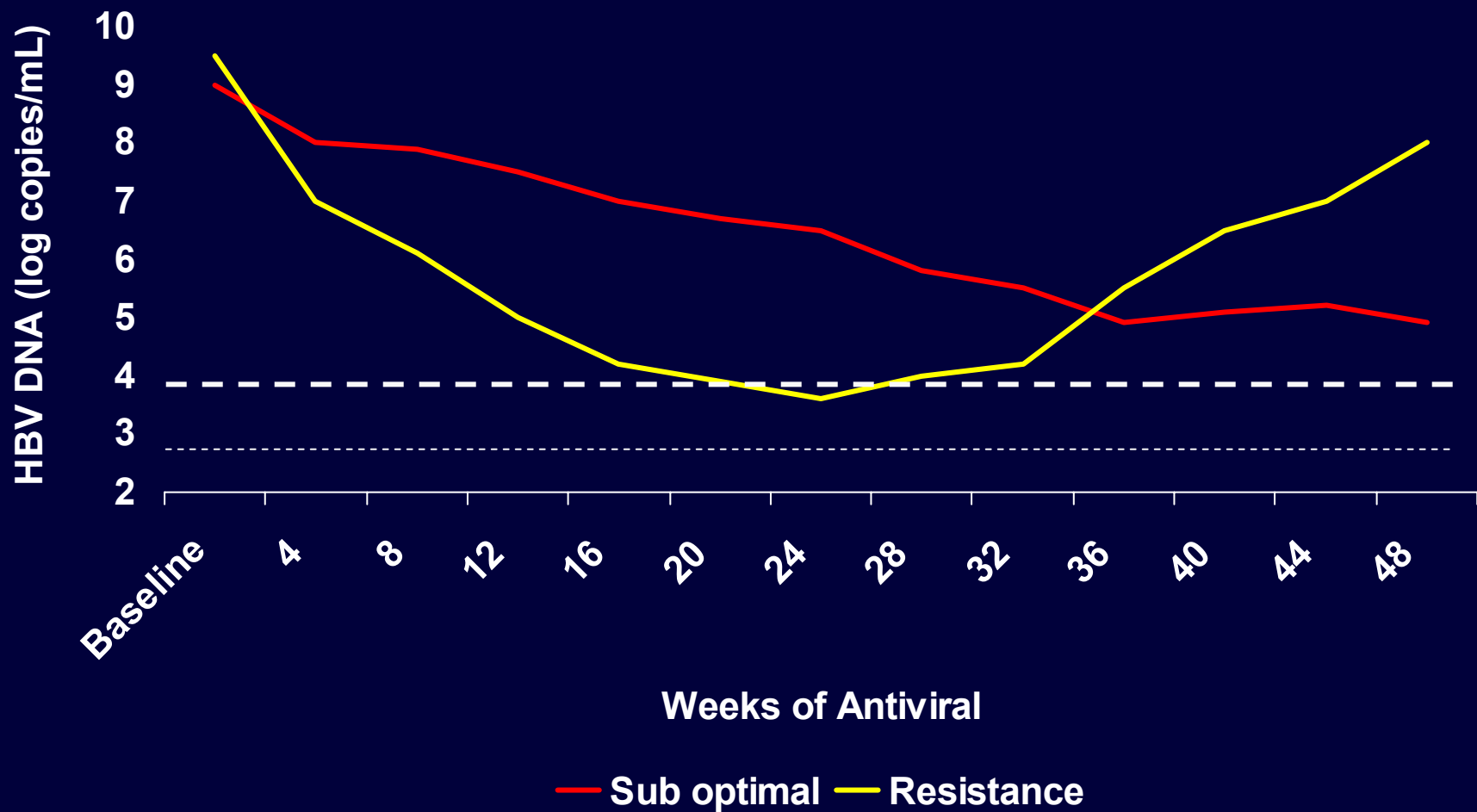


WHEN TO CHANGE

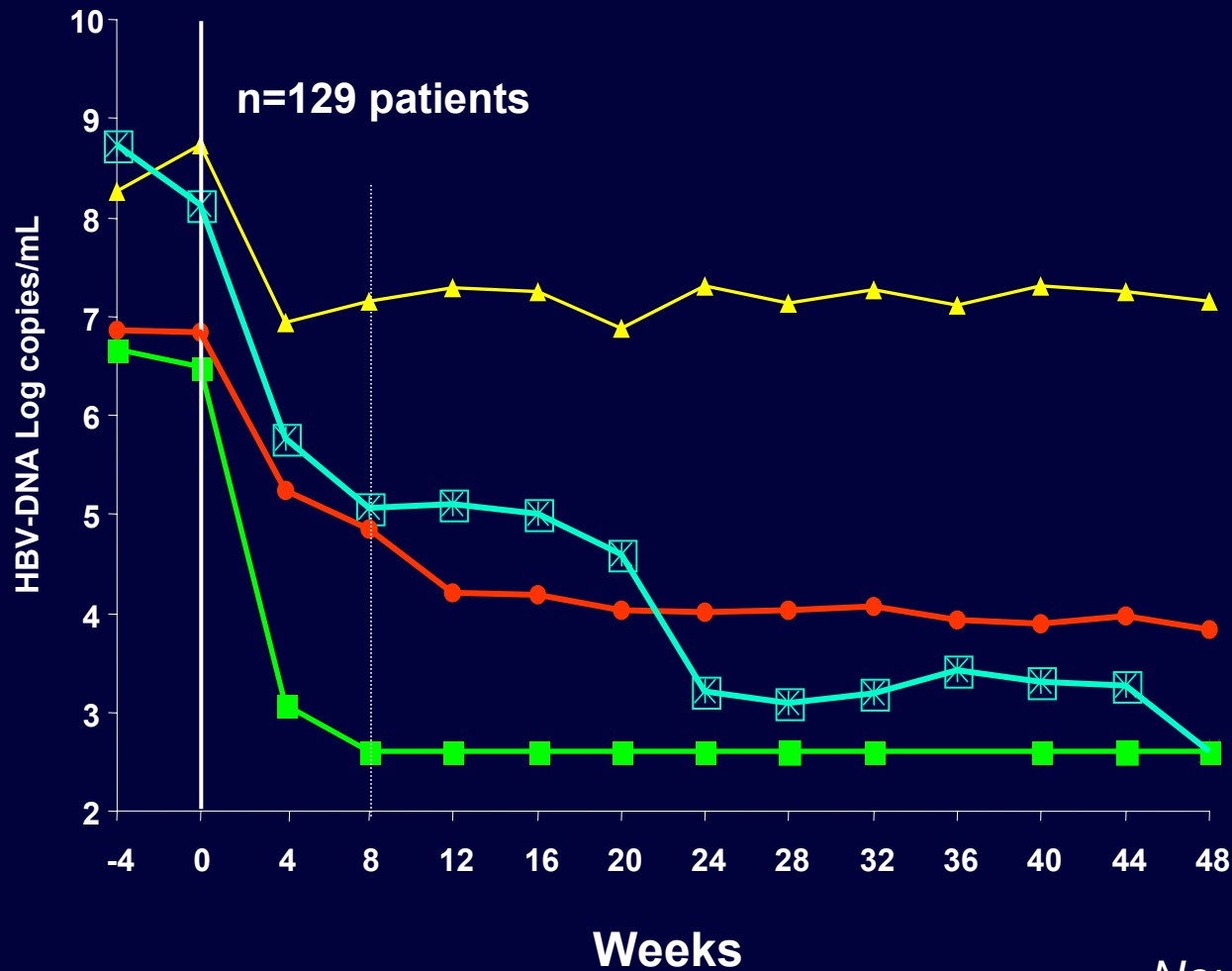
When to Change

- Treatment Failure in compliant patient
 - “Sub optimal” response
 - Expose to resistance
 - Reduces the chance of seroconversion in e+ patients
 - Resistance

