The Chronic Liver Disease Foundation
Presents

Managing Hepatitis B in the At-Risk Community

A CME Program Series

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CLDF
Chronic Liver Disease Foundation

The Management of Hepatitis B in the At-Risk Community

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of the Purdue University College of Pharmacy and the Chronic Liver Disease Foundation (CLDF). Purdue is accredited by the ACCME to provide continuing medical education for physicians.

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Chronic Liver Disease Foundation

Educational Objectives

- Understand the natural history and management of hepatitis B virus (HBV)
- Describe algorithms and guidelines for treatment
- Compare and contrast currently available treatment modalities
- Highlight the latest clinical research in HBV

Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C

Available at: http://www.iom.edu/viralhepatitis

Accessed March 20, 2010.

IOM Report and Updated HBV CDC Screening Guidelines (cont.)

…"**API Americans** account for **more than 50%** of Americans who are living with chronic HBV infection…

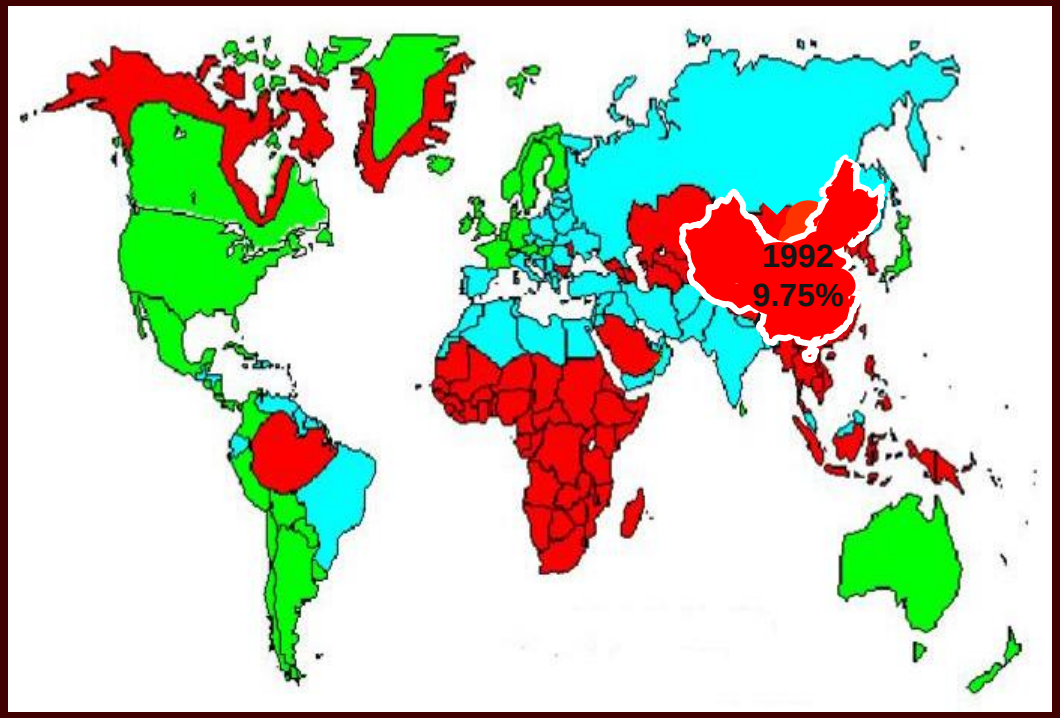
…the **prevalence** of chronic HBV infection in API Americans is as high as **15%** in some studies…

…almost **two-thirds** of chronically infected API Americans are **unaware** of their infection status because they have not been tested for HBV

– 2010 IOM Report

CDC. Travelers' health; yellow book. Atlanta, GA: US Department of Health and Human Services, CDC; 2008. http://wwwn.cdc.gov/ travel/yellowbookch4-HepB.aspx. Accessed March 20, 2010.
IOM. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. http://www.nap.edu/catalog/12793.html. Accessed March 20, 2010.

Geographic Pattern of Hepatitis B Prevalence



HBsAg Prevalence

- >8% High
- 2-8% Intermediate
- <2% Low

1. WHO. Available at: www.who.int/csr/disease/hepatitis/en/
2. Z Sun et. al., J Med Virol 2002, 67:447-

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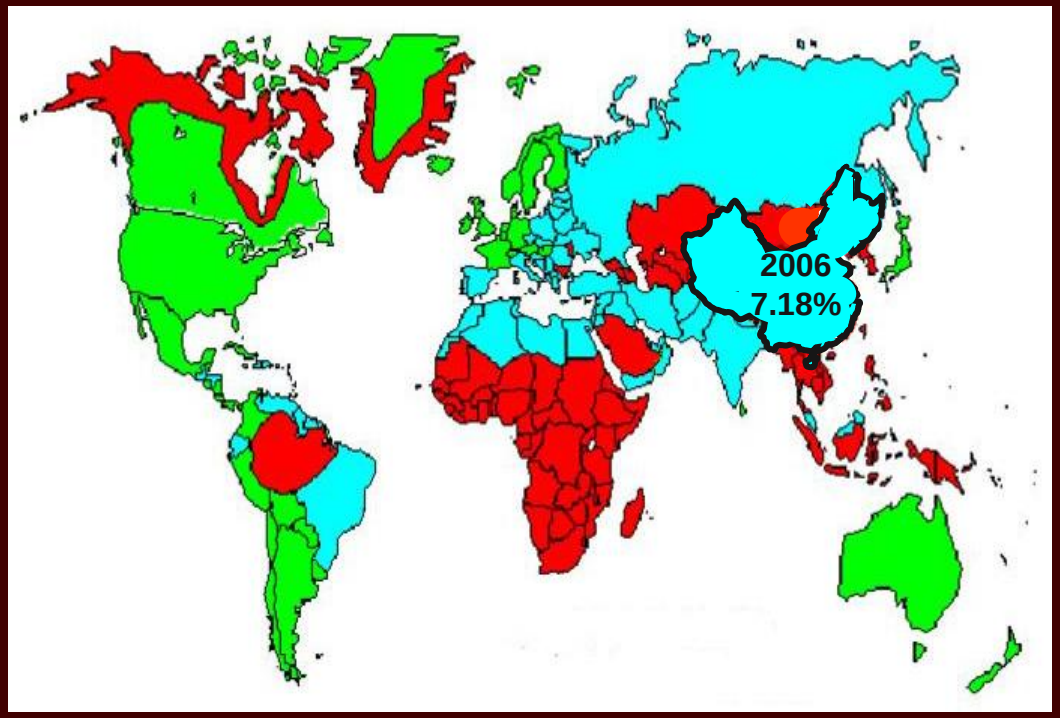

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1. WHO. Available at: www.who.int/csr/disease/hepatitis/en/
2.Z Sun et. al., J Med Virol 2002, 67:447-
3.1992 National Survey for HBV Prevalence, China

Serologic Markers and Clinical Profiles of HBV

Diagnostic Interpretation of HBV Serologic Markers

Serologic Marker				Interpretation
HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	
–	–	–	–	Never infected and no evidence of immunization
+	+	–	–	Chronic infection
+	+	+	–	Acute Infection
–	+	–	+	Recovered from past infection and immune
–	–	–	+	Immune after immunization
–	+	–	–	Past exposure with undetectable anti-HBs titers, previous chronic infection with loss of HBsAg or a false positive test

Adapted from Weinbaum CM et al. *MMWR.* 2008;57(RR08):1-20.

Clinical Profiles of Chronic HBV Infection

	Immune Tolerant	HBeAg (+) CHB	Inactive HBsAg Carrier	HBeAg (-) CHB (Precore Mutant)
HBsAg	+	+	+	+
HBeAg	+	+	–	–
Anti-HBe	–	–	+	+
ALT	Normal	↑	Normal	↑
HBV DNA	>20,000 IU/mL (>10^5 copies/mL)	>20,000 IU/mL (>10^5 copies/mL)	<200 IU/mL (<10^3 copies/mL)	>2,000 IU/mL (>10^{4*} copies/mL)
Histology	Normal/Mild	Active	Normal	Active

HBeAg, hepatitis B e antigen.

*Expert opinions vary as to this value.

Adapted from Hoofnagle JH et al. *Hepatology.* 2007;45:1056-1075.

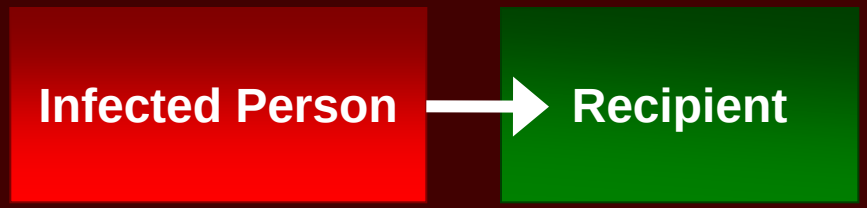
HBV Genotypes

- HBV classified into 10 genotypes (A-H); I and J have been proposed
- Distribution:
  - **A**: North America, northern Europe, India and Africa
  - **B and C**: Asia
  - **D**: Southern Europe, Middle East and India
  - **E**: West Africa and South Africa
  - **F**: Central and South America
  - **G**: United States and Europe
  - **H**: Central America and California
  - **I**: Vietnam
  - **J**: Japan
- B associated with less active disease, slower progression, and lower incidence of hepatocellular carcinoma (HCC) than C
- A and B respond better to interferon than C and D

Adapted from Keeffe EB et al. *Clin Gastroenterol Hepatol*. 2004;2:87-106.

