

Hepatitis B Treatment Today

Mindie H. Nguyen, MD, MAS

Assistant Professor of Medicine

Gastroenterology and Hepatology

Liver Transplant Program

Stanford University Medical Center

June 10, 2006

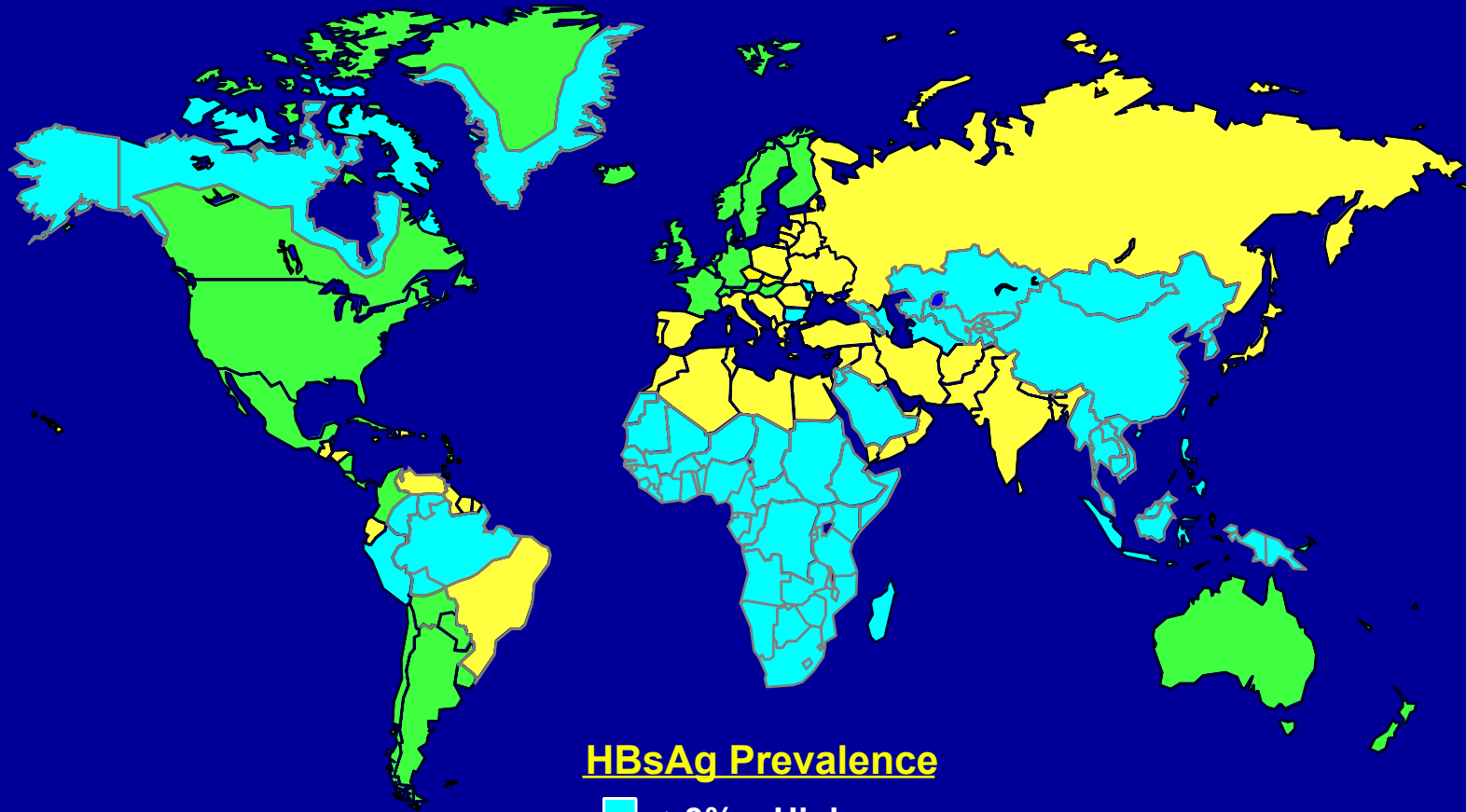
- **Disease burden?**
- **Why treat HBV infection?**

- **How to treat HBV infection?**
 - **Who to treat?**
 - **What to treat with?**
 - **Efficacy**
 - **Side effects**

Disease Burden?

Why treat HBV infection?

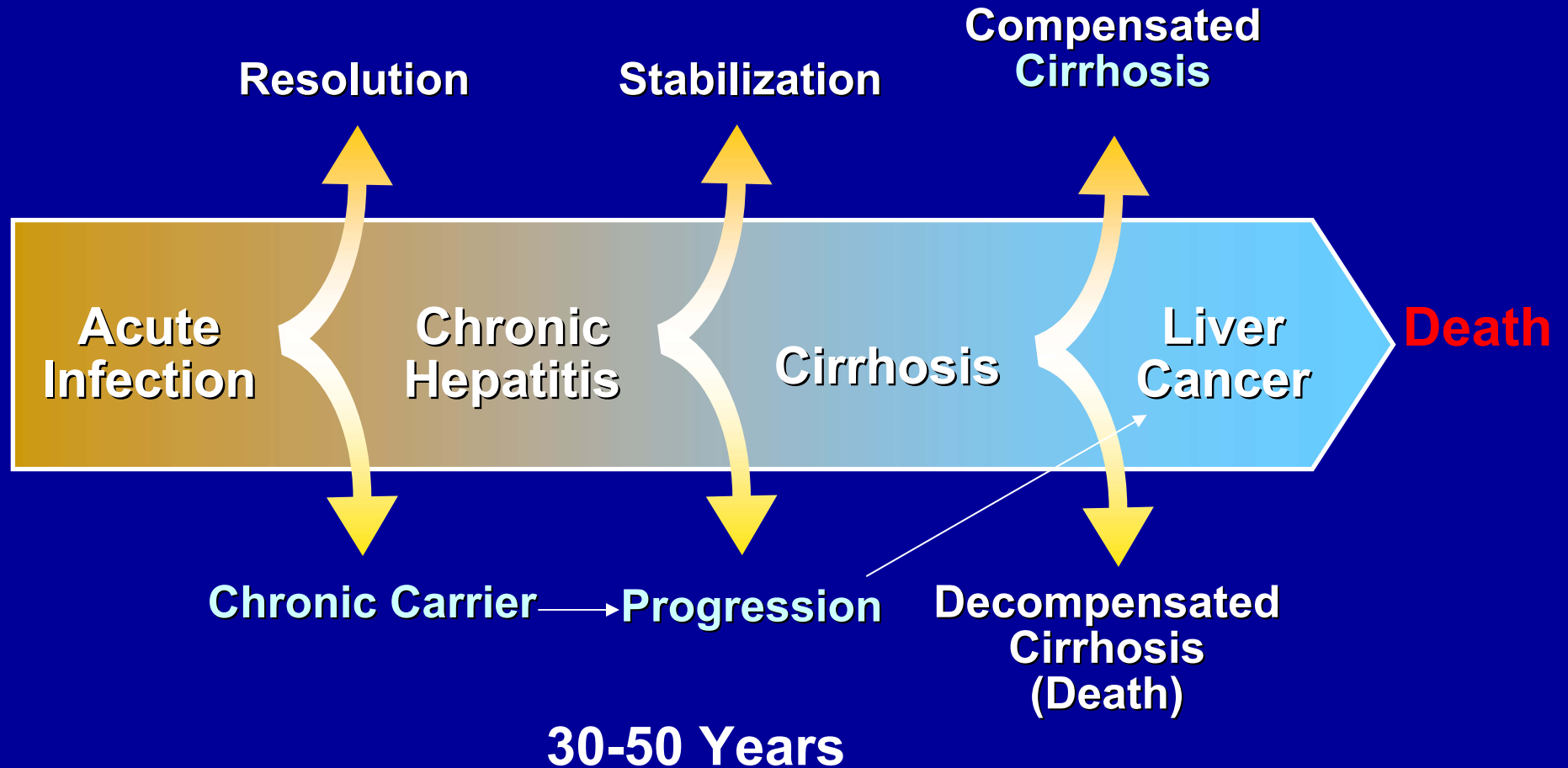
Geographic Distribution of Chronic HBV Infection



HBsAg Prevalence

- $\geq 8\%$ – High
- 2%-7% – Intermediate
- $< 2\%$ – Low

Natural History of Chronic Hepatitis B



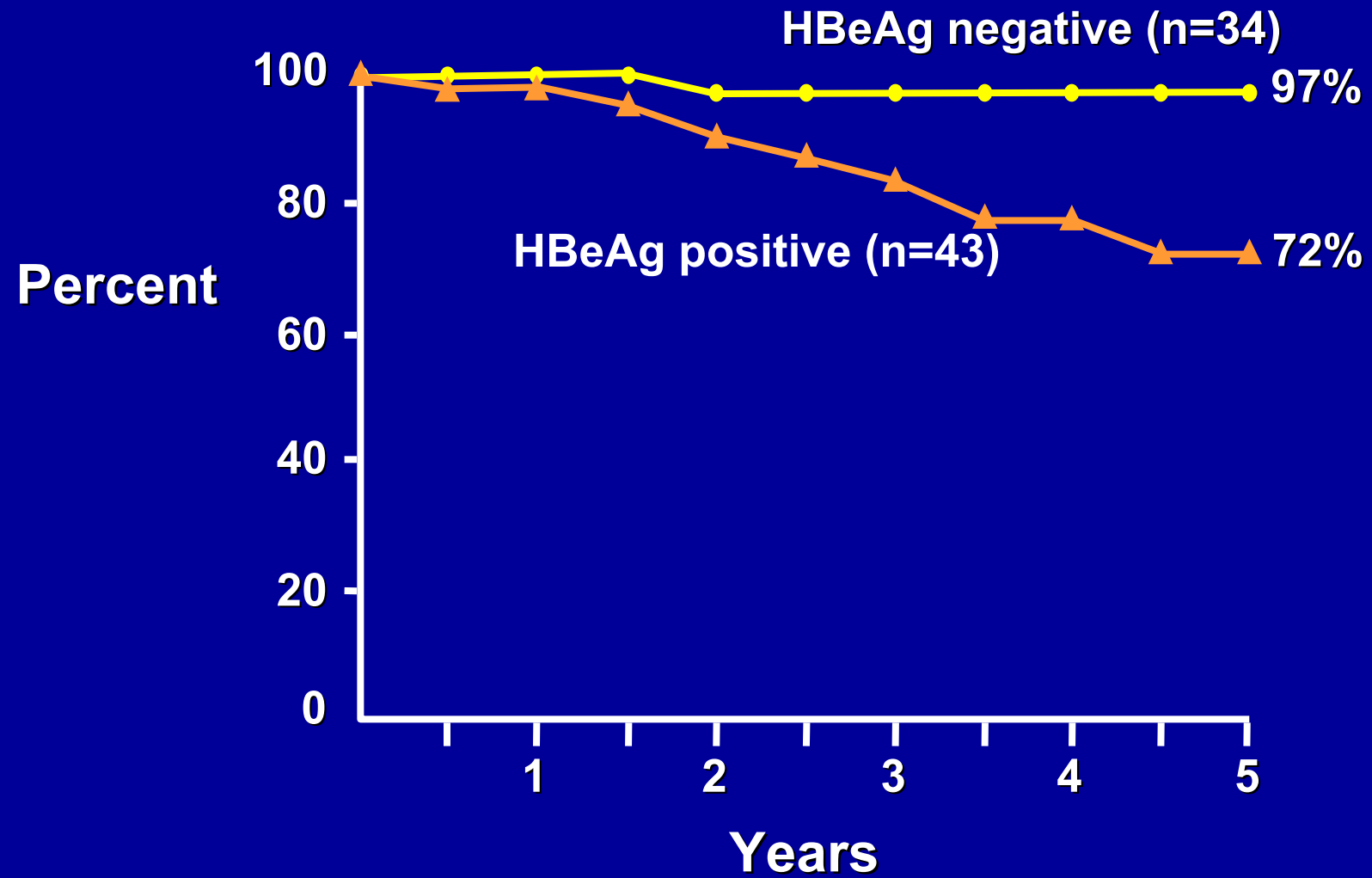
Adapted from Feitelson, Lab Invest 1994

Chronic Hepatitis B

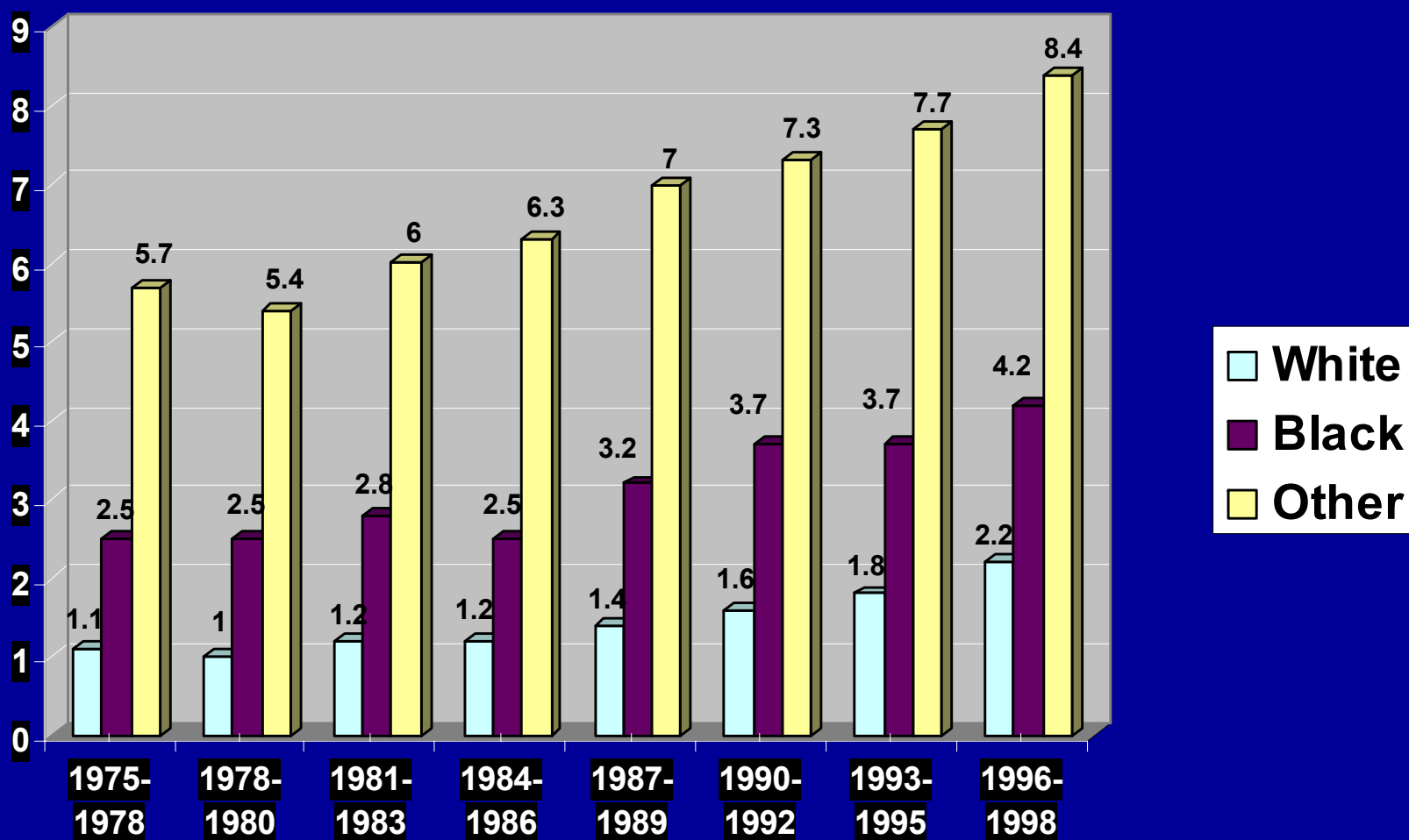
- **Globally**
 - 50 million new cases per year
 - 350-400 million chronic carriers; 75% in Asia
 - 520,000 deaths per year
- **United States**
 - 140,000-320,000 new cases per year
 - 1.25 million chronic carriers; 0.3% of adult population
 - 4-5,000 deaths per year
- **Premature mortality from cirrhosis or HCC: 20-25%**
- **Antiviral therapy can eradicate viremia and delay disease progression**

Chronic HBV with Compensated Cirrhosis

Survival: HBeAg Positive vs Negative



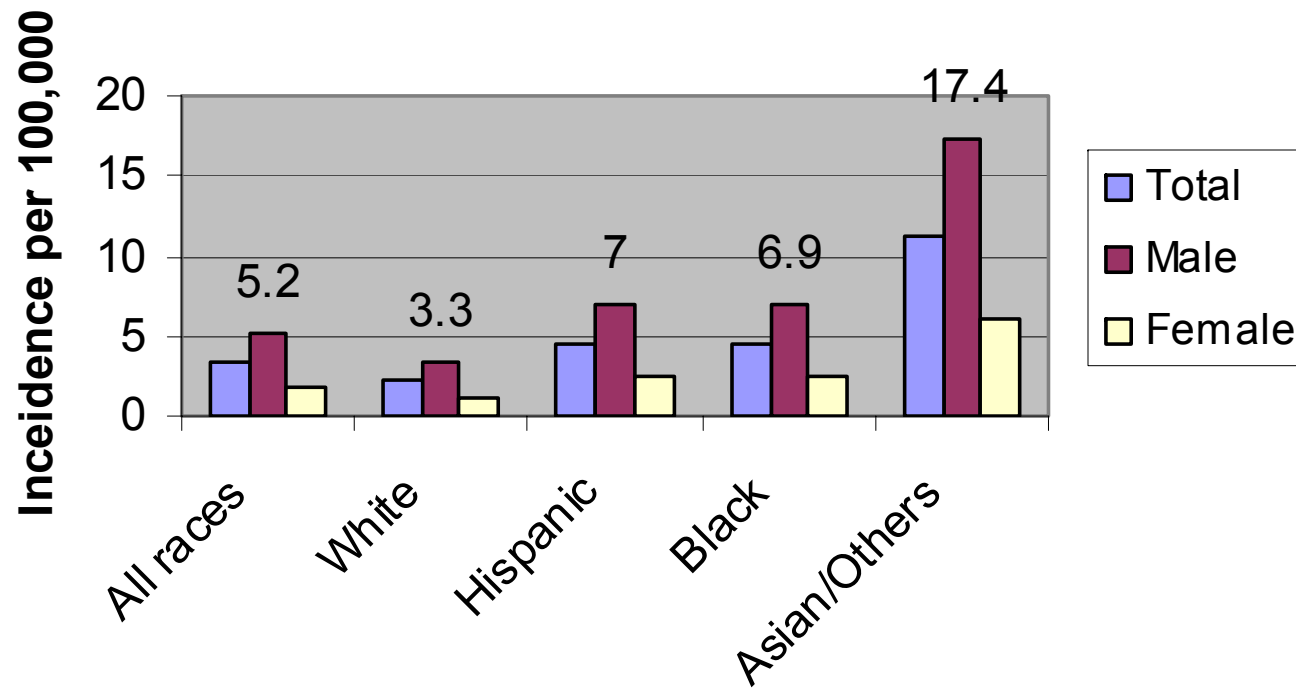
Age-Adjusted Incidence Rate per 100,000 Patients



HCC - California

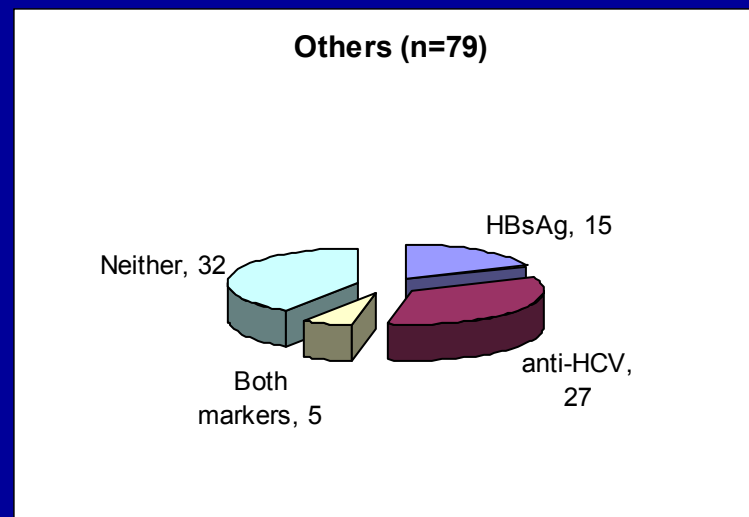
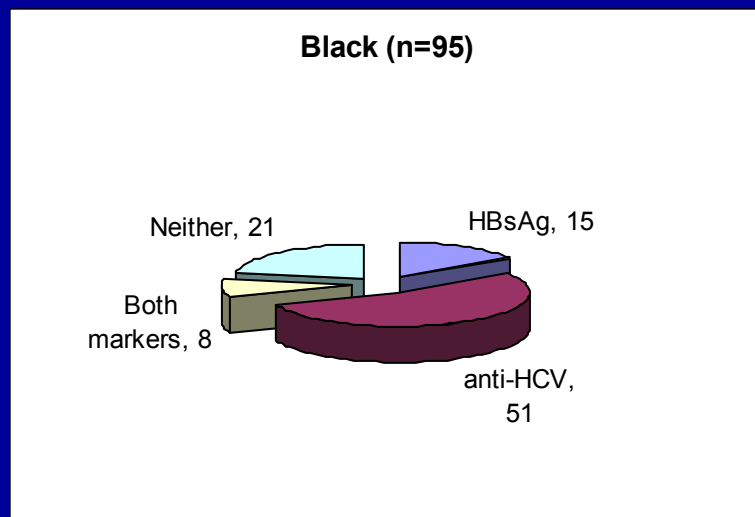
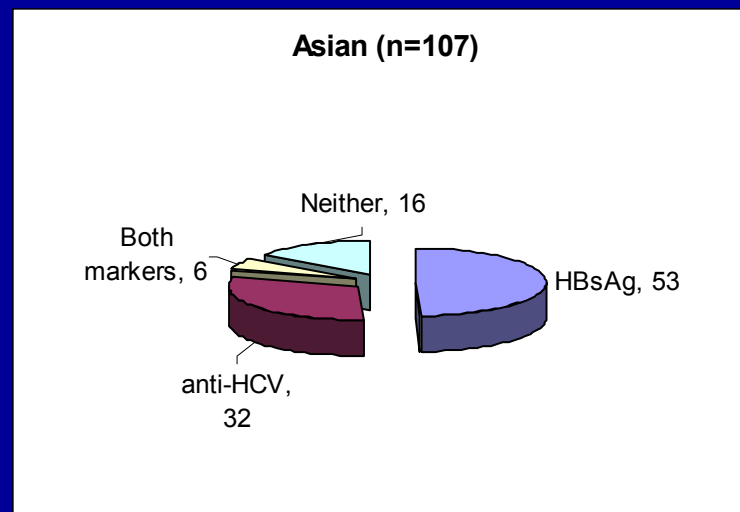
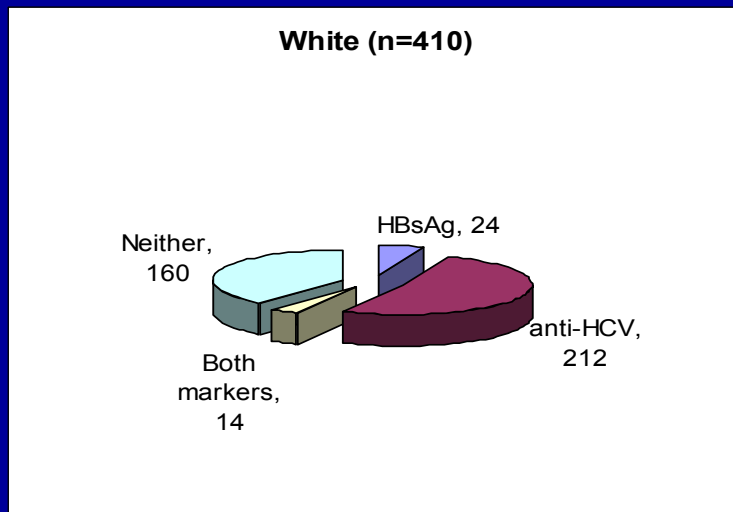
California Cancer Registry, Accessed 10/2004

