Chronic Hepatitis B: Emerging Therapies

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Discovery of Hepatitis B virus

- In 1965, Dr. Baruch S. Blumberg at Fox Chase Cancer Center discovered an antigen in the blood of Australian Aborigine and named Australia antigen which was found to be HBsAg
- Made the first HBV vaccine (plasma vaccine Heptavax B), The First "Anti-Cancer Vaccine"
- Received the Nobel Prize in Medicine in 1976

Courtesy of Dr. HW Hann

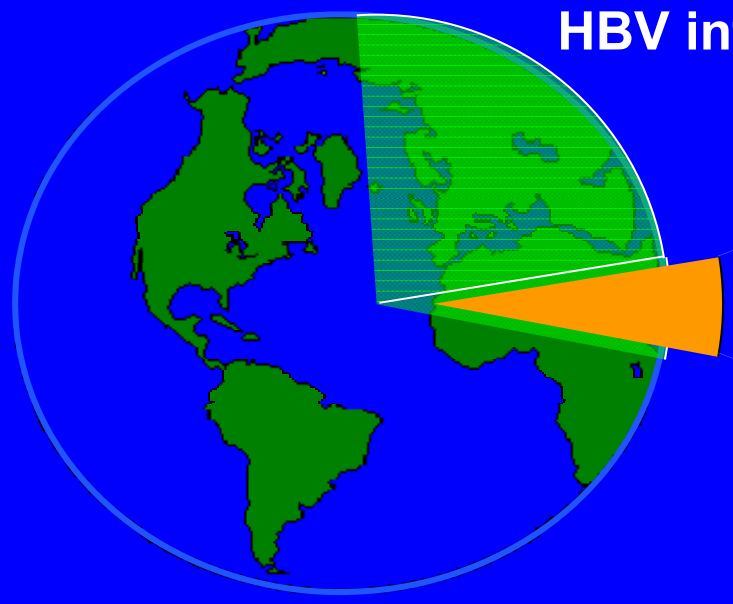
How Old Is HBV ?

- HBV associated with humans for > 1,000 years but no definitive evidence
- Recent evidence establishes ≥ 500 years
- Naturally mummified body of a Korean child found virtually intact
- Laparoscopy: Large organ in RUQ and biopsies sent for pathology and HBV DNA testing
- HBV DNA genotype C isolated from the liver
- Pathology: appeared to be normal liver

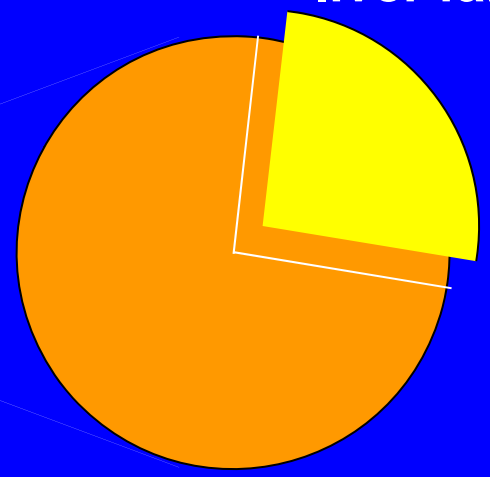
Klein A, et al. 58th AASLD; Boston, MA; November 2-6, 2007. Poster 925.

Global Impact of Hepatitis B

2 billion with past/present HBV infection



15-40% develop cirrhosis, liver failure or HCC



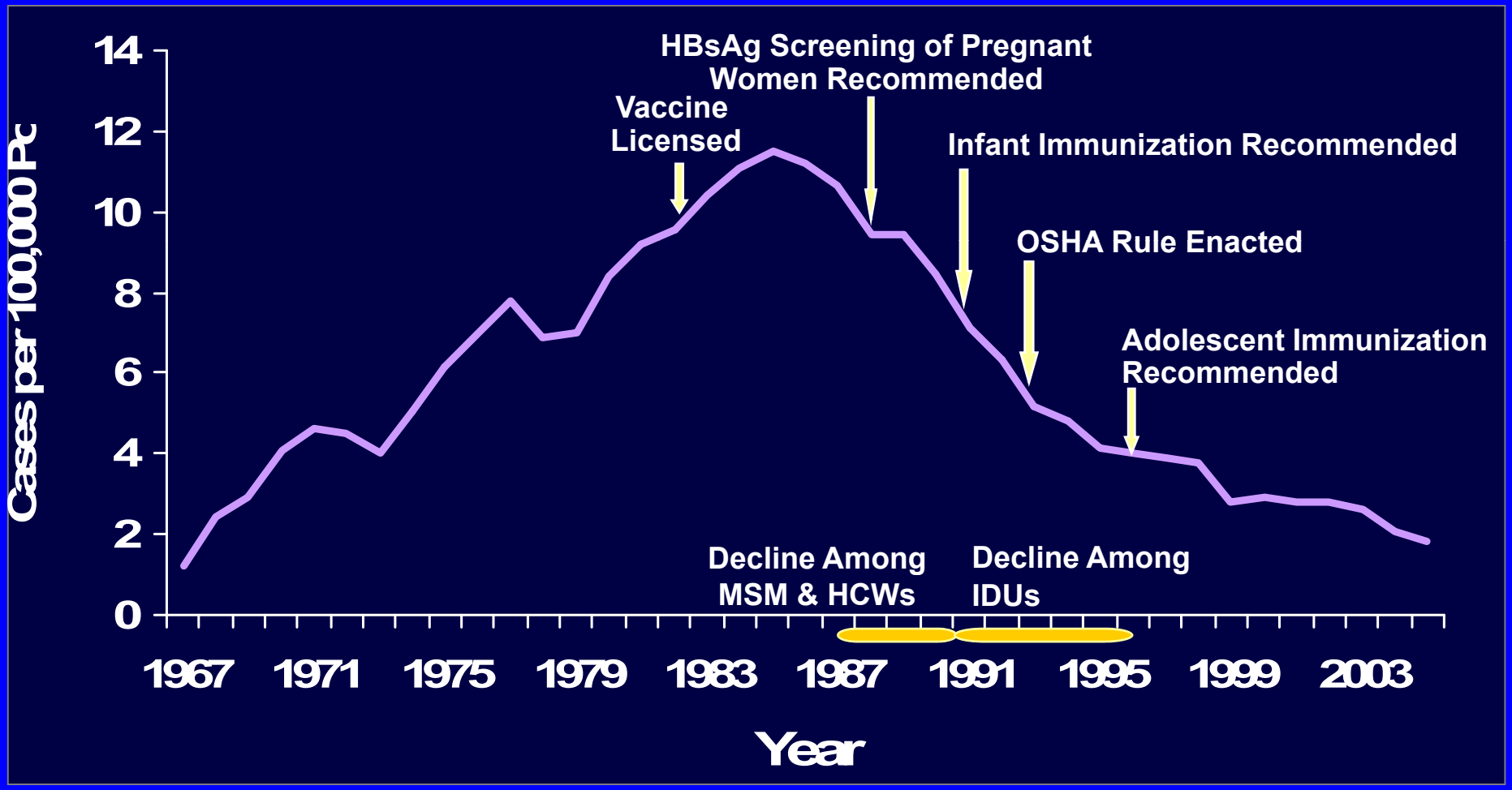
World population 6 billion

350–400 million with chronic hepatitis B

~1 million/year die from HBV-associated liver disease

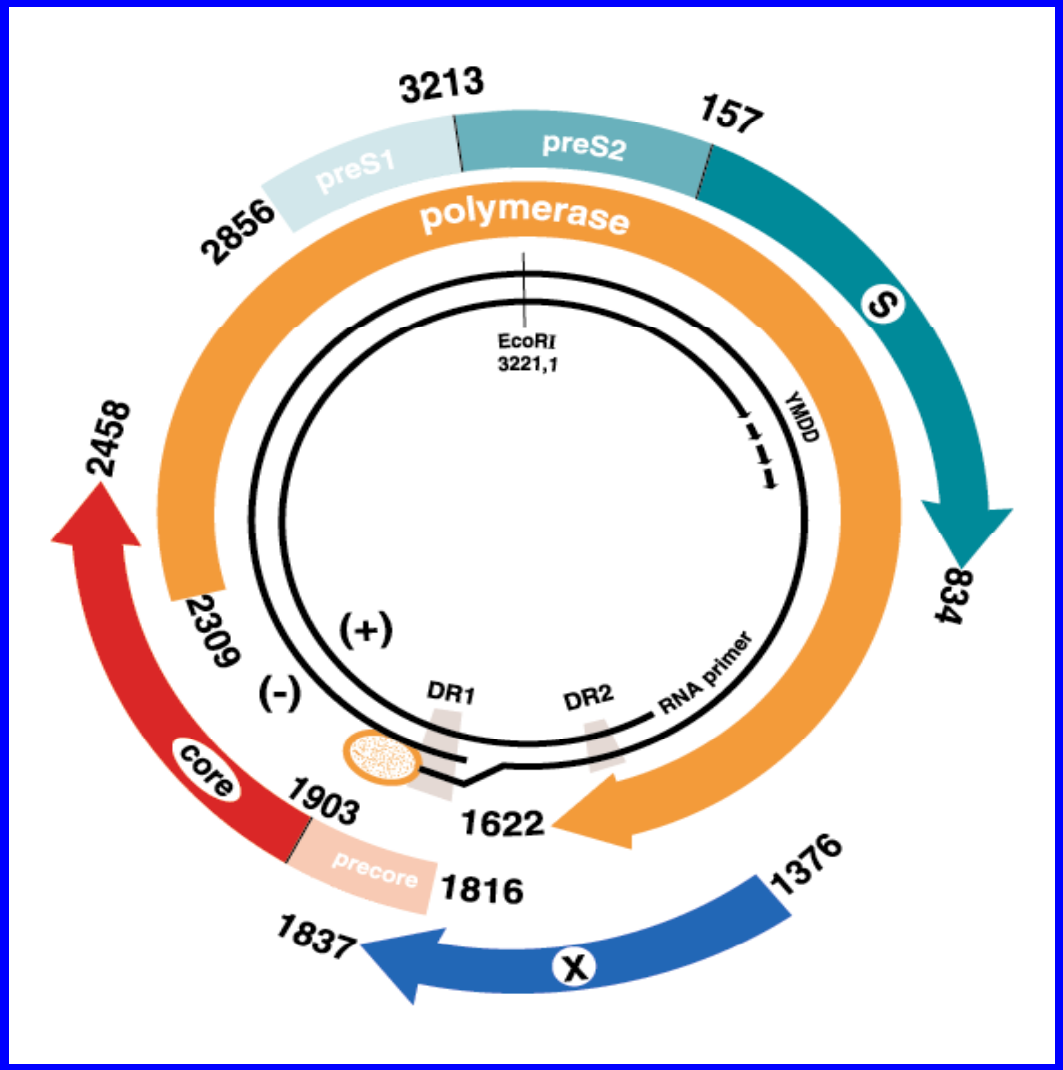
WHO Fact Sheets, available at www.who.int. Accessed: September 24, 2004.
Conjeevaram, et al. *J Hepatology.* 2003;38:S90-S103.
Lee. *N Engl J Med*. 1997;337:1733-1745.
Lok. *N Engl J Med.* 2002;346:1682-1683.

HBV by Year: United States (1966-2005)



Wasley A, et al. *MMWR Surveill Summ*. 2007;56(3):1-24.

Hepatitis B Virus (HBV)



- 4 overlapping open reading frames
- Reverse transcriptase/ DNA polymerase domain overlaps with surface gene
- 100 times more infective than HIV
- Found in blood and body fluids

MMWR. 2003;52:1-33.
Ott et al. *J Pediatr Health Care*. 1999;13(5):211.
Ribeiro et al. *Microbes and Infection*. 2002;4:829.

Hepatitis B Virus:
Naturally Occurring Molecular Variants

- HBeAg-positive
  - Wild-type
  - Associated with higher viral load and greater infectivity
- HBeAg-negative
  - Genetic mutations at precore or core promoter regions
  - Associated with poorer long-term clinical response to therapy and lack of spontaneous remission

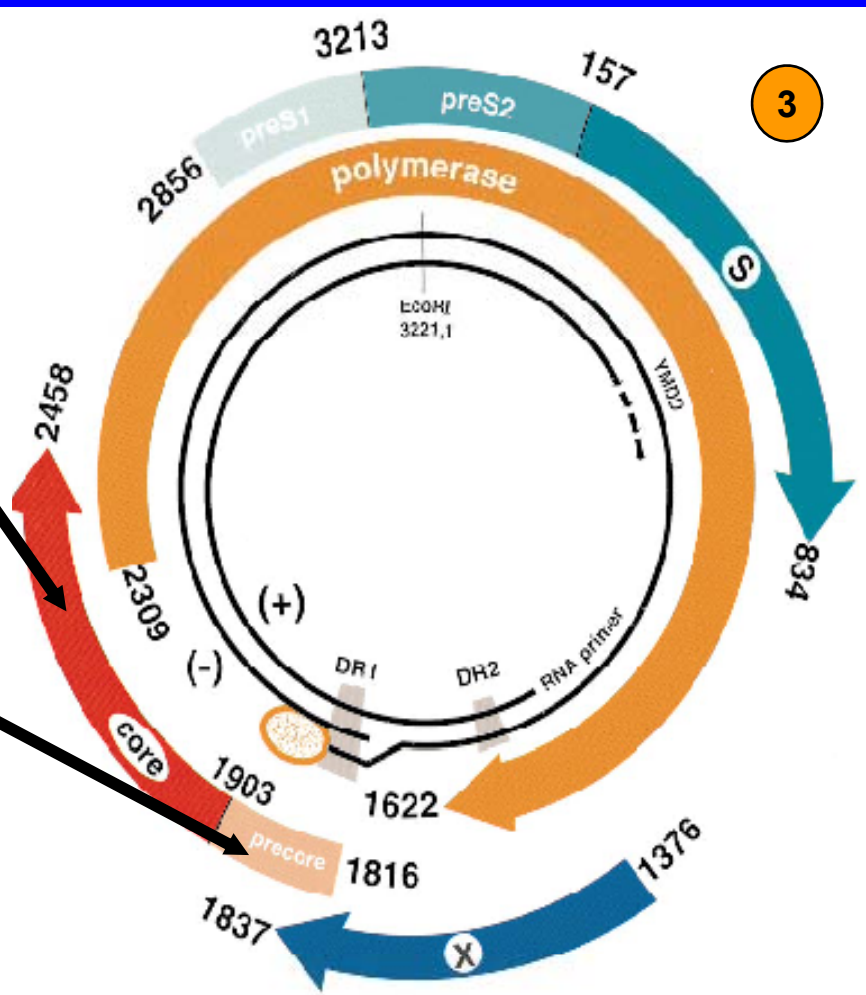
Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2006;4:936-962.