Suboptimal response and Resistance



HBe Negativation and Response to Antivirals: ADV



HBe Ag -

0%

P<.01

28%

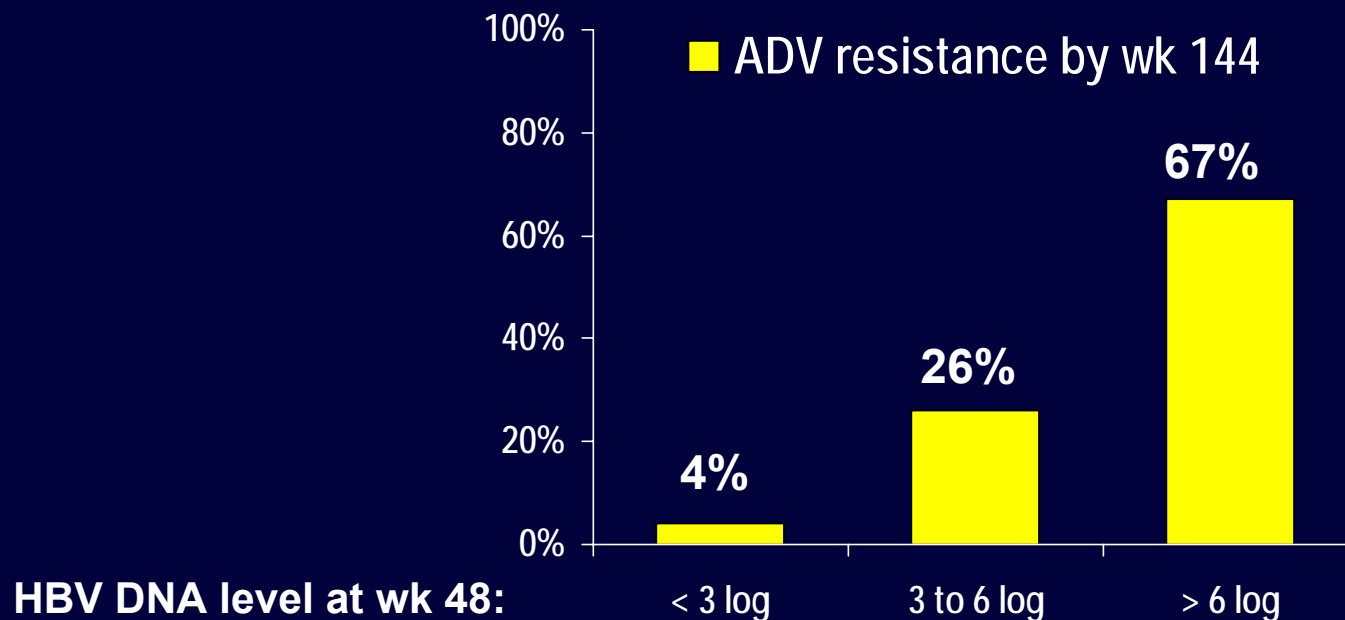
43%

77%

Neuman et al, EASL 2003