**HCC Incidence per 100,000 Population,
California 1990-1994**



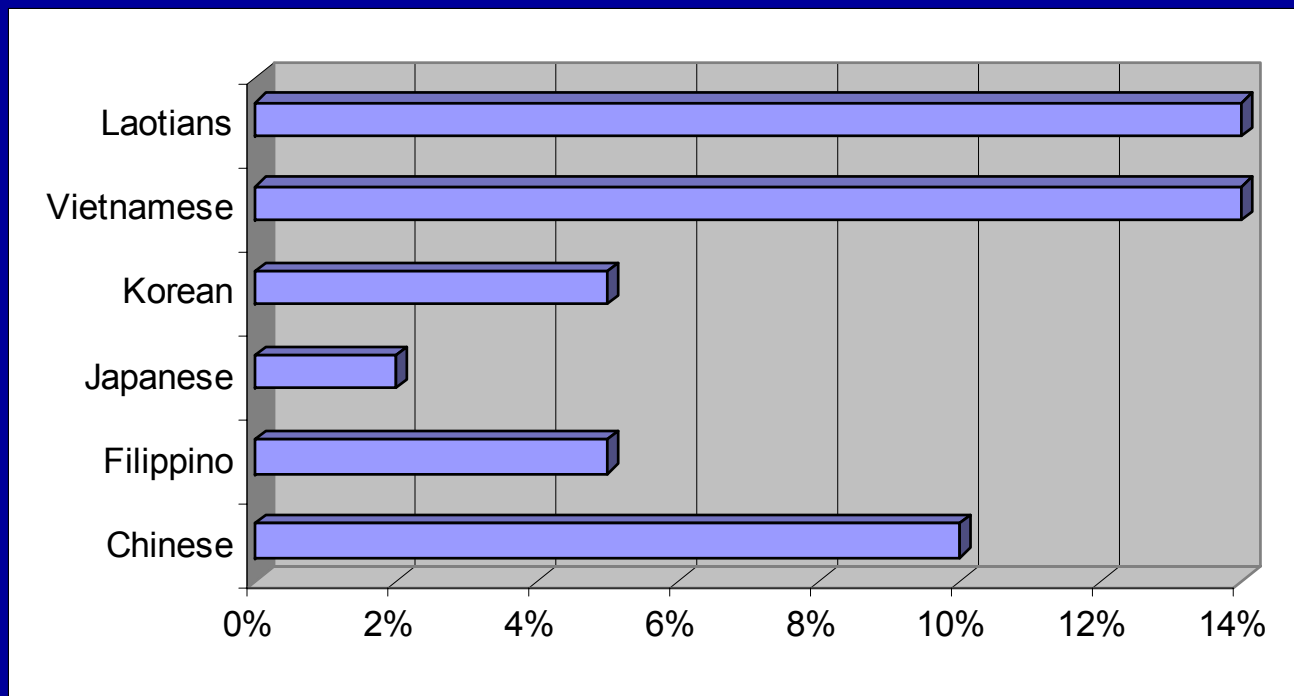
Etiology of HCC in Asians

*Results from survey of 21 US transplant centers between 1997-1999 (n=691):



Hepatitis B prevalence

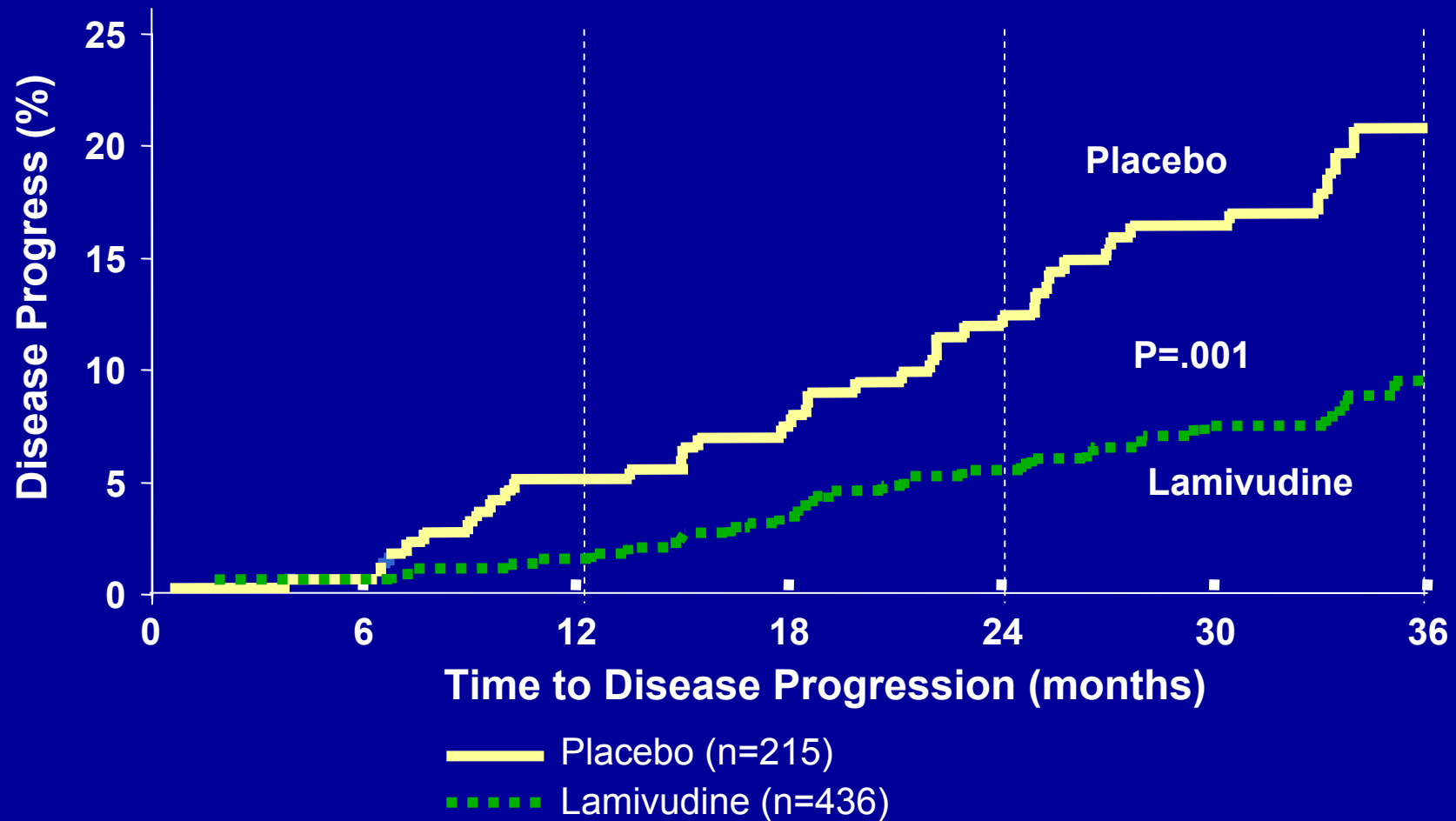
- Low overall U.S. prevalence: 0.3%.
- Asians: ~10-13%



HBV DNA Associated with Increased Risk of HCC

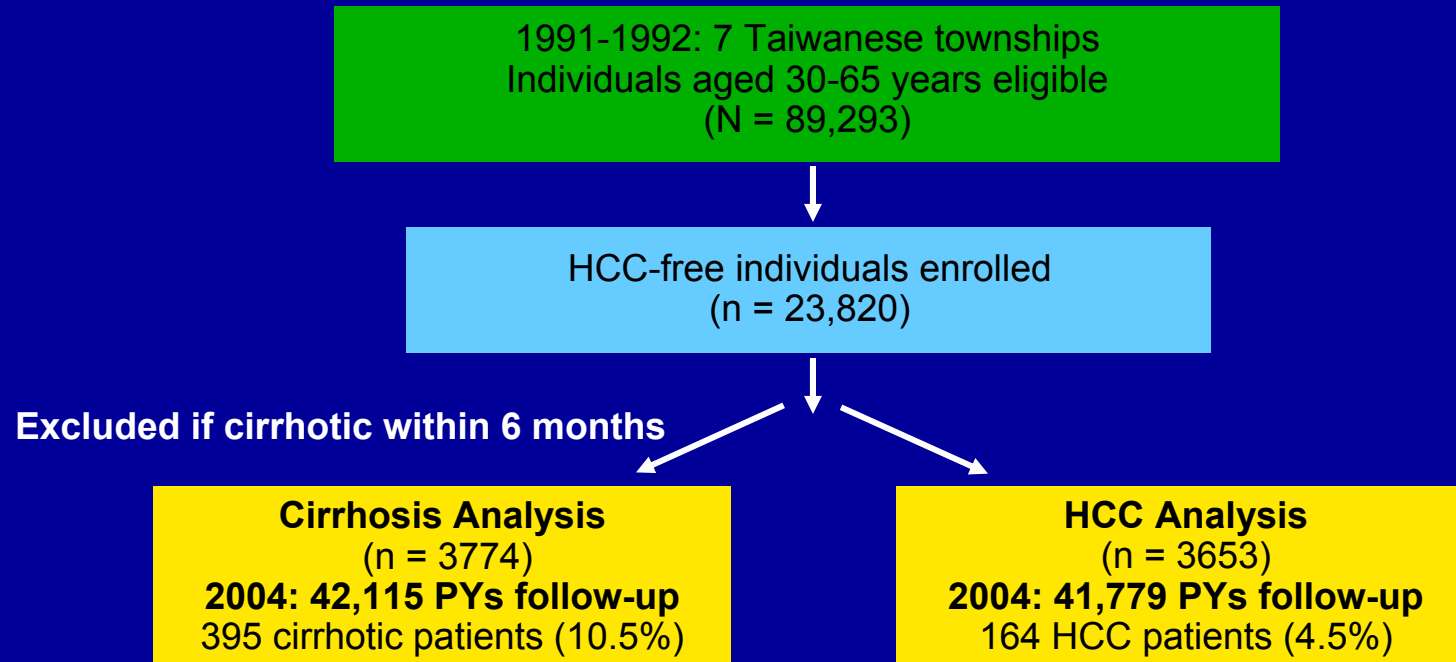
- Likelihood of HCC in individuals with detectable HBV DNA is **3.9** times more than those with undetectable HBV DNA
 - Risk associated with increasing HBV DNA levels
- These data support possibility of preventing long-term risk of HCC by inducing sustained suppression of HBV replication

Time to Disease Progression in Patients with CHB and Cirrhosis



REVEAL: Baseline HBV DNA and Liver Disease Progression

- Prospective, multicenter, observational cohort study



REVEAL: Relationship Between Baseline Viral Load and Cirrhosis

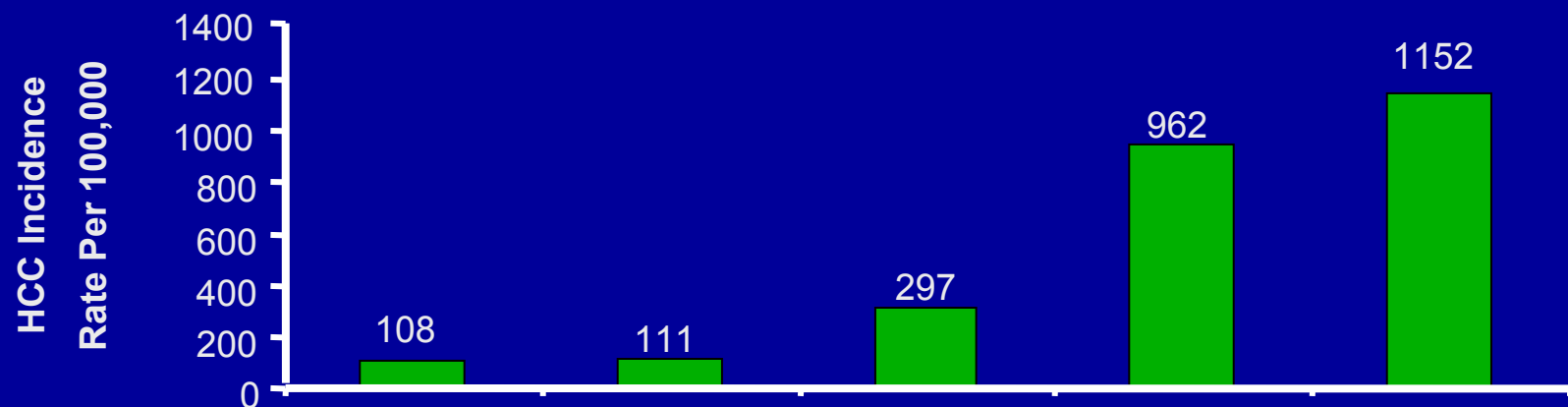
- Baseline HBV DNA predicted progression to cirrhosis
 - Relationship independent of HBeAg status

Serum HBV DNA	Total Patients	Cases of Cirrhosis	Adjusted RR* (95% CI)	P Value
(copies/mL) HBeAg-Negative Patients				
< 10 ⁴	2132	104	1.0 (reference)	--
≥ 10 ⁴ to < 10 ⁵	631	55	1.9 (1.4 - 2.7)	< .001
≥ 10 ⁵	451	96	4.9 (3.7 - 6.4)	< .001
HBeAg-Positive Patients				
< 10 ⁴	22	2	2.6 (0.6 - 10.5)	NS
≥ 10 ⁴ to < 10 ⁵	18	3	6.2 (1.9 - 19.5)	< .01
≥ 10 ⁵	520	135	8.6 (6.6 - 11.2)	< .001

* Adjusted for gender, age, anti-HCV levels, smoking, and alcohol use. NS, not significant

REVEAL: Relationship Between Baseline HBV DNA Levels and HCC

- Baseline HBV DNA predicted incidence of HCC
 - Independent predictor of HCC in multivariate analysis



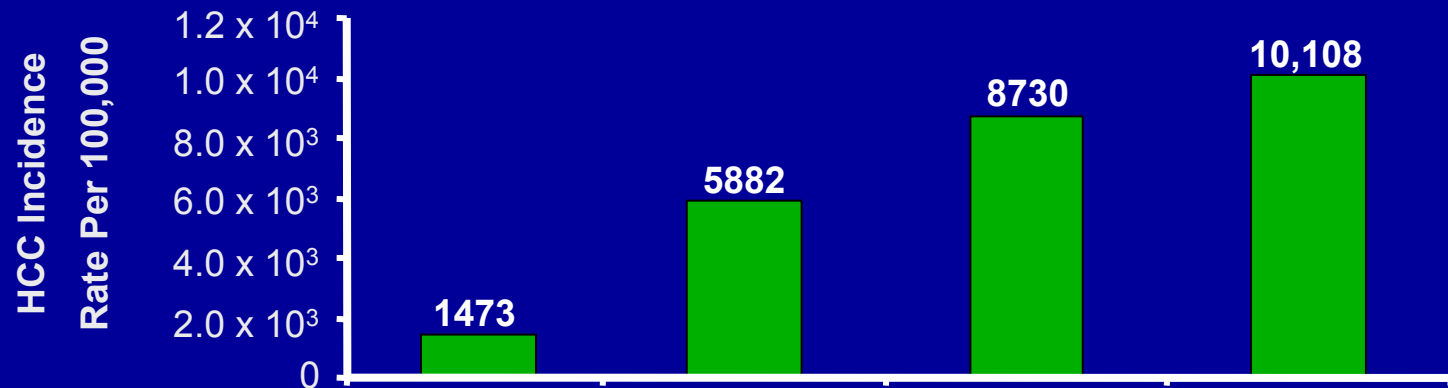
HBV DNA (copies/mL)	< 300	300 to < 10 ³	1.0-9.9 x 10 ⁴	1.0-9.9 x 10 ⁵	≥ 1.1 x 10 ⁶
Adjusted RR (95% CI)	1.0 (ref)	1.0 (0.5-2.2)	2.7 (1.3-5.6)	8.9 (4.6-17.5)	10.7 (5.7-20.1)
P Value	--	NS	.006	< .001	< .001

Chen CJ, et al. *JAMA* 2006;295:65-73.

REVEAL: Relationship Between Persistent Viremia and HCC Incidence

- Persistent HBV DNA associated with greater risk of HCC
 - Examined in those with levels $\geq 10^4$ copies/mL at baseline (n = 1376)

Chen CJ, et al. *JAMA* 2006;295:65-73.



Baseline HBV DNA, copies/mL	$< 10^4$	$\geq 10^5$	$\geq 10^5$	$\geq 10^5$
Follow-up HBV DNA, copies/mL	--	$< 10^4$	10^4 to $< 10^5$	$\geq 10^5$
Adjusted RR (95% CI)	1.0 (reference)	3.8 (1.7-8.4)	7.3 (3.5-15.3)	10.1 (6.3-16.2)
P Value	--	$< .001$	$< .001$	$< .001$

HBV DNA Associated with Increased Risk of HCC

- Serum HBV DNA $\geq 10^4$ copies/mL may be an independent predictor of the development of cirrhosis and HCC in dose-response fashion
 - Unknown if results can be generalized to all HBV carriers
- These data support possibility of preventing long-term risk of cirrhosis and HCC by sustained suppression of HBV replication
 - Hypothesis needs to be proven prospectively

How To Treat HBV Infection

Who To Treat?

What To Treat With?

Serological Markers: HBV

- **HBsAg:** Marker of infection
Presence > 6 months = chronic
- **HBeAg:** Active viral replication
Absent in pre-core mutant - common in Asian, higher treatment relapse, poorer survival.
- **Anti-HBs:** Indicates recovery and/or immununity (after vaccine)
- **Anti-HBe:** Inactive viral replication
- **Anti-HBc:** Infection or immunity

Hepatitis B Virus *Variants*

- **Wild type**
 - Usual HBeAg (+) hepatitis
- **Precore mutation (27% U.S. patients)**
 - Abolishes HBeAg production (e-CHB)
- **Core promoter mutation (44% U.S. patients)**
 - Down-regulates HBeAg production (e-CHB)
- **Treatment-induced mutations**
 - YMDD (M204V/I +/- L180M and others): induced by lamivudine (~20%/year)
 - N236T and A181V: induced by adefovir (~2% at year 2 and ~4% at year 3)
 - I169, T184, S202 and M250: induced by entecavir in patients with prior lamivudine resistance.

Hepatitis B Virus

Genotypes

- **HBV classified into 7 genotypes (A-G)**
 - **A: North America and Western Europe**
 - **B and C: Asia**
 - **D: Southern Europe and India**
 - **E and G: Africa**
 - **F: Central and South America and Alaska**
 - **H: Central America**
- **B associated with less HCC, less active and more slowly progressive liver disease than C**
- **A and B respond better to IFN than C and D**
- **Genotype does not predict response to oral agents**

HBV Infection: Definitions

- **Chronic hepatitis B**
 - Chronic necroinflammatory liver disease > 6 mo
 - ALT ↑, HBeAg-positive or -negative, HBV DNA > 10^{4-5}
- **Inactive HBsAg carrier**
 - Persistent infection without necroinflammatory disease
 - ALT normal, HBeAg-negative, HBV DNA < 10^{4-5}
- **Resolved hepatitis B**
 - Previous HBV infection without virological, biochemical, or histological evidence of active disease
- **Acute exacerbation or flare of hepatitis B**
 - Elevated ALT > 10 x ULN or > 2 x baseline
- **Reactivation of hepatitis B**
 - Reappearance of necroinflammatory disease in person known to be inactive carrier or resolved hepatitis B

Phases of Chronic Hepatitis B

- **Immunotolerant phase**

- HBeAg-positive; HBV DNA high (10^{5-10}); ALT normal

*Candidates for therapy

- **Immunoactive phase (chronic hepatitis B)**

- HBeAg-positive (wild type) or HBeAg-negative (mutants)
- HBV DNA high (10^{4-10}); ALT elevated; symptoms +/-

- **Non-replicative phase (inactive HBsAg carrier)**

- HBeAg-negative; HBV DNA low ($<10^4$); ALT normal
- HBsAg may later become undetectable

Natural Clearance of HBeAg and HBsAg

- **HBeAg**
 - 4% to 12% of carriers per year
 - 40% to 50% in 5 years
 - 70% to 80% in 10 years
 - More frequent in older carriers and with ↑ ALT
 - Up to 20% who clear HBeAg have ≥ 1 HBeAg reversions
- **HBsAg**
 - 0.5% of carriers per year; most develop anti-HBs

General Management and Counseling

Chronic Hepatitis B

AASLD Practice Guideline

- **Routine, periodic follow-up of all carriers should be performed by a health care provider**
- **Follow-up interval of every 6 months seems reasonable, although no evidence-based data exists to support this recommended interval**
 - **Tests: ALT and AST; AFP; consider US**
 - **Inactive HBsAg carrier: if ALT/AST increase, re-evaluate**
 - **Chronic hepatitis B: CBC, LFTs, HBeAg, anti-HBe**

Chronic HBV Infection

Counseling

- **HAV vaccination of those who are not immune**
- **Abstinence or limited use of alcohol**
- **Counseling regarding infectivity**
- **Sexual and household contacts tested for HBV and receive HBV vaccine if negative**
- **HBIG and HBV vaccine to newborns of HBV-infected mothers**

Screening for HCC

Recommendations

- **Screening should be considered in all carriers**
 - HCC begins as a single lesion in 70-90% of cases
 - Doubling time long: 1-12 mo (average = 6 mo)
- **Minimum screening: AFP q 6 months in inactive carriers from endemic populations**
- **AFP plus US q 6 months in HBV carriers with:**
 - Cirrhosis
 - Family history of HCC
 - Age > 35-40 years

Treatment of Chronic Hepatitis B

Goals of Treatment

- Prevent long-term clinical outcomes (cirrhosis, HCC, death) by durable suppression of HBV DNA
- Treatment endpoints in clinical trials and practice
 - Improve liver histology*
 - Decrease serum HBV DNA
 - Decrease or normalize serum ALT
 - Induce HBeAg loss or seroconversion
 - Induce HBsAg loss or seroconversion

***Clinical trials only; not routinely assessed in practice**

Goals of Therapy

Two Distinct Patient Populations

- **HBeAg-positive (wild-type)**
 - HBeAg loss \pm seroconversion
 - Durable suppression of HBV DNA to low or undetectable levels
 - Therapy discontinued after seroconversion; durability of response \approx 80%
- **HBeAg-negative (precore and core promoter mutants)**
 - HBeAg seroconversion not an endpoint
 - Durable suppression of HBV DNA to low or undetectable levels
 - Relapse common after stopping oral therapy; therapy usually administered long-term