Hepatitis B Virus Variants

- **Wild Type**
  - Unmutated HBeAg-positive hepatitis
- **Basal core promoter mutations** (44% US patients)[1]
  - Lower rate of HBeAg production("HBeAg-negative CHB")

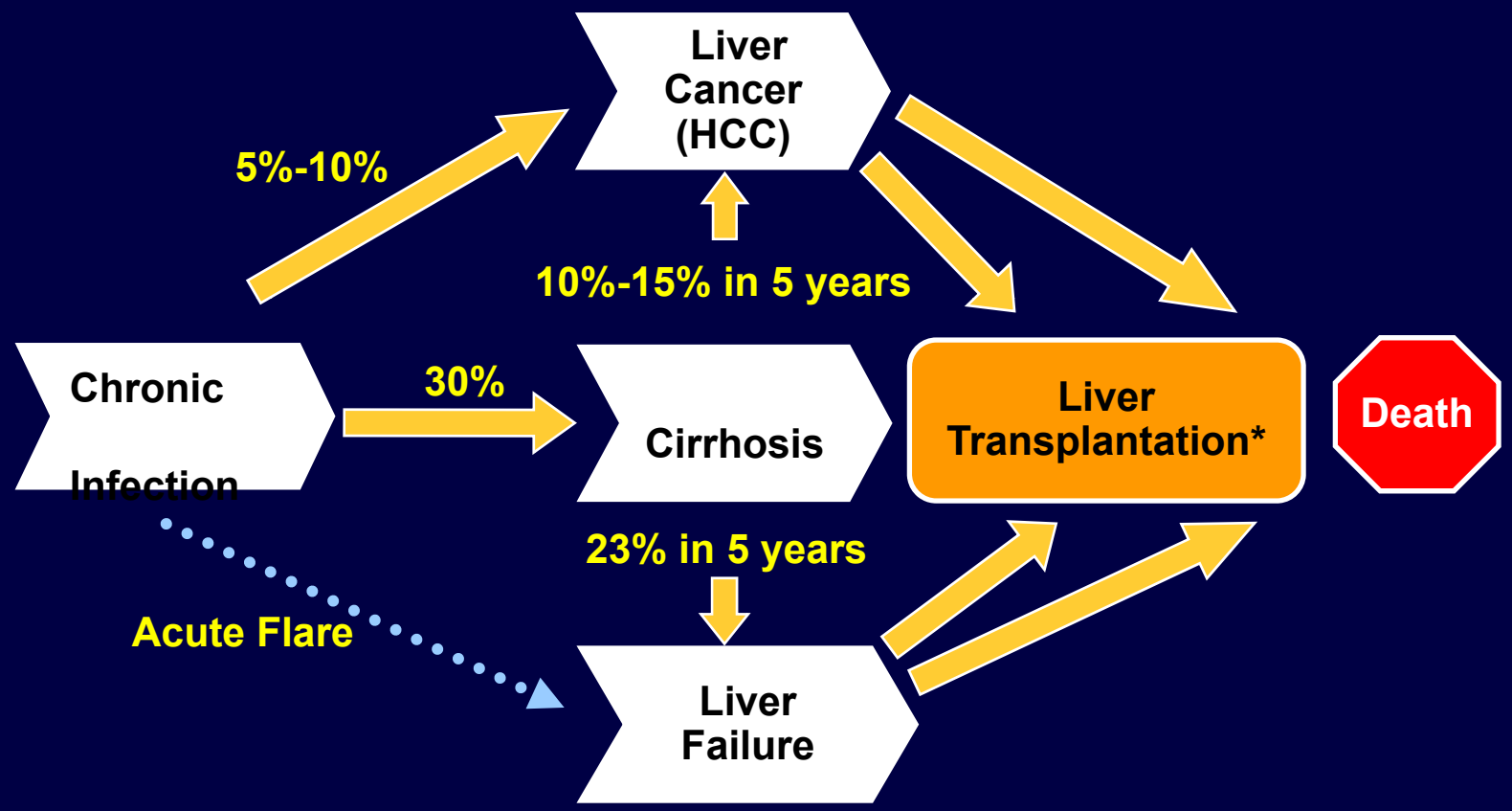
Precore mutations

(27% US patients)[2]
  - Abolishes HBeAg production (HBeAg-negative CHB)
- **Treatment-induced mutations**



2. Chu C-J et al. *Gastroenterology* 2003;125:444-451.
3. Hunt CM et al. *Hepatology* 2000; 31:1037-1044.

Disease Progression Occurs in 15% to 40% of Chronic HBV Patients



*HBV is the 6th leading cause of liver transplantation in the United States.

Fattovich G, et al. *Gastroenterology.* 2004;127:S35-S50.
Seef LB, et al. *Hepatology.* 2001;33:455-463.
Torresi J, et al. *Gastroenterology.* 2000;118:S83-S103.
Fattovich G, et al. *Hepatology.* 1995;21:77-82.

Viral Load Predicts Disease Progression The REVEAL Study

Risk Evaluation of Viremia Elevation & Associated Liver Disease

- Prospective, multicenter, observational cohort study

1991-1992 Recruitment

7 Taiwanese townships aged 30–65 years (n=89,293)

↓

Baseline HBsAg+ (n=9800)

↓

Baseline HBV DNA (n=3851)

- 24% PCR neg
- 85% HBeAg neg
- 94% ALT<45 IU/L
- 98% non-cirrhotic (on ultrasound)

↓

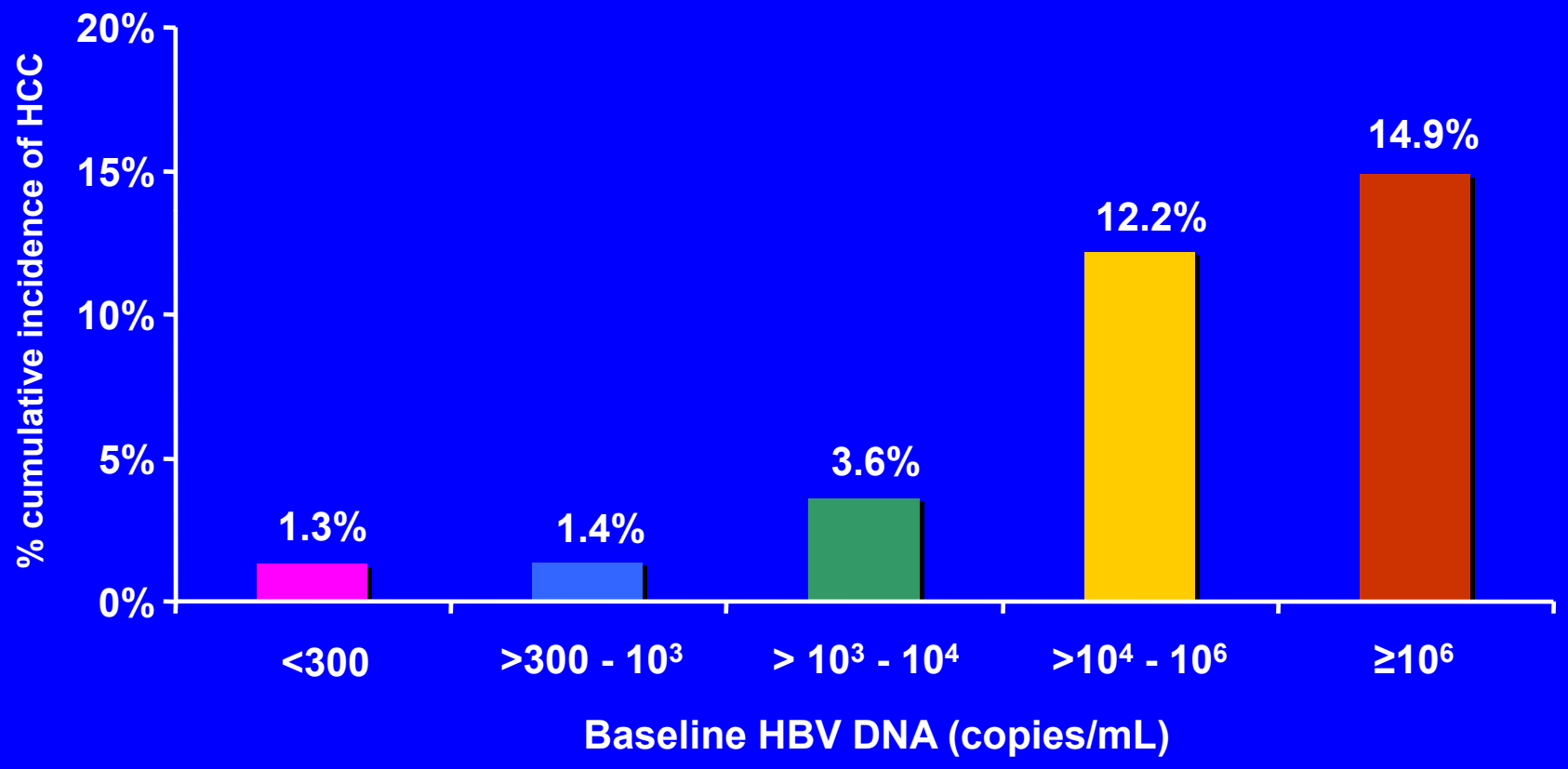
Follow-up analysis for cirrhosis/HCC (n=3774)

↓

June 2004: 43,993 PYs follow-up

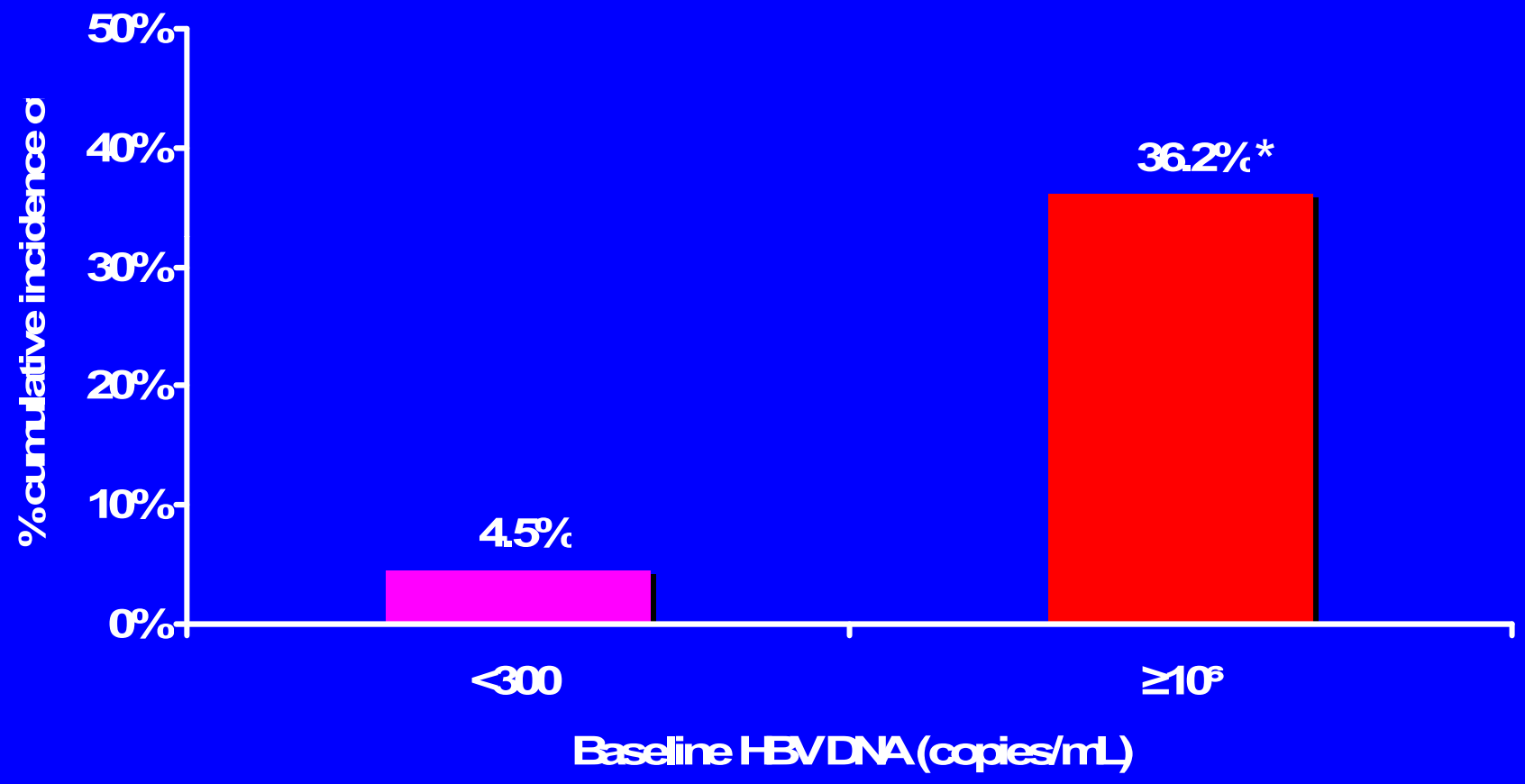
Chen CJ. *JAMA.* 2006;295:65-73.

REVEAL-Incidence of HCC Increases with Increasing HBV DNA Baseline Viral Level



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

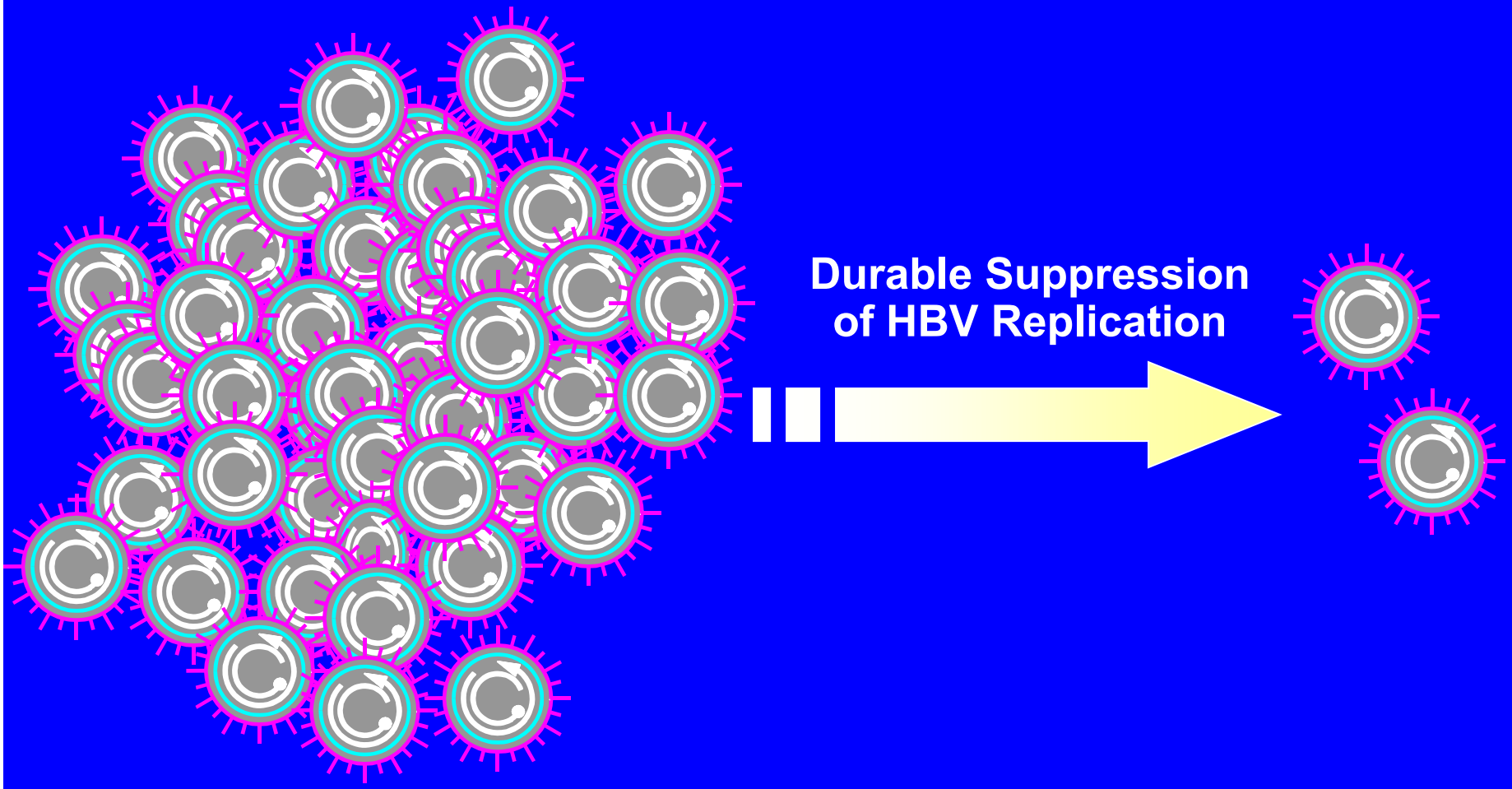
REVEAL-Incidence of Cirrhosis Increases with Increasing Baseline Serum HBV DNA Level



Iloeje U H, et al. Gastroenterology 2006;130:678-86.