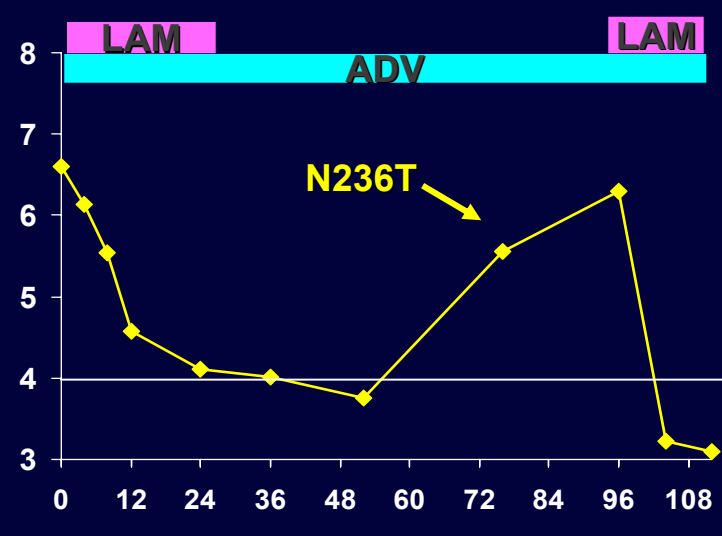
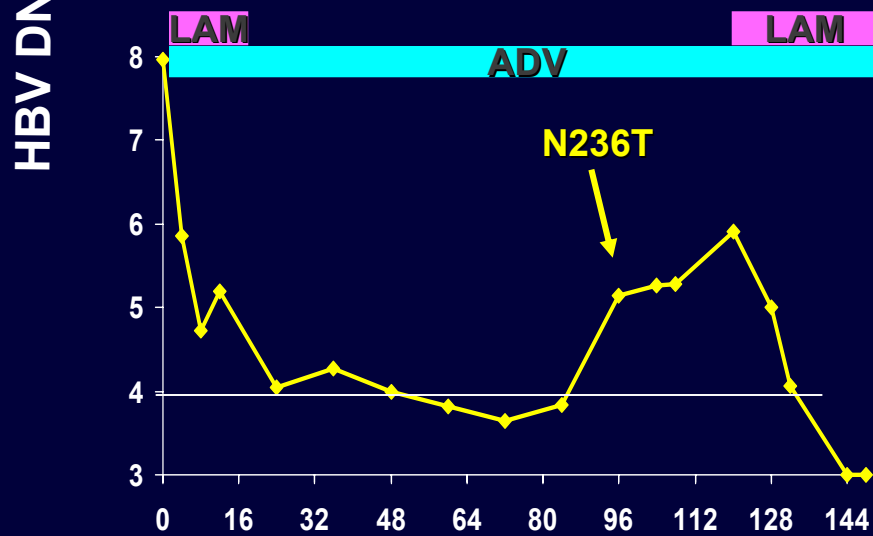
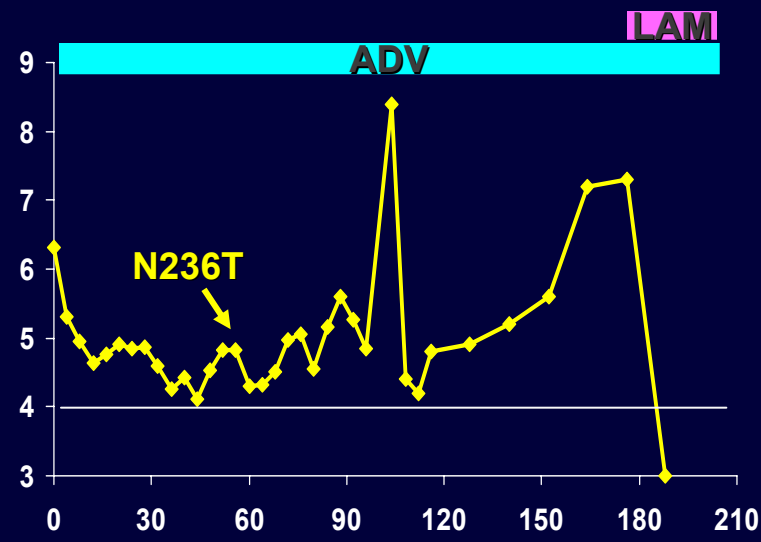
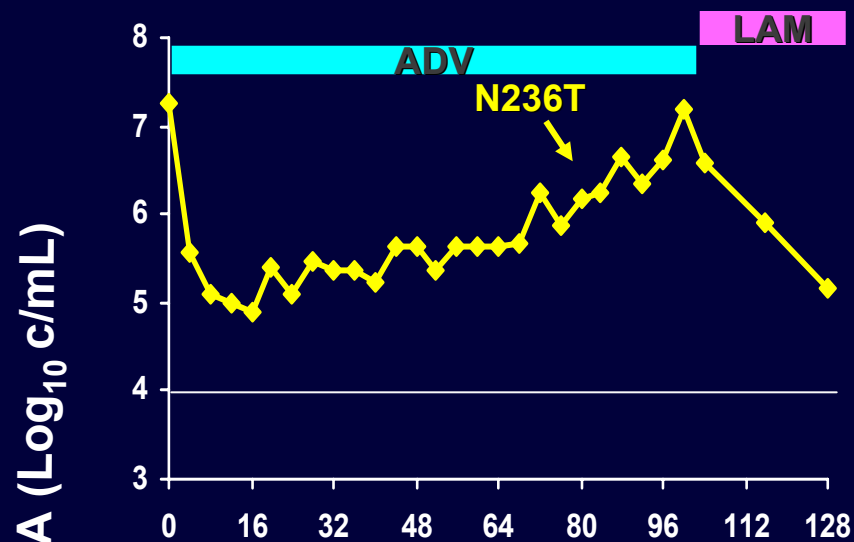
Week 144 ADV Resistance by Serum HBV DNA at Week 48