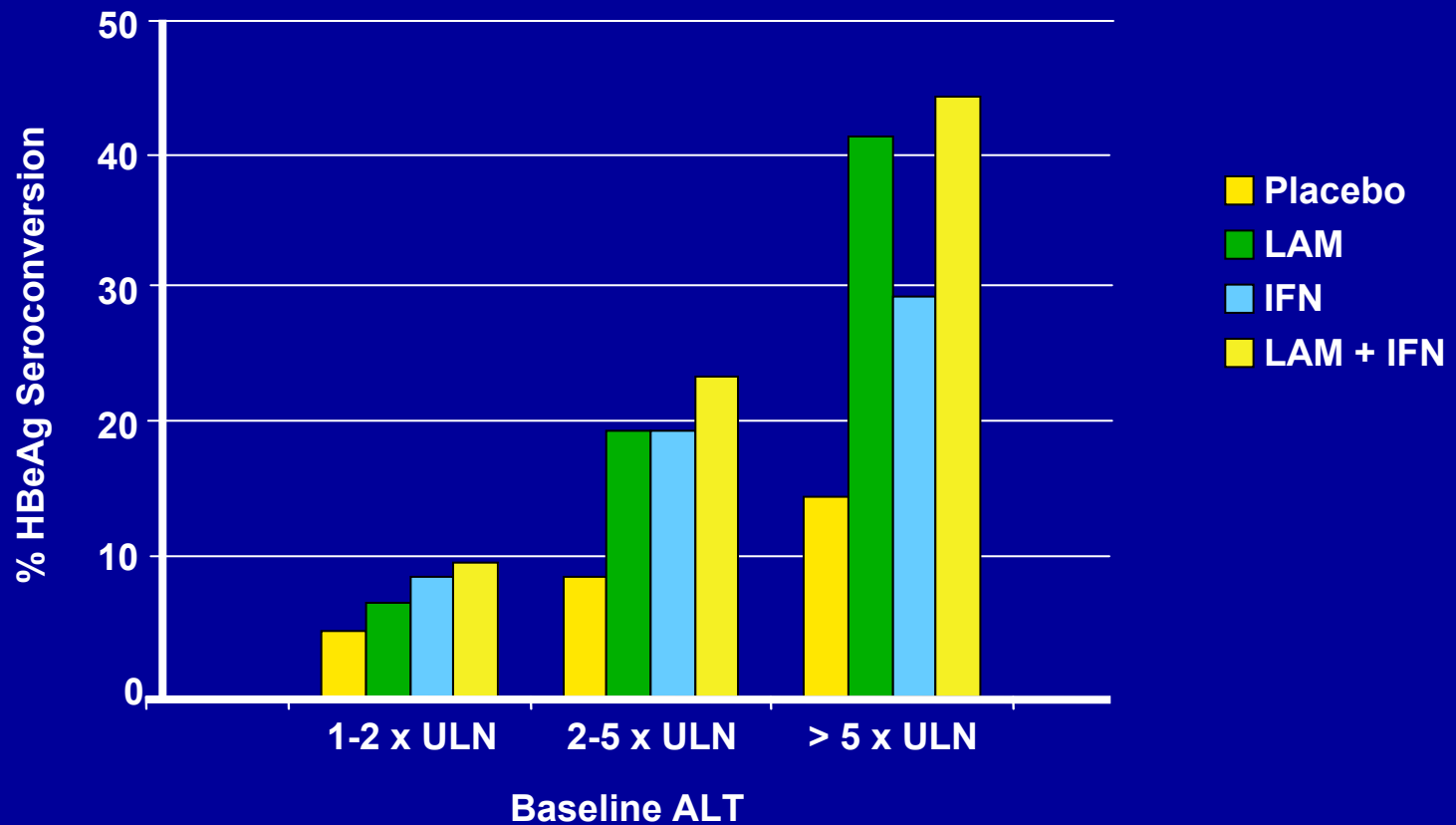
Standard Treatments for Chronic Hepatitis B

- **Interferon**
 - Interferon alfa-2b (Intron A) 5 MU/d or 10 MU tiw x 4 months
 - Peginterferon alfa-2a (Pegasys) 180 mcg/week x 24-48 weeks
- **Nucleoside/nucleotide analogues**
 - Lamivudine (Epivir-HBV): 100 mg/d
 - Adefovir dipivoxil (Hepsera): 10 mg/d
 - Entecavir (Baraclude): 0.5-1.0 mg/d
 - New nucleoside analogues and other oral agents under study
- **Liver transplantation (decompensated chronic hepatitis B with cirrhosis)**

Treatment Guidelines & Algorithm

- Usually commissioned by professional societies or government advisory committees
- Some guidelines commissioned by pharmaceutical companies by independent panel
- Current guidelines for chronic hepatitis B
 - AASLD: Lok and McMahon, *Hepatology* 2004;39:857
 - EASL: de Franchis et al, *J Hepatol* 2003;39:533
 - APASL: Liaw et al, *Liver Int* 2005;25:472
 - NIH: Lok et al, *Gastroenterology* 2001;120:1828
 - Treatment algorithm: Keeffe et al, *CGH* 2004;2:87
- Guidelines have similarities and differences

Baseline ALT and Response to Treatment of HBeAg(+) Patients



Treatment Recommendations for HBeAg(+) Patients

ALT	HBV DNA	Recommendations
$\leq 2 \times \text{ULN}$	+	No treatment, monitor ^{1,2,3} Grey zone: ALT 1–2 x ULN or intermittently elevated; liver biopsy → moderate/severe inflammation or advanced fibrosis → treatment ¹
$> 2 \times \text{ULN}$	+	Observe × 3–6 months; treat if no spontaneous HBeAg seroconversion ^{1,2,3} Immediate treatment if bilirubin increases ³ or decompensation ^{1,3}

HBV DNA: + defined as $>100,000$ copies/mL
Guidelines: ¹AASLD; ²EASL; ³APASL

Treatment Recommendations for HBeAg(-) Patients

ALT	HBV DNA	Recommendations
$\leq 2 \times \text{ULN}$	$< 100,000$ copies/ml	No treatment, monitor ^{1,2,3} Grey zone: ALT 1–2 ULN; HBV DNA 10,000 – 100,000 copies/mL Liver biopsy → moderate/severe inflammation or advanced fibrosis → treatment ¹
$> 2 \times \text{ULN}$	$> 100,000$ copies/ml	Treatment ^{1,2,3}

HBV DNA: $<$ or $> 100,000$ copies/mL
Guidelines: ¹AASLD; ²EASL; ³APASL

Panel Recommendations: 2006

- New recommendations
 - Revised normal ALT levels should be used in determining criteria of elevated ALT for treatment
 - Adefovir may be preferred for patients with LAM-resistance because of novel mutations with entecavir

Updated Definitions of Healthy Ranges for ALT Levels

- Retrospective cohort study; university hospital in Milan; 6,835 first time blood donors 1995-1999; anti-HCV negative and no contraindication to donation
- ALT activity independently related to: BMI, and abnormal lipid or carbohydrate metabolism
- Updated upper limits
 - Males 40 → 30 U/L (-25%)
 - Females 30 → 19 U/L (-37%)

Normal Serum AST and ALT and Risk of Mortality from Liver Disease

DESIGN

- Prospective, cohort study
 - Cause of death from death certificates
 - 94,533 males and 47,522 females ages 35-59 with 8 years follow-up
- Number with CHB unknown*

OBJECTIVE

- Determine liver mortality in individuals with normal ALT (<40 IU/L)

OUTCOMES

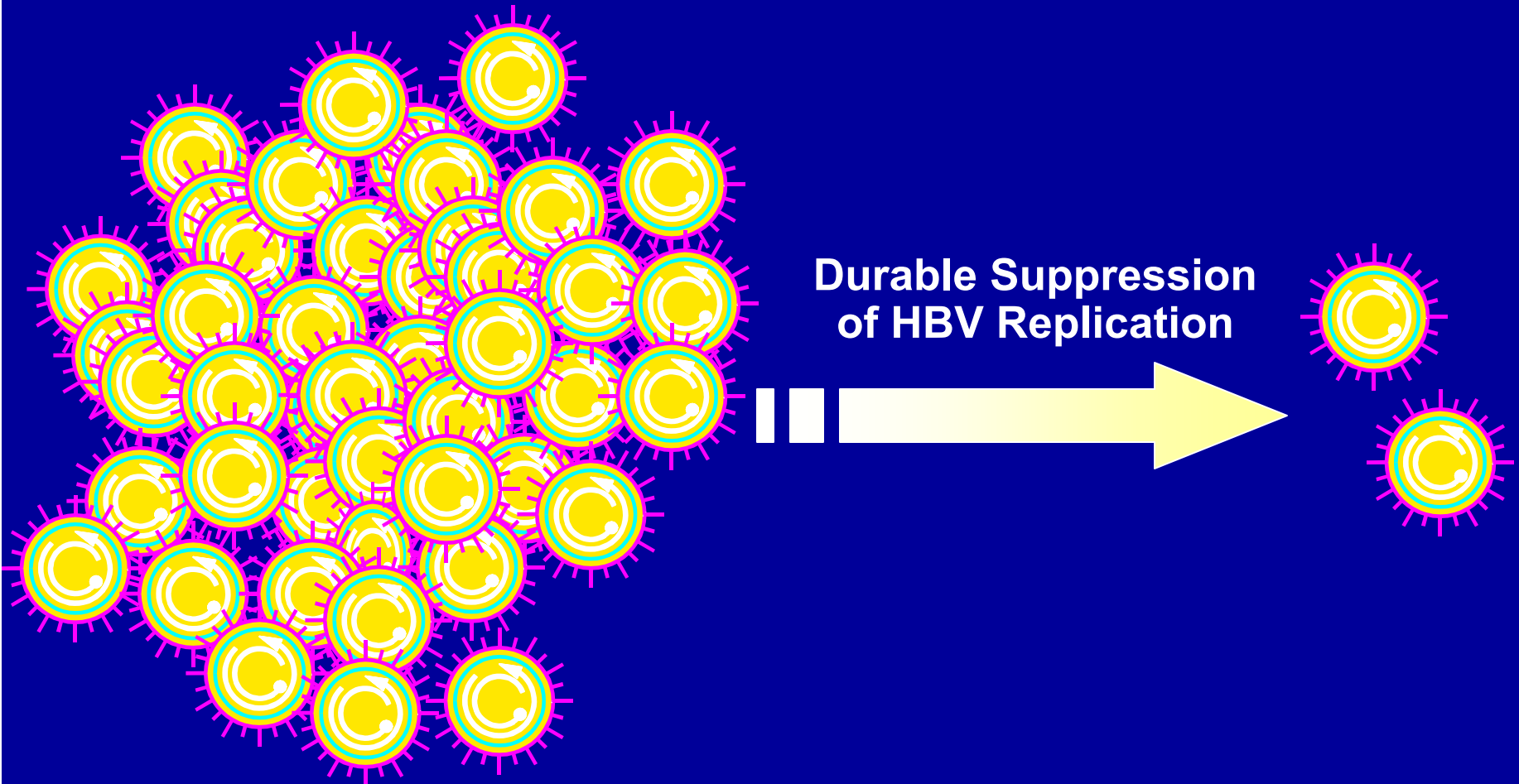
- 690 deaths from liver disease (LD)
- Death from LD associated with baseline age, AST, BP, FHx of LD, elevated glucose or cholesterol
- ALT >20 associated with increased risk for death from LD

Risk of death from liver disease based on ALT and AST

	RR of Death from LD	
	Male	Female
AST		
<20	1	1
20-29	2.5	3.3
30-39	8	18.2
ALT		
<20	1	1
20-29	2.9	3.8
30-39	9.5	6.6

Kim HC, et al. *BMJ* 2004;328:983.

Primary Goal of Hepatitis B Therapy: Preventing Cirrhosis, HCC, and Death



Interferon Therapy

IFN α Therapy for HBeAg +ve HBV *Long-term Follow-up*

- Meta-analysis of 12 studies (n=1975)
- 765 IFN-treated and 1210 untreated
- Follow-up range: 2.1–8.9 yr (mean, 6.1)

	IFN	Untreated
Loss of HBsAg	11.4%	2.6%
Disease decompensation	9.9%	13.3%
Development of HCC	1.9%	3.16%
Liver-related death	4.9%	8.7%

IFN α Therapy for HBeAg - ve HBV

Undetectable HBV DNA and ALT normalization (EOT)¹⁻⁴	28%–69%
Sustained response (EOF)^{1,2,4}	6%–33%
HBsAg loss (EOF)^{2,4,5}	4.5%–13%
Long-term (72 mo. post-Rx)⁵	27%

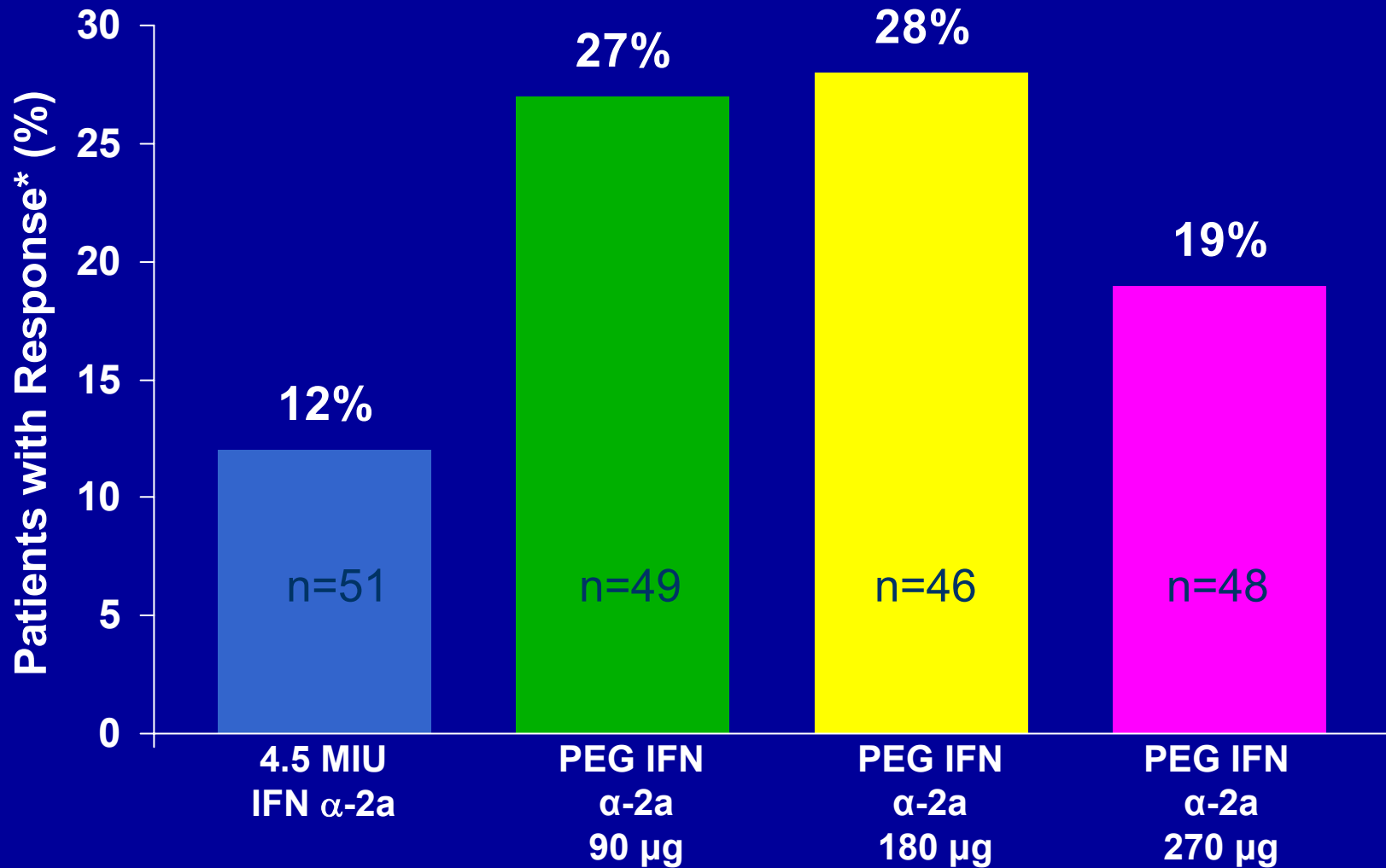
[1] Lampertico, et al, 1997; [2] Oliveri, et al, 1999; [3] Brunetto, et al, 2002;

[4] Manesis, et al, 2001; [5] Papatheodoridis, et al, 2001

Treatment of HBeAg +ve Chronic HBV with PEG INF alfa-2a

- **Study objective: compare the efficacy and safety of PEG IFN α -2a 90 μ g, 180 μ g, or 270 μ g administered qw with IFN α -2a 4.5 MIU tiw in the treatment of HBeAg +ve chronic hepatitis B**
- **Patients treated for 24 weeks followed by 24 weeks of follow-up**

Combined Response* at Week 48



*HBeAg loss, HBV DNA <500,000 copies/mL, ALT normalization

Combination Therapy with Nucleoside Analogues and IFN

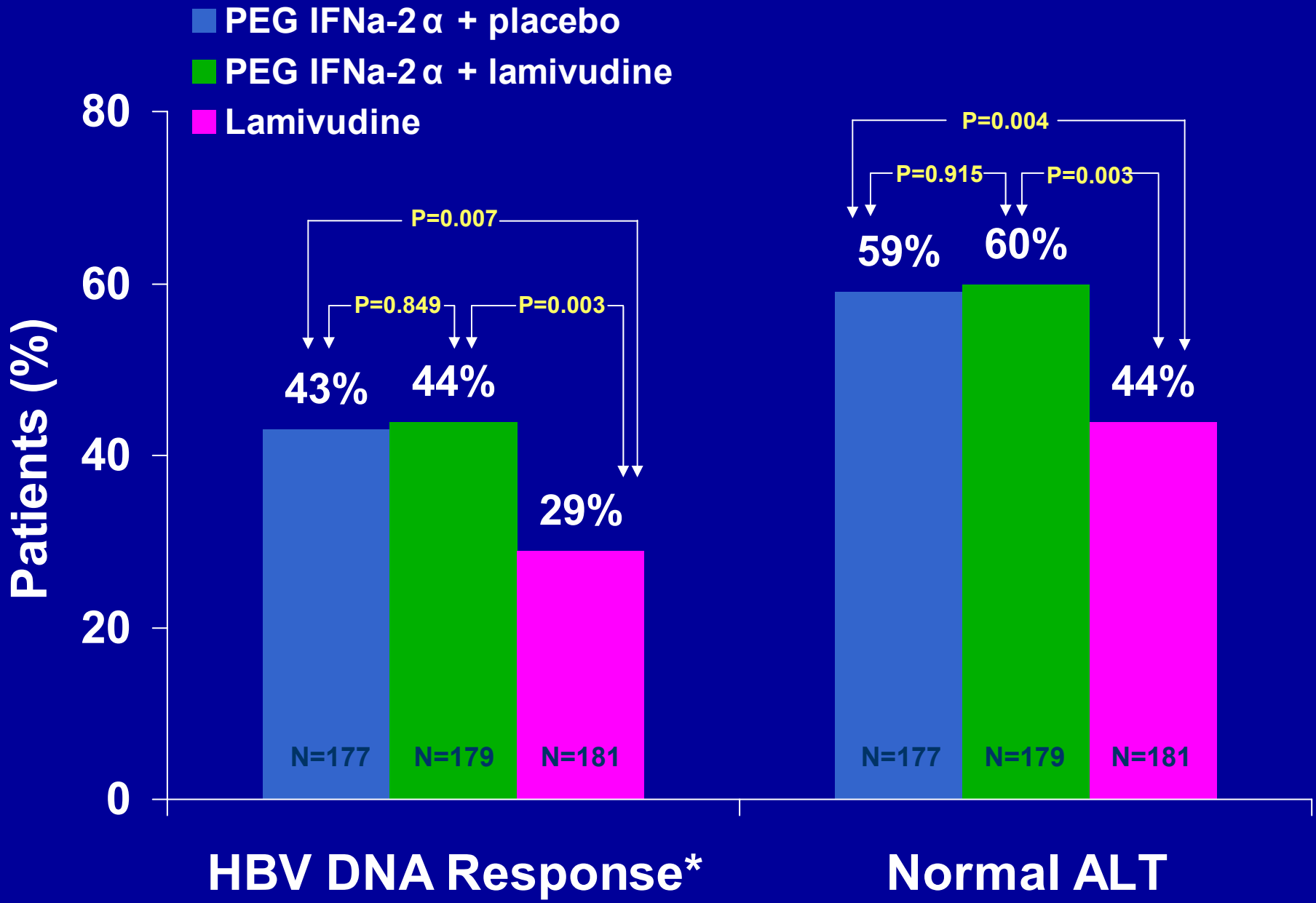
- Different mechanisms of action may enhance therapeutic effectiveness of antiviral therapy
- Suppression of serum HBV DNA may be greater with combination therapy
- Higher rates of response shown in pilot studies in humans and in the woodchuck model

- No significant differences in sustained response for both HBeAg positive and negative patients in preliminary reports

Lau and Marcellin, 2004

Treatment of HBeAg -ve Chronic HBV with PEG IFN alfa-2a

- **Objective: compare the efficacy and safety of PEG IFN α -2a 180 μ g/wk monotherapy, PEG IFN plus lamivudine 100 mg/d, and lamivudine monotherapy in the treatment of HBeAg-ve chronic hepatitis B**
- **Patients at 54 sites in 13 countries treated for 48 weeks followed by 24 weeks of follow-up**

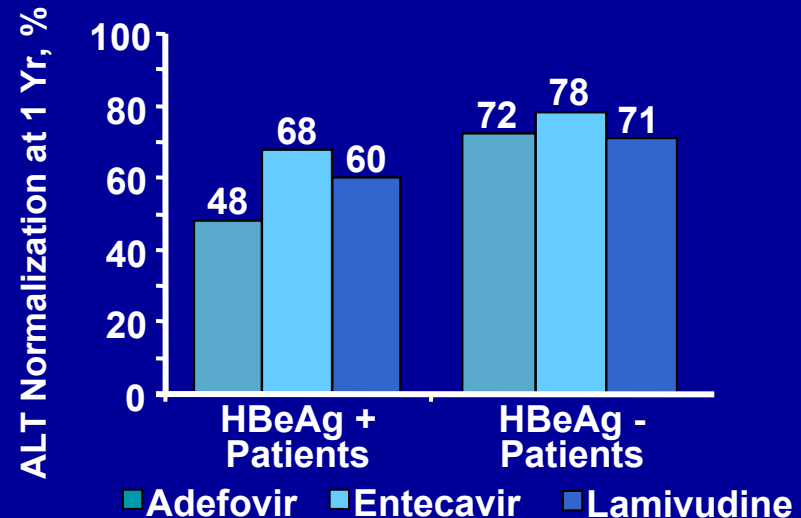
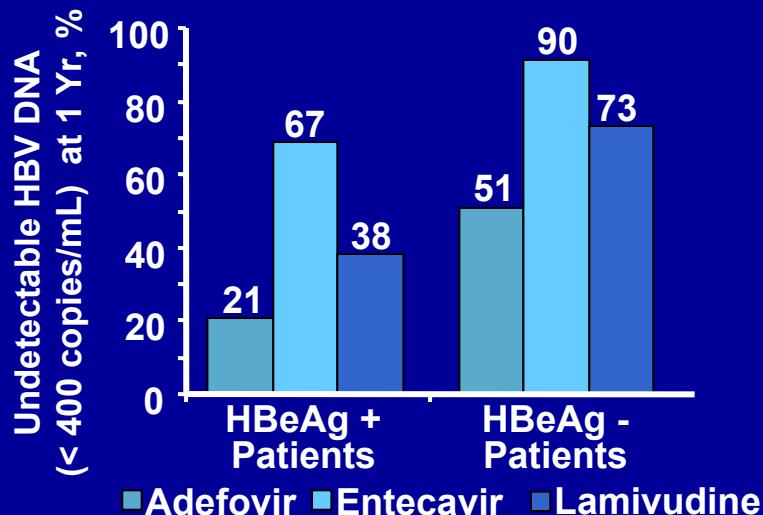


Marcellin, P et al. *N Engl J Med* 2004;351:1206-17.