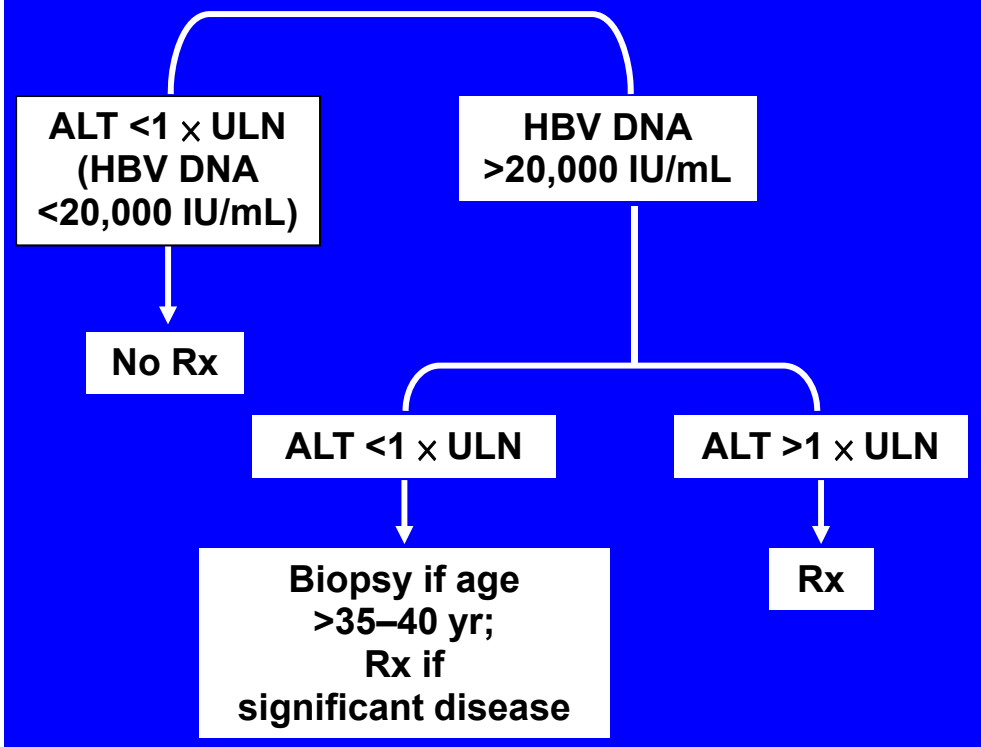
* $p < 0.001$ test for trend

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

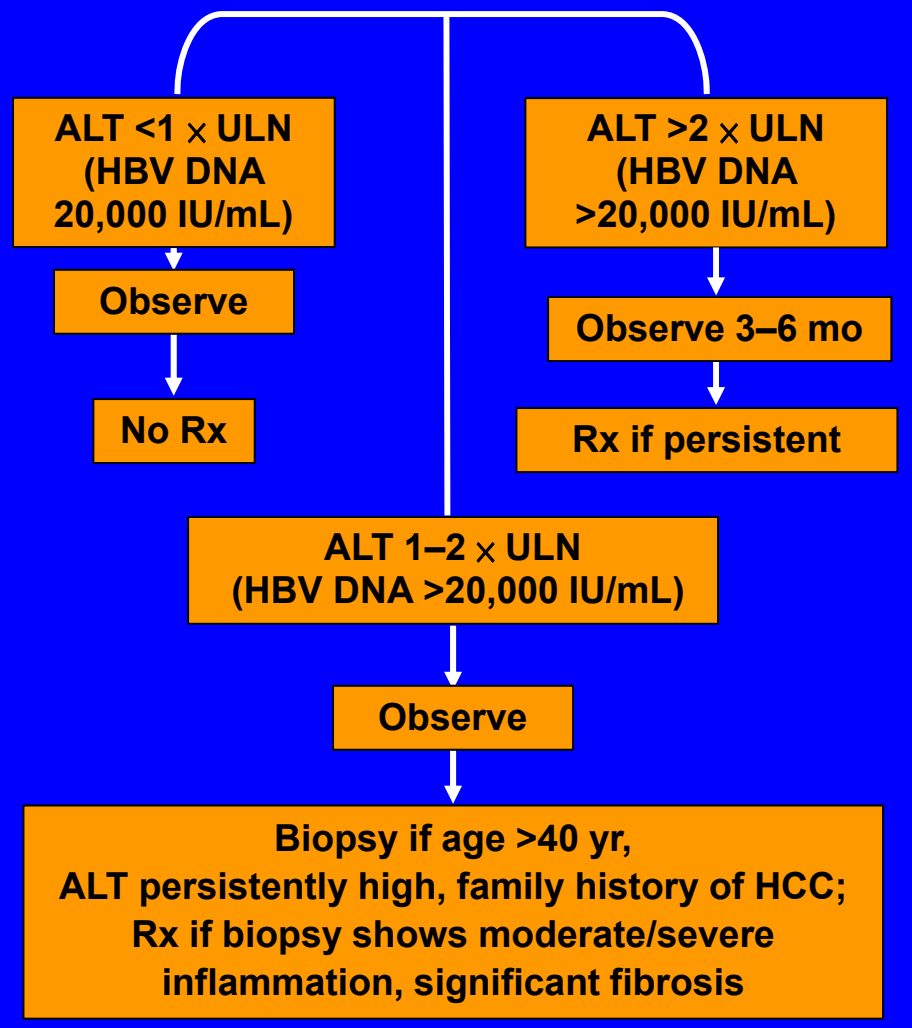


Differences Between the Treatment Algorithm and AASLD 2007 Guidelines: HBeAg-Positive Patients

Treatment Algorithm[1]



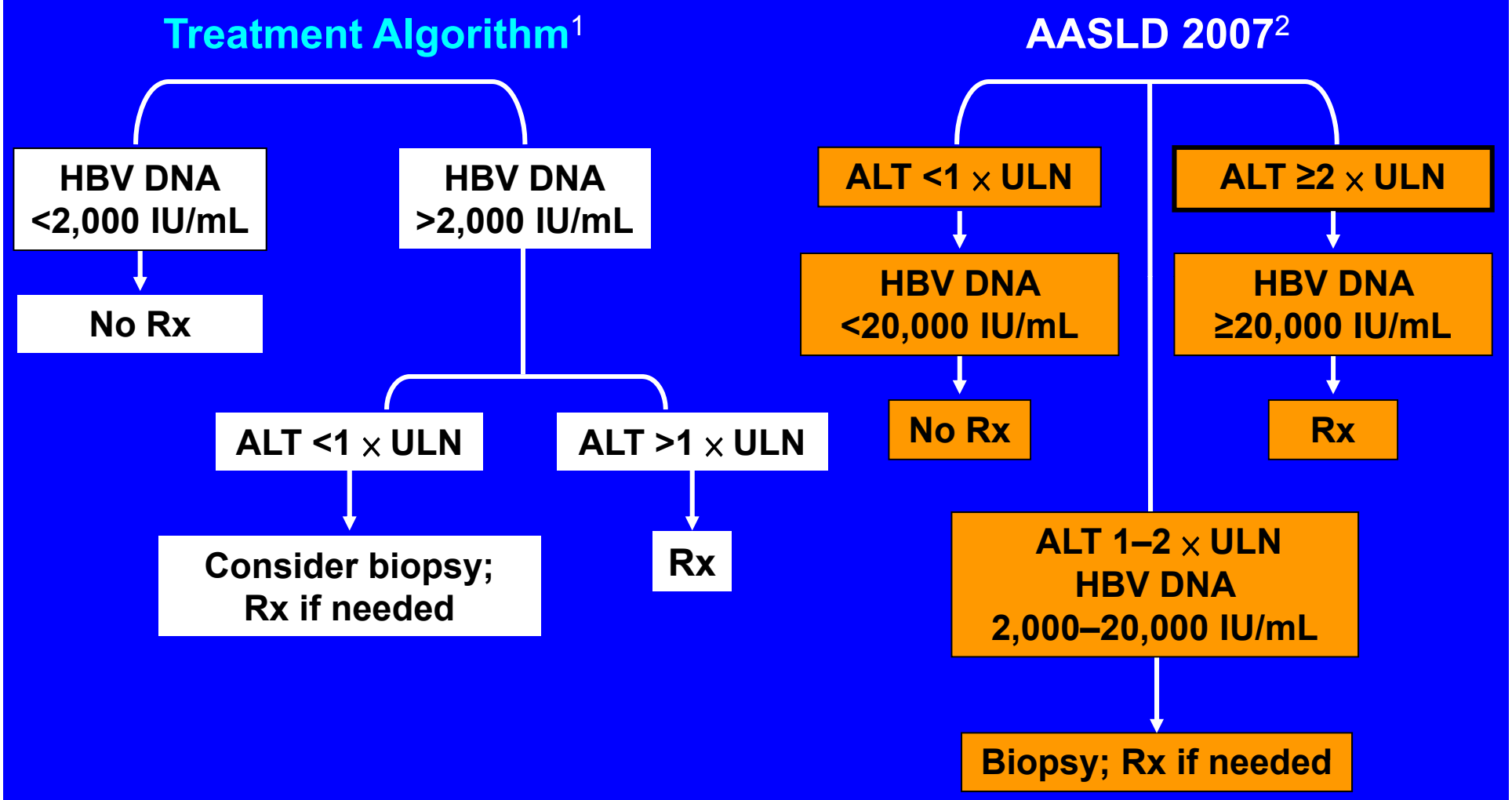
AASLD 2007[2]



1. Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2006;4:936–962.
2. Lok AS, McMahon BJ. *Hepatology*. 2007;45:507–539.

Courtesy of Dr. Ira Jacobson

Differences Between the Treatment Algorithm and AASLD 2007 Guidelines: HBeAg-Negative Patients



1. Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2006;4:936–962.
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Courtesy of Dr. Ira Jacobson

Upper Limit of Normal ALT Levels Has Been Lowered

- Updated upper limits
  - Males: 30 U/L (-25% from prior ULN)
  - Females: 19 U/L (-37% from prior ULN)
- Based on retrospective cohort study
  - 6835 first time blood donors 1995-1999
    - Anti-HCV negative and no contraindication to donation
- ALT activity independently related to
  - BMI
  - Abnormal lipid or carbohydrate metabolism

Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2006;4:936-962.
Prati D, et al. *Ann Intern Med*. 2002;137:1-9.

Normal ALT and Risk of Mortality From Liver Disease

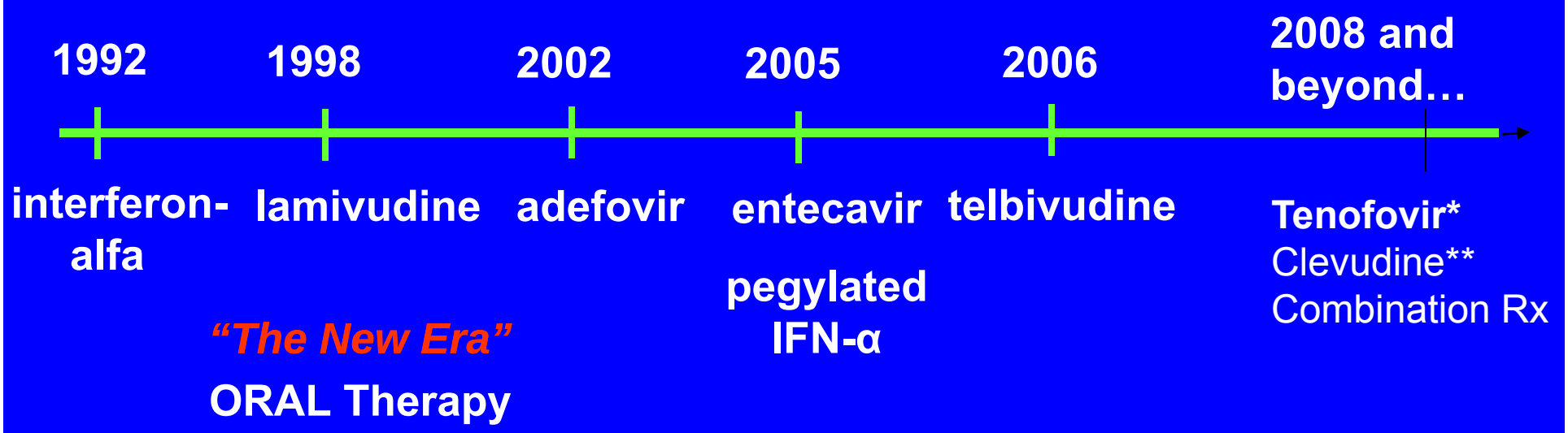
- Prospective, cohort study
  - 94,533 males and 47,522 females ages 35-59 years
  - Follow-up: 8 years
- Cause of death from death certificates
  - Number with chronic HBV unknown
- ALT ≥20 was associated with increased risk for death from liver disease

Relative Risk of Mortality From Liver Disease

ALT (U/L)	Male	Female
<20	1	1
20-29	2.9	3.8
30-39	9.5	6.6

Kim HC, et al. *BMJ*. 2004;328:983-988.