- Week 48 serum HBV DNA (n=114)^a
 - DNA < 3 log: 70% - DNA > 6 log: 3%



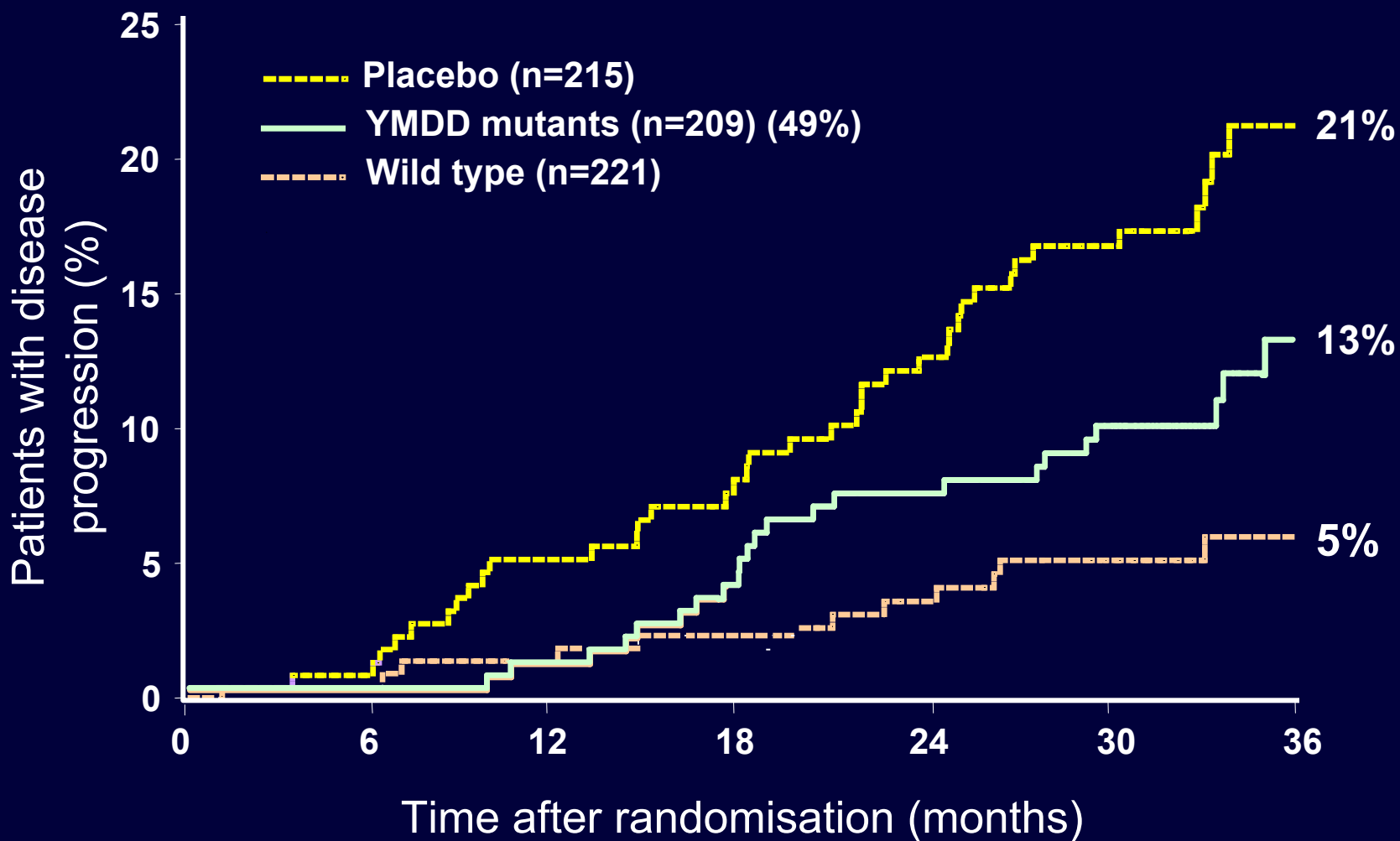
a. Missing wk 48 HBV DNA in 10/124 patients included in the predictor analyses. All ten patients had no ADV-R mutations by wk 144