*Less than 20,000 copies/mL

Overview of Efficacy with Current Oral Agents for Hepatitis B

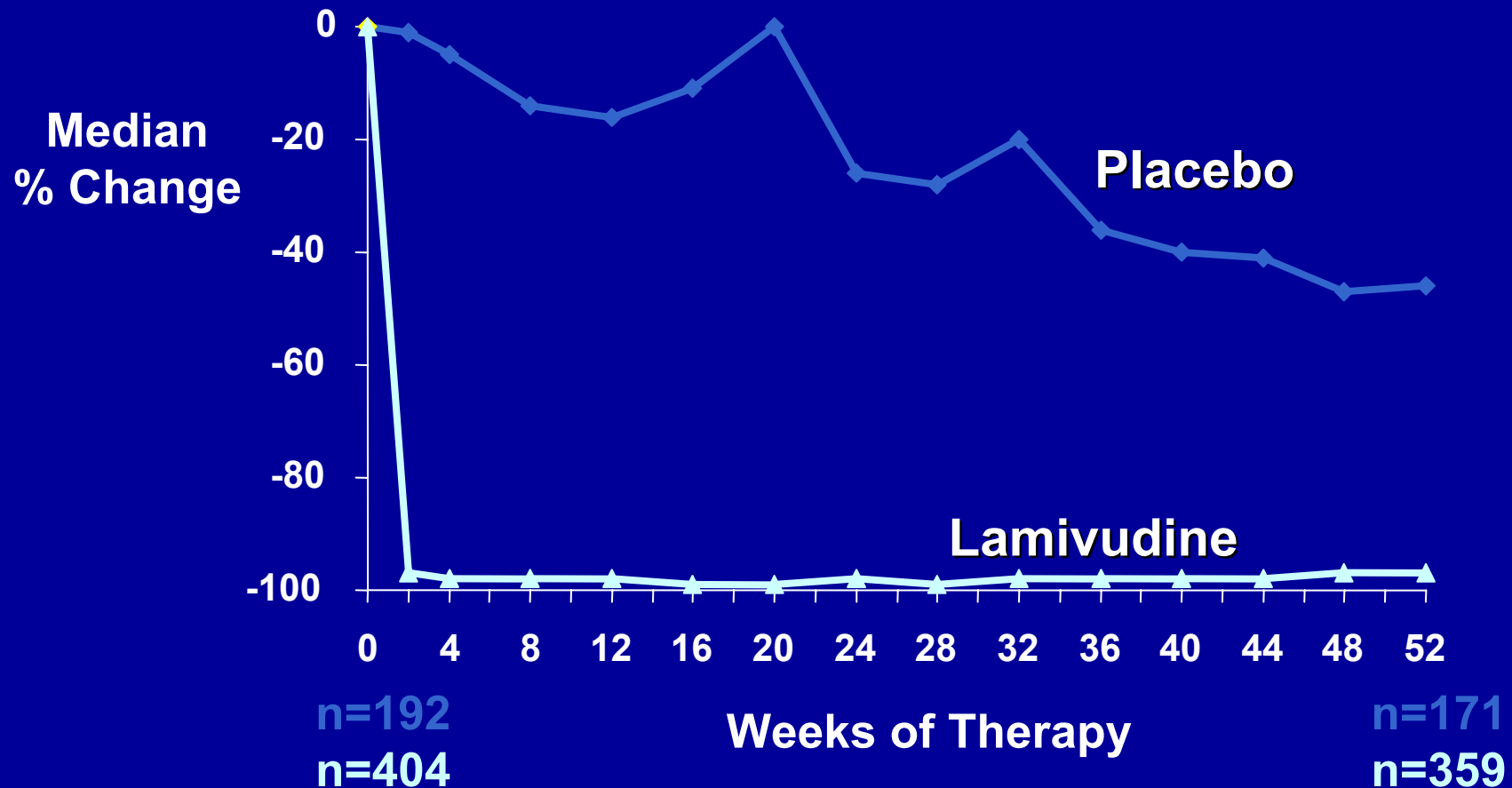
- HBV DNA comparison at yr 1
 - Mean drop, log₁₀ copies/mL
 - Entecavir, 5.04-6.86
 - Lamivudine, 4.53-5.39
 - Adefovir, 3.57-3.65
- HBeAg seroconversion at yr 1
 - Entecavir, 21%
 - Lamivudine, 18%
 - Adefovir, 12%
- ALT normalization at yr 1



Lamivudine Therapy: 1-Year Data

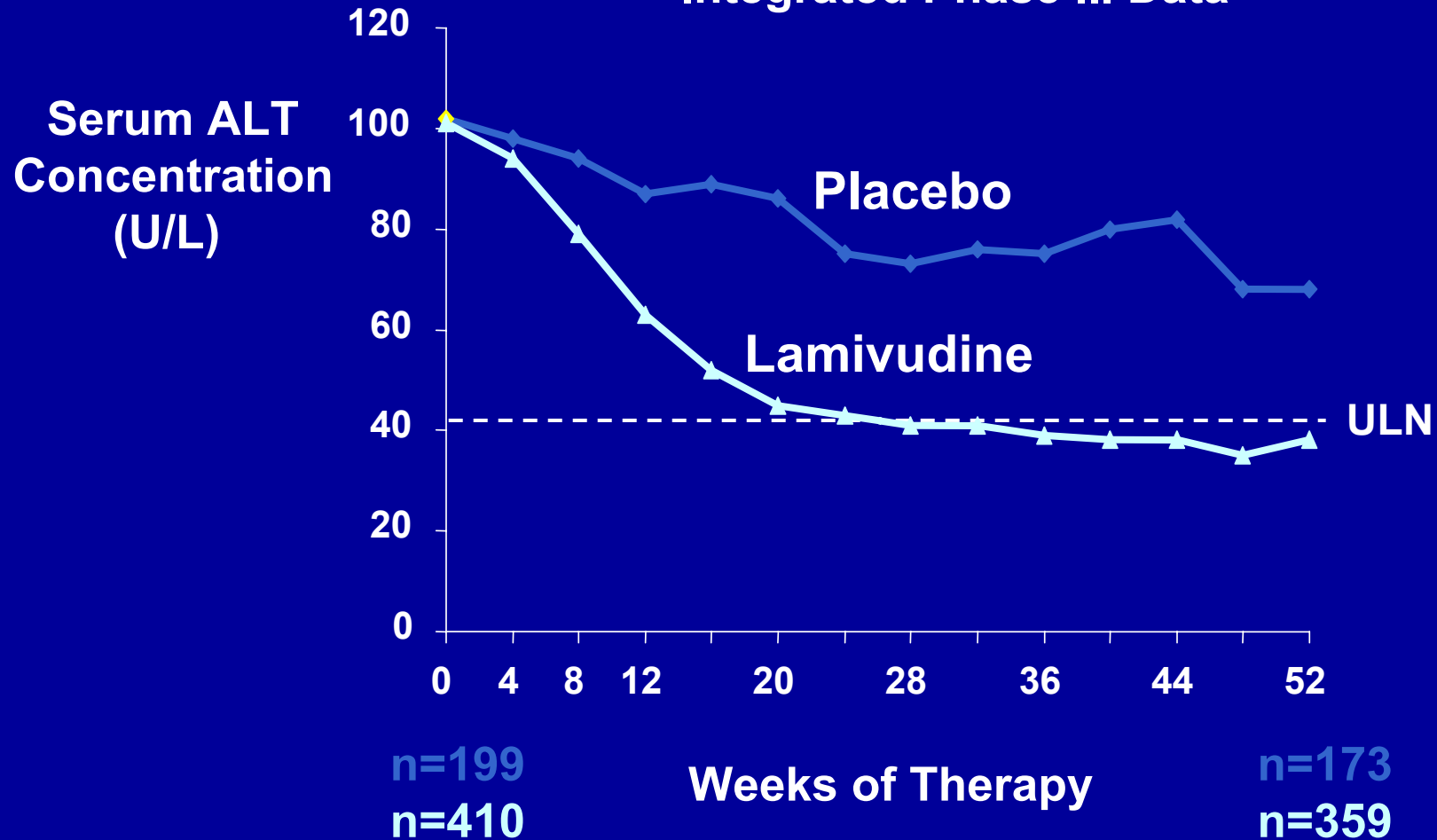
Suppression of Serum HBV DNA with Lamivudine

Integrated Phase III Data



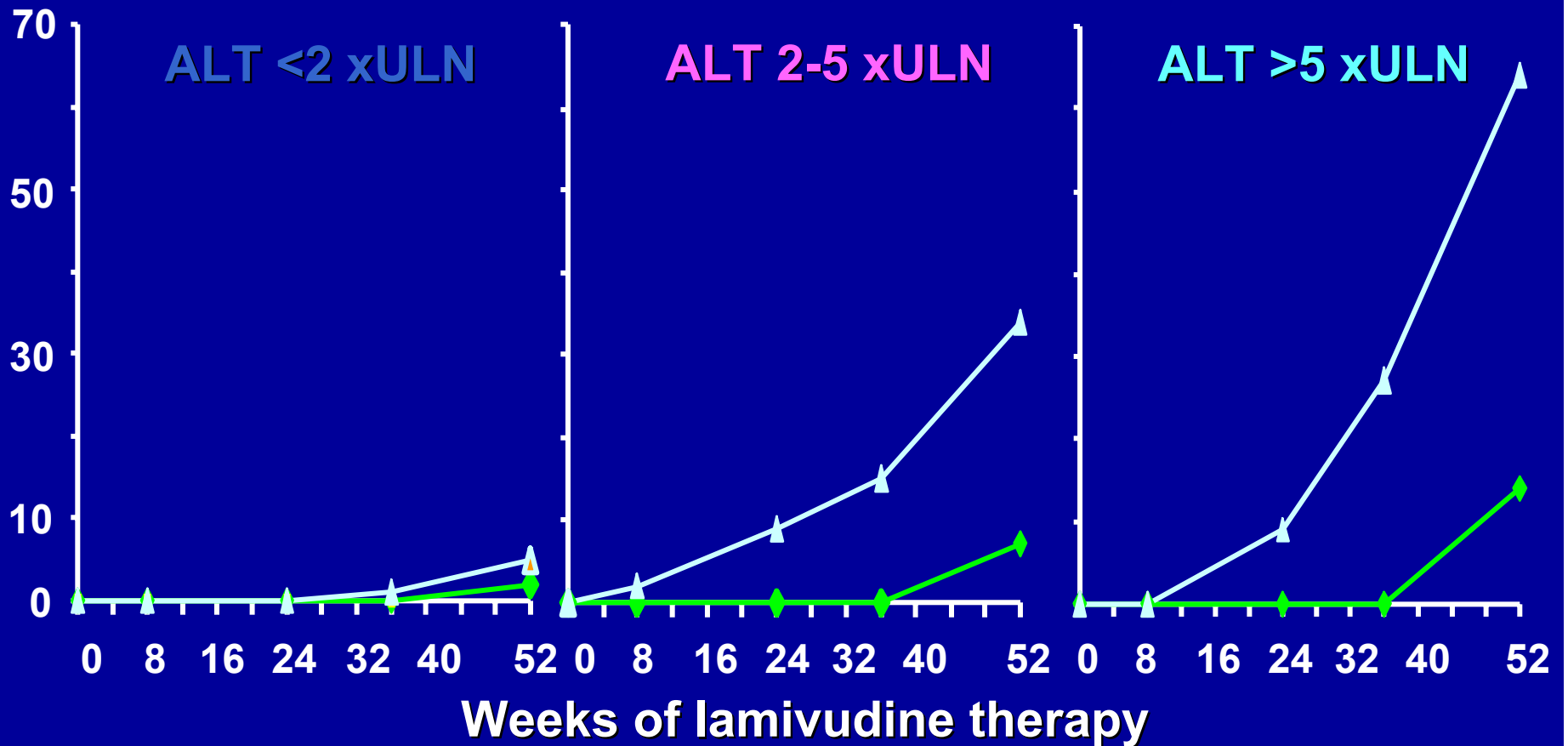
Effect of Lamivudine on Serum ALT

Integrated Phase III Data



HBeAg Seroconversion Relative to Baseline Serum ALT

HBeAg Seroconversion (%)

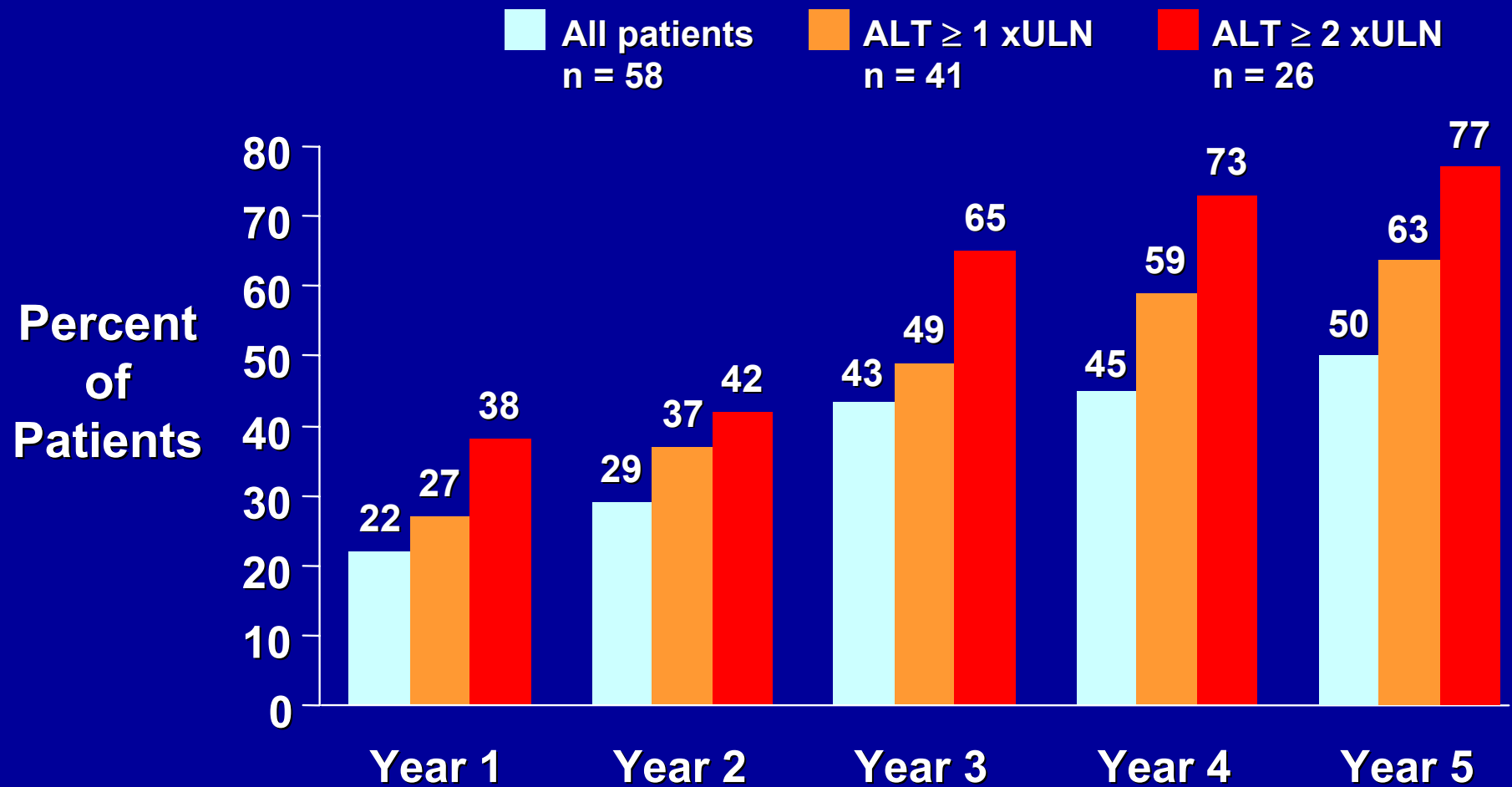


◆ Placebo ▲ Lamivudine

Chien, et al. *Hepatology* 1999

Lamivudine Therapy: 5-Year Data

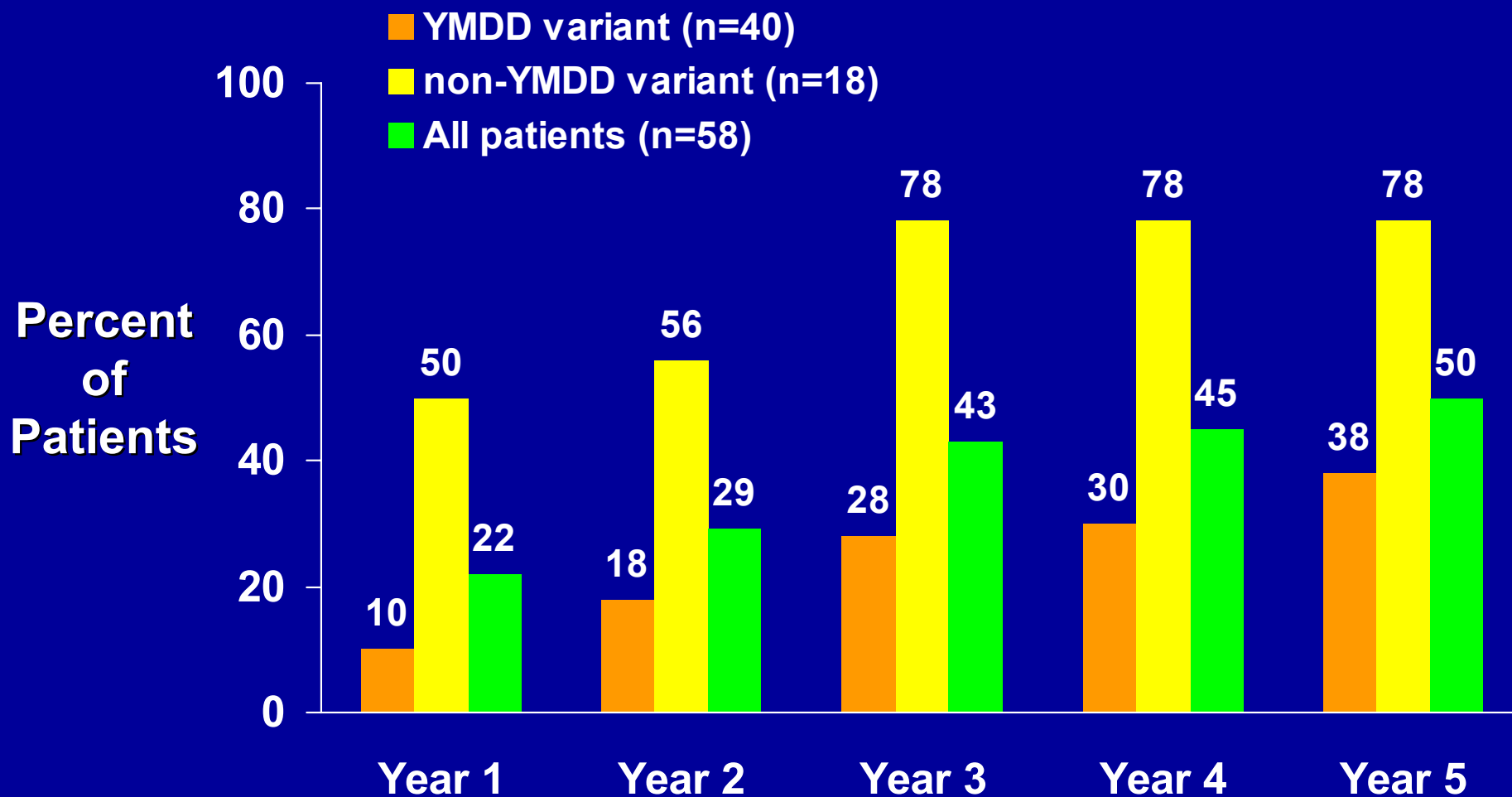
HBeAg Seroconversion: Effect of Treatment Duration and Baseline ALT



Asian study - Lai, Leung, Liaw, Guan

HBeAg Seroconversion over 5 Years

Effect of YMDD-Variant HBV



Lamivudine-Resistant YMDD Variants

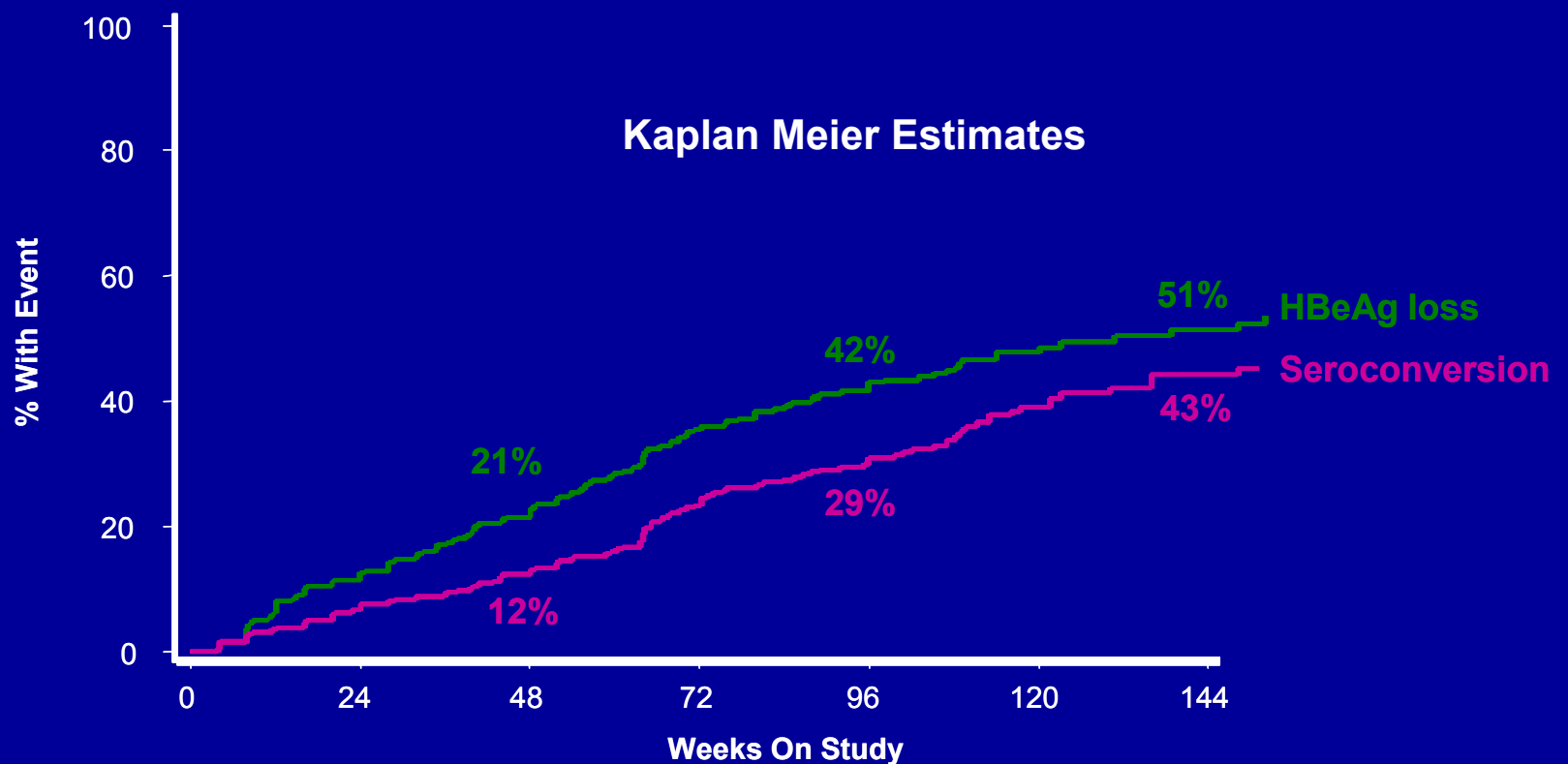
	Incidence of YMDD variants				
Year	1	2	3	4	5
% of Patients	14	30	50	67	69