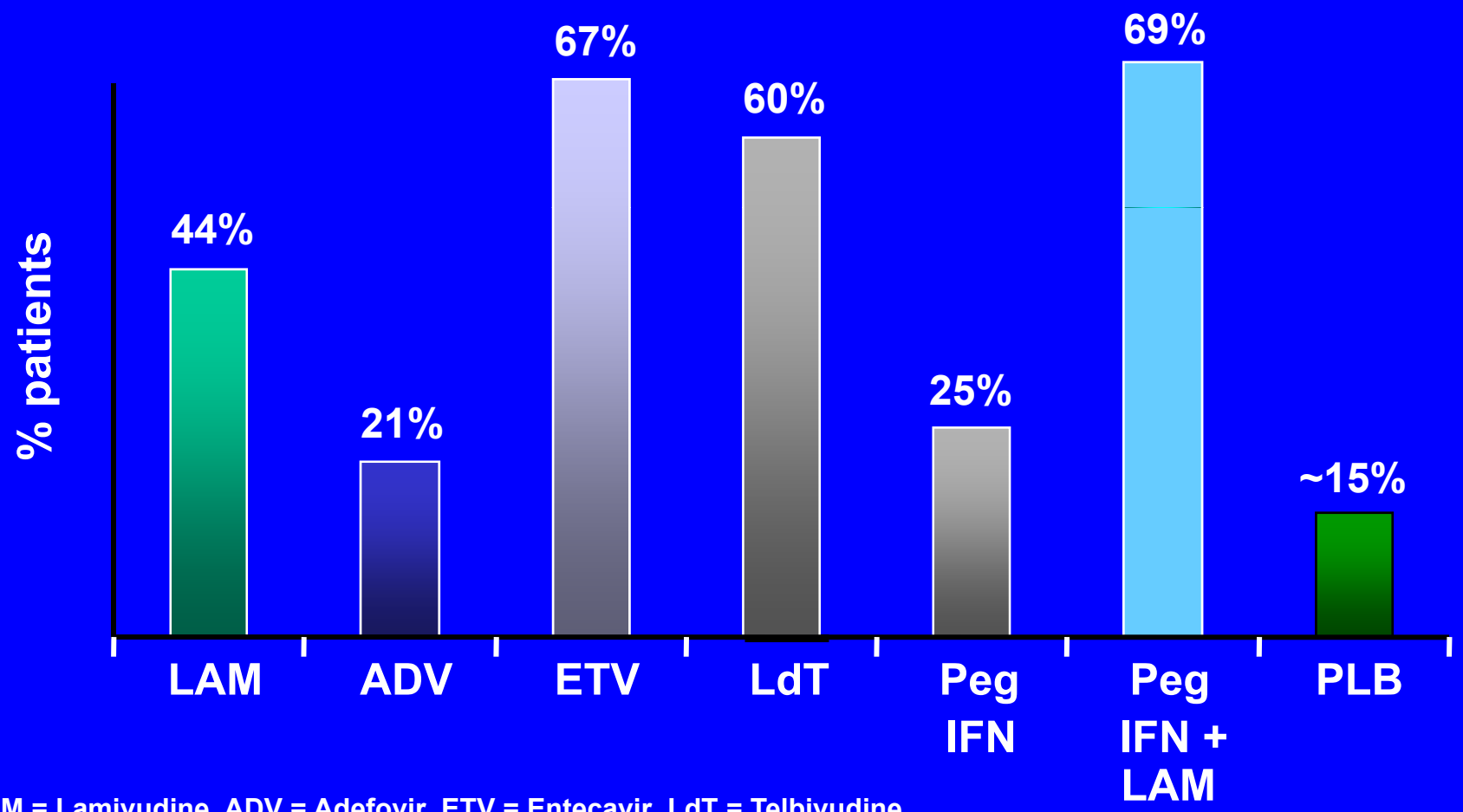
Therapy for Chronic Hepatitis B: 2008



*FDA-approved for HIV and in review by FDA for HBV indication
** in phase III trial

Virological Response in HBeAg+ patients (undetectable HBV DNA by PCR at week 48-52)

Not Head to Head Trials, Different Patient Populations

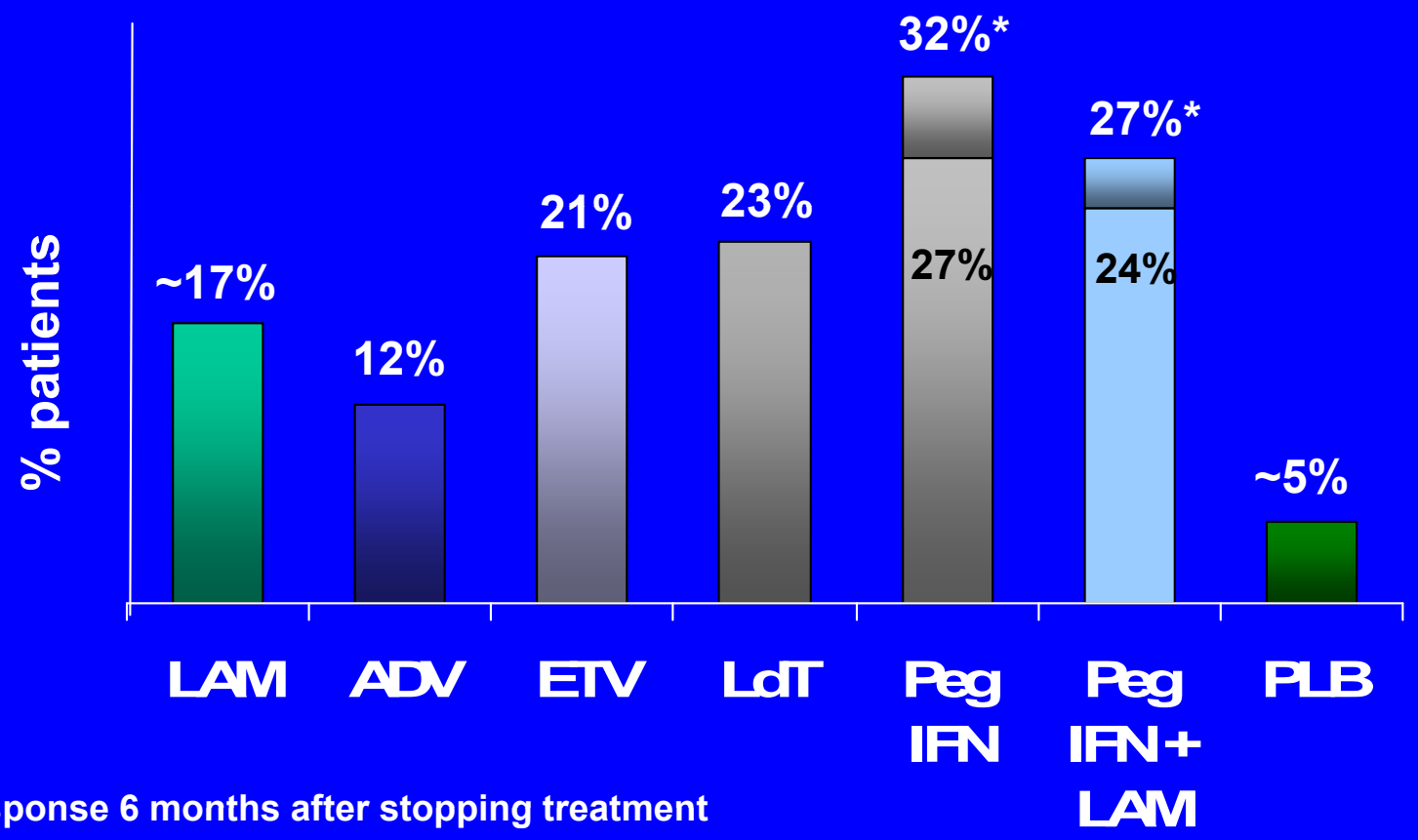


LAM = Lamivudine ADV = Adefovir ETV = Entecavir LdT = Telbivudine
PEG IFN = Pegylated Interferon PLB = Placebo

Adapted from Lok and McMahon, *Hepatology* 2007; 45: 507-539

Virological Response in HBeAg+ patients (HBeAg seroconversion at week 48-52)

Not Head to Head Trials, Different Patient Populations



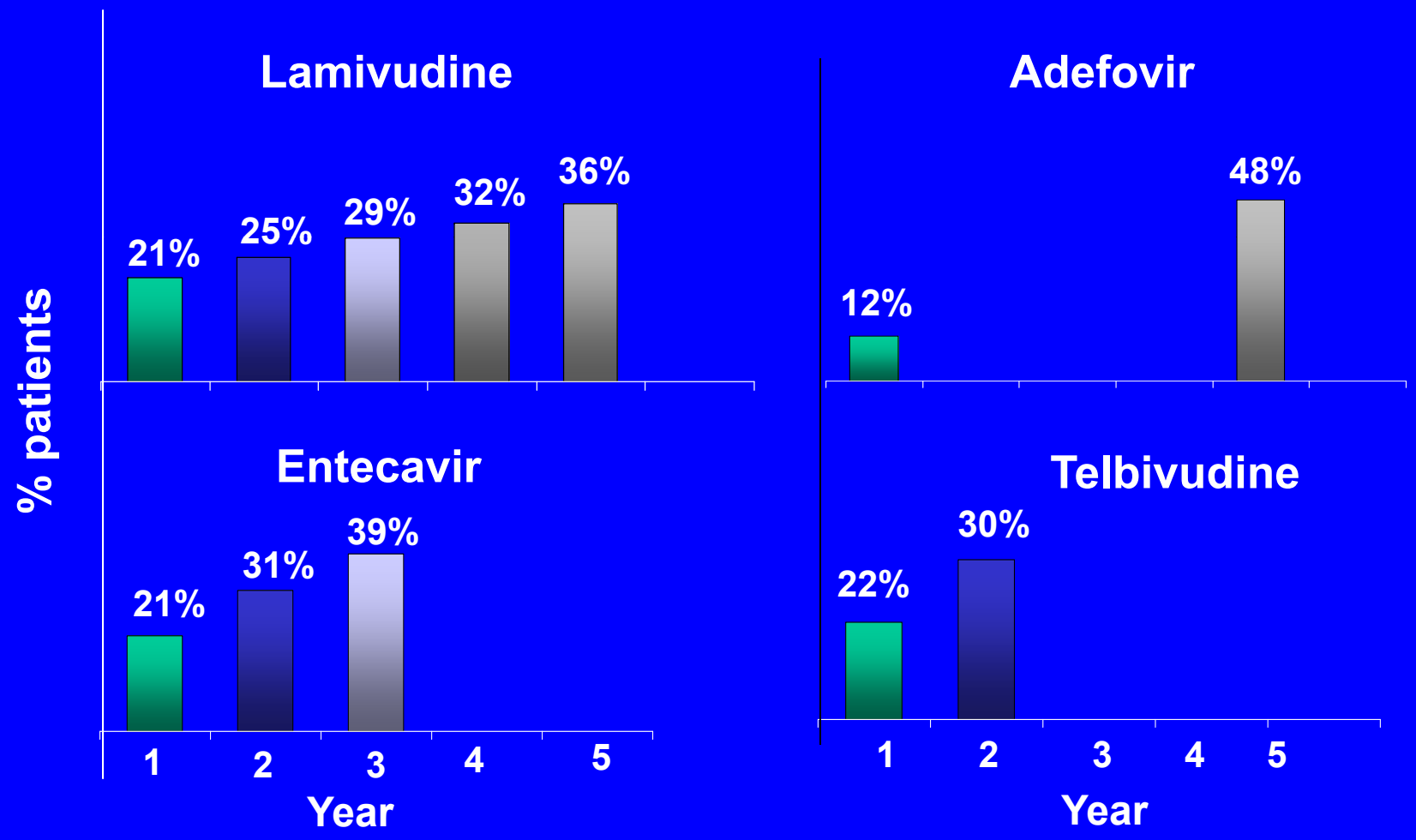
* Response 6 months after stopping treatment

LAM = Lamivudine ADV = Adefovir ETV = Entecavir LdT = Telbivudine
PEG IFN = Pegylated Interferon PLB = Placebo

Adapted from Lok and McMahon, *Hepatology 2007;* 45: 507-539

HBeAg seroconversion during continued treatment

Not Head to Head Trials, Different Patient Populations and Trial Design

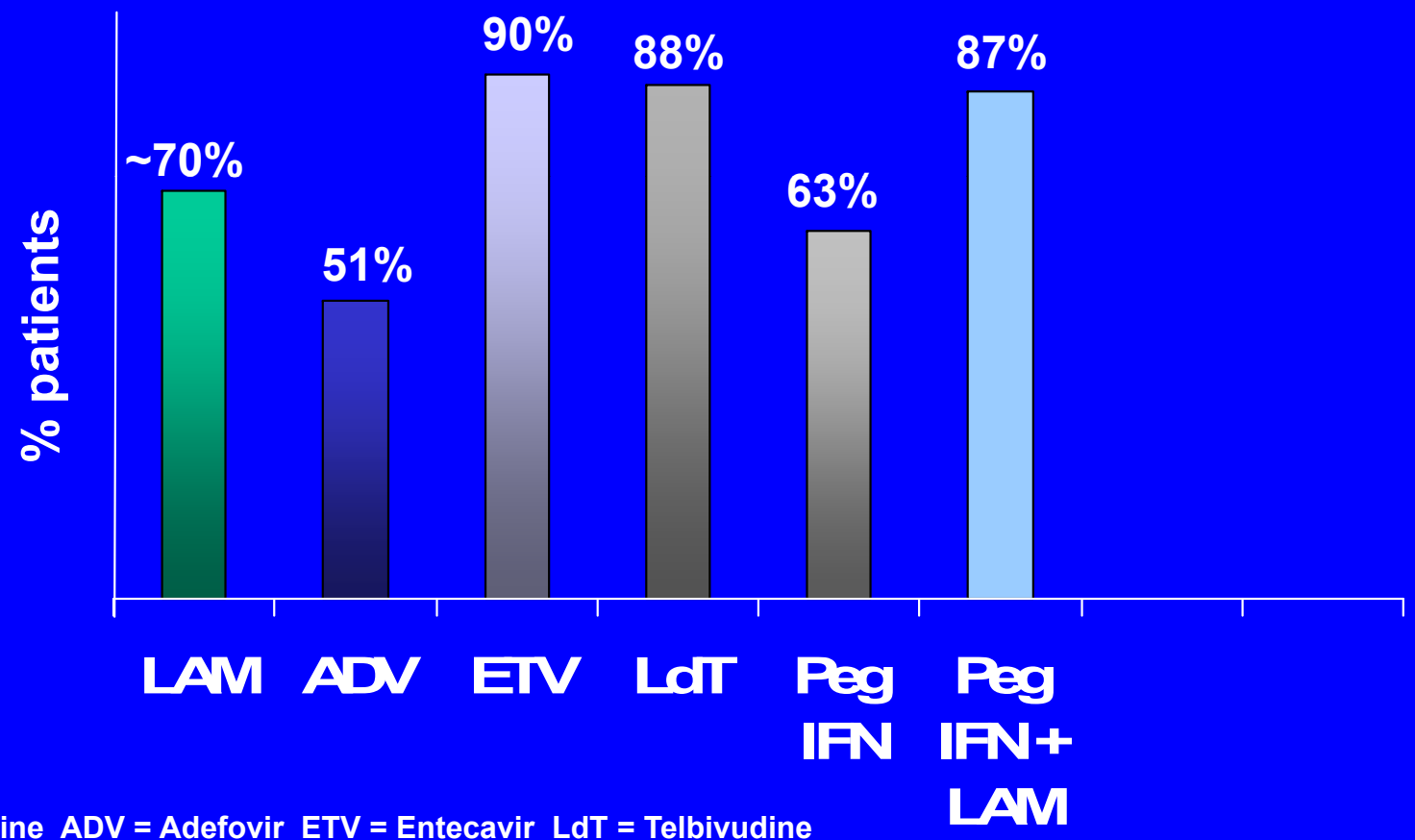


Marcellin P, Hepatology Chang T, AASLD 2006 abs
Lai C, AASLD 2006 abs

Adapted from:
Lok and McMahon, *Hepatology* 2007; 45: 507-539
Lok AS, *Gastro* 2003; 125: 1714-1722

Virological response in HBeAg-patients (HBV DNA undetectable by PCR at week 48-52)