ADV Resistance

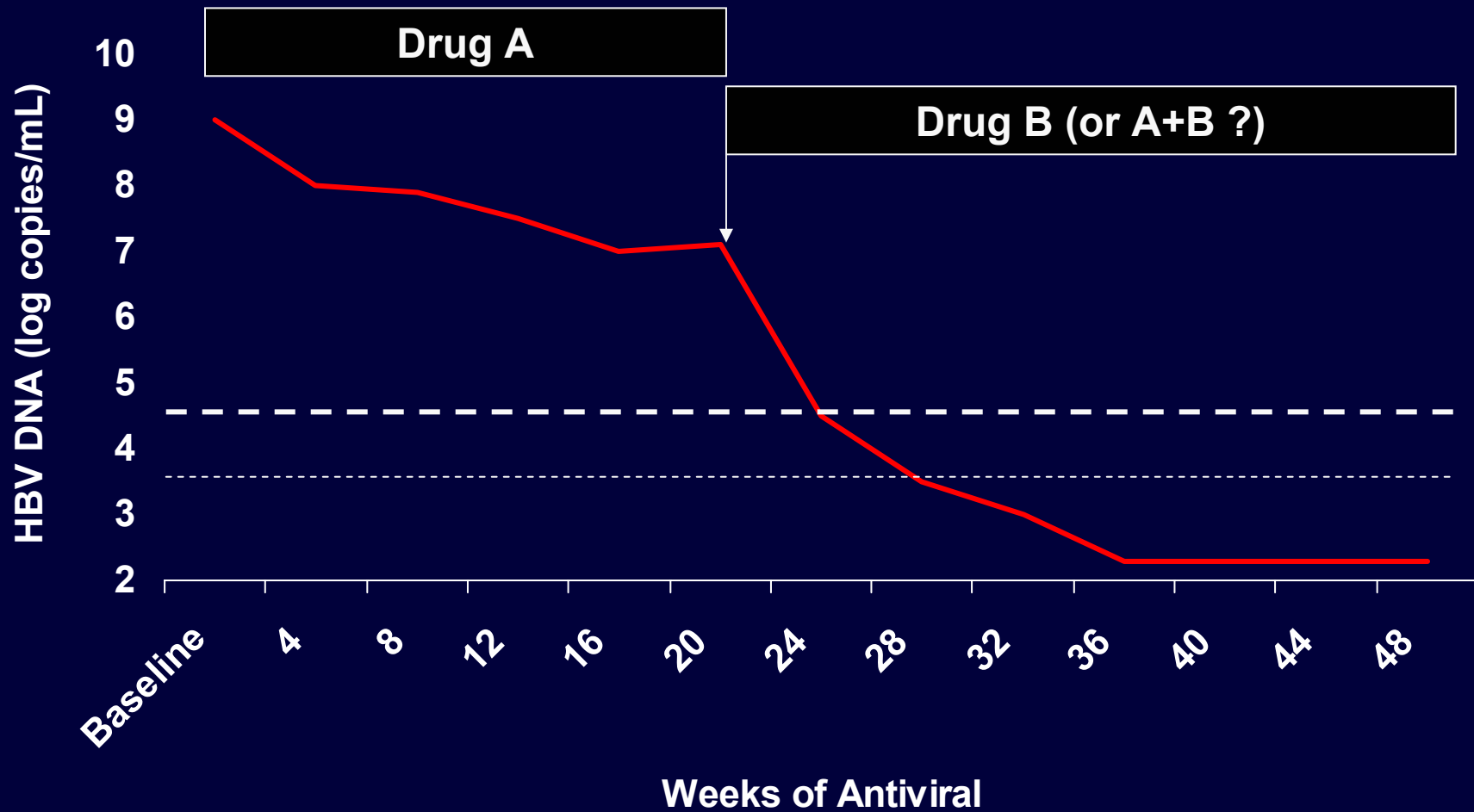


Weeks

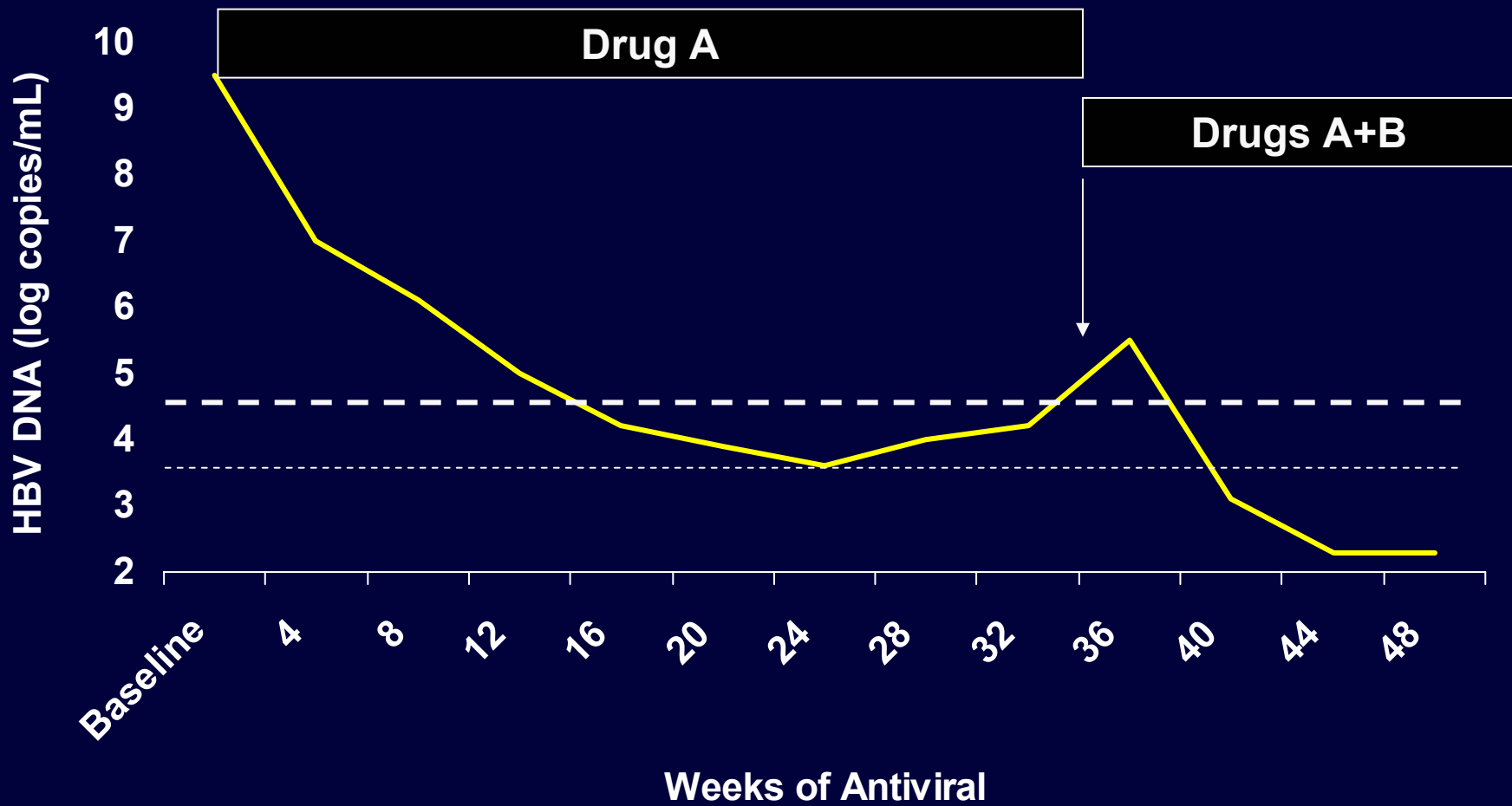
Time to Disease Progression According to YMDD Mutant Status



When to Change Suboptimal response