- Unusual before 6 months of therapy
- HBV DNA and ALT levels usually below pretreatment values
- Asian study: histological deterioration after 3 years
- Patients can still experience HBeAg seroconversion
- Flares may follow YMDD variant emergence
- Current approach: switch to adefovir 10 mg daily

Adefovir 3-year and 5-year Therapy

ADV for HBeAg-Positive CHB

3-Year Data: HBeAg Loss

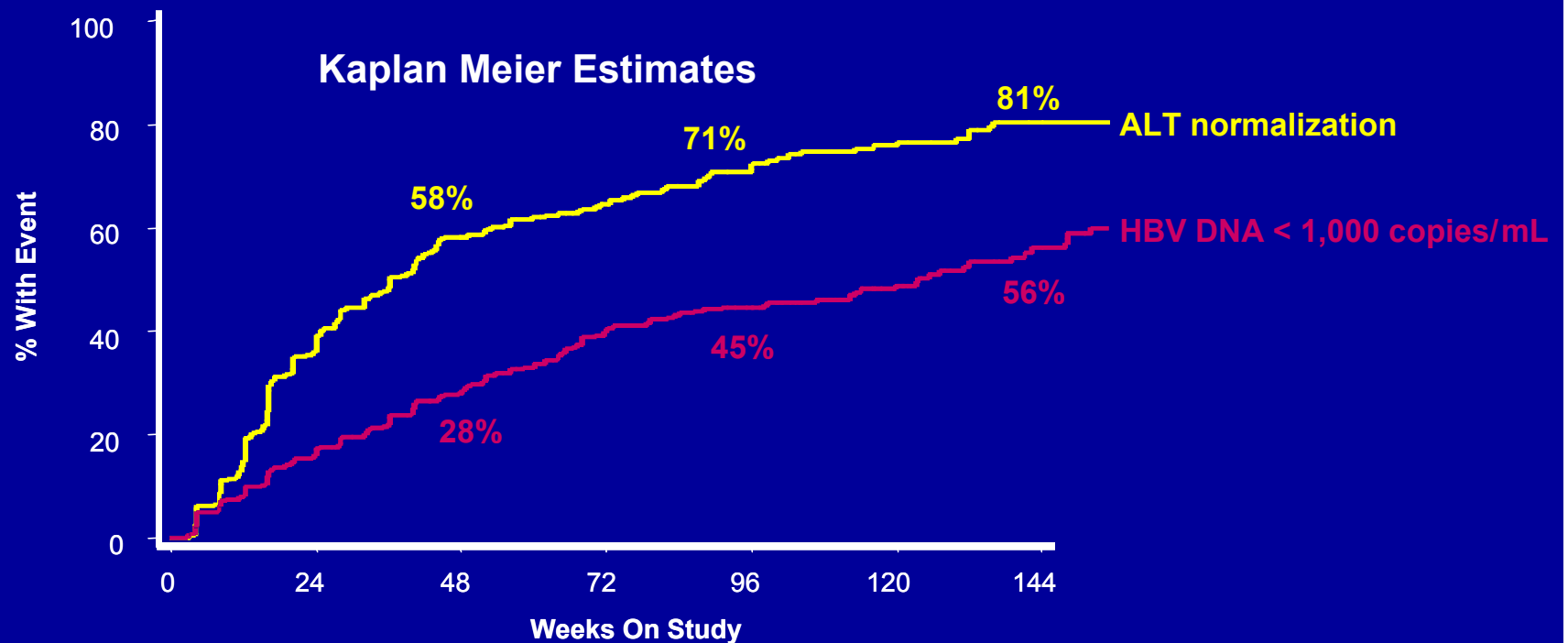


HBeAg Loss:	288	252	215	158	128	75	45
HBeAg Seroconversion:	288	267	240	191	157	90	53

Marcellin P, et al. *Hepatology* 2004;40:655A

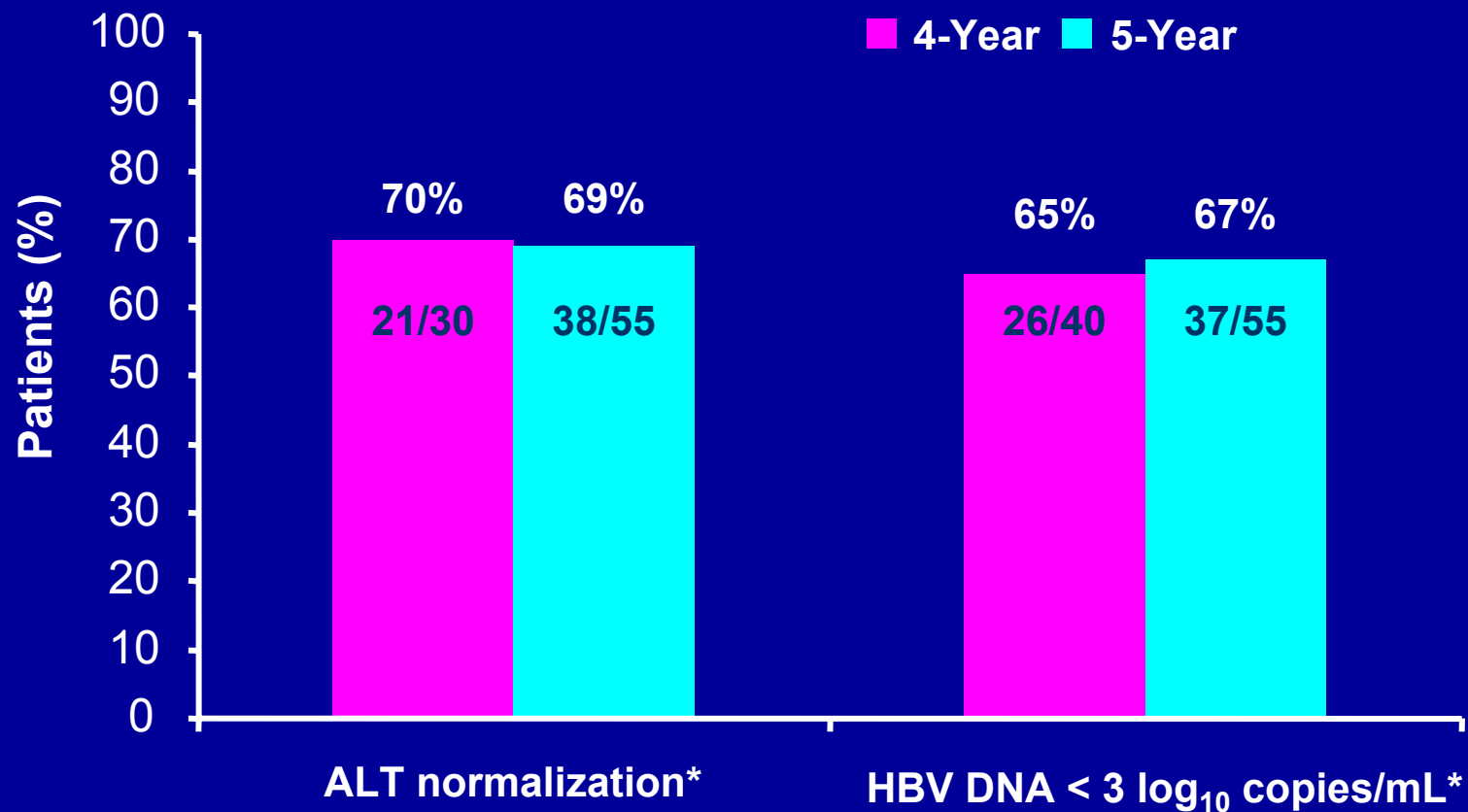
ADV for HBeAg-Positive CHB

3-Year Data: HBV DNA and ALT



ALT Normalization:	282	179	110	83	61	35	22
HBV DNA < 1,000:	307	254	210	156	132	83	48

Virologic and Biochemical Efficacy of Adefovir Similar in 4- and 5-year Cohorts



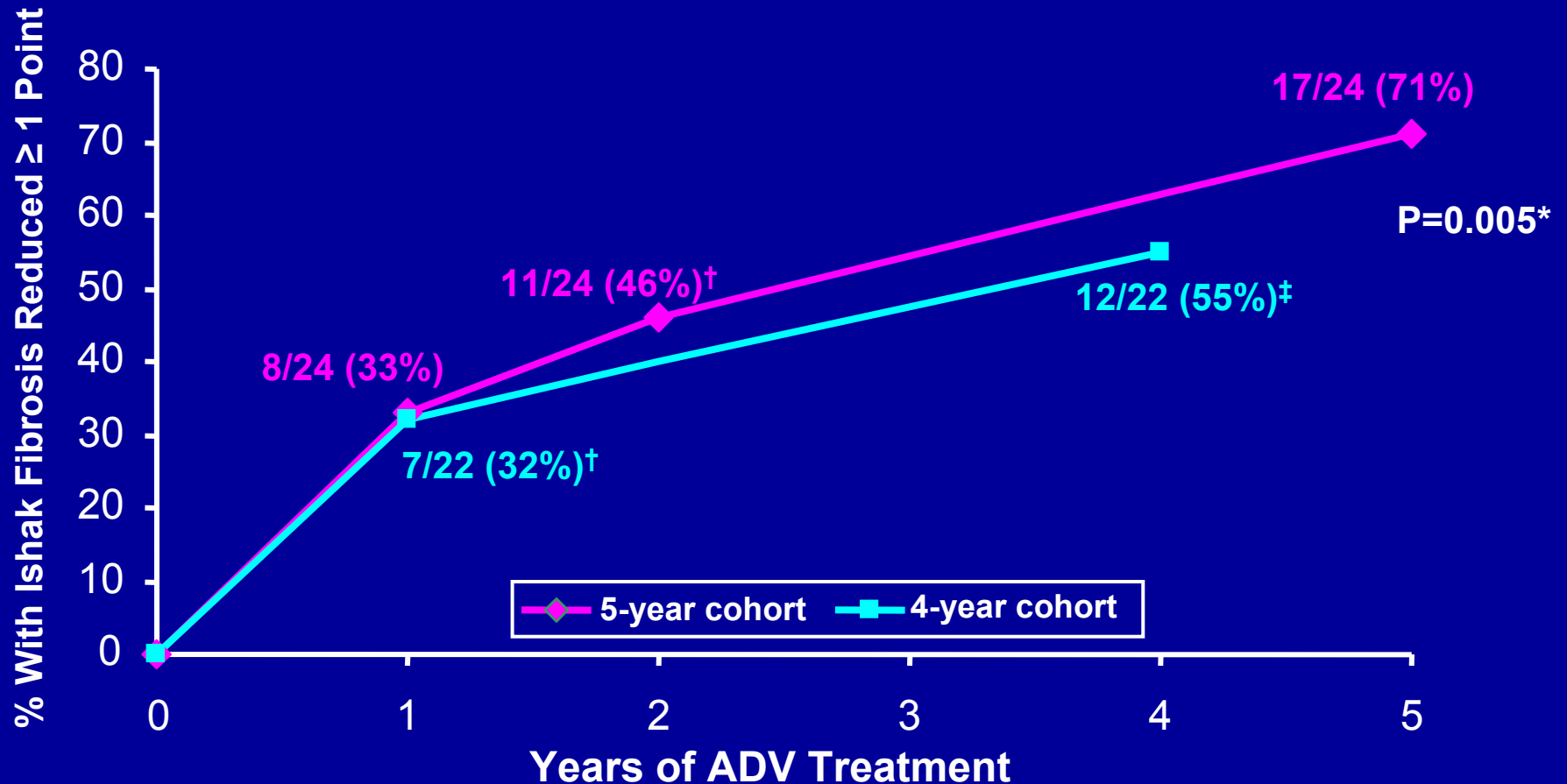
* Missing = failure for resistance or hepatocellular carcinoma.

HBsAg Seroconversion on Adefovir Dipivoxil

- **Six patients (5%) had HBsAg loss**
- **Five of the six patients had anti-HBs at the last available time point**
- **One patient lost HBsAg in < 0.5 year, one patient in < 1.5 years, and four patients after > 3.5 years of adefovir dipivoxil**

ADV for HBeAg-Negative CHB

5-Year Data: Fibrosis Scores



*Cochran-Armitage exact test of trend over time for 5Y cohort.

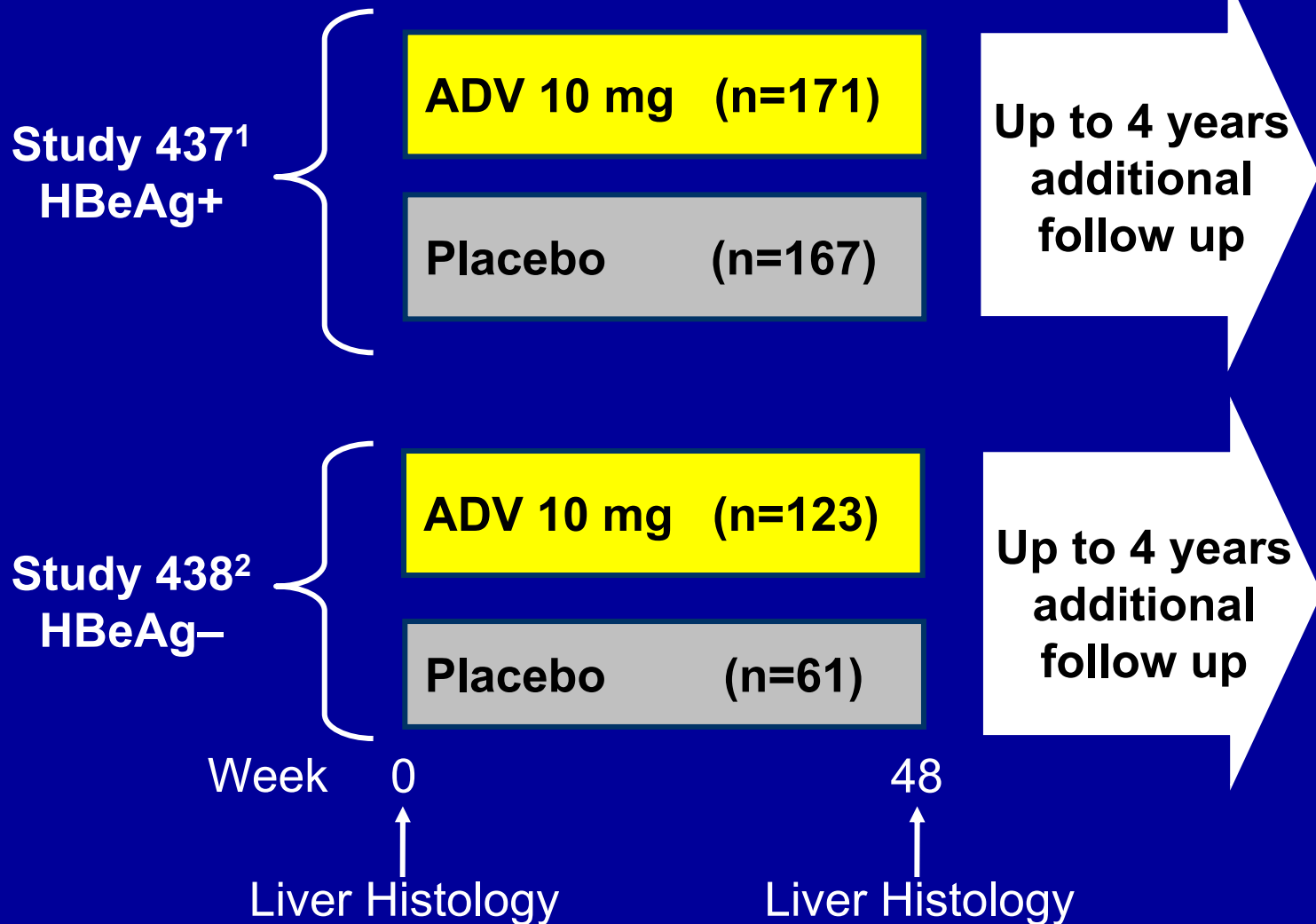
†No fibrosis improvement: n=9 for 4Y cohort; n=15 for 5Y cohort.

‡1 patient received concomitant lamivudine.

Adefovir: Genotypic Resistance

- Year 1: 0%
- Year 2: 3%
- Year 3: 11%
- Year 4: 18%
- Year 5: 29%

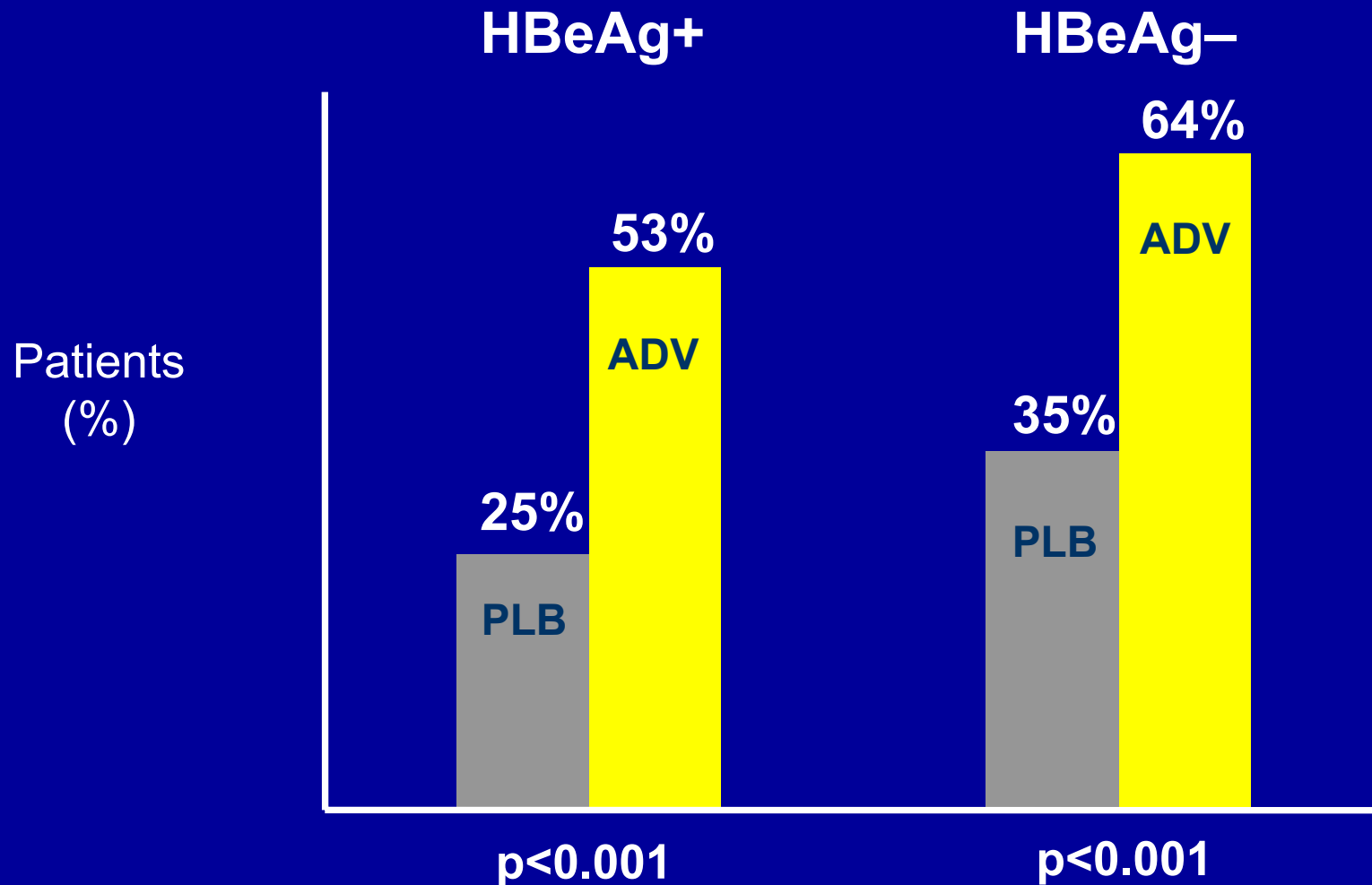
Adefovir Dipivoxil Pivotal Studies



¹Marcellin P, et al. *N Engl J Med*. 2003;348:808-816.

²Hadziyannis SJ, et al. *N Engl J Med*. 2003;348:800-807.