Not Head to Head Trials, Different Patient Populations



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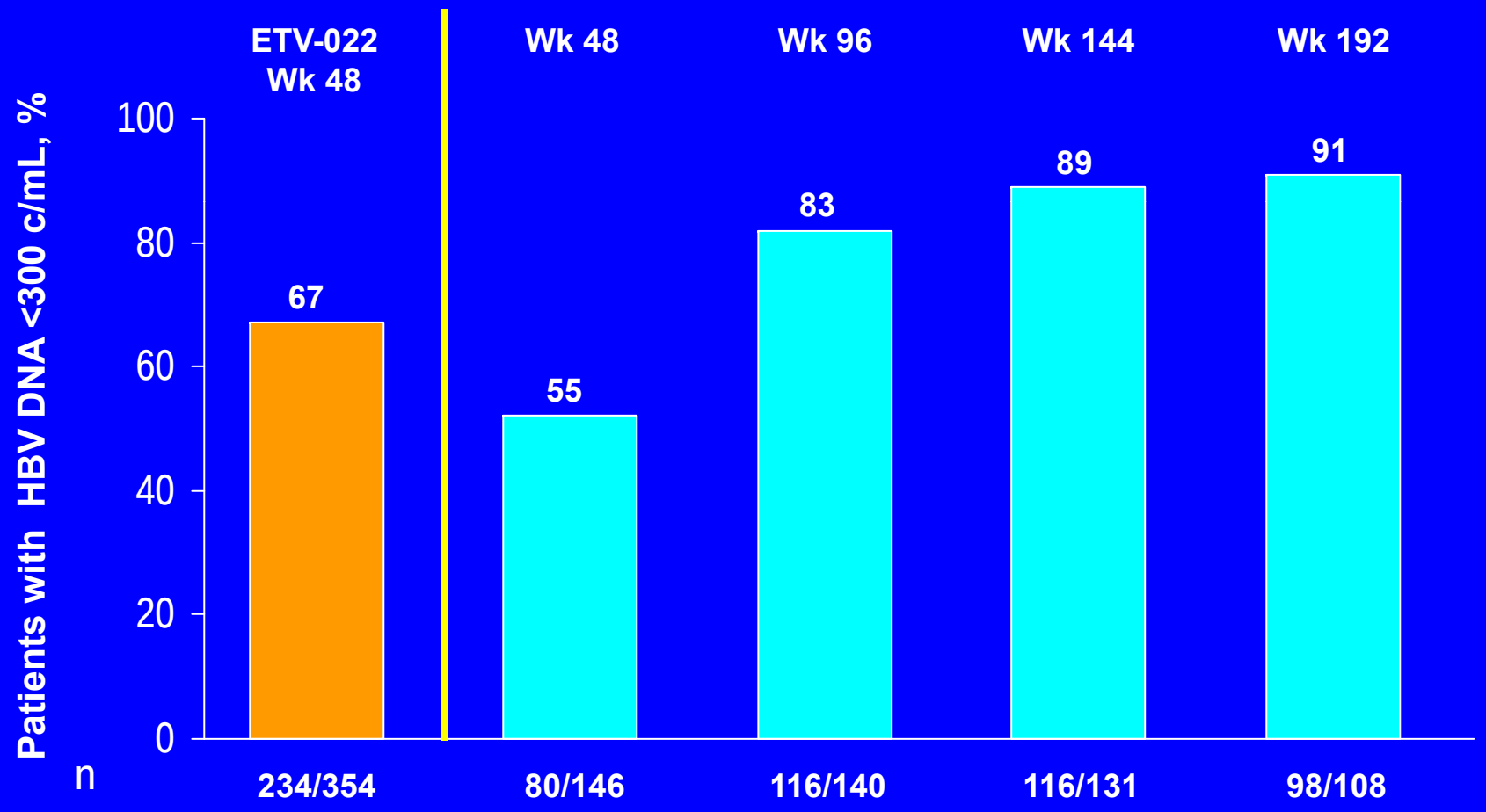
Adapted from Lok and McMahon, *Hepatology* 2007; 45: 507-539

Proportion of HBeAg-Positive Patients Achieving HBV DNA Levels of <300 c/mL Through 4 Years of Entecavir Therapy

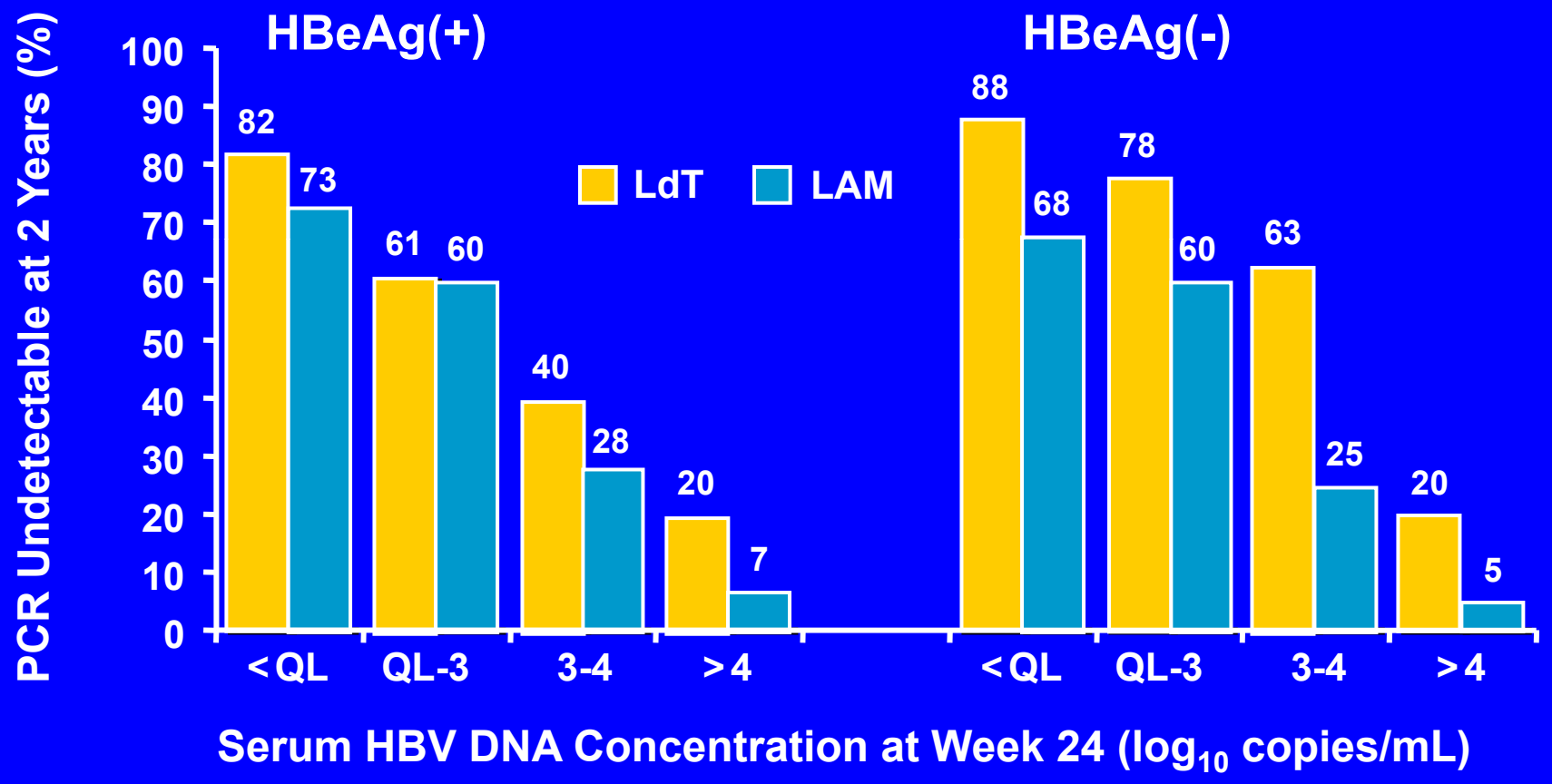


Han S, et al. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases, November 2–6, 2007, Boston, Massachusetts; abstract no. 938.

Entecavir: Genotypic Resistance and Virologic Breakthroughs in Nucleoside-Naïve Patients

Colonno RJ, et al. Presented at the 42nd Annual Meeting of the European Association for the Study of the Liver, April 11–15, 2007, Barcelona, Spain.

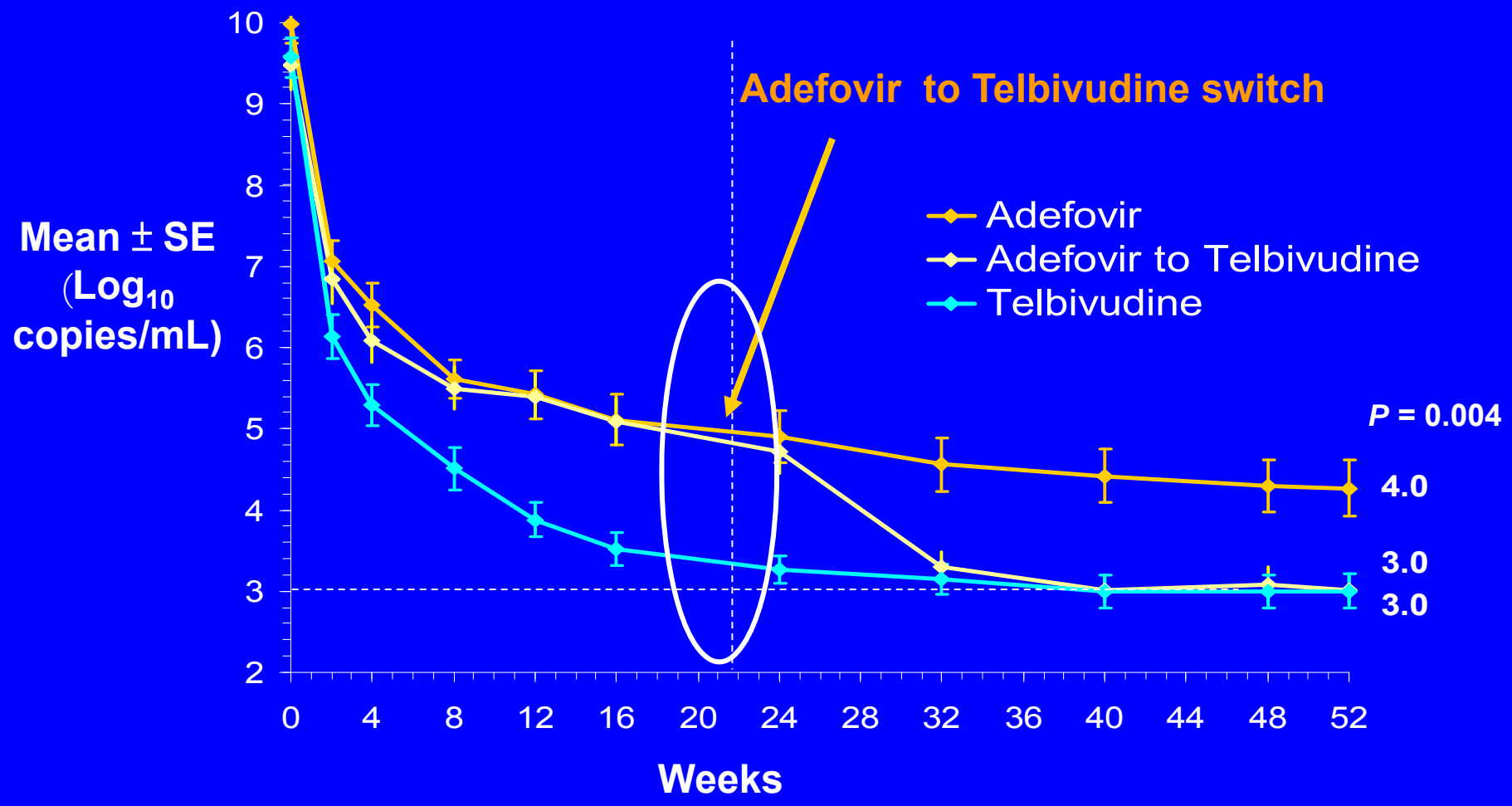
Telbivudine (LdT): Week 24 Serum HBV DNA Concentration Predicts Year-2 PCR Undetectability



QL, quantification limit

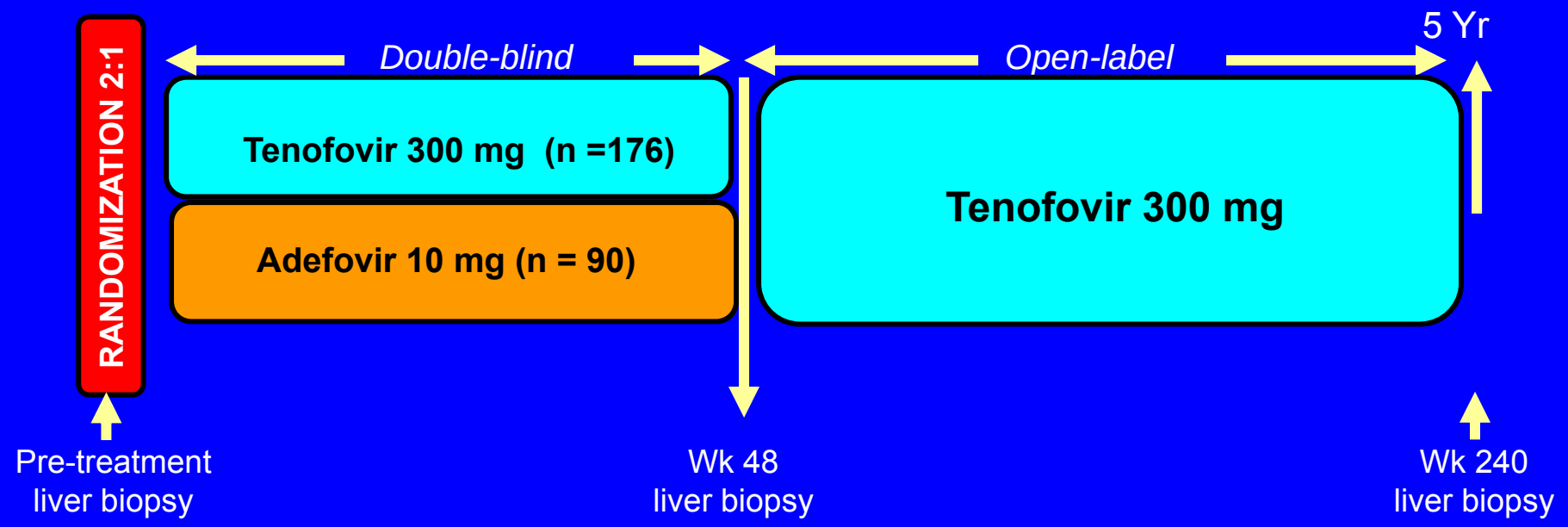
DiBisceglie et al. 57th AASLD; October 27-31, 2006; Boston, MA. Abstract 112.

Effects of Switching from Adefovir to Telbivudine in Patients with Suboptimal Response to Adefovir (HBV DNA >3 $\log_{10}$ copies/mL at 24 Weeks)



Chan et al. Ann Inter Med 2007;147;epub.