When to Change Resistance



When to Stop

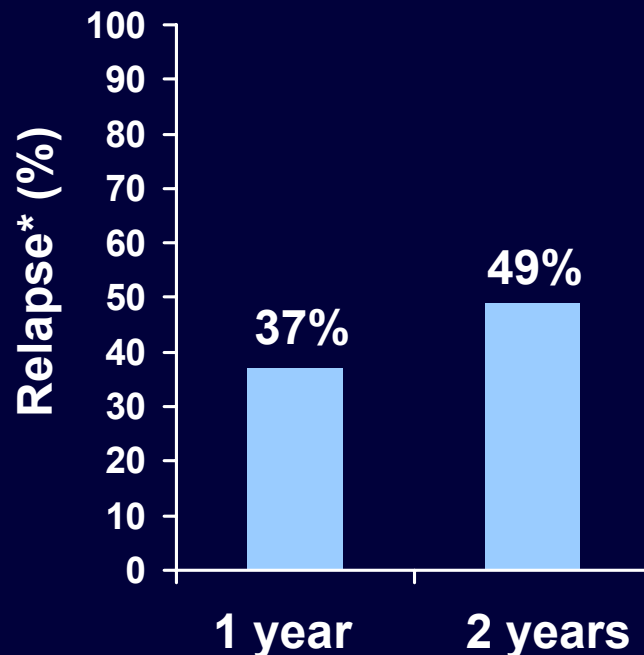
When to Stop Seroconversion

- Durability of HBsAg/HBe seroconversion ?
- Significance of HBeAg seroconversion with persistent low DNA (<4 log)?