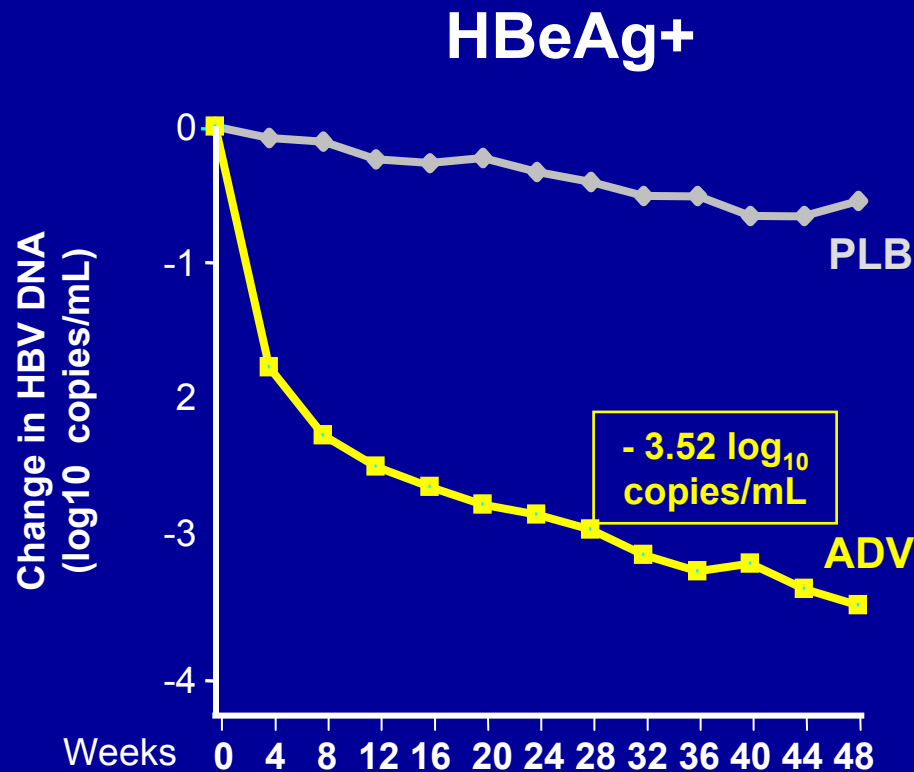
Adefovir Studies at 48 Weeks Improvement in Liver Histology*



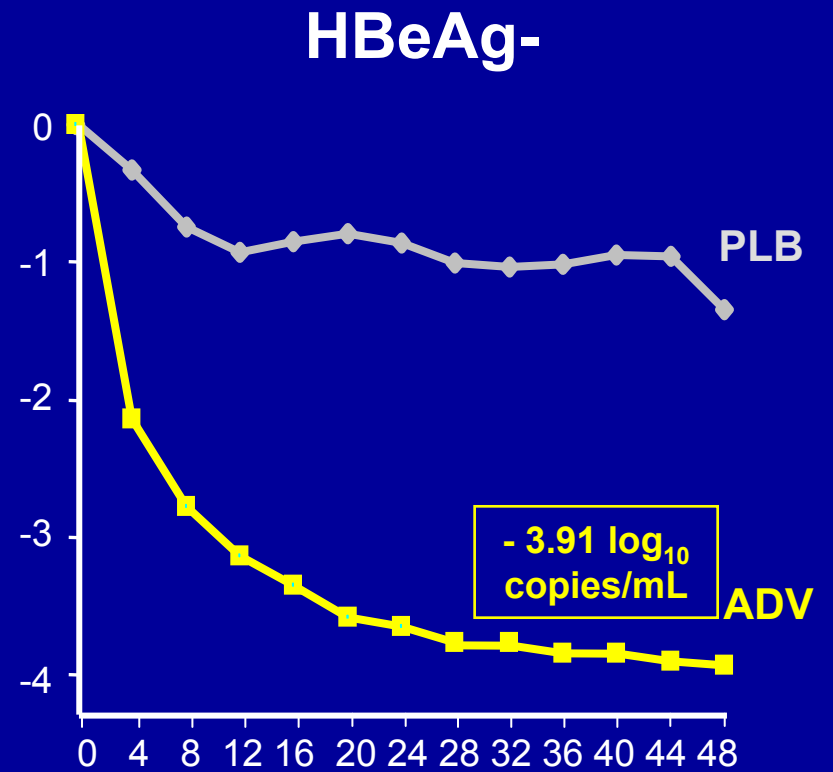
* Defined as > 2 point reduction in HAI score with no worsening in fibrosis score

Adefovir Studies

Median Change from Baseline in HBV DNA



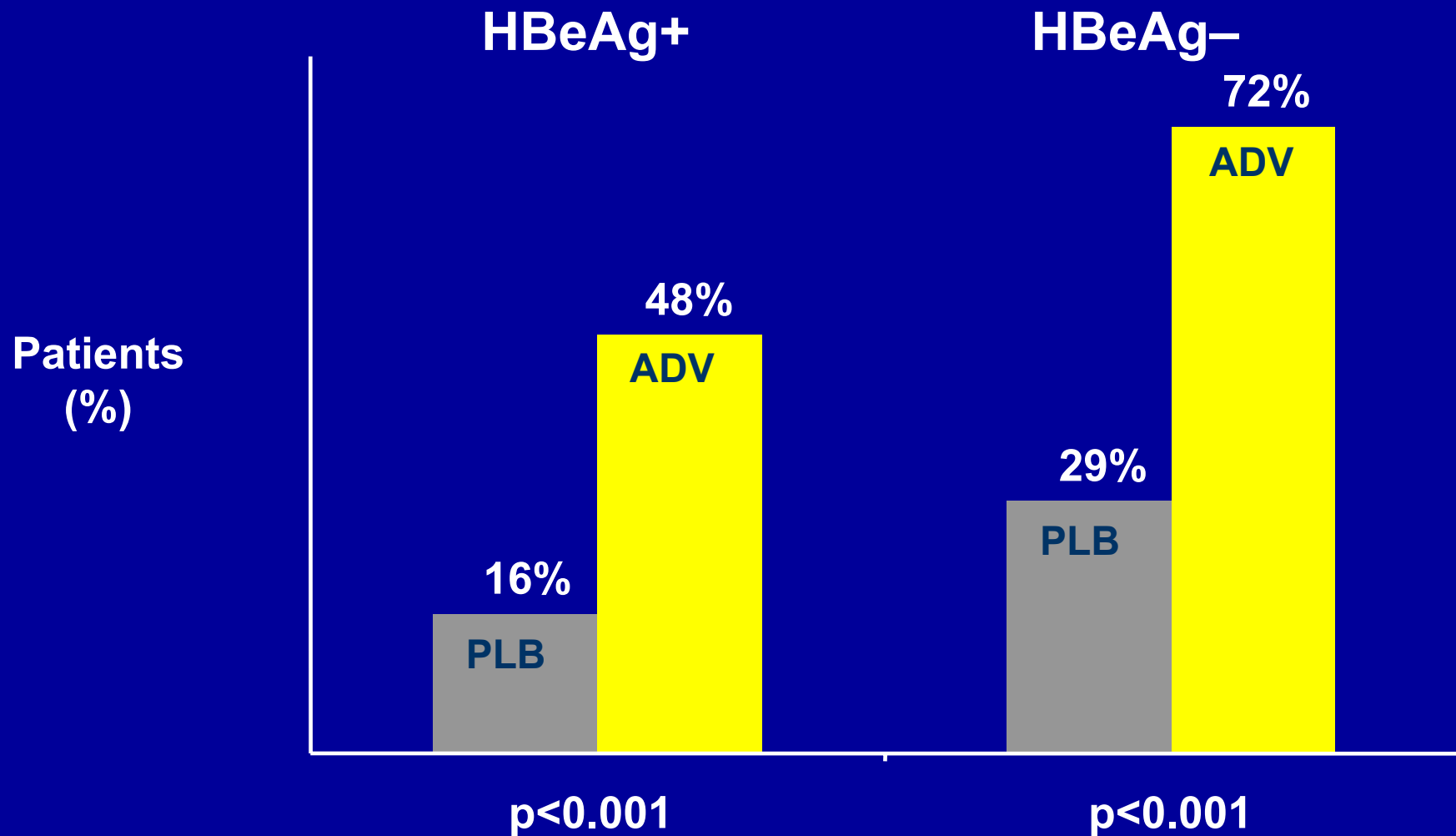
p<0.001



p<0.001

Adefovir Studies at 48 Weeks

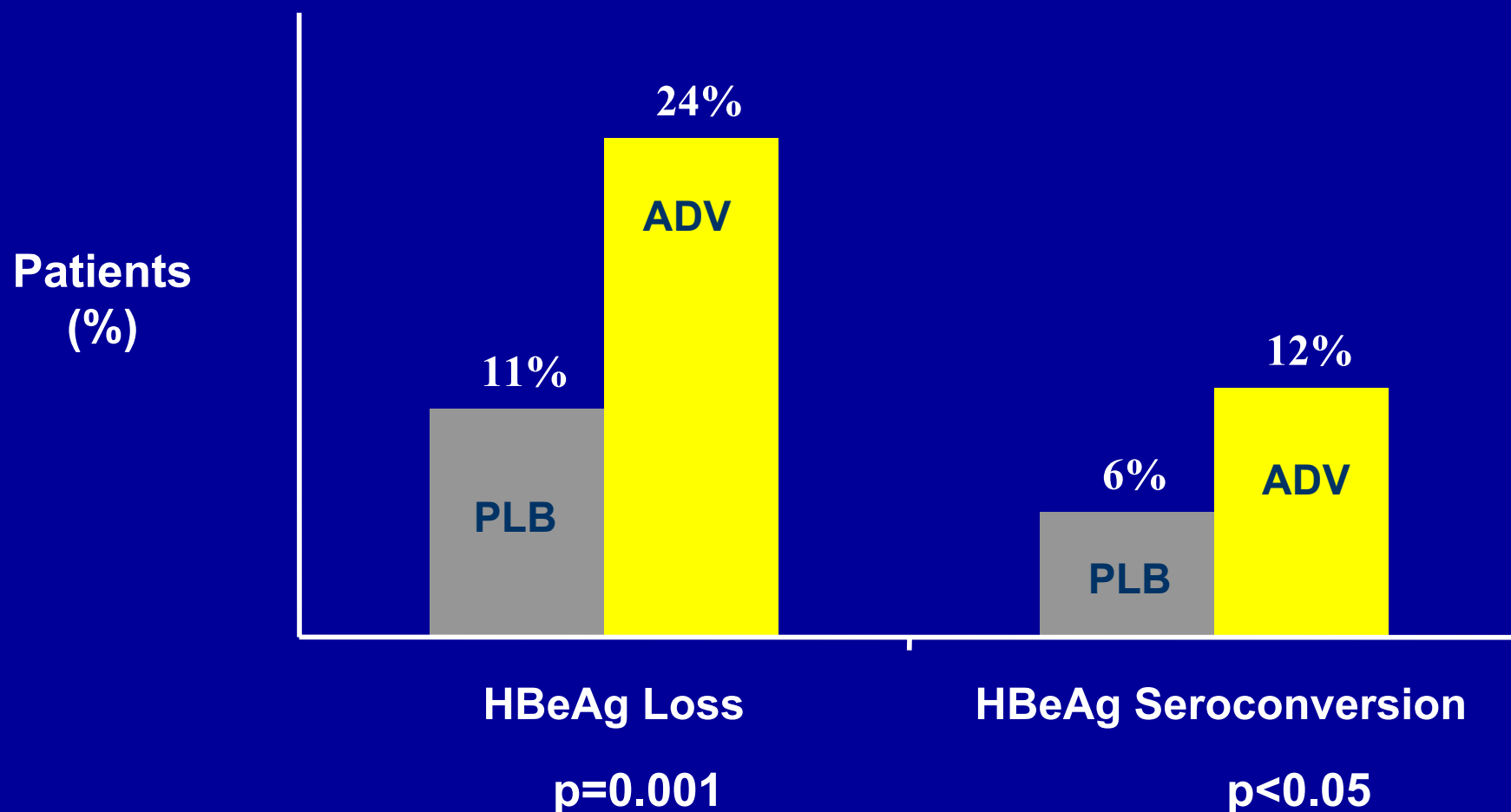
ALT Normalization



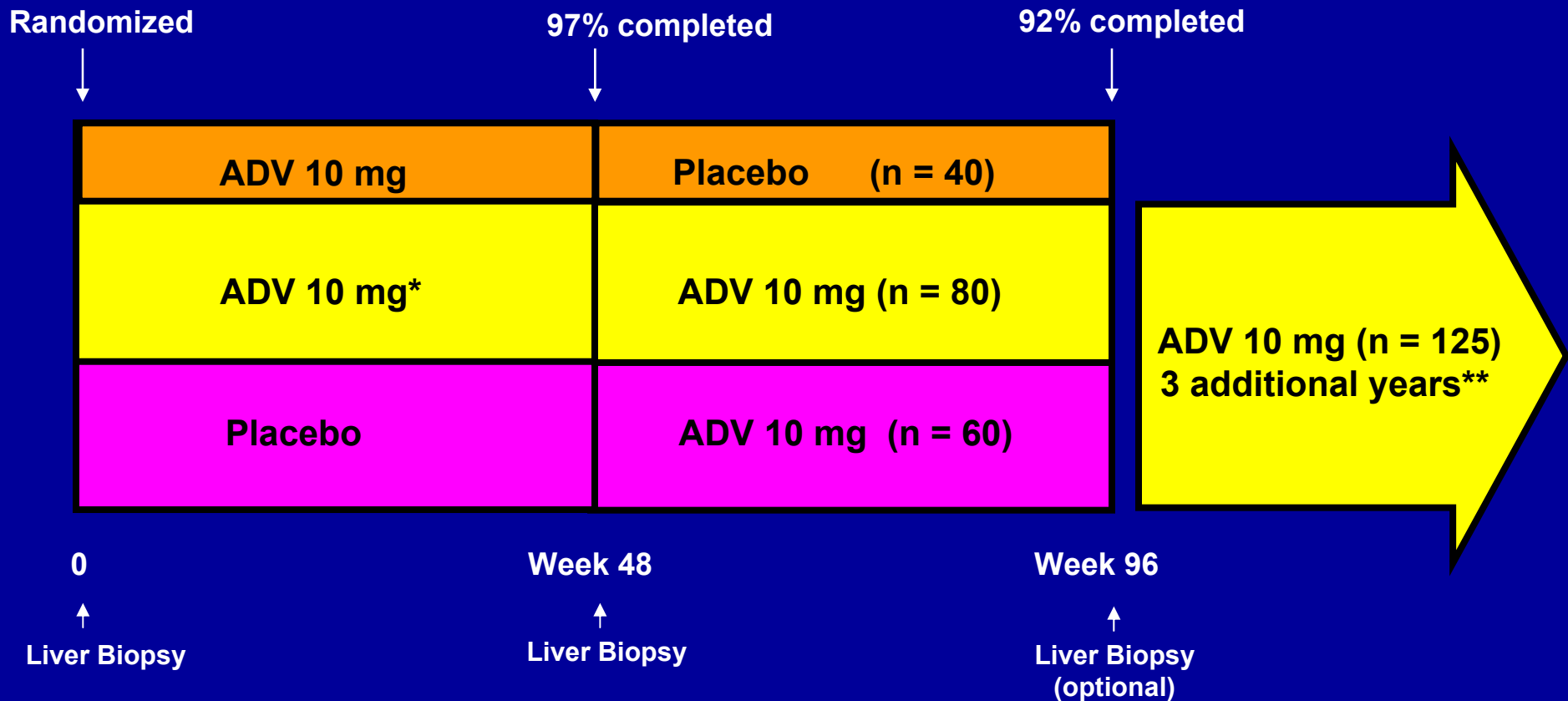
HBeAg Positive Study at 48 Weeks

HBeAg Loss and Seroconversion

HBeAg+



HBeAg -ve CHB Rollover Study

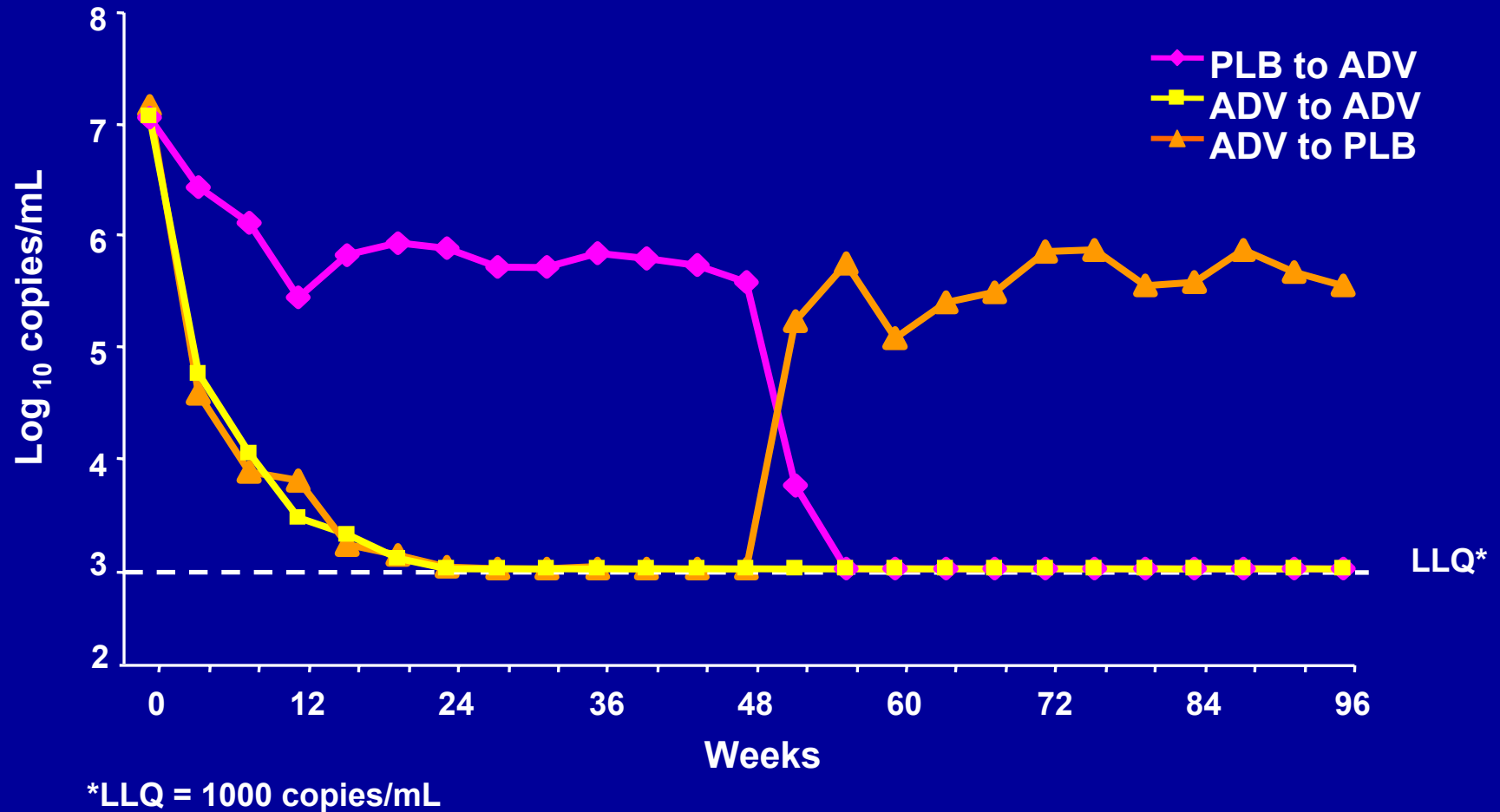


* Patients in ADV 10 mg group re-randomized in a 2:1 fashion at week 48

** All patients who received ADV 10 mg in second 48 week period

Efficacy in HBeAg -ve CHB

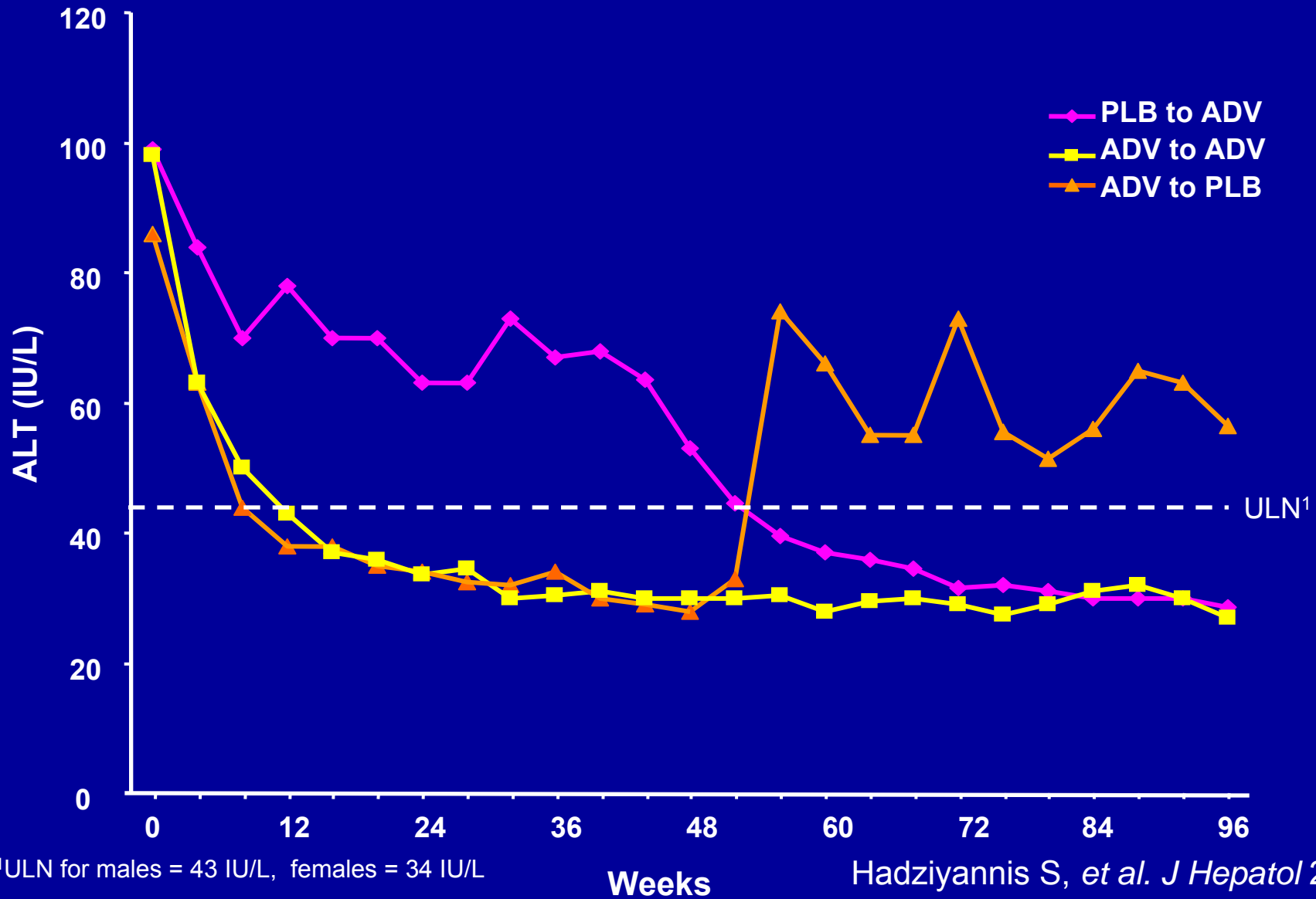
Median HBV DNA: 96 Week Data



Hadziyannis S, et al. J Hepatol 2003 (Abstract).