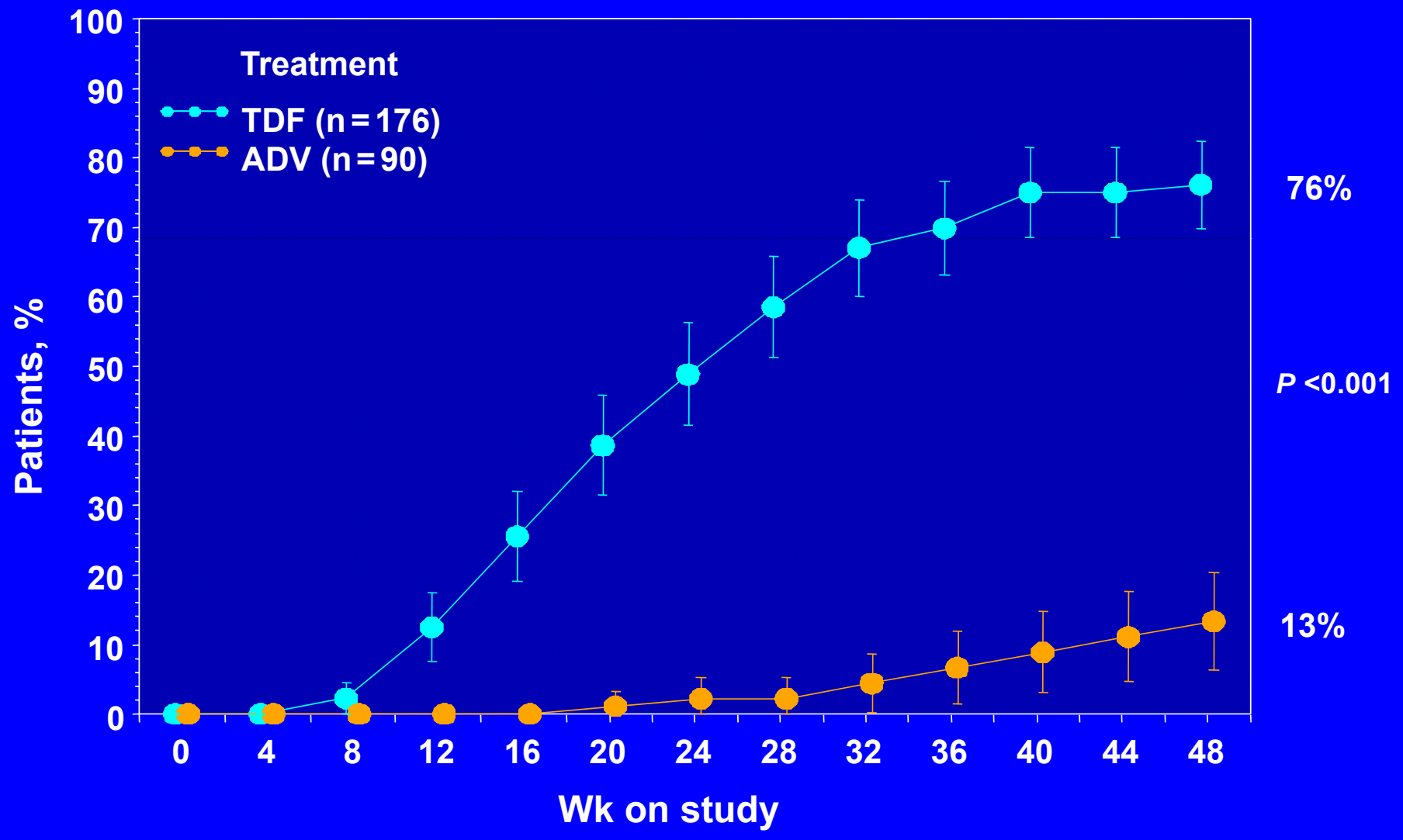
Randomized, Double-Blind Comparison of Tenofovir and Adefovir in HBeAg-positive CHB: Study Design



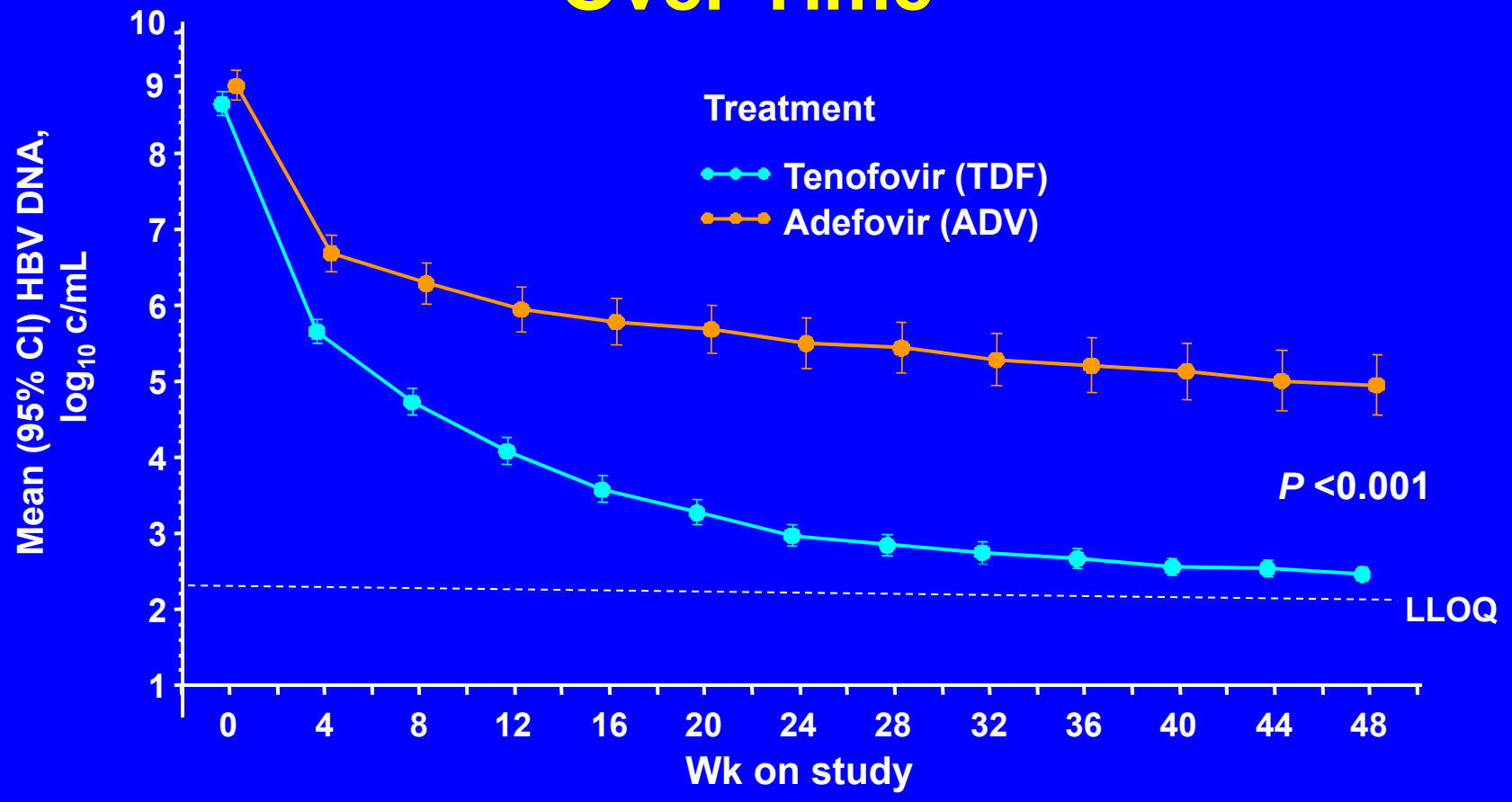
Primary end point = complete response:
HBV DNA <400 c/mL *and* histologic improvement (≥2-point reduction in the Knodell score without worsening in fibrosis)

Heathcote J, et al. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases, November 2–6, 2007, Boston, Massachusetts; abstract no. LB6.

Tenofovir vs Adefovir in HBeAg-positive CHB: Patients With HBV DNA Levels of <400 c/mL



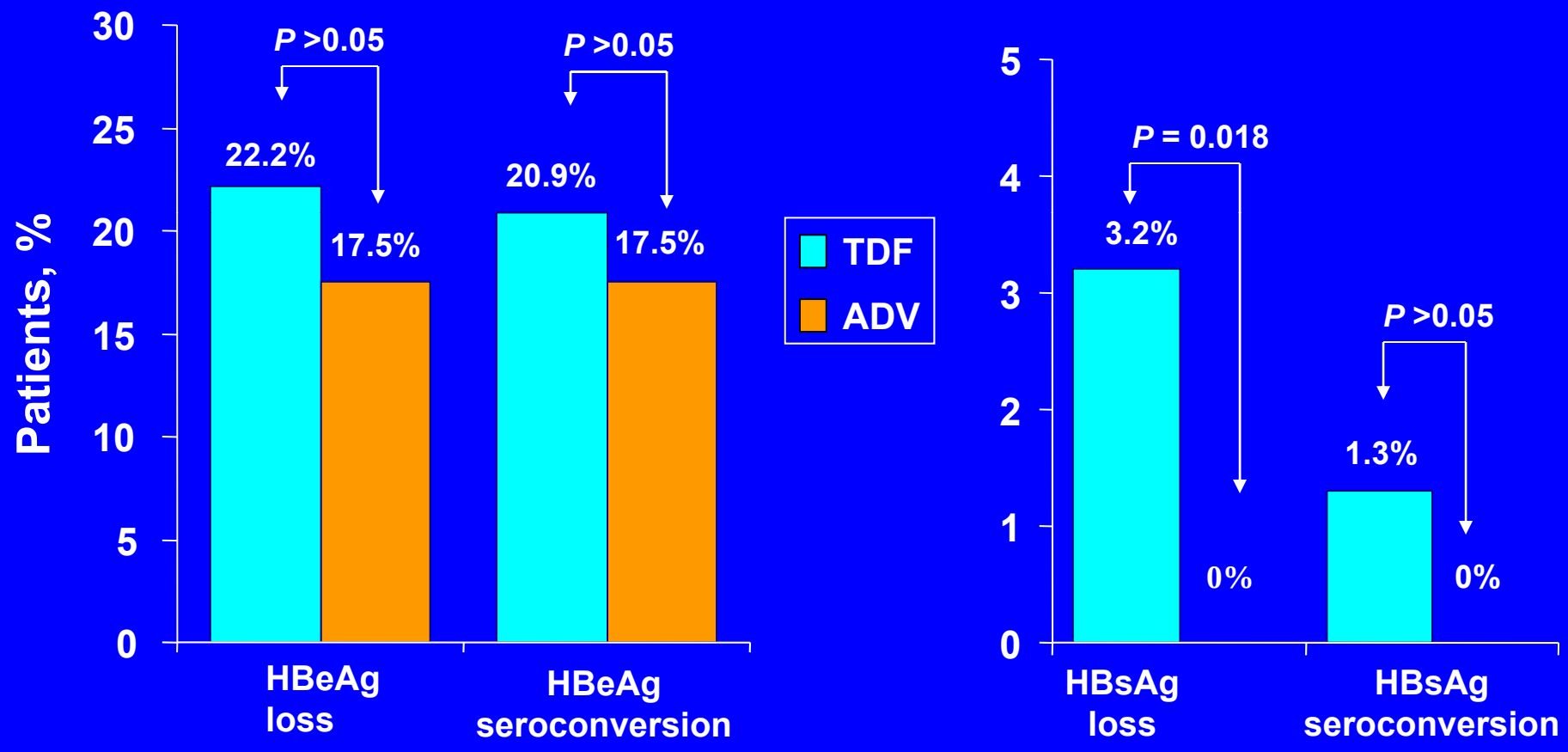
Tenofovir vs Adefovir for HBeAg-positive CHB: Mean HBV DNA Levels (log_{10} c/mL) Over Time



ADV	N = 90	88	85	84	84
TDF	N = 176	173	165	166	160

Heathcote J, et al. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases, November 2–6, 2007, Boston, Massachusetts; abstract no. LB6.

Tenofovir vs Adefovir in HBeAg-positive CHB: HBeAg and HBsAg Loss and Seroconversion at Week 48

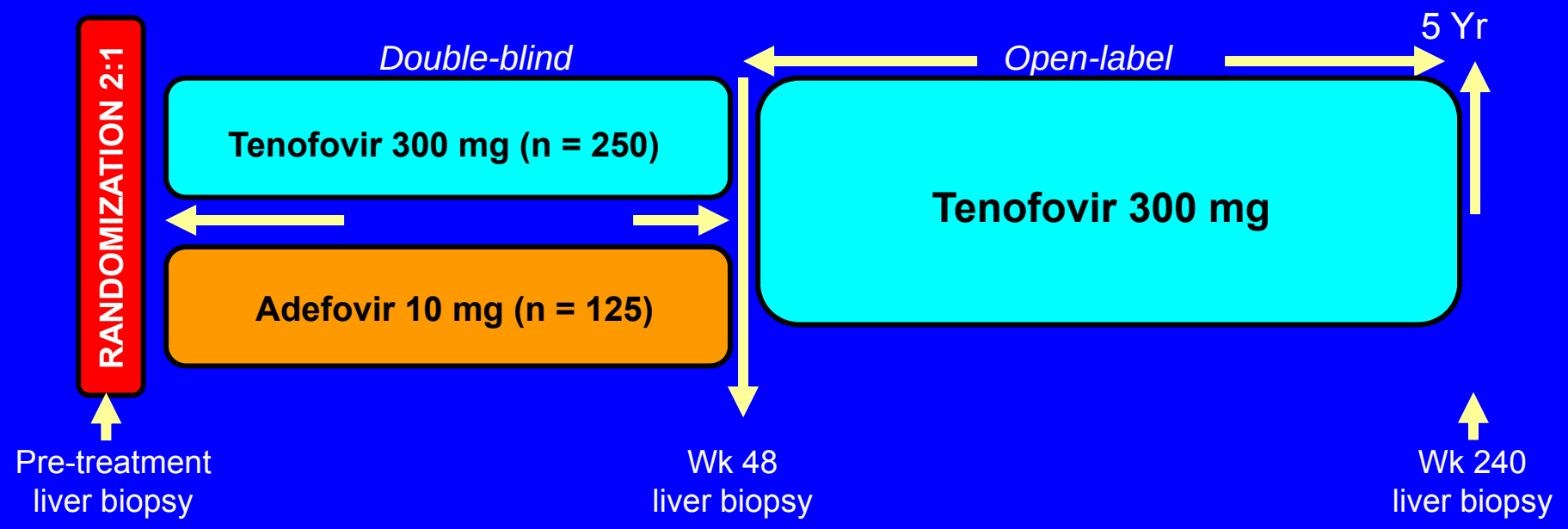


N = 153 TDF patients, N = 80 ADV patients

N = 158 TDF patients, N = 82 ADV patients

Heathcote J, et al. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases, November 2–6, 2007, Boston, Massachusetts; abstract no. LB6.

Randomized, Double-Blind Comparison of Tenofovir vs Adefovir in HBeAg-negative CHB: Study Design