Transmission of HBV

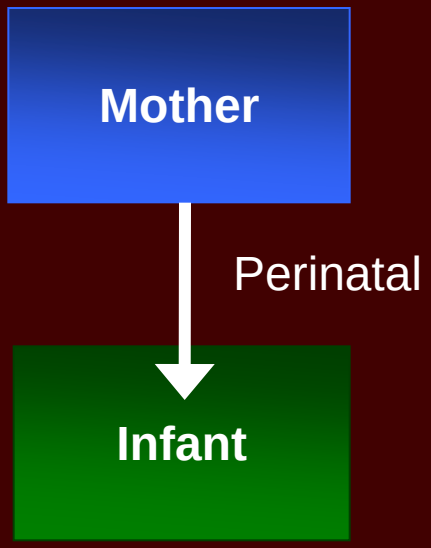
Horizontal Transmission



- Child-to-Child
- Contaminated Needles
- Sexual
- Health Care Worker
- Transfusion
- Hemodialysis

No clear risk factors in 20%-30% of patients

Vertical Transmission

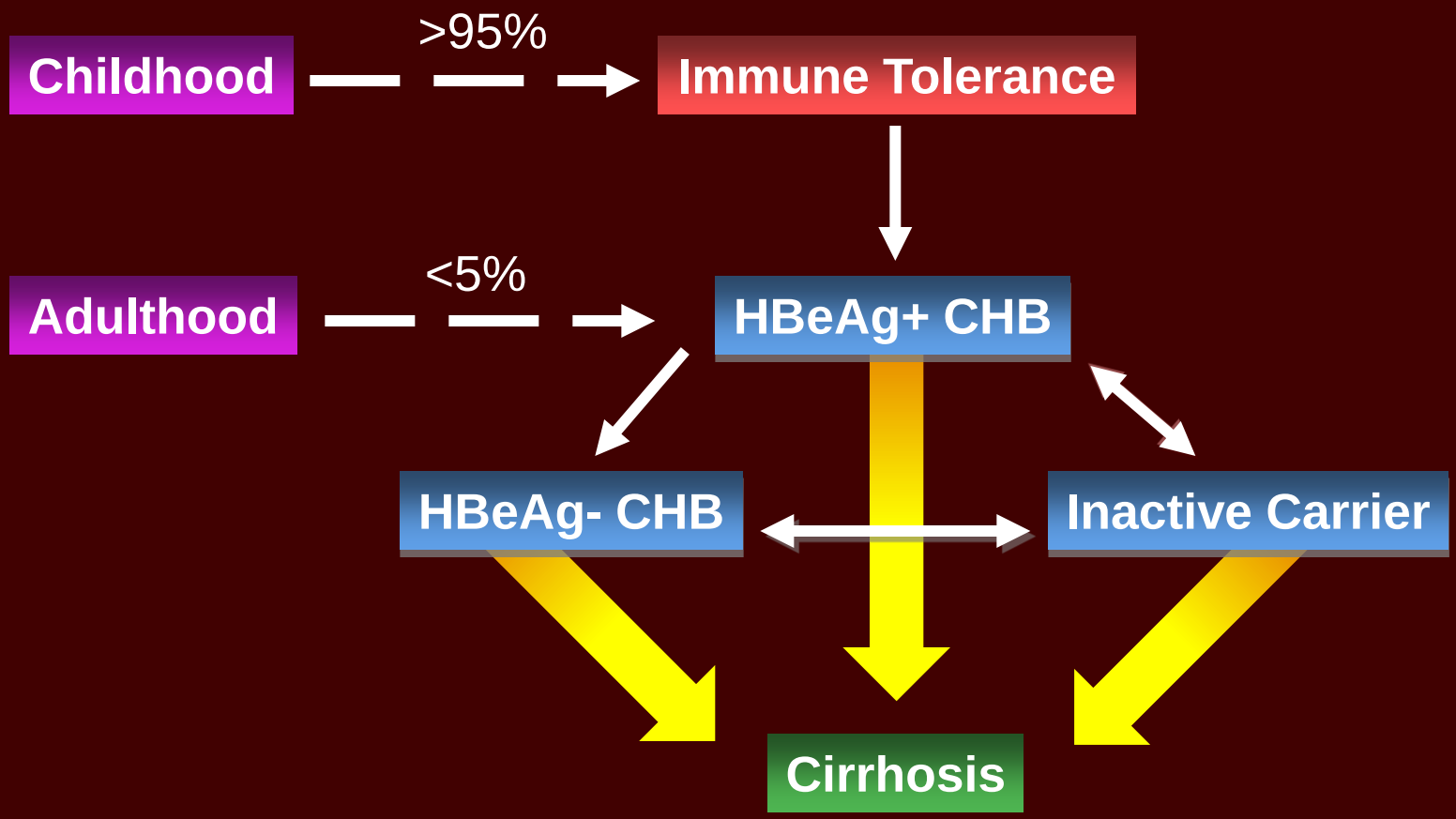


Common in regions with HBsAg prevalence of >2%

CDC Fact Sheet. http://www.cdc.gov/hepatitis/B/PatientEduB.htm. Accessed August 13, 2009.
Lee WM. *N Engl J Med*. 1997;337:1733-1745.
Lavanchy D. *J Viral Hepat*. 2004;11:97-107.

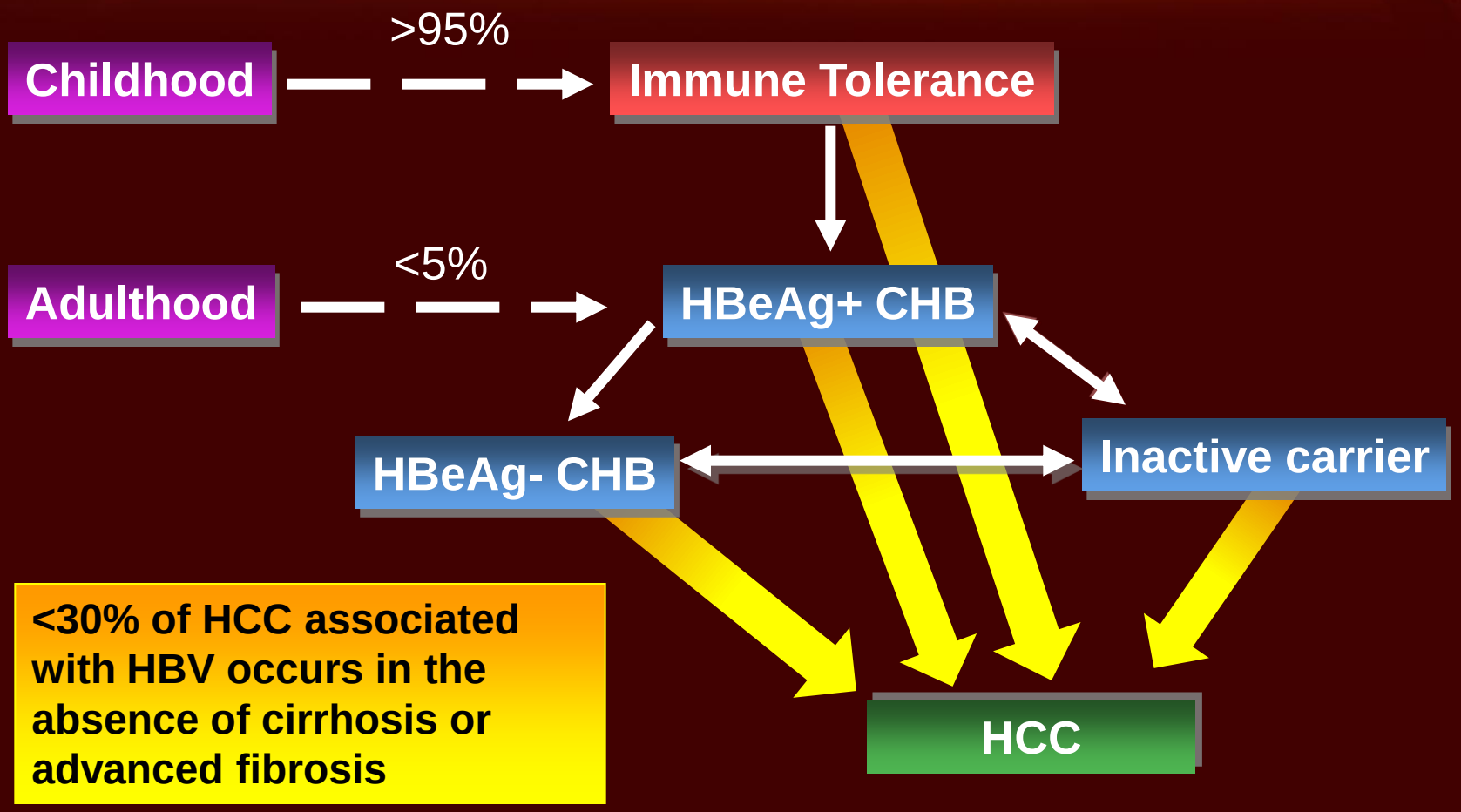
Natural History of HBV

Natural History of HBV Infection



Pungpapong S et al. *Mayo Clin Proc*. 2007;82:967-975.
Chen DS. *J Gastroenterol Hepatol*. 1993;8:470-475.
Seeff LB et al. *N Engl J Med.* 1987;316:965-970.