Post LAM HBe Reactivation

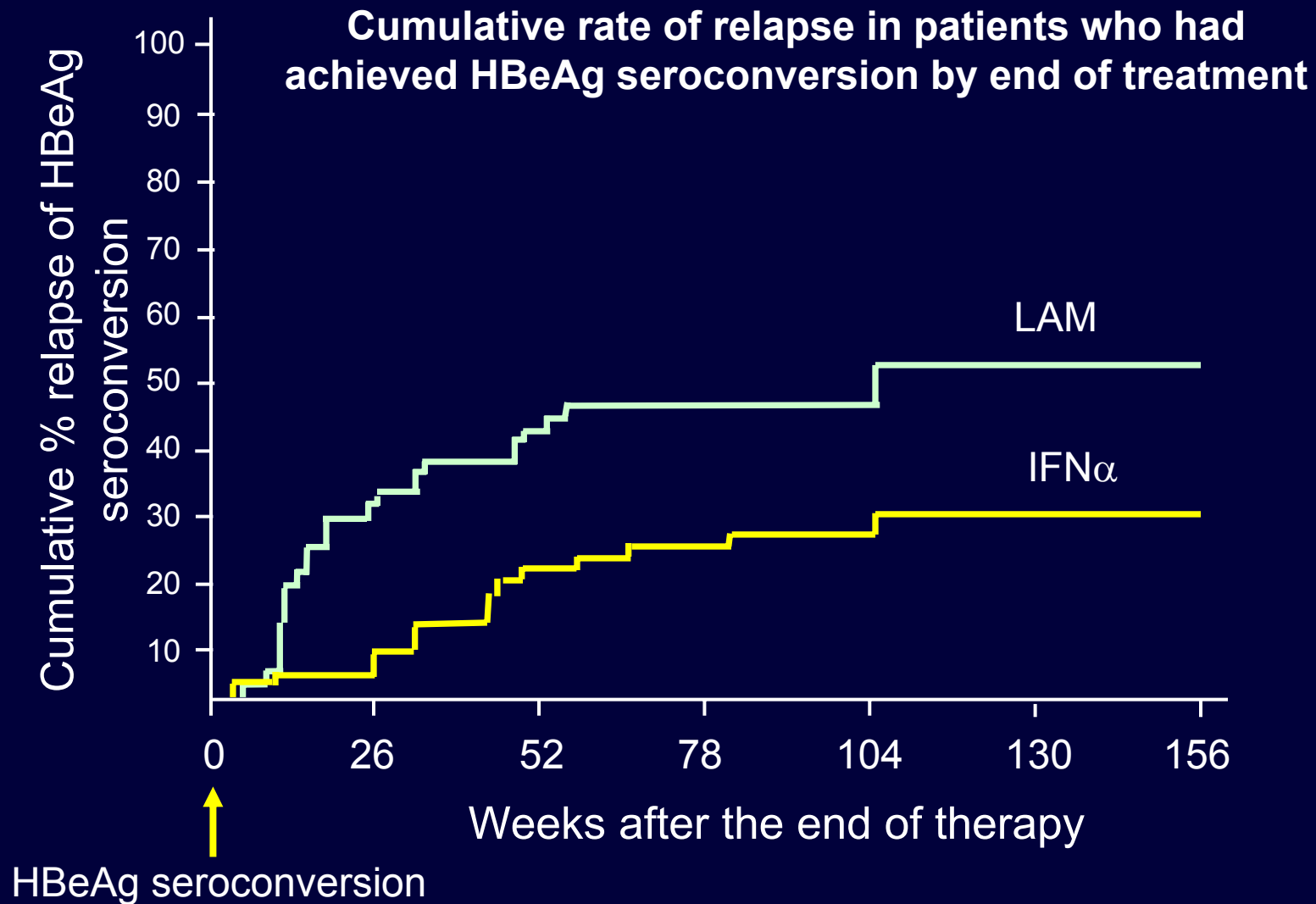
- 98 patients with HBeAg-positive CHB treated with LAM
- Mean duration of treatment in seroconverters 9.3 ± 3 months
- Lamivudine stopped 2–4 months after HBeAg seroconversion

Post-treatment relapse*



* Elevation of ALT (94%),
reappearance of HBeAg (81%)

Post LAM HBe Reactivation



When to Stop

Now !!