Primary end point = complete response:
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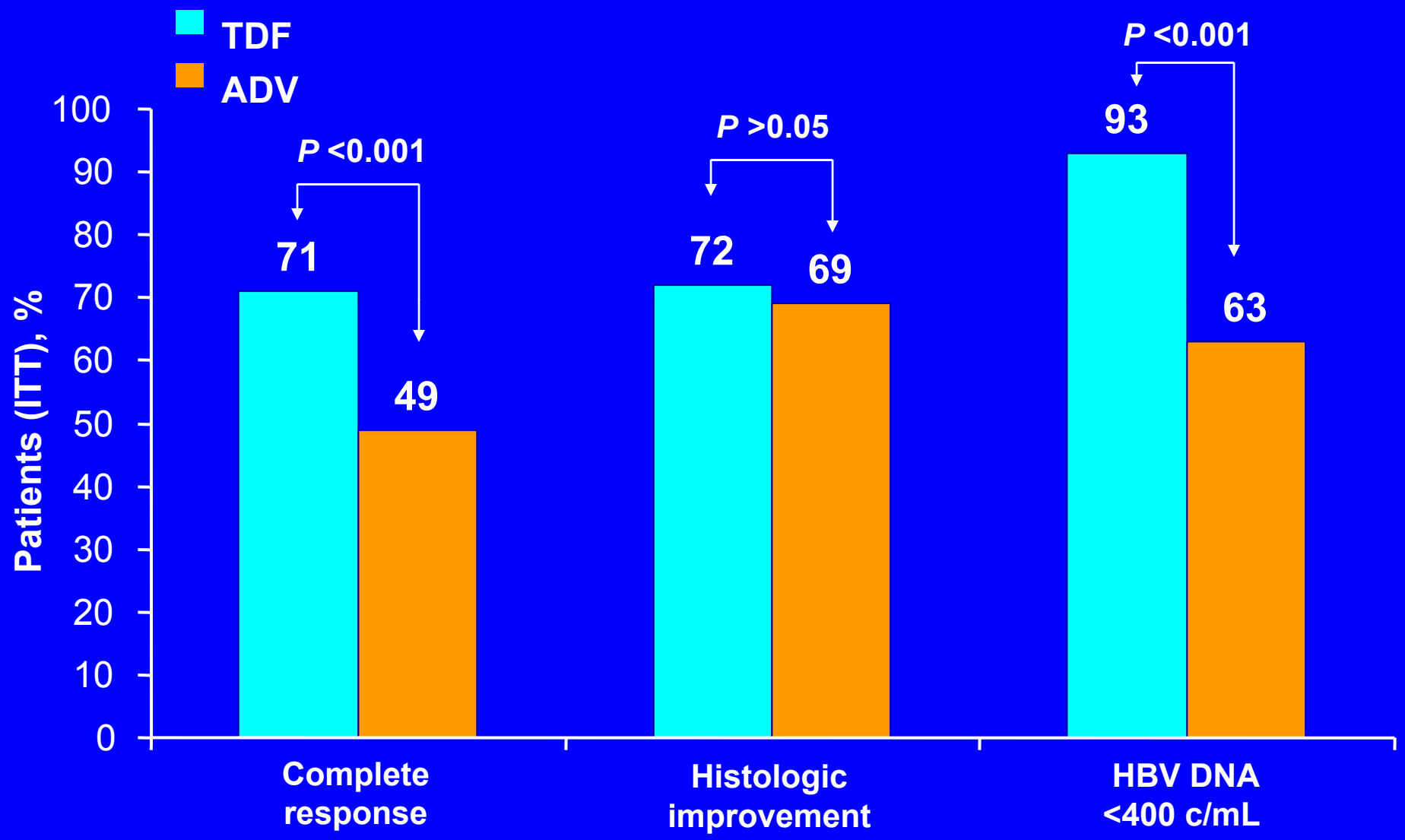
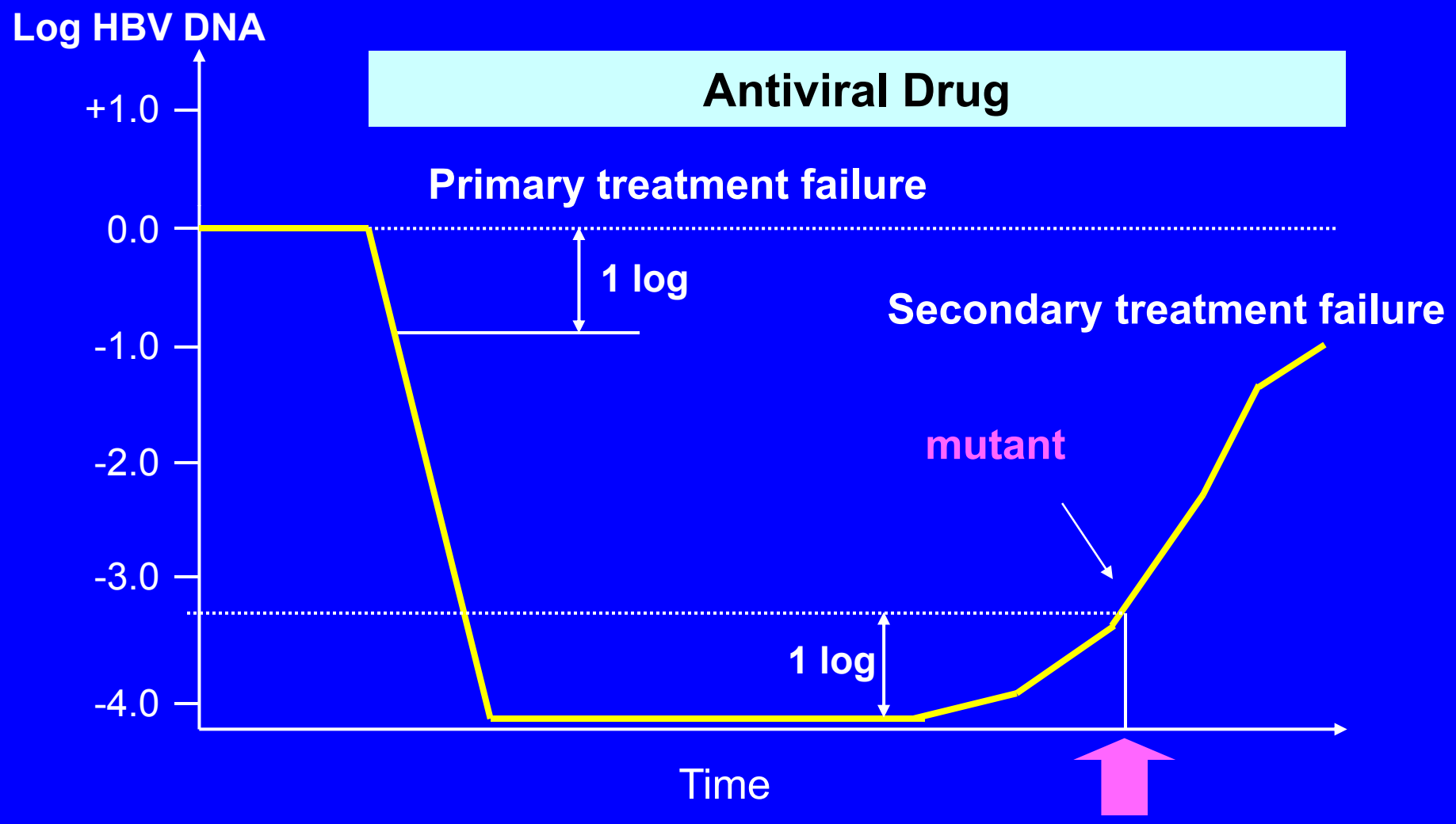
Marcellin P, et al. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases, November 2–6, 2007, Boston, Massachusetts; abstract no. LB2.

Primary and Secondary End Points

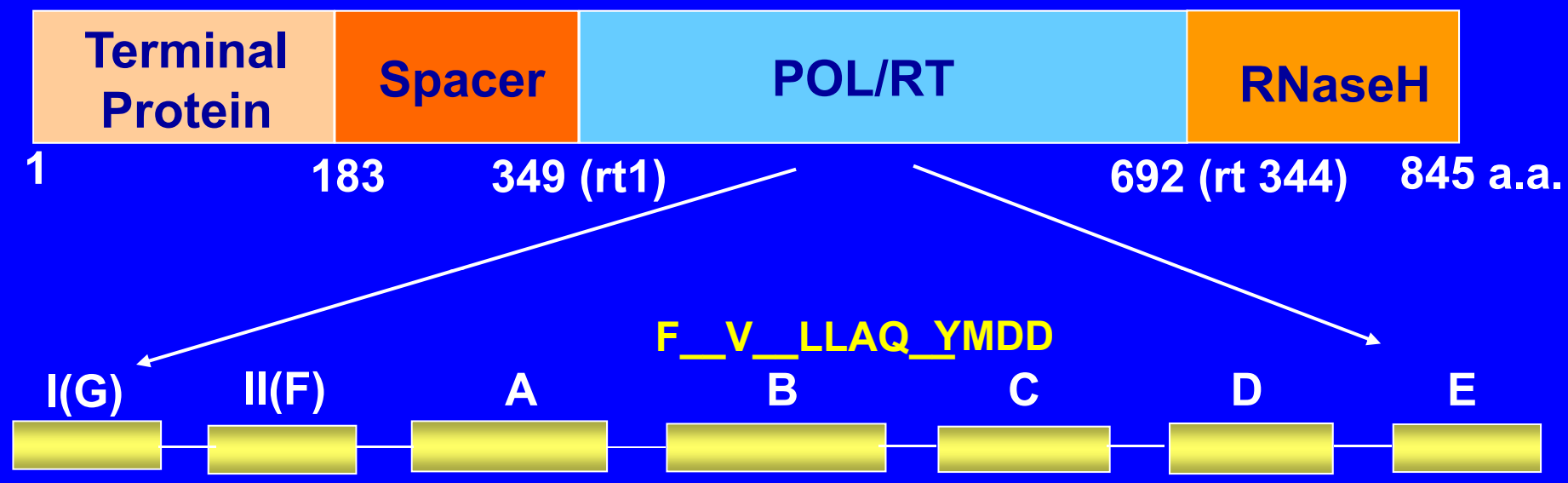


Marcellin P, et al. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases, November 2–6, 2007, Boston, Massachusetts; abstract no. LB2.

Antiviral Treatment Failure in HBV

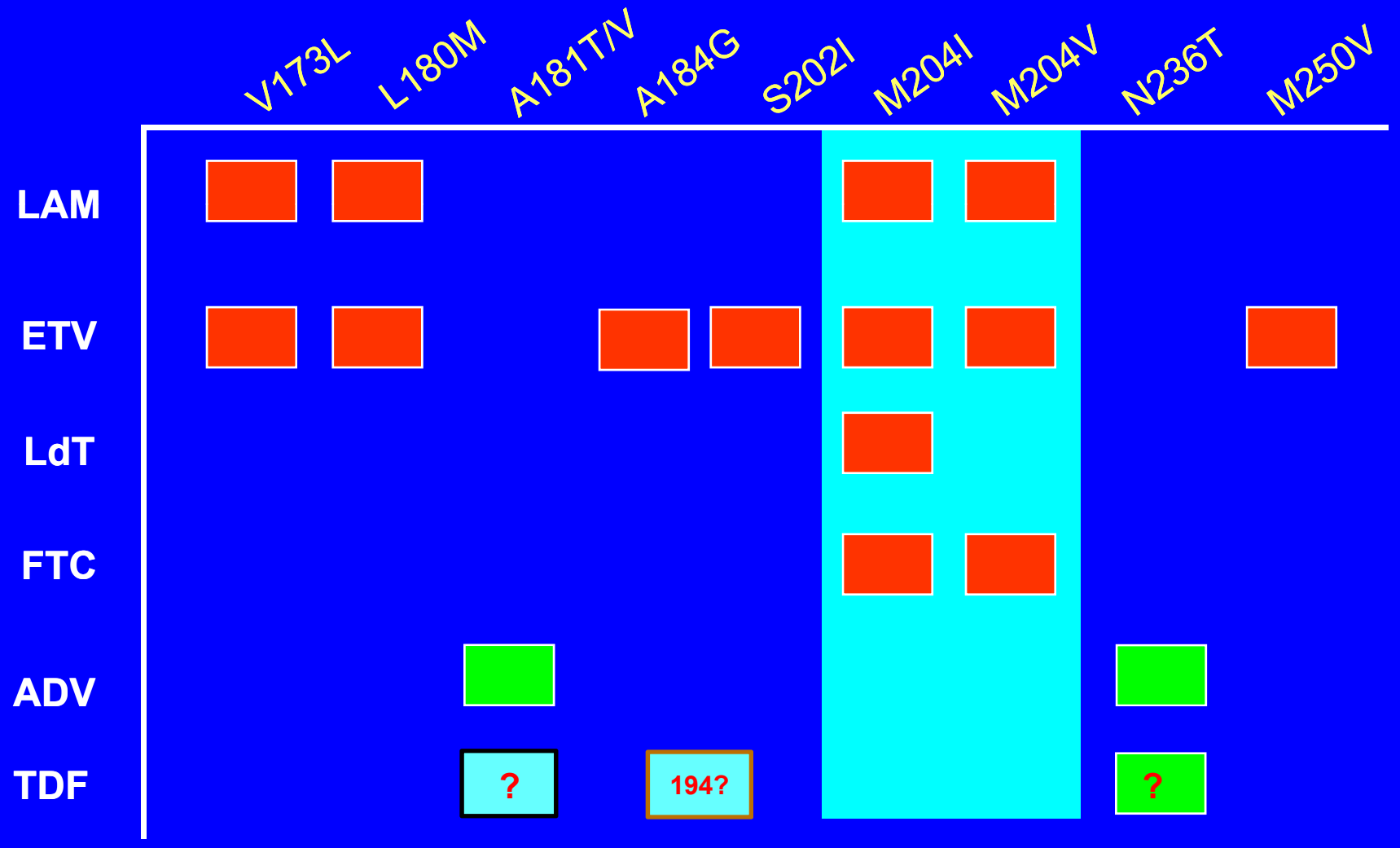


Primary Resistance Mutations



LMV Resistance		rtA181T/V	rtM204V/I	
LdT Resistance		rtA181T/V	rtM204I	
ADV Resistance		rtA181T/V		rtN236T
TDF Resistance		rtA181T/V	rtA194T/rtM204V/I	
ETV Resistance	rtI169T rtL180M rtS184S/A/I/L/G/C/M			
			rtS202C/G/I rtM204V	rtM250I/V

HBV Antiviral Therapy
Cross Resistance *In Vitro*



Management Roadmap According to 24 Week Virologic Response

Week 24: Early predictors of efficacy

Complete response
<60 IU/mL
(<300 copies/mL)

→ Continue
Monitor every 6 months

Partial response
60-2,000 IU/mL

→ Add***
another drug
or
Continue***
Monitor every 3 months

Inadequate response
>2,000 IU/mL
(>10,000 copies/mL)

→ Add
another drug
without
cross resistance
Monitor every 3 months

***Depends on
- Genetic barrier to resistance of drug used
- Level of residual viremia
- Degree of viral load reduction

Keeffe et al. Clin Gastroenterol Hepatol 2007;5:890-97

ADV Add-On Therapy In 145 LAM-R Patients

	Years of treatment*			
Patterns of response	1 (n=145)	2 (n=112)	3 (n=78)	4 (n=39)
HBV-DNA undetectable*	89 (61%)	78 (70%)	62 (79%)	32 (82%)
HBV-DNA >35 to <2,000 copies/ml	10 (7%)	11 (10%)	6 (8%)	1 (2%)
HBV DNA level ≥ ** 2,000 copies/ml	46 (32%)	23 (20%)	10 (13%)	6 (15%)
Virologic breakthrough***	0	0	0	0

Note: all values are expressed as n (%)
*Lower limit of quantification of real-time PCR: 35 copies/ml (1.5 log copies/ml)
** Lower limit of quantification of Versant 3.0: 2,000 copies/ml (3.3 log copies/ml)
*** > 1 log increase of HBV-DNA compared to on treatment nadir, comfirmed on 2 occasions.

Lampertico P, et al. Gastroenterology 2007; 133-1445-1451.