Natural History of HBV Infection



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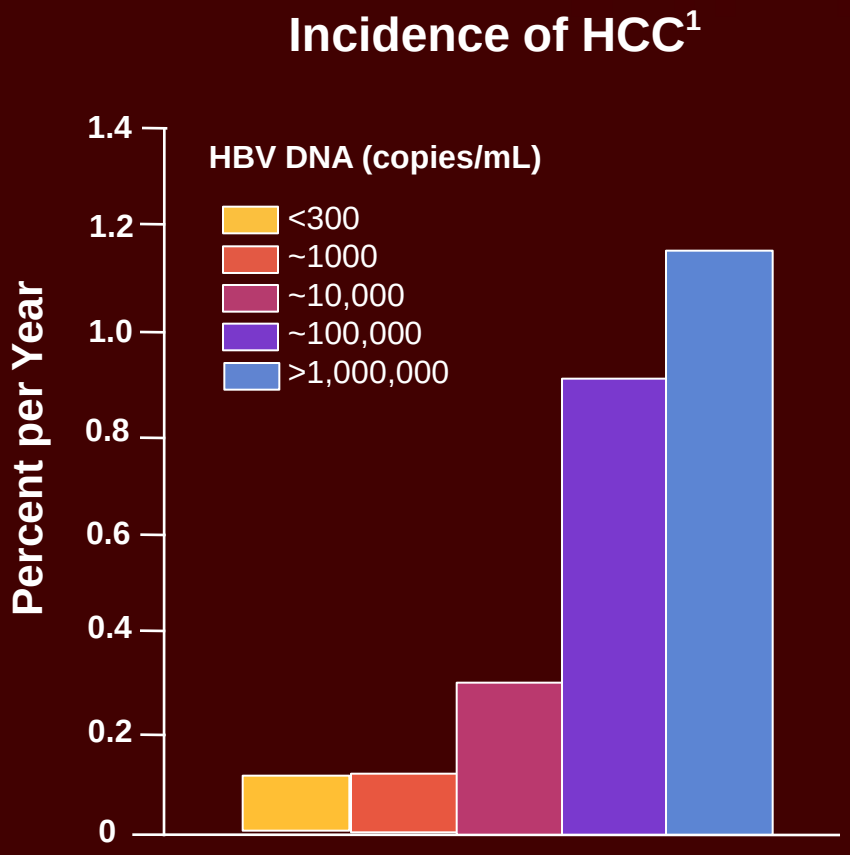
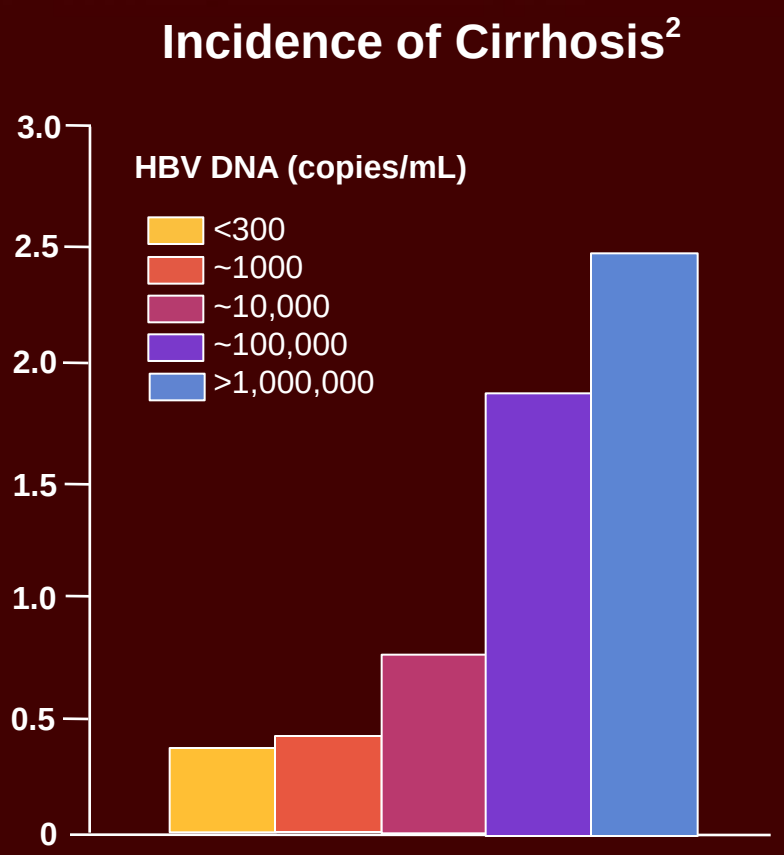
Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

HBV DNA and Natural History





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

2. Iloeje UH et al. *Gastroenterology.* 2006;130:678-686.

Patients With Normal ALT May Have Significant Liver Disease

- 37% of patients with chronic HBV and persistently normal alanine aminotransferase (ALT) had significant fibrosis (stage 2) or inflammation (grade 2)[1]
- In a large cohort (140,000 Koreans) an ALT >20 was associated with increased risk of death from chronic liver disease (CLD) over 8 years follow-up[2]
- Patients with ALT 0.5-1.0 upper limit of normal (ULN) had increased risk of adverse outcomes from CLD[3]

1. Lai M et al. *J Hepatol.* 2007;47:760-767.
2. Kim HC et al. *BMJ.* 2004;328:983-987.
3. Yuen M-F et al. *Gut.* 2005;54:1610-1614.

Normal Serum AST and ALT and Risk of Mortality From Liver Diseases

Design

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

Outcomes

- 690 deaths from liver disease (LD)
- ALT >20 increased risk of death from LD

	RR of Death from LD	
AST	**Male**	**Female**
<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

AST, aspartate aminotransferase.

Kim HC et al. *BMJ.* 2004;328:983-986.

The Treatment of Chronic Hepatitis B

Chronic Hepatitis B
Goals of Treatment

- **Long-term outcomes:**
  - Sustained suppression of HBV replication
  - Prevention of end stage liver disease, HCC, transplant, and death
  - Similar goals for both HBeAg+ and HBeAg-
- **Therapeutic goals:**
  - Undetectable serum HBV DNA
    - Cannot eradicate HBV ccc DNA
  - Normalization of serum ALT level
  - Clearance of HBeAg
  - Loss of HBsAg
  - Improvement in liver histology

NIH Consensus Conference on HBV Guidelines for Therapy

- **Therapy is indicated**
  - Cirrhosis, both compensated and decompensated
- **Therapy may be indicated**
  - Immune active phase (HBeAg+), particularly by the late ‘30s or early ‘40s and active inflammation is present
  - Reactivation phase (HBeAg-) with elevated HBV DNA and elevated ALT
- ***Immediate* therapy not routinely indicated**
  - Inactive carriers and low replicative phase (low DNA, normal ALT, minimal inflammation/fibrosis)

Sorrell MF et al. *Ann Intern Med.* 2009;150:104-110.

Parameters Used to Determine Candidates for Treatment of HBV

- **ALT**
  - "New" normal ALT: <30 for men and <19 for women[1]
  - Presence of one normal value does not exclude significant disease or subsequent complications
- **HBV DNA**
  - Predicts development of cirrhosis and HCC[2,3]
  - Interpret in conjunction with ALT and/or histology
- **Liver biopsy**
  - Useful in situations where ALT or HBV DNA do not provide clear guidelines for treatment[1]

1. Keeffe EB et al. *J Clin Gastroenterol Hepatol.* 2008;6:1315-1341.
2. Iloeje UH et al. *Gastoenterology.* 2006;130:678-686.
3. Chen CJ et al. *JAMA.* 2006;295:65-73.

Treatment Criteria for Chronic Hepatitis B

Guideline	HBeAg+		HBeAg-	
	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL	ALT U/L
EASL 2009[1]	>2,000	>ULN	>2,000	> ULN
US Algorithm 2008[2]	≥20,000	>ULN or (+) biopsy	≥2,000	>ULN or (+) biopsy
APASL 2008[3]	≥20,000	>2x ULN	≥2,000	>2x ULN
AASLD 2009[4]	>20,000	>2x ULN or (+) biopsy	>20,000 or >2,000	≥2x ULN or (+) biopsy

1. European Association for the Study of the Liver. *J Hepatol.* 2009;50:227-242.
2. Keeffe EB et al. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.
3. Liaw Y-F et al. *Hepatol Int.* 2008;2:263-283.
4. Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

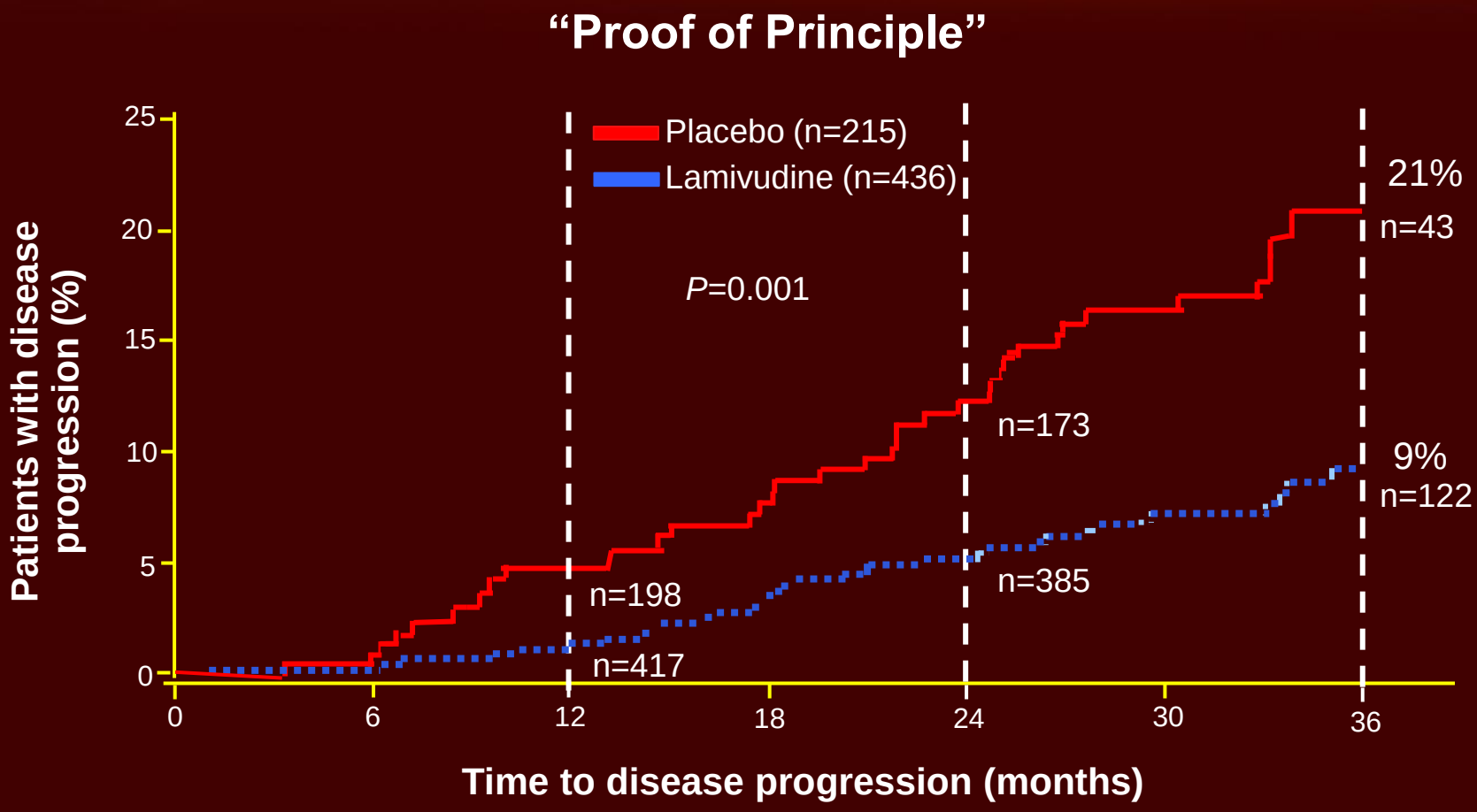
FDA-Approved Therapies for Chronic HBV

First-Line Therapy			
Peginterferon alfa-2a	PEGASYS®	Roche Laboratories	2005
Tenofovir	VIREAD®	Gilead Sciences	2008
Entecavir	BARACLUDE™	Bristol-Myers Squibb	2005
Second-Line Therapy			
Adefovir dipivoxil	HEPSERA™	Gilead Sciences	2002
Telbivudine	TYZEKA™	Idenix and Novartis	2006
Third-Line Therapy			
Lamivudine	EPIVIR-HBV®	GlaxoSmithKline	1998

Interferon alfa-2b, recombinant (INTRON® A, Schering Corporation, 1992) is the only agent approved for pediatric use and is largely reserved for that use.

Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed February 18, 2010.

Antiviral Therapy Delays Overall Disease Progression in Chronic Hepatitis B



Liaw Y-F et al. *N Engl J Med.* 2004;351:1521-1531.

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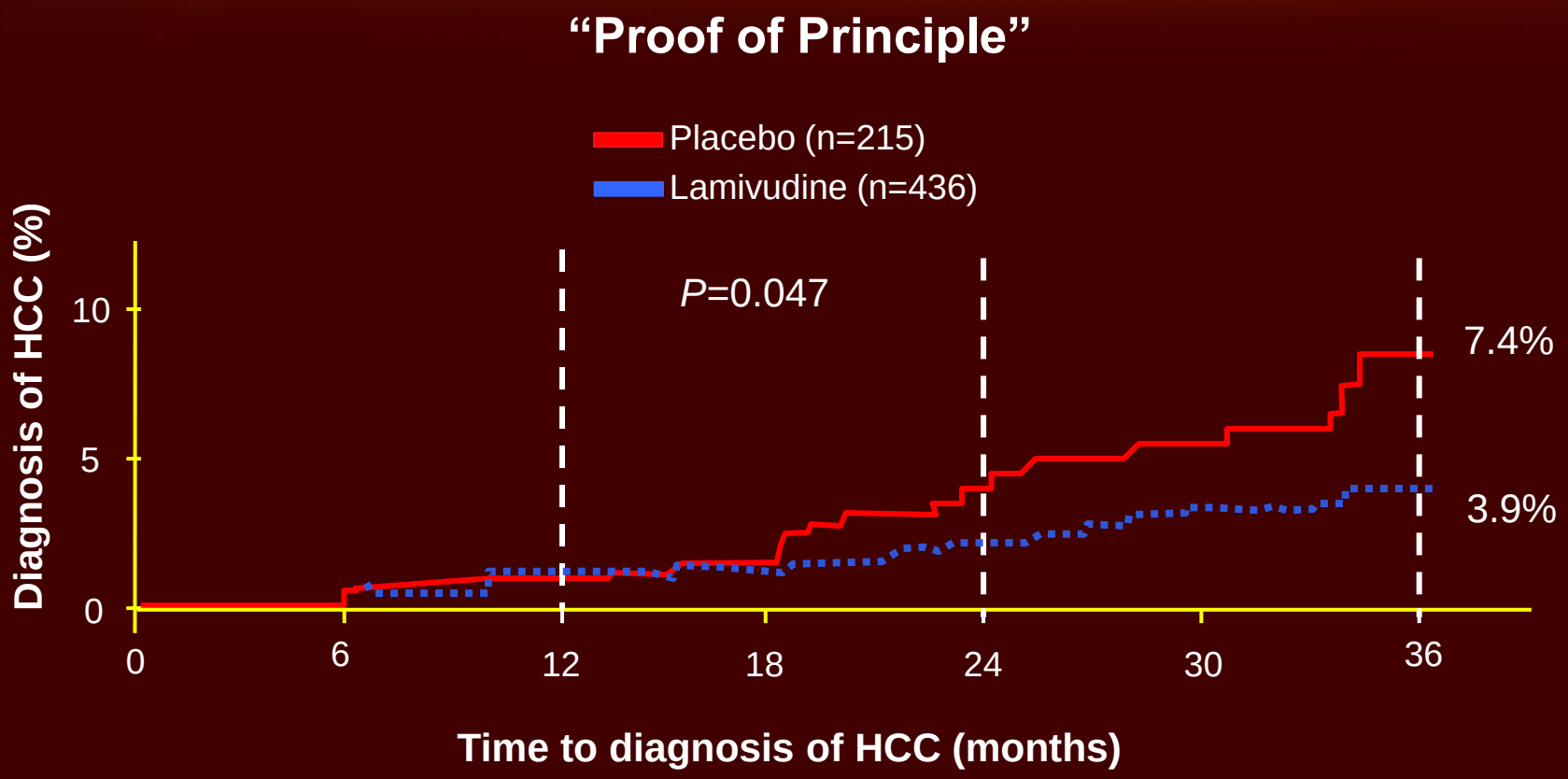


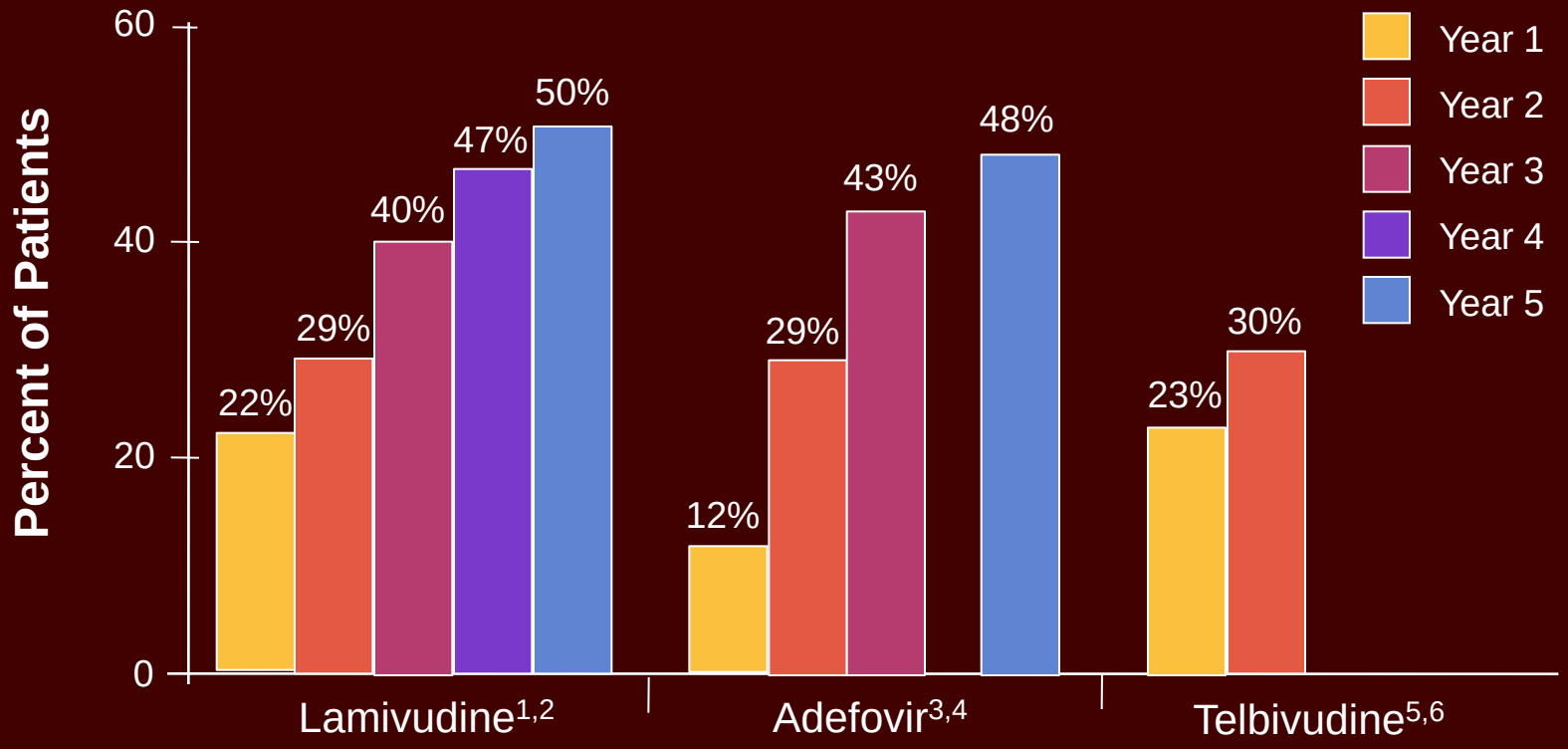
Liaw YF et al. *N Engl J Med.* 2004;351:1521-1531.

HBeAg-Positive CHB First-Line Treatment Efficacy: Loss of HBV DNA

- Patients have a 90% chance of achieving HBV DNA negativity after 2 to 3 years of therapy with first-line therapies

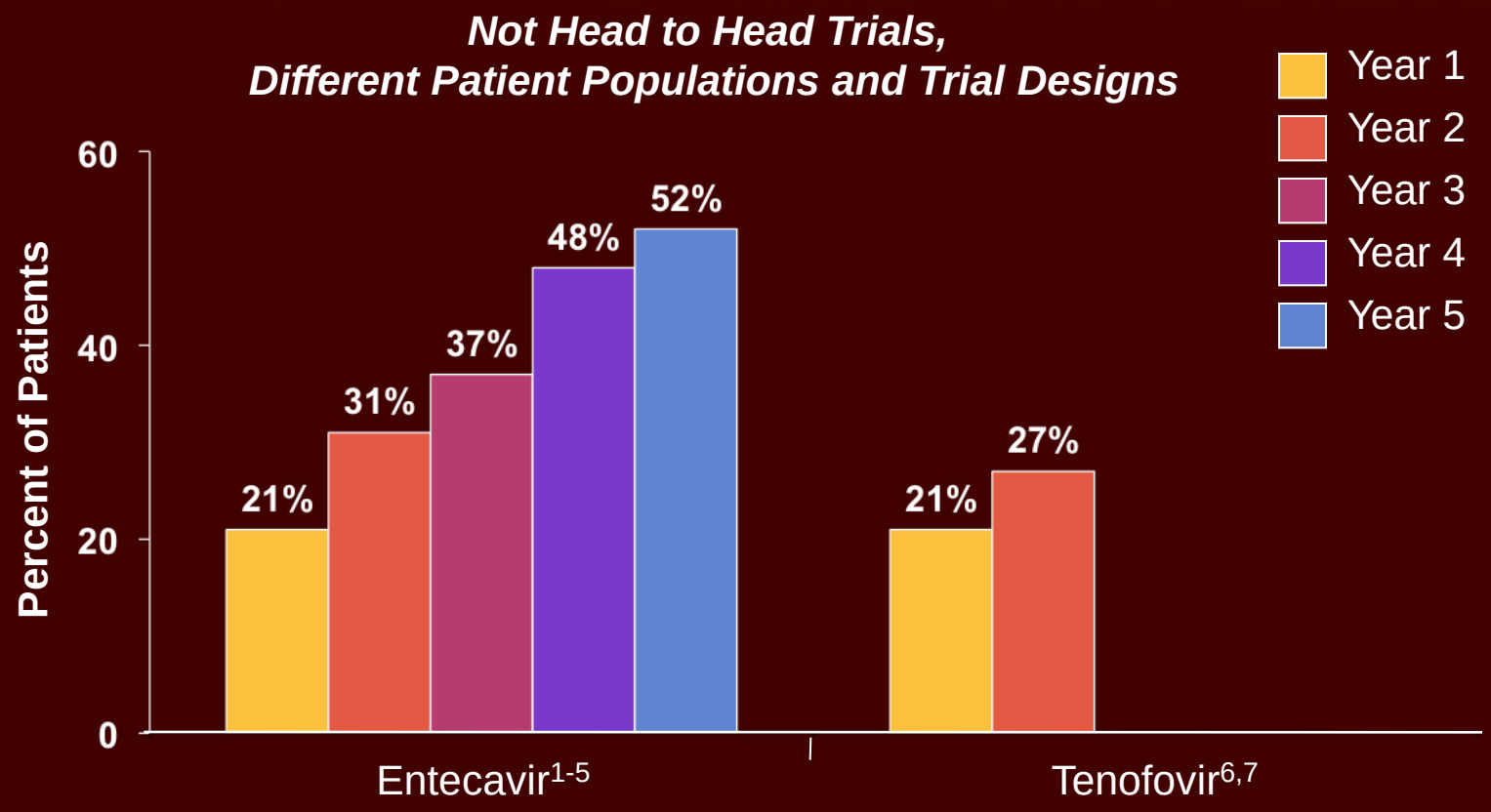
HBeAg Seroconversion During Continued Treatment