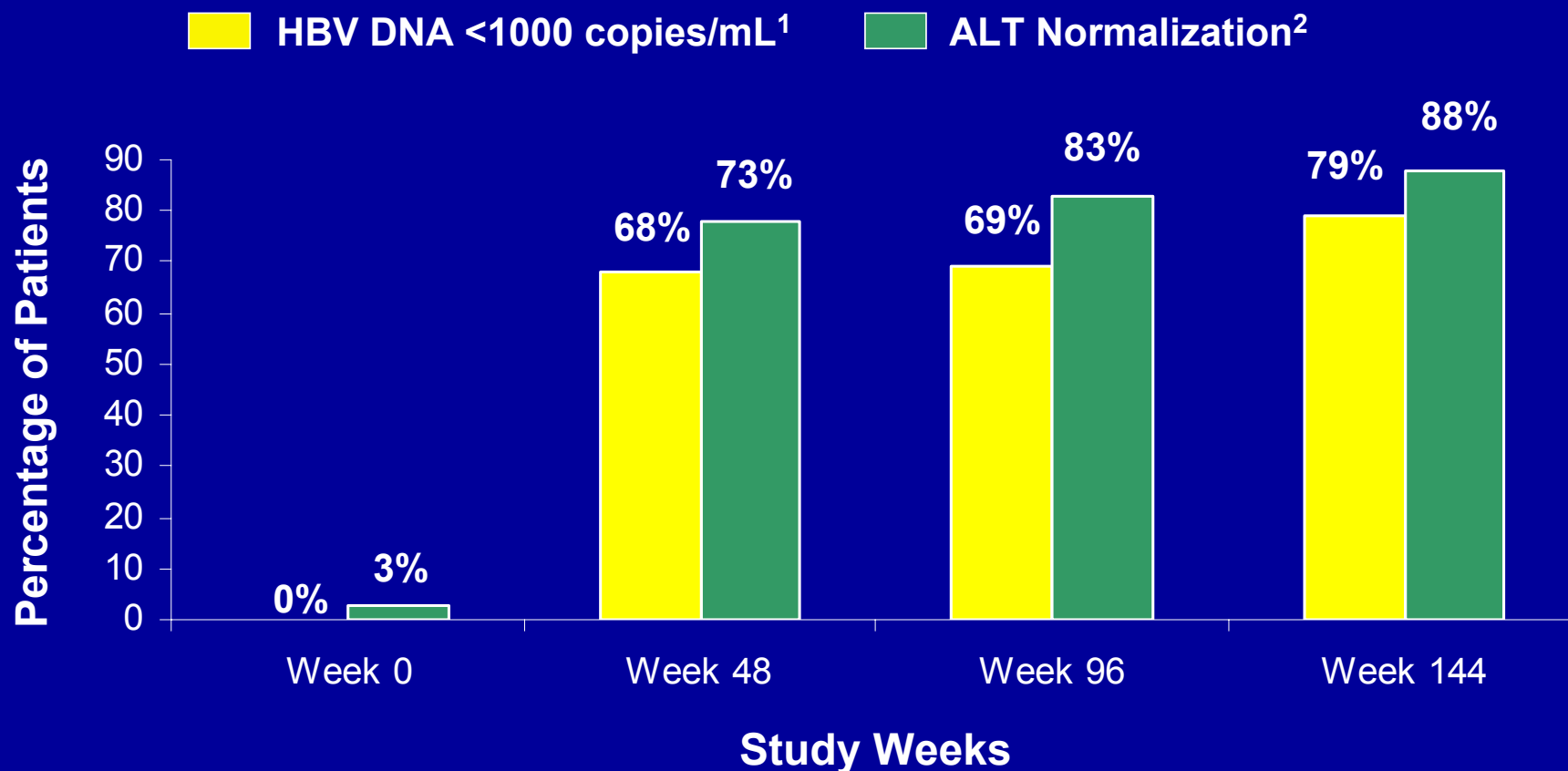
Efficacy in HBeAg -ve CHB

Median ALT: 96 Week Data



ADV for HBeAg-Negative CHB

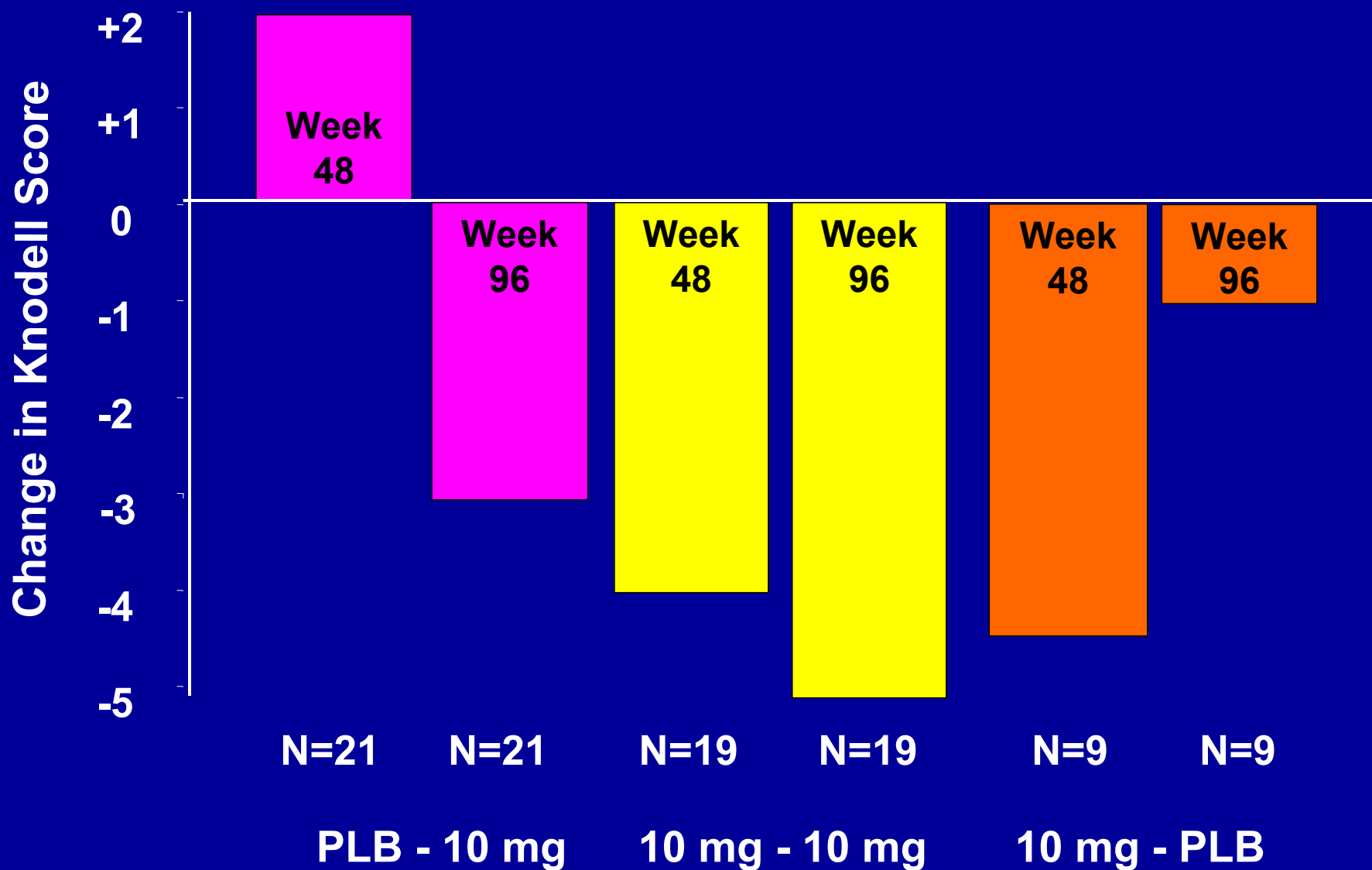
3-Year Data



¹Patients with HBV DNA >1000 copies/mL at baseline (n=70); ²patients with ALT > ULN at baseline (n=64)

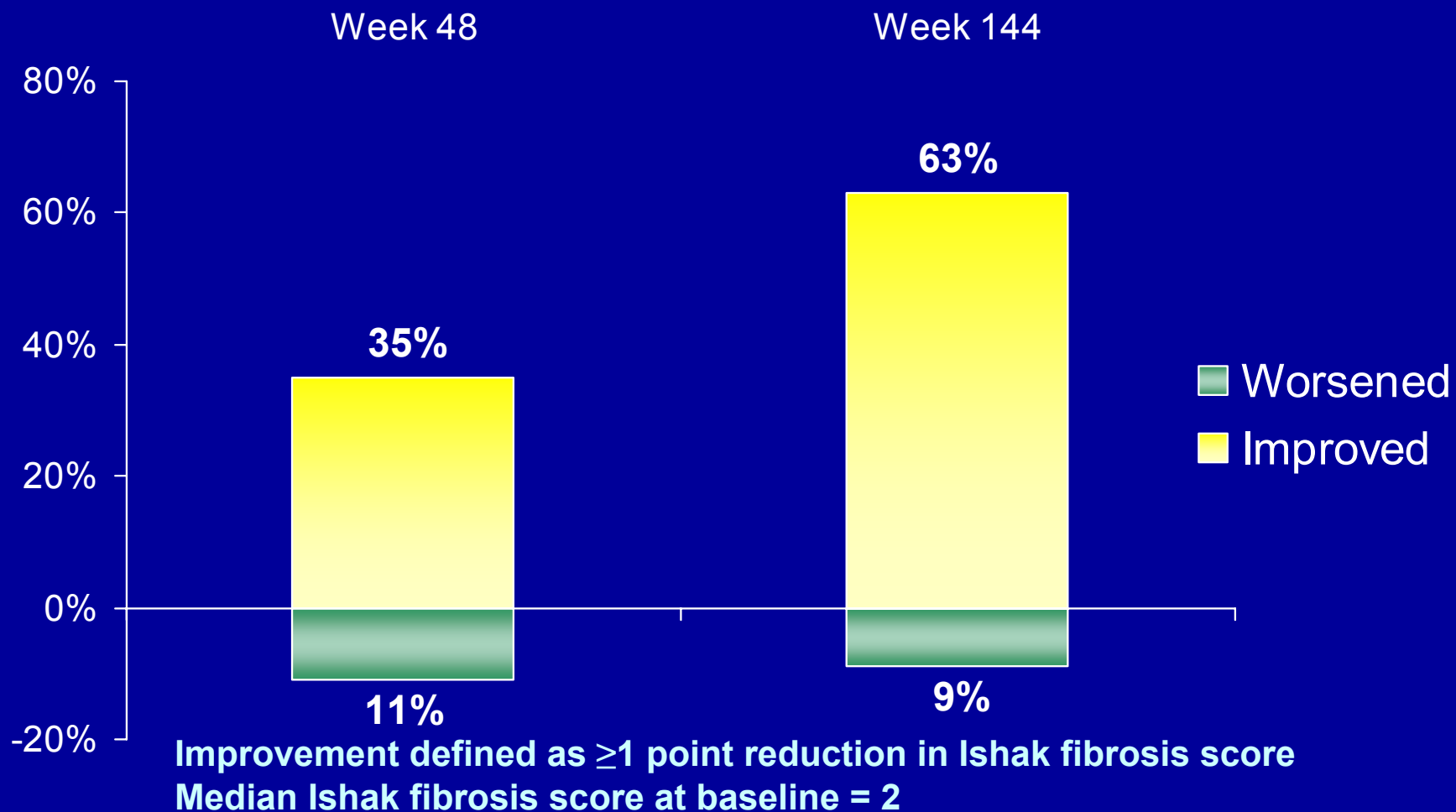
ADV for HBeAg-Negative CHB

Change in Total Knodell Score: Week 96

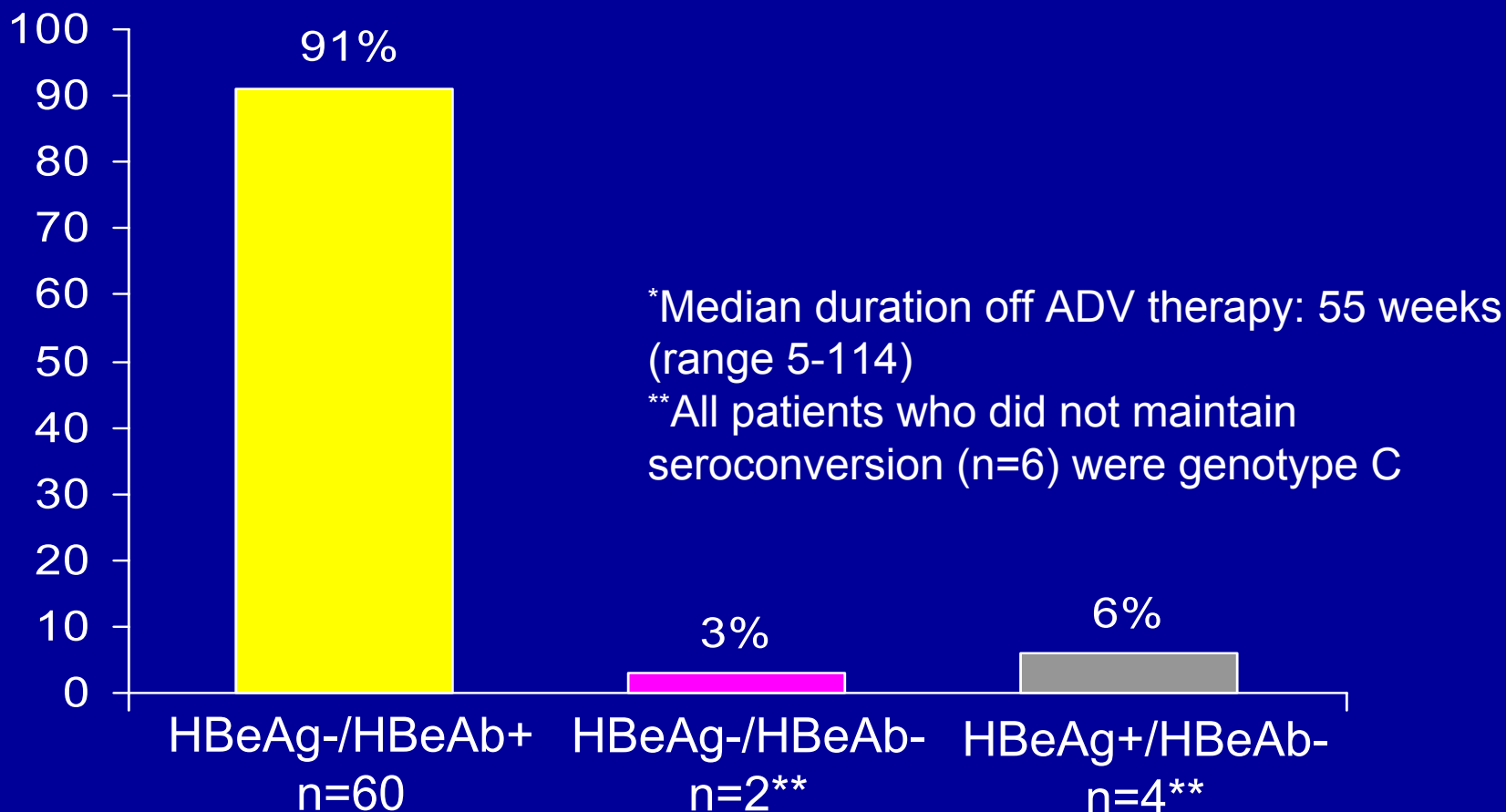


ADV for HBeAg-Negative CHB

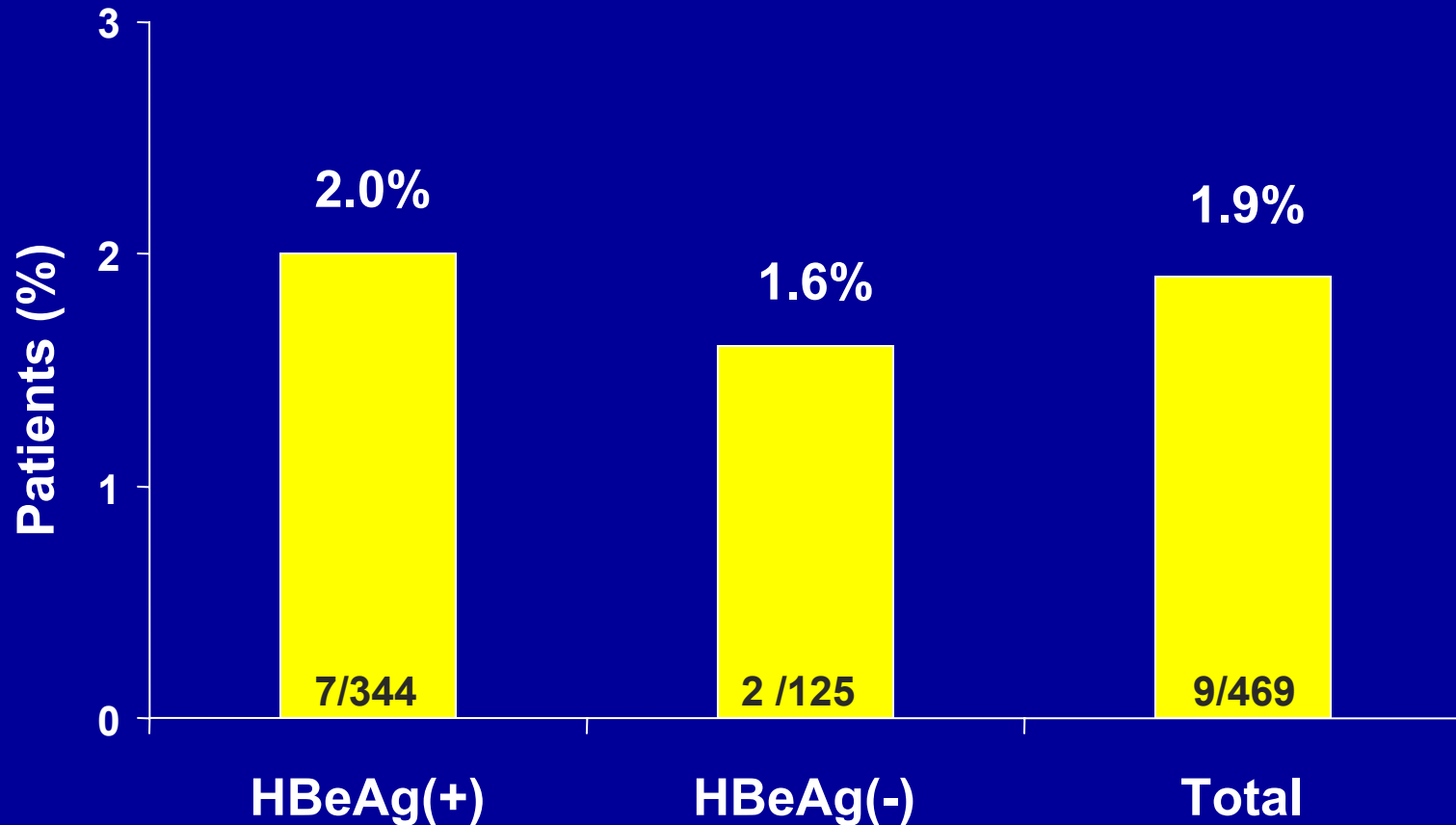
3-Year Fibrosis Data



Durability of HBeAg Seroconversion Following ADV Discontinuation*



HBsAg Seroconversion Associated with ADV Therapy



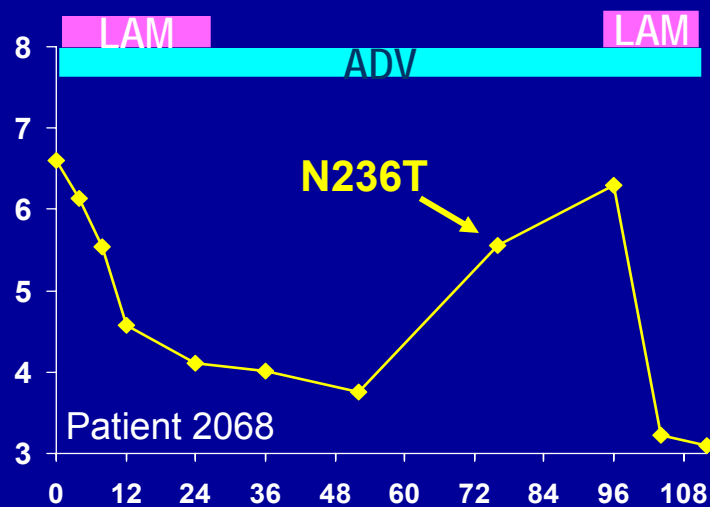
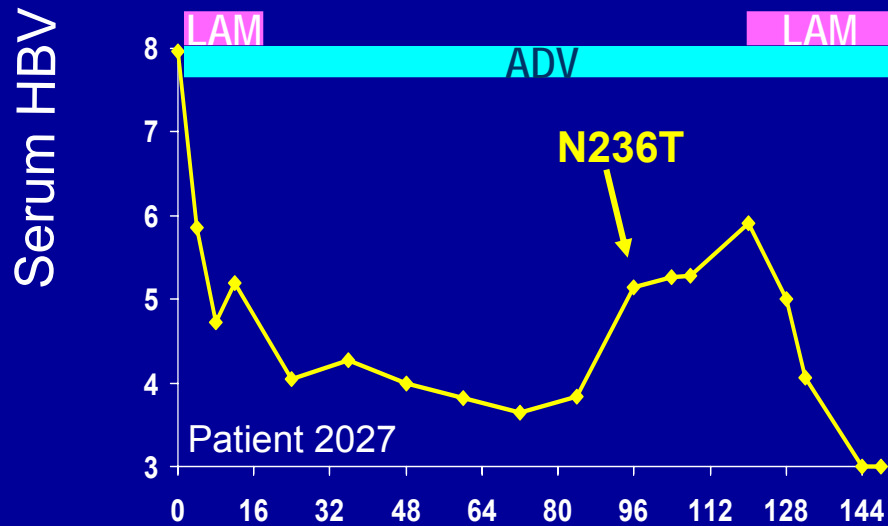
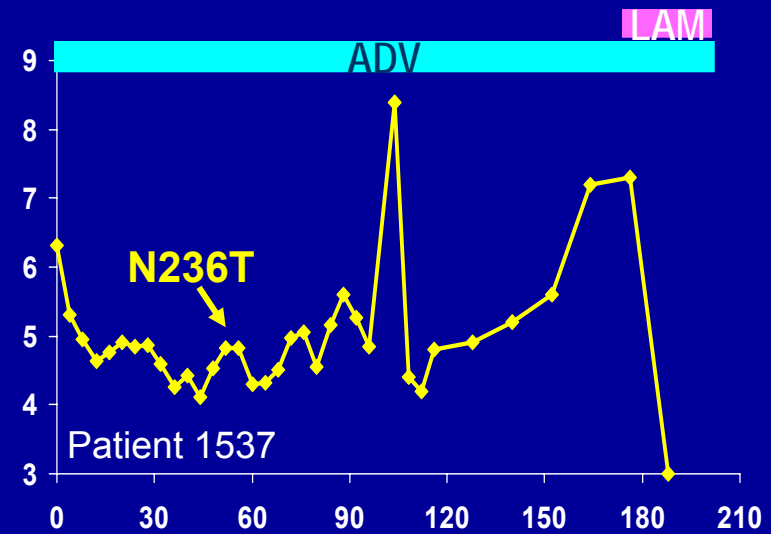
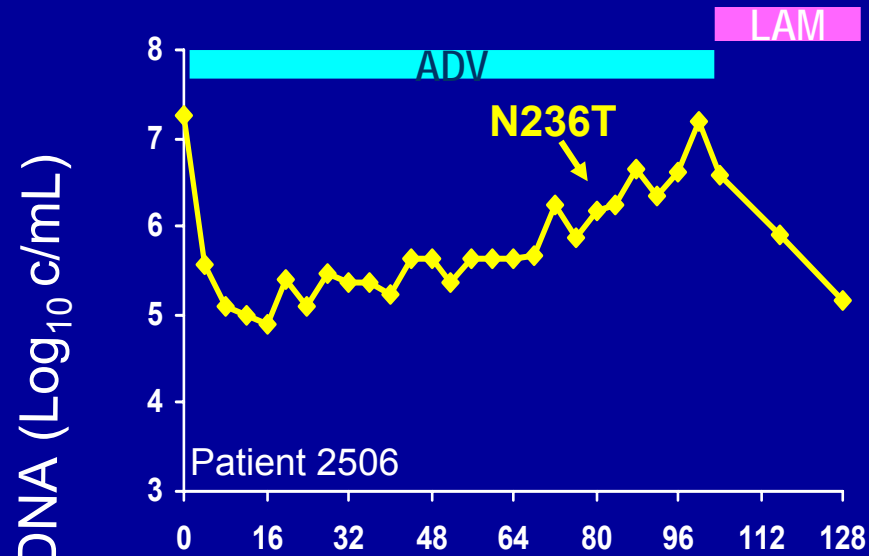
All patients had HBV DNA < LLQ and normal ALT at the time of HBsAg seroconversion

Shiffman M, et al. *J Hepatol* 2004; 40(Suppl 1):45A

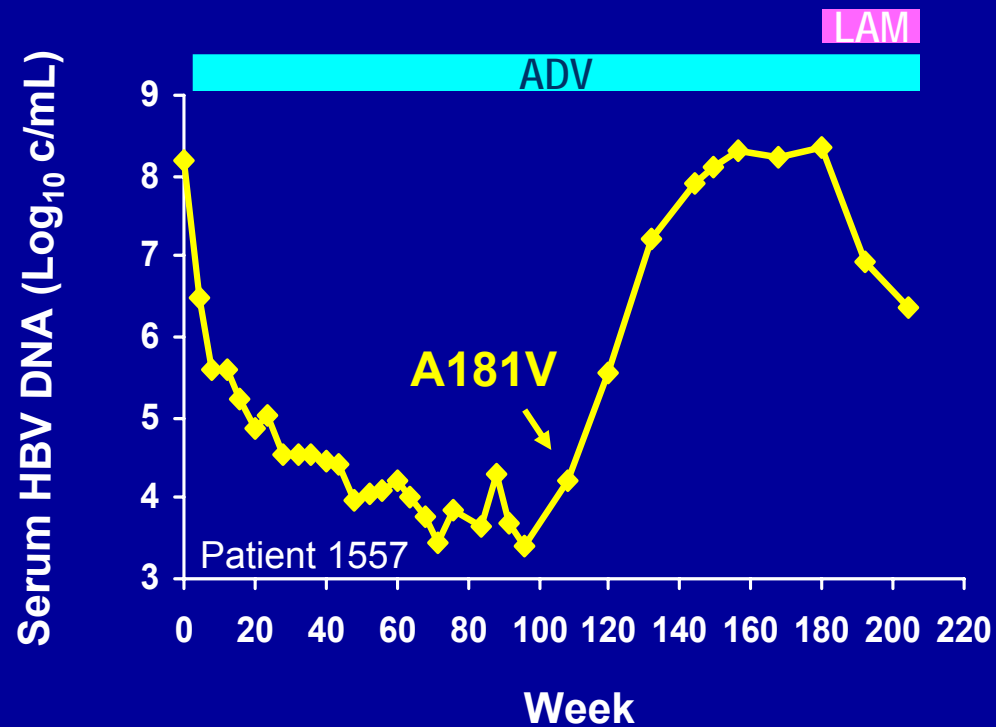
Virology Resistance Summary

- No adefovir resistance mutations were identified in patients treated with adefovir dipivoxil for 48 wk
- Adefovir-resistant mutations (N236T and A181V) identified in patients treated for ≥ 2 yr in extension studies (rate $\sim 2\%$ at yr 2 and $\sim 4\%$ at yr 3)
 - N236T and A181V mutations are susceptible to lamivudine
- No cross resistance
 - Active against all major patterns of lamivudine resistant HBV *in vitro* and *in vivo*