Future Directions

- Monotherapy versus combination therapy
  - Is it necessary to routinely use combination therapy when we have drugs with excellent long term resistance profiles?
- Drugs or regimens capable of higher rates of sustained viral suppression
  - Includes higher rates of HBeAg seroconversion and higher rates of durable suppression in HBeAg neg pts
  - Higher rates of HBsAg clearance
- Novel approaches

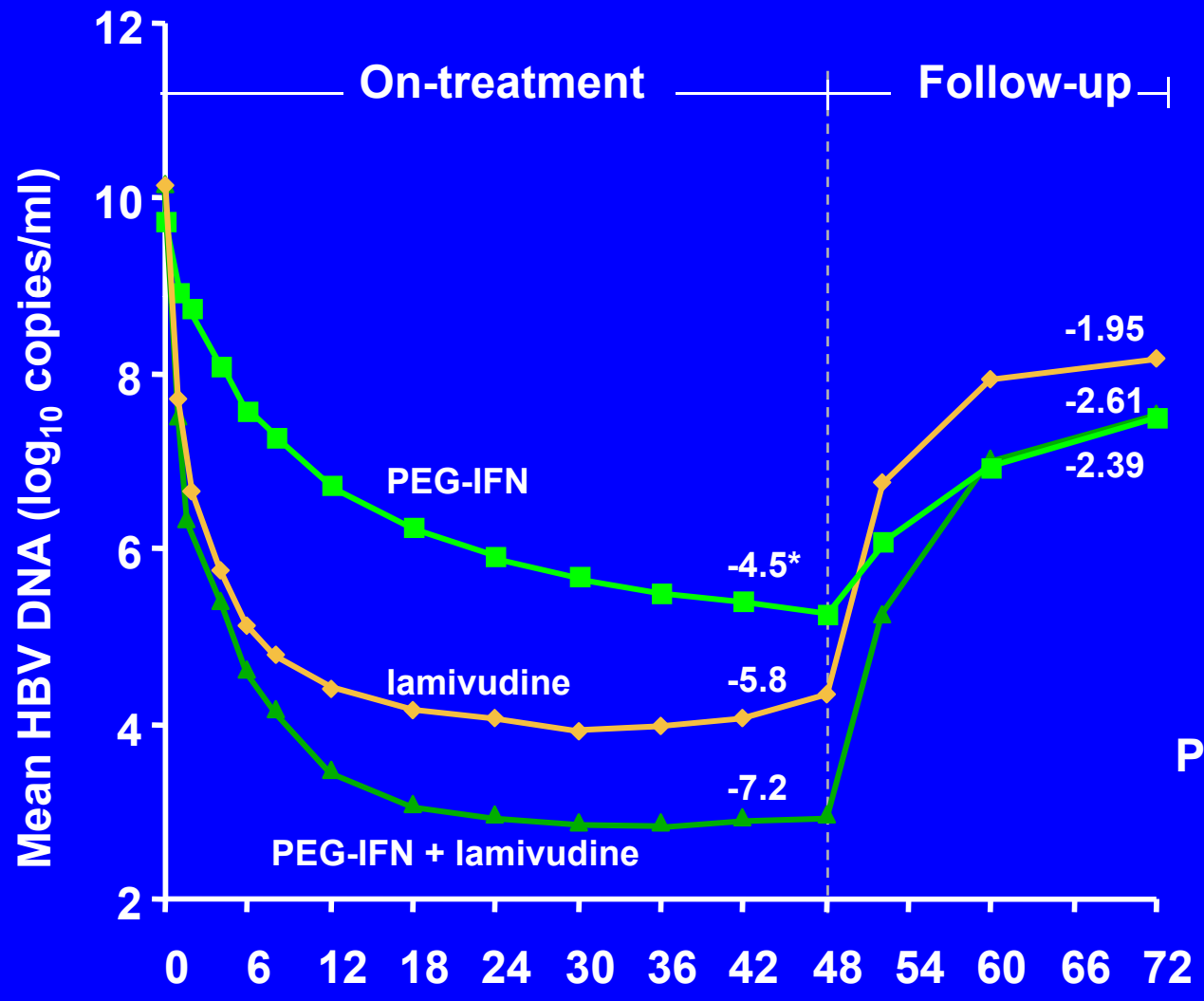
Combination Therapy for CHB

- HIV pandemic is a paradigm for combination therapy:
  - Upfront combination prevented resistance and is superior to sequential monotherapy
  - De novo combination better than adding second agent after resistance occurs
- Potential Limitations?
  - Cost vs Benefit
  - Will it be as important with newer, more potent oral agents (entecavir, telbivudine, tenofovir) and roadmap concept

Delta Coordinating Committee. Lancet 1996; 348: 283-291.

Hammer et al. N Engl J Med 1997; 337: 725-733.

On-therapy HBV DNA Suppression and End of Follow-up Responses



PEG-IFN

HBeAg seroconversion at EOF = 32%

Lamivudine

HBeAg seroconversion at EOF = 19%

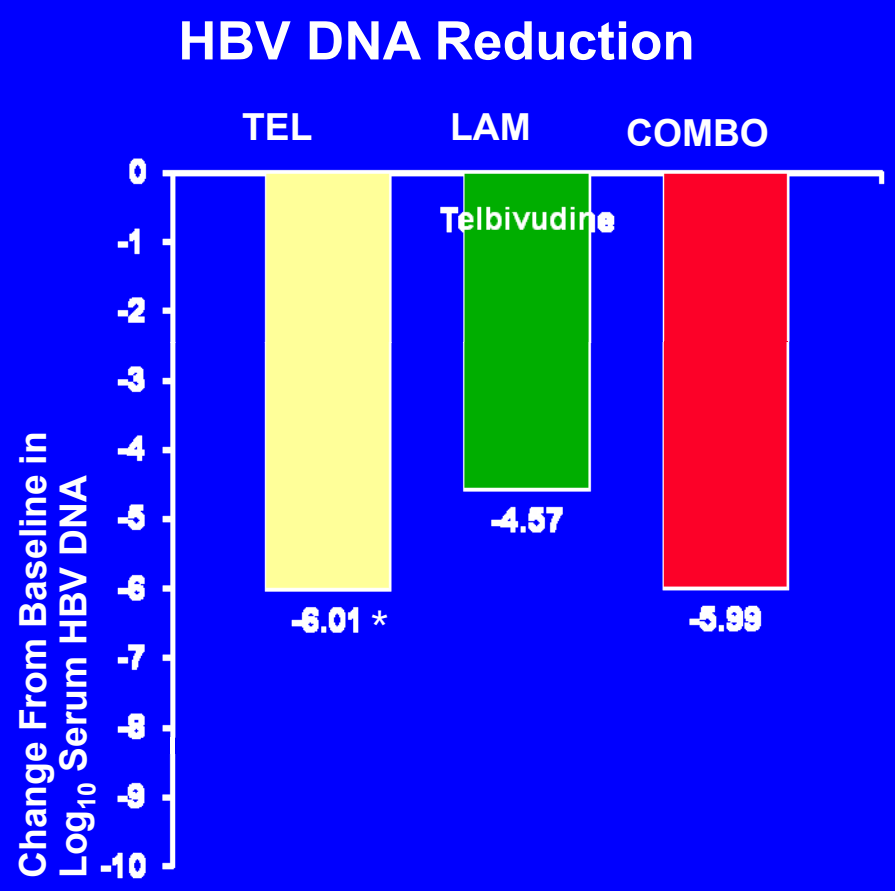
PEG-IFN + lamivudine

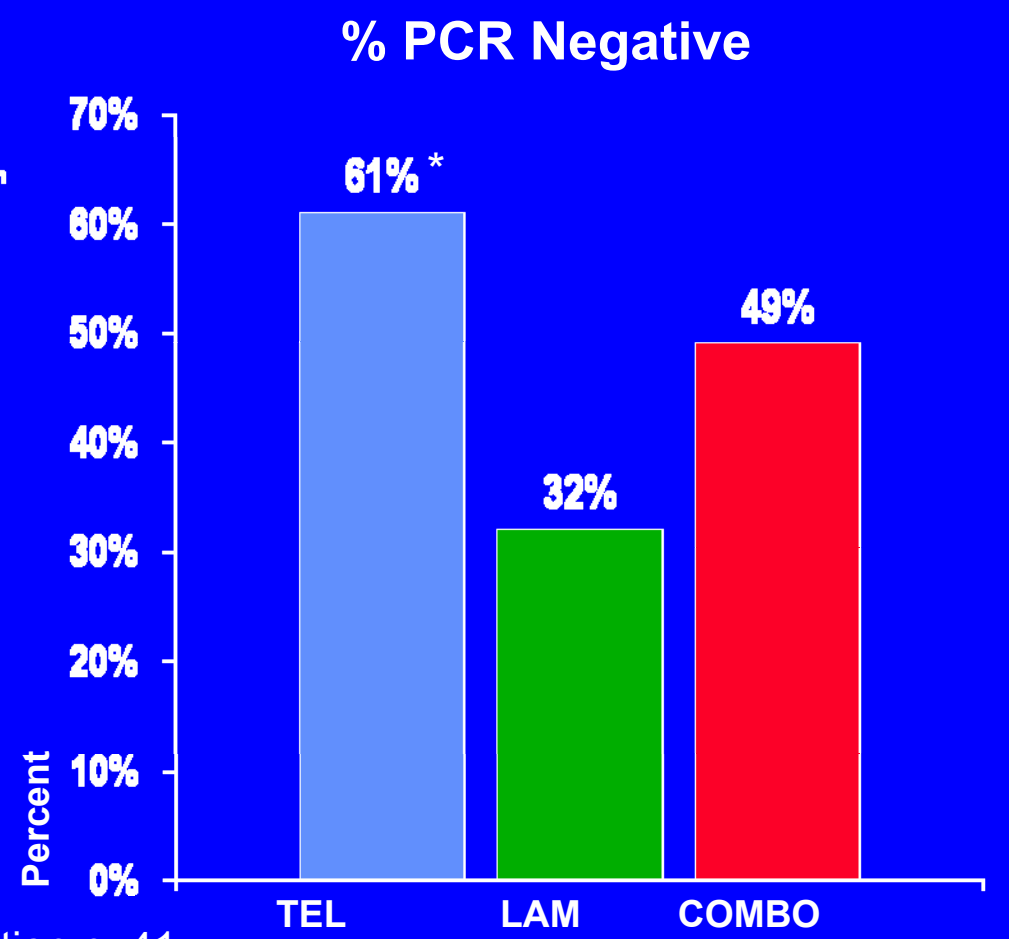
HBeAg seroconversion at EOF = 27%

*all numbers shown are $\log_{10}$ reduction from baseline

Lau G. et al. N Engl J Med 2005;352:2682-95.

De Novo Combination Therapy with Telbivudine + Lamivudine in Patients with HBeAg(+) Chronic HBV





Telbivudine n=44, lamivudine n=19, combination n=41
*$P<0.05$ vs lamivudine monotherapy.

Lai CL. *Gastroenterology*. 2005;126(2):528-536.

ADV Plus LAM vs LAM Monotherapy in Treatment Naïve CHB

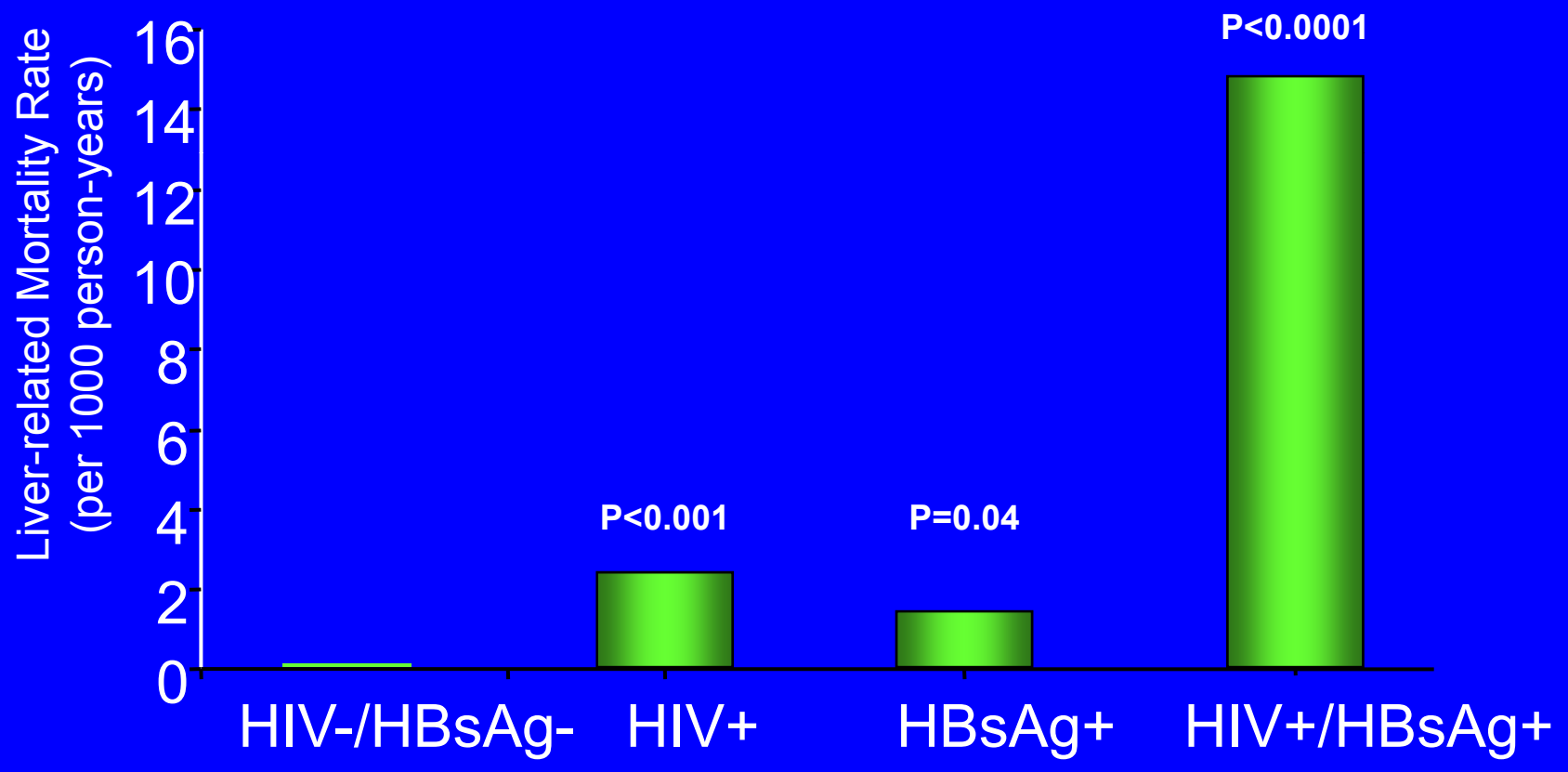
- N=115 treatment naïve
- Randomized to LAM or LAM +ADV

- At wk 104:

	LAM+ADV		LAM
– serum HBV DNA undetectable	14%	vs	26%
– ALT normalization	41%	vs	47%
– HBeAg Serconversion	20%	vs	13%
– LAM-R	15%	vs	43%

Sung et al. J Hepatol 2003:25

HIV/HBV Coinfection: Effect on Liver-related Mortality



Thio CL, et al. *Lancet*. 2002;360:1921-1926.

Treatments for Chronic Hepatitis B in HIV-Infected Persons

FDA-Approved Drugs

- Interferon alfa-2b
- Peginterferon alfa-2a
- Lamivudine**
- Adefovir
- Entecavir**
- Telbivudine

Active vs. HBV but Not FDA Approved

- Tenofovir disoproxil fumarate**
- Emtricitabine (FTC)**
- Truvada™ / Atripla™**
- Peginterferon alfa-2b
- Famciclovir

**Also have proven activity against HIV.

Treatment of HBV in HIV Co-infection Need to Treat Both HIV and HBV

Recommended Combinations

- Lamivudine plus tenofovir
- Emtricitabine plus tenofovir (Truvada®) plus protease inhibitor or non-nucleoside reverse transcriptase inhibitor
- Emtricitabine, tenofovir and efavirenz (Atripla®)

1. DHHS Panel. Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents - October 10, 2006. At: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf
2. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology.* 2007; 45:507-539
3. McMahon et al, N Eng J Med 2007;356:2614-21

Treatment of Chronic Hepatitis B in 2008: Efficacy Data

	HBeAg (+) Patients		HBeAg (-) Patients
Drug	**HBeAg Seroconversion at Yr 1, %**	**HBV DNA Negative at Yr 1,* %**	**HBV DNA Negative at Yr 1,* %**
Interferon alfa	~ 18	37	60-70
Lamivudine	18	40-44	60-70
Adefovir	12	21	51
Entecavir	21	67	90
Peginterferon alfa-2a	27	25	63
Telbivudine	23	60	88
Tenofovir†	21	76	93

*Interferon and lamivudine: hybridization assay; adefovir, entecavir, and peginterferon: PCR assay.
†Licensed for treatment of HIV infection; under review by FDA for treatment of chronic hepatitis B.

Chronic Hepatitis B : Who Should Be Treated and with What ?

Long-Term Benefits

Efficacy

Durability of response

Long-Term Risks

Side effects

Drug resistance

Patient's age
Contraindications
Ease of administration
Duration of Rx
Costs of Rx and monitoring
Patient and provider preference

Courtesy of Anna Lok, MD