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



1. Chang T-T et al. *J Gastroenterol Hepatol.* 2004;19:1276-1282.
2. Lok ASF, McMahon BJ. *Hepatology.* 2007;45:507-539.
3. Marceellin P et al. *Hepatology.* 2004;40(suppl 1):655A.
4. Marcellin P et al. *Hepatology.* 2006;44(suppl 1):548A.
5. Lai C-L et al. *N Engl J Med.* 2007;357:2576-2588.
6. Liaw Y-F et al. *Gastroenterology.* 2009;136:486-495.

HBeAg Seroconversion During Continued Treatment



1. Chang TT et al. *N Engl J Med.* 2006;354:1001-1010.
2. Gish RG et al. *Hepatology.* 2005;42(suppl 1):267A.
3. Chao Y-C et al. *Hepatology.* 2006;44(suppl 1):229A.
4. Han S et al. *Hepatology*. 2007;46(suppl 1):654A.
5. Han S-H et al. *Hepatology.* 2008;48(suppl 1):705A-706A.
6. Marcellin P et al. *N Engl J Med.* 2008;359:2442-2455.
7. Heathcote EJ et al. *Hepatology.* 2008;48(suppl 1):366A.

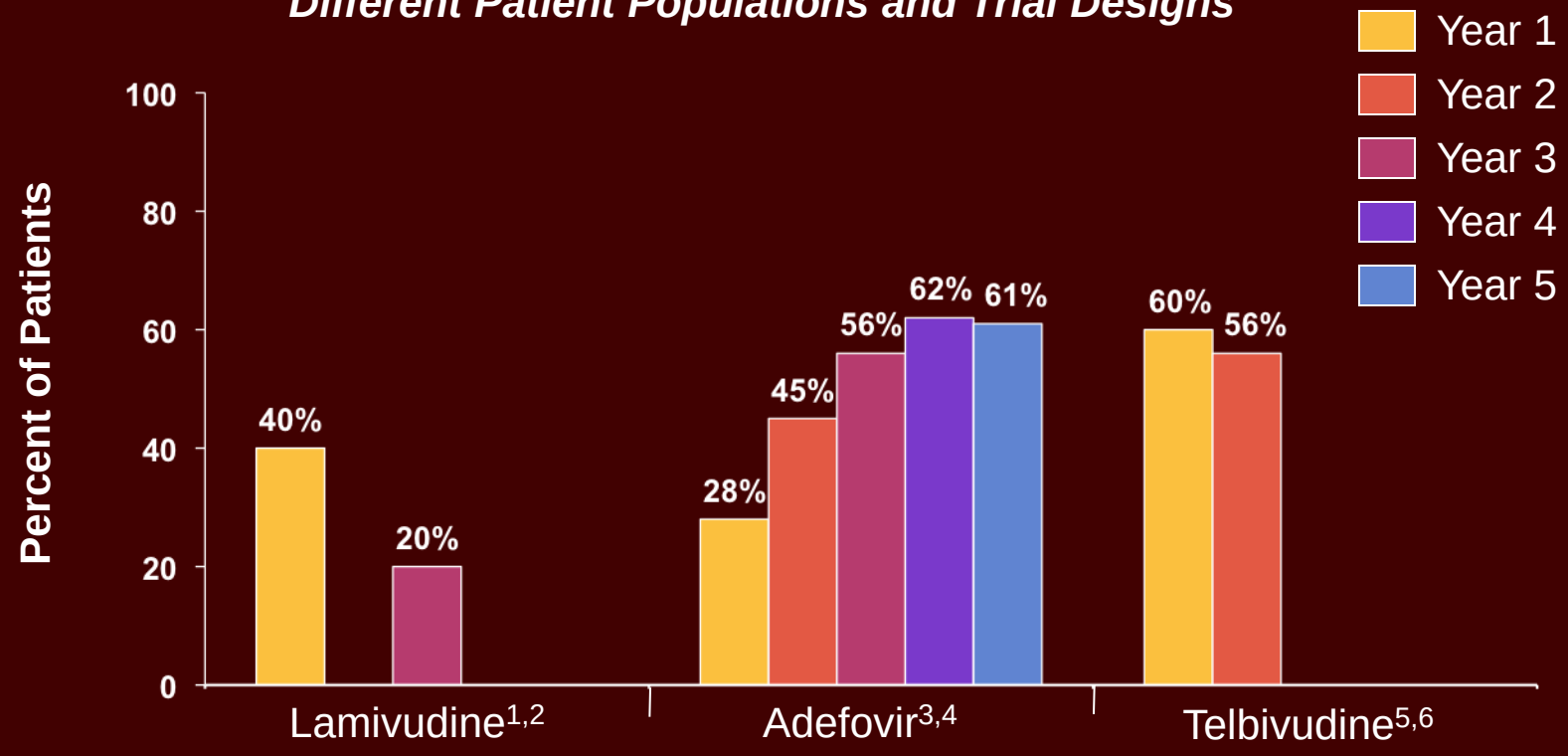
Treatment Associated HBeAg Seroconversion

- **Durability:**
  - 65% to 90% for oral therapy
  - Higher with interferons at one year

- **Factors that affect seroconversion**
  - Duration of therapy
  - Use of “consolidation” therapy

HBV DNA Undetectable During Continued Treatment

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



1. Lai C-L et al. *N Engl J Med.* 2007;357:2576-2588.
2. Leung NWY et al. *Hepatology.* 2001;33:1527-1532.
3. Marceellin P et al. *Hepatology.* 2004;40(suppl 1):655A.
4. Marcellin P et al. *Hepatology.* 2008;48:750-758.
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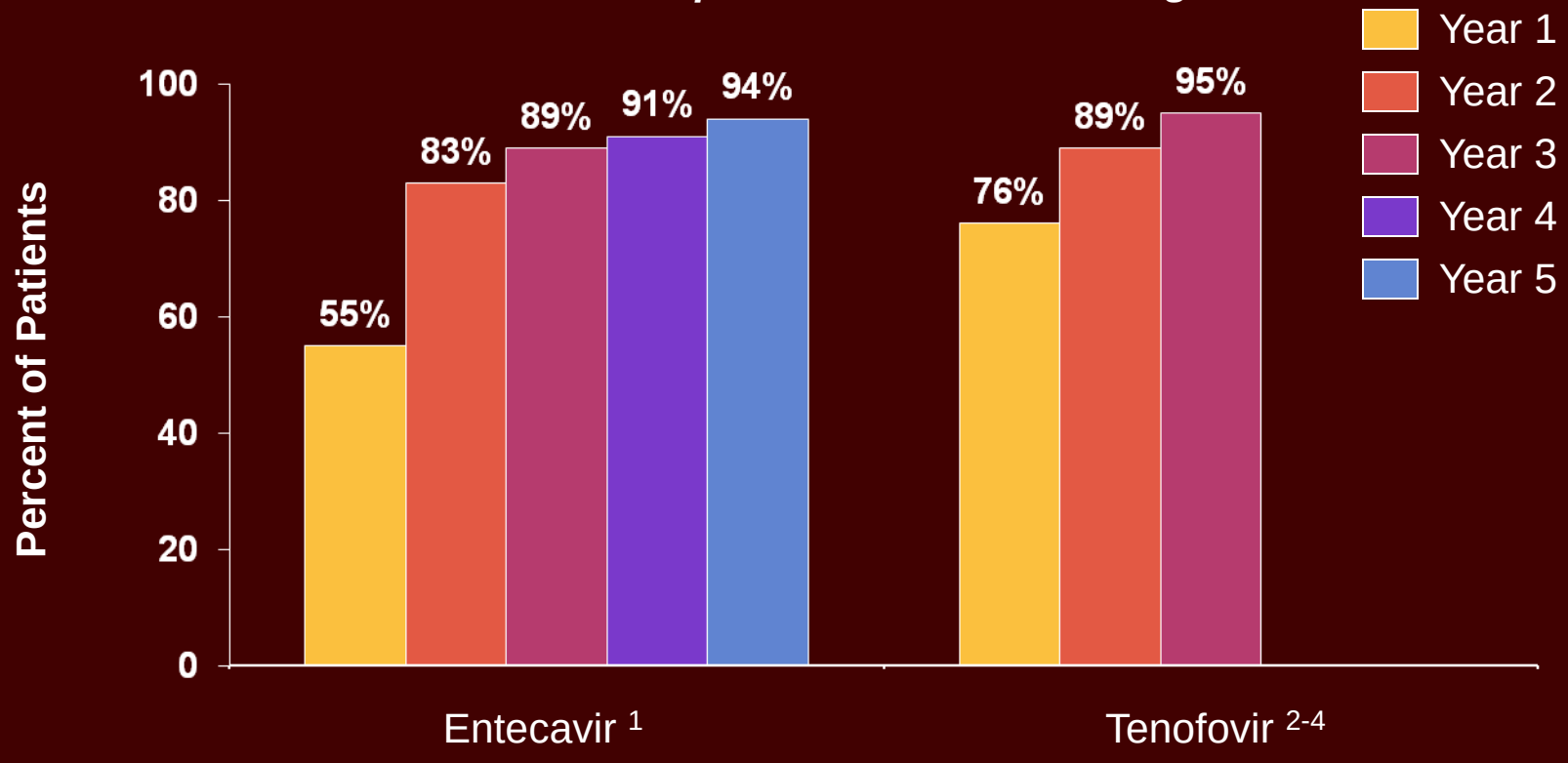

1. Chang TT et al. *Hepatology.* 2010;51:422-430.
2. Marcellin P et al. *N Engl J Med.* 2008;359:2442-2455.
3. Heathcote EJ et al. *Hepatology.* 2008;48(suppl 1):366A.
4. Heathcote E et al. *Hepatology.* 2009;50(suppl 4):533A-534A.