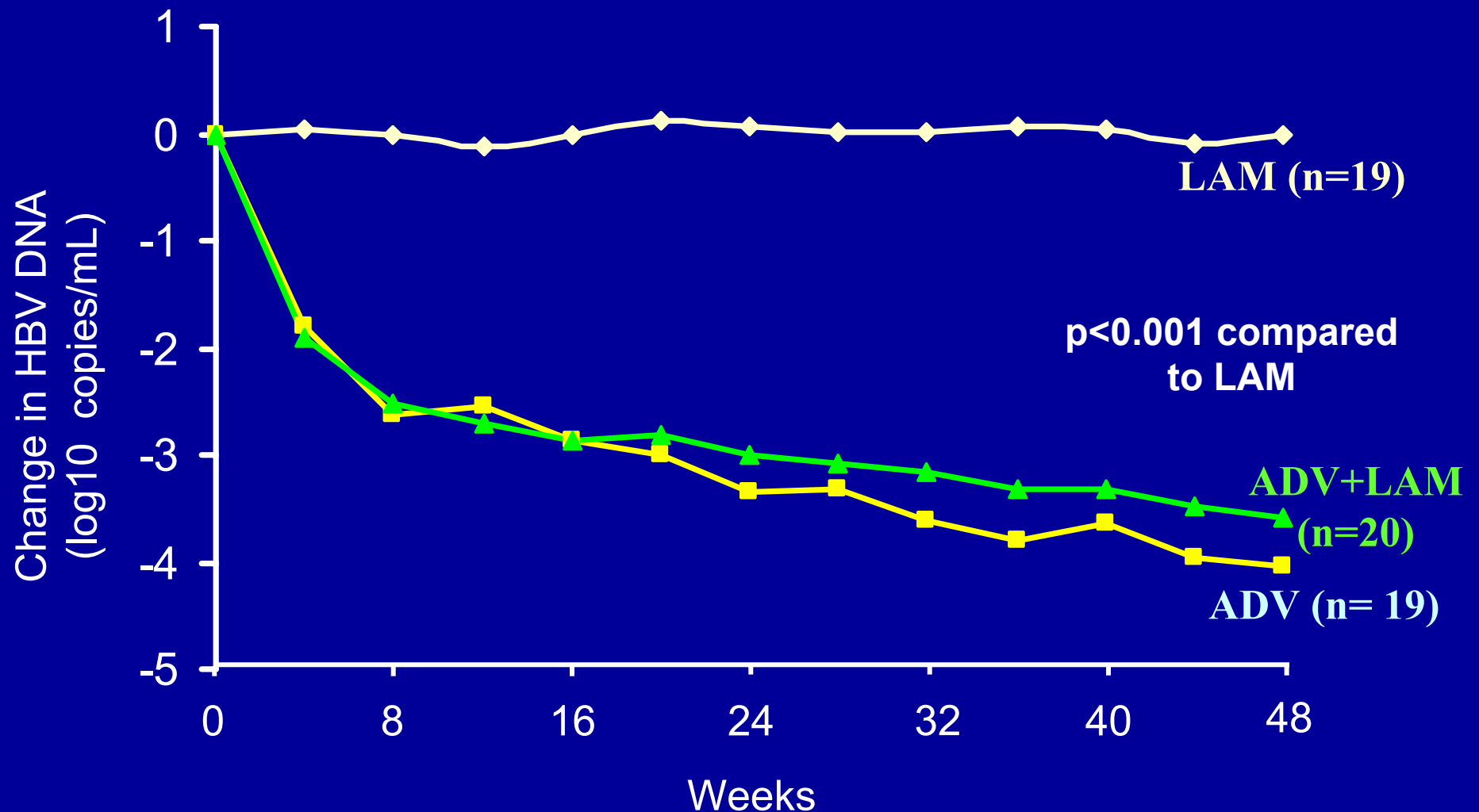
Patients with N236T: Clinical Response to Lamivudine



Patient with A181V: Clinical Response to Lamivudine



Therapy of Lamivudine Resistant HBV with Adefovir: HBV DNA Response



Treatment of Chronic Hepatitis B

	IFN	Lamivudine	Adefovir
Response in yr 1			
e+CHB (HBeAg SC)	~18%	16%–18%	12%
e-CHB (HBV DNA loss*)	60%–70%	60%–70%	51%
Duration of R _x			
e+CHB	4–6 mo	>1yr	>1yr
e-CHB	12 mo	>>1 yr	>>1 yr
Durability of Response			
e+CHB	80%–90%	60%–80%	91%
e-CHB	~20%	<10%	<10%

*IFN and LAM – hybridization assay; ADV – PCR assay

Treatment of Chronic Hepatitis B

	Interferon	Lamivudine	Adefovir
Route	SC	Oral	Oral
Side effects	Many	Negligible	Negligible
Contraindication	++	—	—
Drug resistance	None	~20% yr 1 ~70% yr 5	None yr 1 ~2% yr 2 ~4% yr 3
Costs	High	Low*	Intermediate*

*Based on 1 yr Rx duration

Entecavir

	ETV
More potent antiviral	++
Activity vs. LAM-R HBV	+
Decreased risk of resistance (vs. LAM)	++
More durable viral suppression	?
Less side effects (vs. ADV)	±
More affordable	?

New Treatment of Chronic Hepatitis B Compared to Approved Treatments

	ETV	FTC	LdT	CLV
More potent antiviral	++	±	++	±
Activity vs. LAM-R HBV	++	—	±	—
Decreased risk of resistance (vs. LAM)	+	+	?	?
Effective in all subsets of patients	—	—	—	—
More durable viral suppression	±	?	?	+
Less side effects (vs. ADV)	+	+	+	?
More affordable	?	?	?	?

Treatment Guidelines

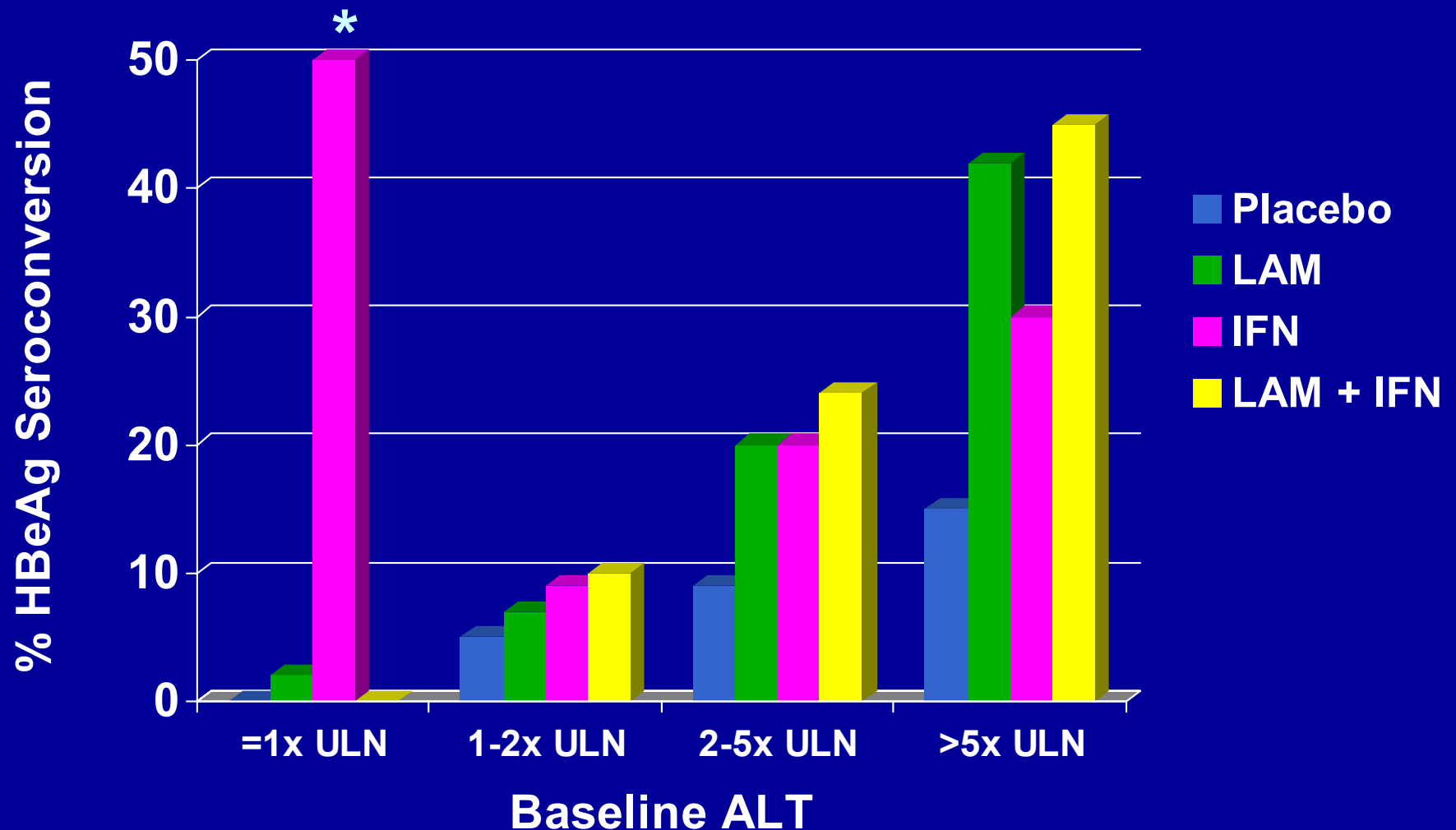
- **Usually commissioned by professional societies or government advisory committees**
- **Some guidelines commissioned by pharmaceutical companies**
- **Guidelines for chronic hepatitis B**
 - **American Association for the Study of Liver Diseases (AASLD)**
 - **European Association for the Study of the Liver (EASL)**
 - **Asian Pacific Association for the Study of the Liver (APASL)**
 - **NIH workshop on management of hepatitis B-2000**
 - **Chronic HBV treatment algorithm-2004**
- **Guidelines have similarities and differences**

Treatment Recommendations for HBeAg +ve Patients

ALT	HBV DNA	Recommendations
$\leq 2 \times \text{ULN}$	+	No treatment, monitor ^{1,2,3} Grey zone: ALT 1–2 x ULN or intermittently elevated; liver biopsy → moderate/severe inflammation or advanced fibrosis → treatment ¹
$> 2 \times \text{ULN}$	+	Observe × 3–6 months; treat if no spontaneous HBeAg seroconversion ^{1,2,3} Immediate treatment if bilirubin increases ³ or decompensation ^{1,3}

HBV DNA: + defined as $>100,000$ copies/mL
Guidelines: ¹AASLD; ²EASL; ³APASL

Baseline ALT and Response to Treatment of HBeAg +ve Patients



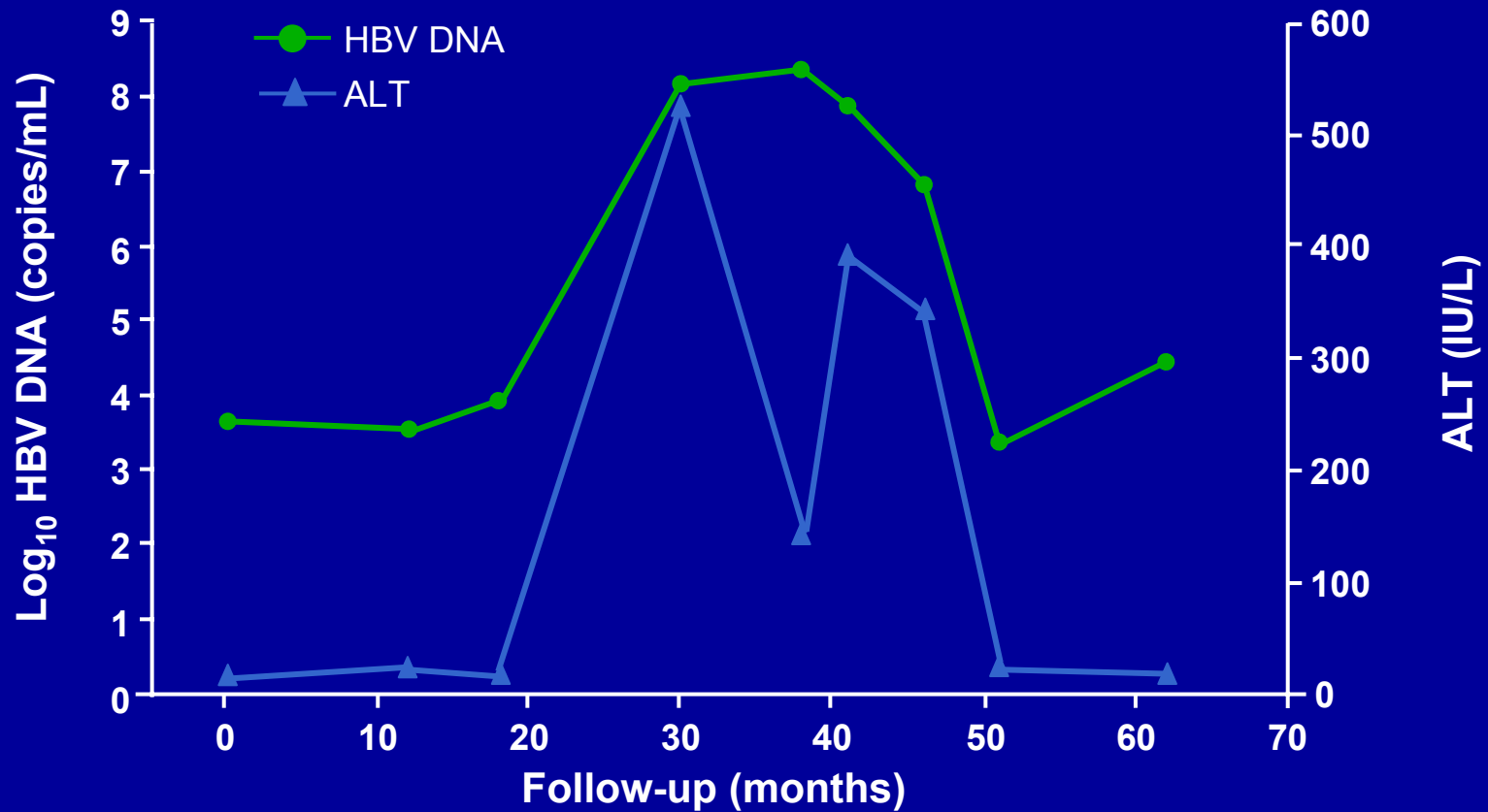
Treatment Recommendations for HBeAg -ve Patients

ALT	HBV DNA	Recommendations
$\leq 2 \times$ ULN	$< 100,000$ copies/ml	No treatment, monitor ^{1,2,3} Grey zone: ALT 1–2 ULN; HBV DNA 10,000 – 100,000 copies/mL Liver biopsy → moderate/severe inflammation or advanced fibrosis → treatment ¹
$> 2 \times$ ULN	$> 100,000$ copies/ml	Treatment ^{1,2,3}

HBV DNA: + defined as $> 100,000$ copies/mL
Guidelines: ¹AASLD; ²EASL; ³APASL

Fluctuating Course of HBeAg -ve Chronic Hepatitis B

HBeAg	-	-	-	-	-	-	-	-	-
Anti-HBe	+	+	+	+	+	+	+	+	+
PC 1896	G			G					A>G
CP 1762 1764	AG>TA			TA>AG					AG



Treatment Algorithm for Chronic HBV Roundtable

- **In February 2003, a US physician roundtable developed an HBV treatment algorithm**
 - **Emphasis placed on review of literature, especially recent guidelines**
 - **Goal: provide clear direction to treating physicians regarding diagnosis, treatment and monitoring**
- **Recommendations evidence-based, but when controlled data lacking, the panel relied on clinical experience**

Appropriate HBV DNA Level for Initiation of Treatment: e-CHB

- Retrospective analysis of 165 patients with different stages of chronic hepatitis B¹
 - 1/3 of HBeAg –ve patients had HBV DNA levels greater than 10^5 copies/mL
 - 2/3 of HBeAg –ve patients and all inactive carriers had with HBV DNA levels less than 10^5 copies/mL
 - Thus not possible to define single cutoff HBV DNA to distinguish inactive carrier from e-CHB
- HBV DNA cutoff of $>10^5$ copies/mL may be too high for diagnosis of patients with precore mutation

¹Chu CJ, et al. *Hepatology*. 2002;36:1408-1415.

Classification of HBeAg -ve Chronic HBV Infection: Role of HBV DNA

- **196 patients with HBeAg-negative chronic HBV infection studied: 134 with chronic hepatitis and 62 inactive carriers**
- **ALT normal at baseline in 25 (18.7%) of e-CHB and all inactive carriers throughout study**
- **30,000 copies/mL is a more sensitive cutoff for correctly classifying HBeAg -ve patients**
 - **e-CHB: HBV DNA <30,000 c/mL in 14 (10.5%) and <100,000 c/mL in 17 (12.9%) patients**
 - **All inactive carriers: HBV DNA levels <30,000 c/mL**
 - **Cut-off of 30,000 c/mL correctly classified 93%**

Chronic HBV Infection

Proposed Approach to Therapy

Interferon or lamivudine or adefovir or entacavir

- Presence or absence of HBeAg
- HBV DNA $\geq 10^5$ c/mL for e+CHB ($\geq 10^4$ for e-CHB)
- Elevated ALT (not >2-fold), or repeated flares (not need to wait 3-6 months before treating)
- Presence of chronic hepatitis on biopsy

Lamivudine or adefovir or entacavir

- Cirrhosis: compensated and decompensated
- OLT: prophylaxis, and recurrent HBV after OLT

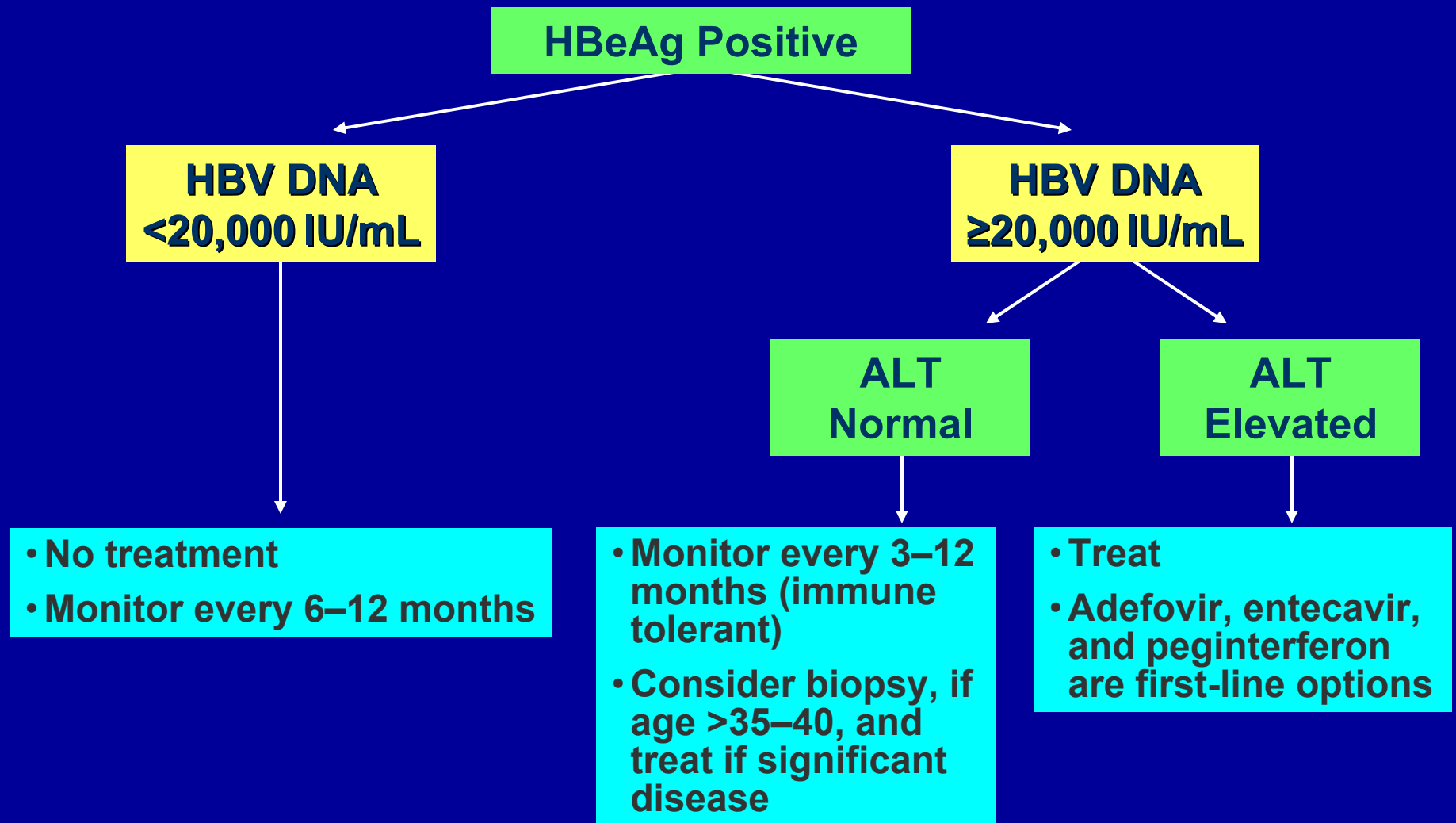
Treatment Recommendations

Summary

	Recommendation
HBeAg +ve chronic hepatitis B	IFN, LAM, ADV, or ENT first line Rx
HBeAg -ve chronic hepatitis B	ADV or ENT or IFN preferred because of need for long-term Rx
Compensated cirrhosis	ADV or ENT or LAM
Decompensated cirrhosis	ADV or ENT or LAM; refer to and coordinate with transplant center
IFN nonresponders or contraindicated	ADV or ENT or LAM
LAM resistance	ADV or ENT or IFN
ADV resistance	LAM or ENT or IFN

Treatment Algorithm

Patients with Compensated Disease



Treatment Algorithm

Patients with Compensated Disease

HBeAg Negative

**HBV DNA
<2,000 IU/mL**

**HBV DNA
≥2,000 IU/mL**

**ALT
Normal**

**ALT
Elevated**

- No treatment
- Monitor every 6–12 months

- Monitor ALT, or
- Consider biopsy, since ALT often fluctuates, and treat if significant disease
- Long-term treatment required

- Treat
- Adefovir, entecavir, and peginterferon are first-line options
- Long-term treatment required (oral agents)

Patients with Compensated Cirrhosis