Entecavir Treatment for Up to 5 Years for HBeAg(+) Chronic Hepatitis B

Endpoint	Wk 48[*†1] (N=354)	Wk 96[2,3] (N=354)	Wk 144[4] (N=122)	Wk 192[*5] (N=146)	Wk 240[*6] (N=98)
HBV DNA <300 copies/mL	236/354 67%	80%	87%	98/108 91%	88/94 94%
ALT ≤1 x ULN	242/354 68%	-	85%	96/112 86%	78/98 80%
HBeAg loss	78/354 22%	-	31%[‡]	39/96[‡] 41%	39/95[‡] 41%
HBeAg seroconversion	74/354 21%	110/354 31%[§]	16%[‡]	15/96[‡] 16%	16/95[‡] 17%
HBsAg loss	6/354 2%	18/354 5%[§]	-	-	-

*Denominator represents patients with available samples.
[†]94/354 (27%) of patients were genotype A.
[‡]Numbers/proportions represent additional patients achieving HBeAg loss or HBeAg seroconversion.
[§]Cumulative value.

1. Chang TT et al. *N Engl J Med.* 2006;354:1001-1010.
2. Gish RG et al. *Hepatology.* 2005;42(suppl 1):267A.
3. Chang T-T et al. *Hepatology.* 2010;51:422-430.
4. Chao Y-C et al. *Hepatology.* 2006;44(suppl 1):229A.
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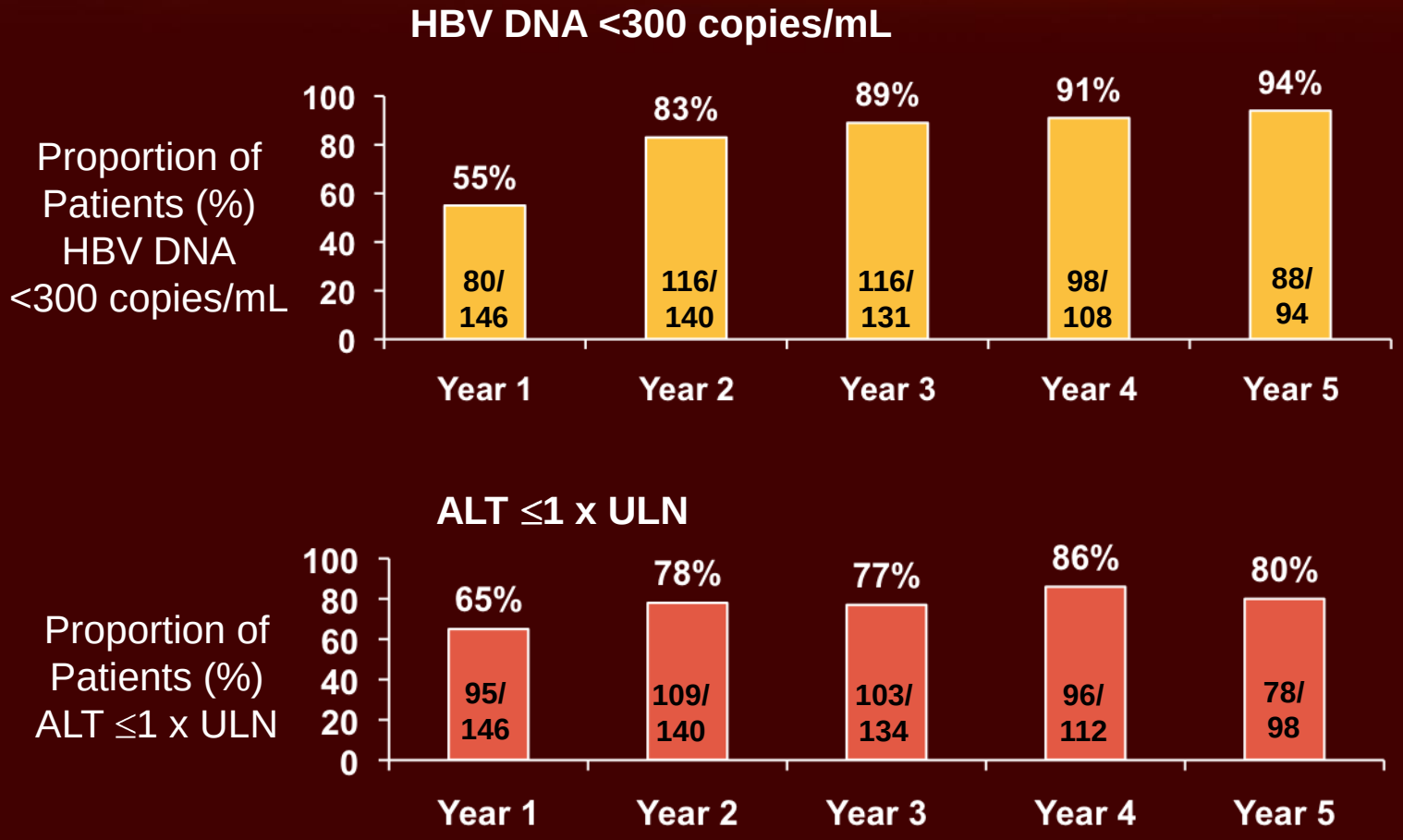
Entecavir Treatment for up to 5 Years for HBeAg (+) Chronic Hepatitis B



38/146 (26%) of patients were genotype A

Chang T-T et al. *Hepatology.* 2010;51:422-430.

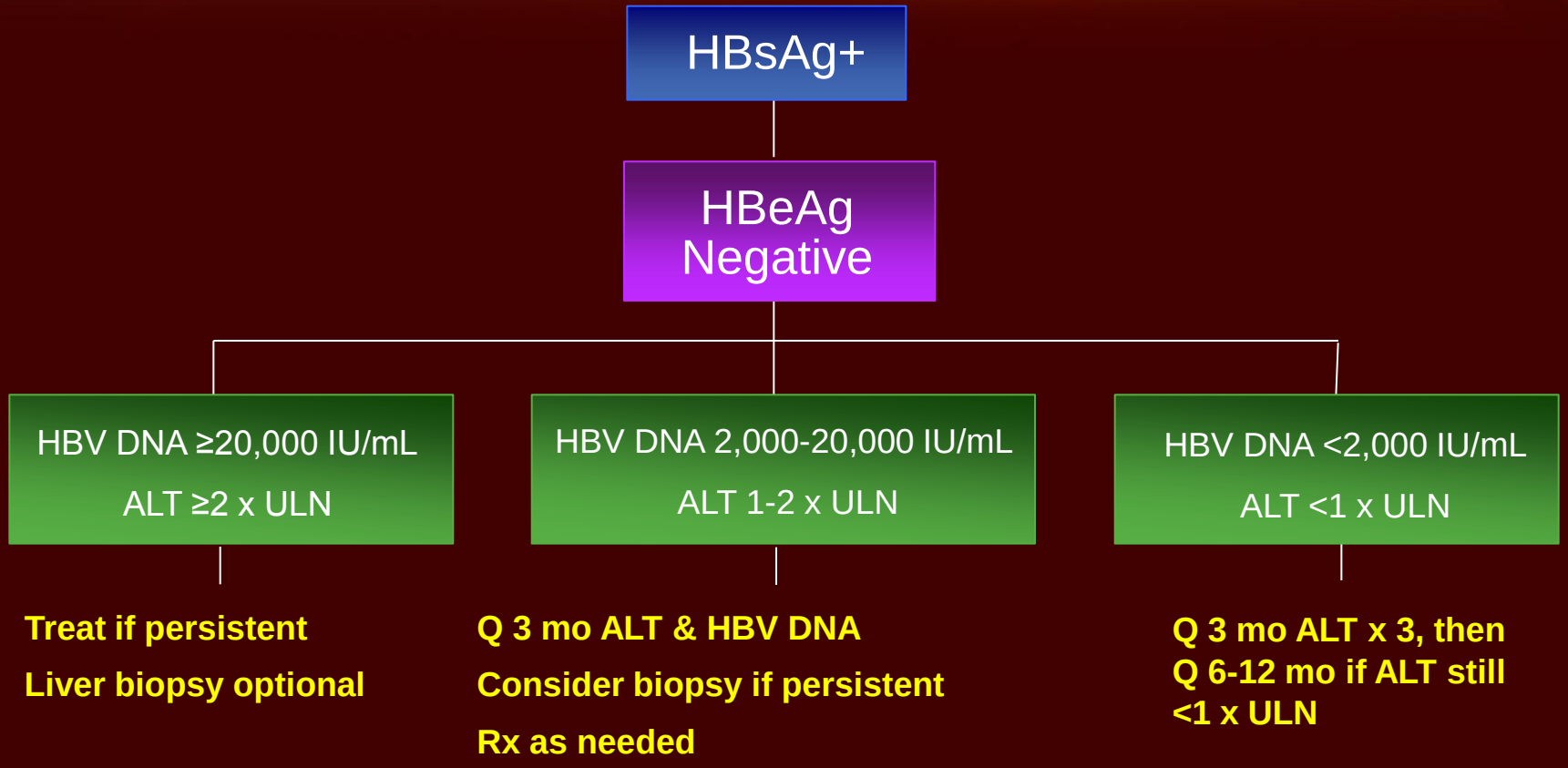
Tenofovir Treatment for up to 3 Years for HBeAg(+) Chronic Hepatitis B

Endpoint	Wk 48*[1] (N=176)	Wk 96[2]	Wk 144[3] (N=214)†
HBV DNA <400 copies/mL	134/176 76%	77%	~78%
ALT ≤1 x ULN	115/169 68%	-	-
HBeAg loss	-	30%	~35%
HBeAg seroconversion	32/153 21%	26%	~26%
HBsAg loss	5/158 3.2%	6%	~8%

*41/173 (24%) of patients were genotype A.
†Values include patients treated with adefovir for the first 48 weeks before being switched to tenofovir.

1. Marcellin P et al. *N Engl J Med.* 2008;359:2442-2455.
2. Heathcote EJ et al. *Hepatology.* 2008;48(suppl 1):366A.
3. Heathcote EJ et al. *Hepatology*. 2009;50(suppl 4):533A.

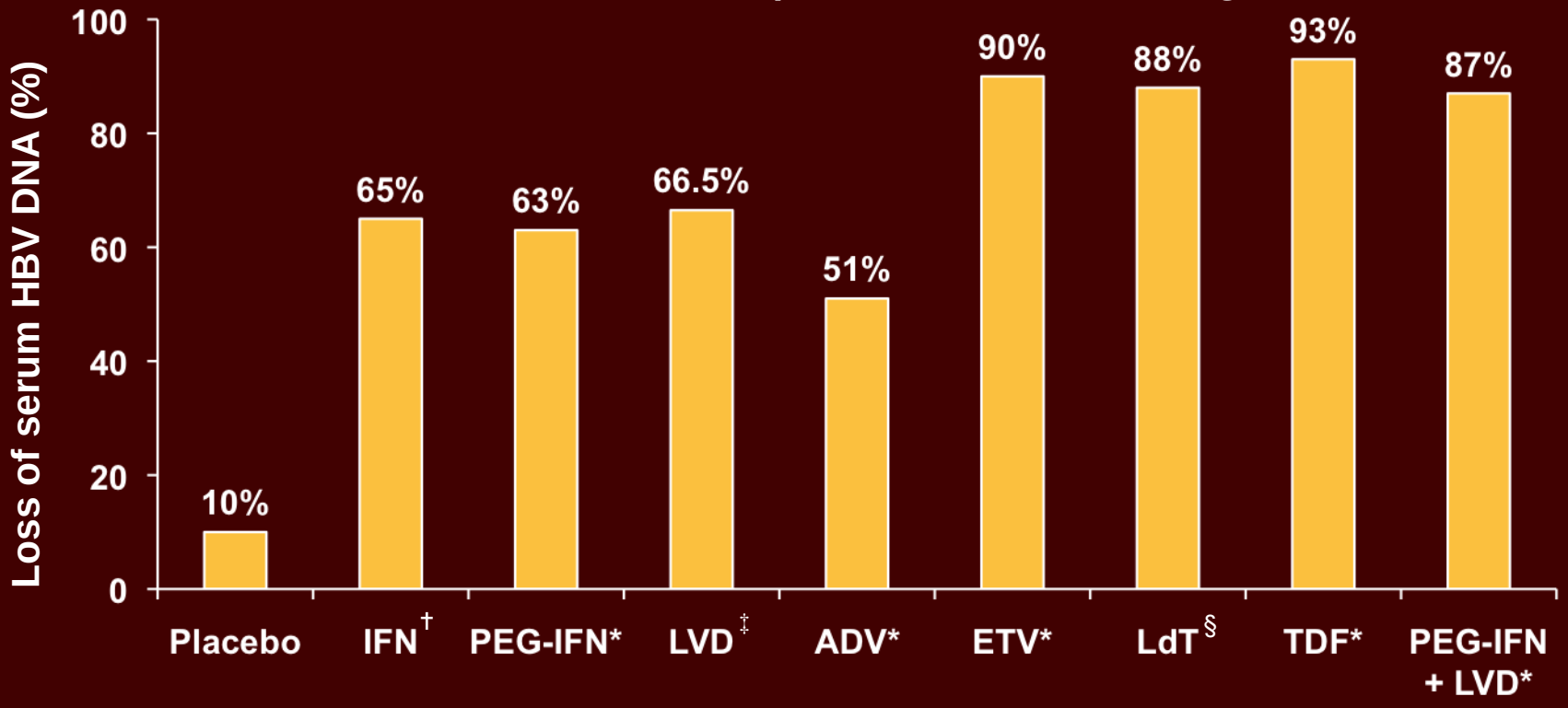
AASLD CHB Treatment Guidelines HBeAg(-): Identifying Appropriate Treatment Candidates



Adapted from Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

HBeAg-Negative CHB Treatment Options: HBV DNA Loss at 1 Year

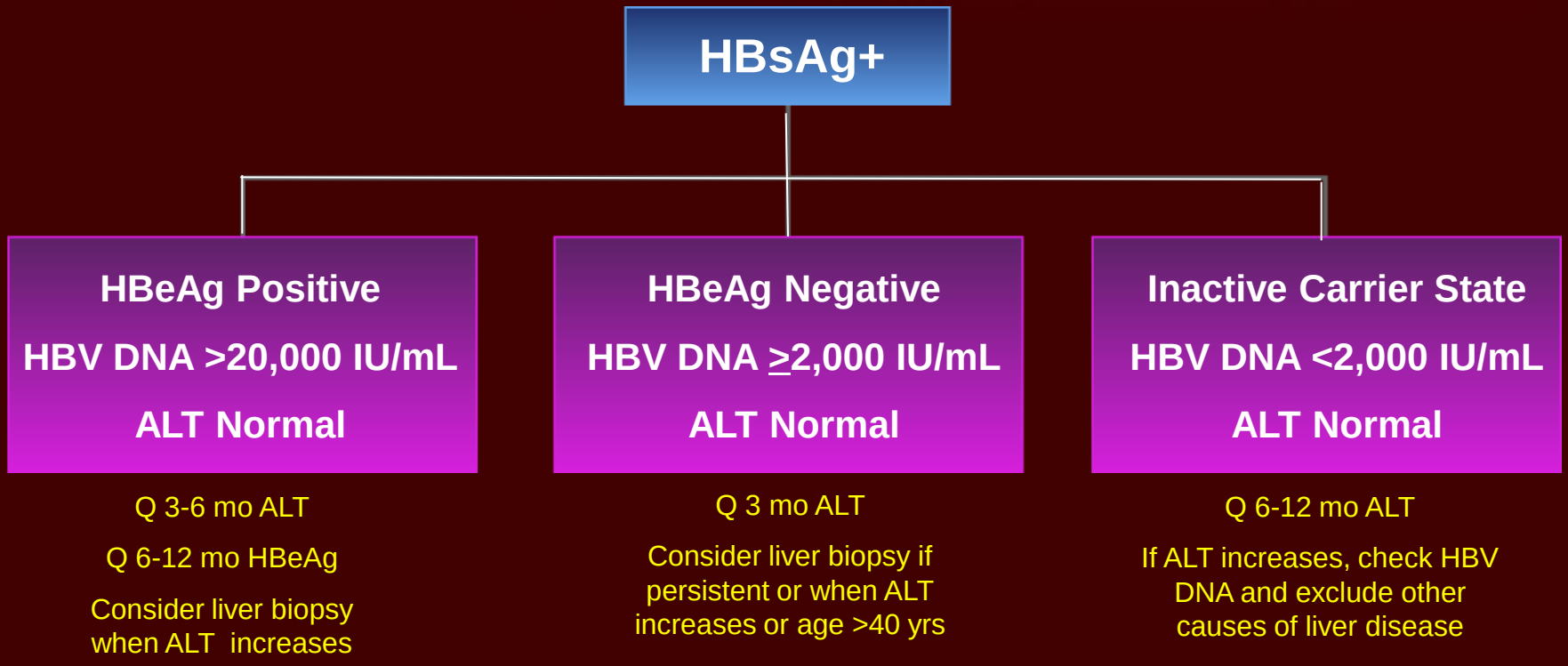
Not Head to Head Trials, Different Patient Populations and Trial Designs



Treatment Duration: †, 6-12 mo; *, 48 wks; ‡, 48-52 wks; § , 52 wks.
IFN = Interferon; PEG-IFN = Pegylated Interferon; LVD = Lamivudine; ADV = Adefovir; ETV = Entecavir; LdT = Telbivudine; TDF = Tenofovir

Adapted from Lok ASF, Mahon BJ. *Hepatology*. 2009;50:1-36.

Guidelines for Follow-up of Patients Initially *Not Considered* for Treatment

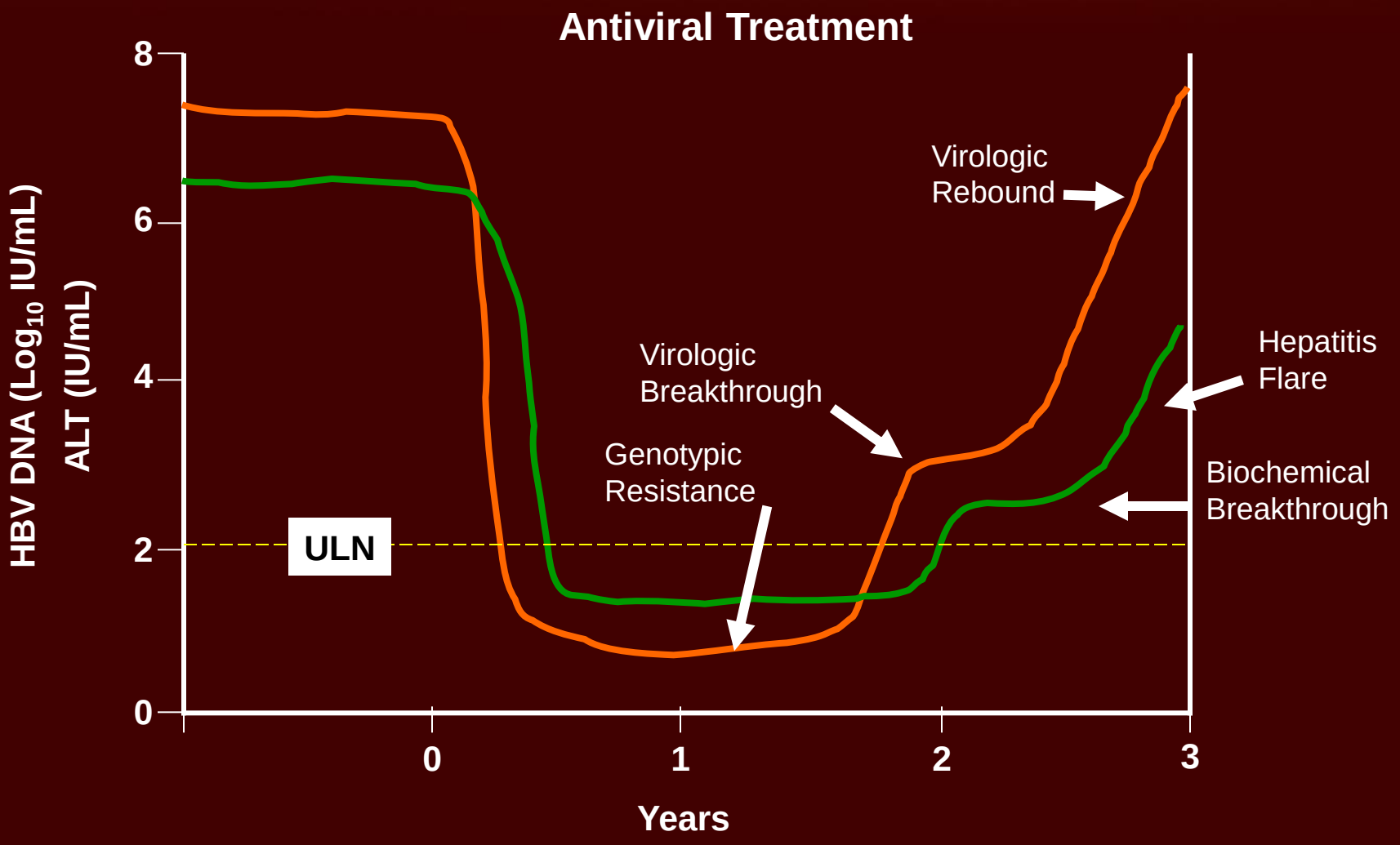


Apply guidelines for surveillance of HCC for all groups as indicated

Adapted from Keeffe EB et al. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.

The Problem of Nucleos(t)ide Resistance in Chronic Hepatitis B

Manifestations of Antiviral Resistance



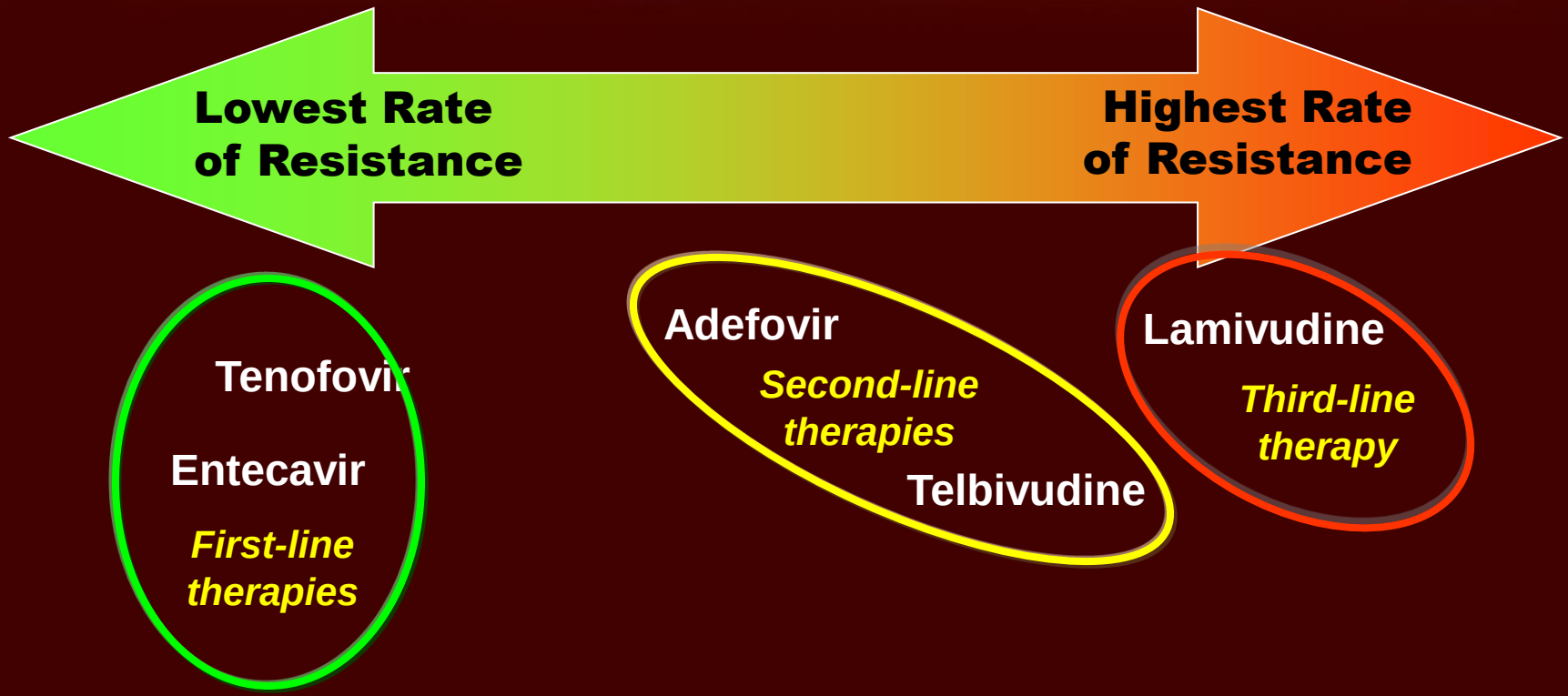
Adapted from Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

Terms Relating to Antiviral Resistance With Nucleoside Analogue Treatment

- **Genotypic resistance:**
  - Detection of mutations that have been shown in *in vitro* studies to confer resistance to the nucleoside analogue that is being administered
  - Sequencing or Line Probe (InnoLipa assay)
- **Phenotypic resistance:**
  In vitro confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the nucleoside analogue administered

Adapted from Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

US Treatment Algorithm—Resistance Profile: First-Line Treatment Options Have the Lowest Resistance Rates



Resistance does not appear to emerge during treatment with IFN α-2b or PEG-IFN α-2a

Adapted from Keeffe EB et al. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.

Factors Affecting the Development of Resistance

- Pretreatment HBV DNA levels
- Potency of the antiviral agent
- Rapidity of viral suppression
- Prior exposure to oral nucleoside or nucleotide antiviral therapy
- Duration of treatment
- Degree of genetic barriers to resistance to the individual drug
- Pharmacologic barrier: Blood and tissue levels

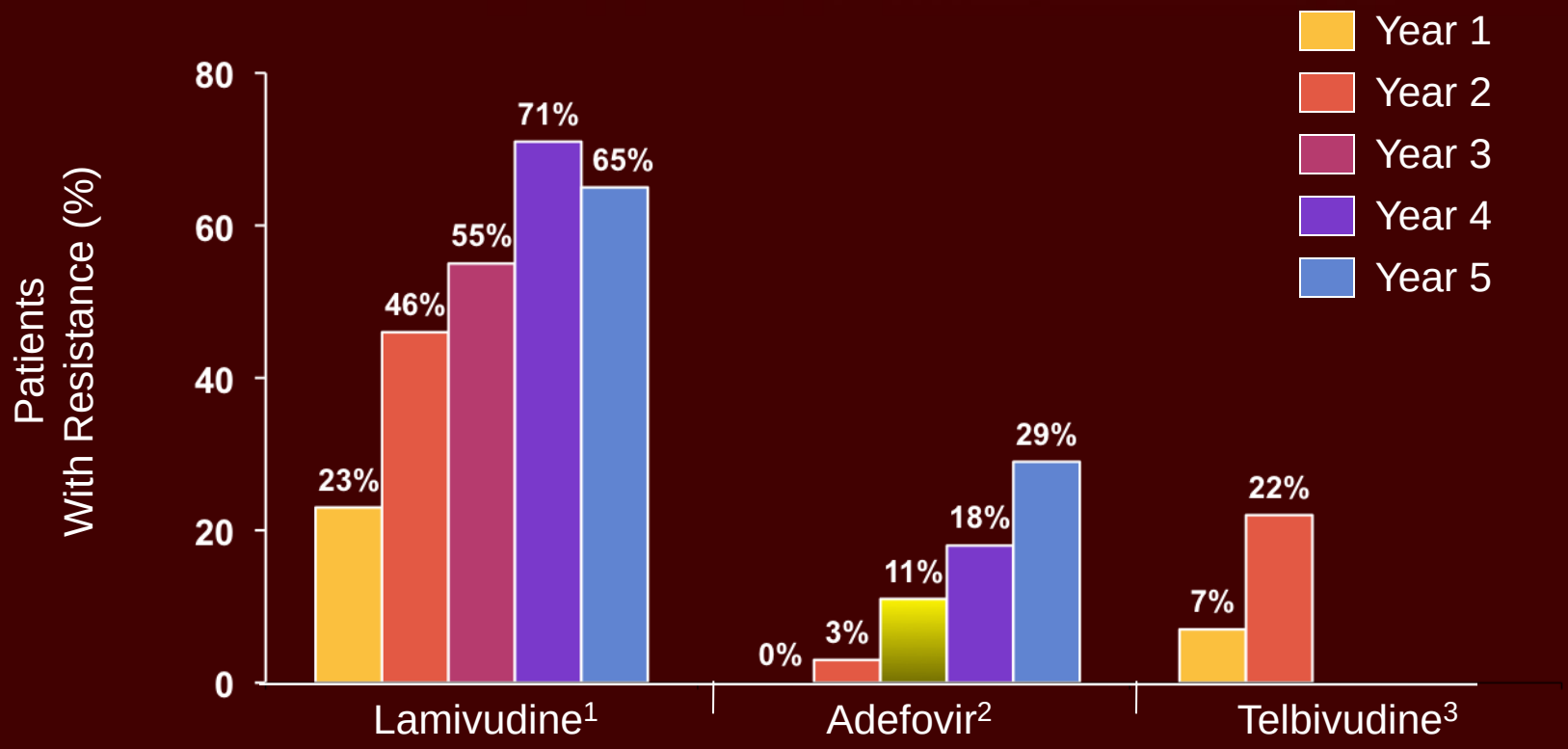
Adapted from Keeffe EB et al. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.

Consequences of Antiviral Resistance

- Virologic breakthrough; loss of initial virologic, biochemical, and histologic response
- Can lead to loss of initial response, and in some cases hepatitis flares and hepatic decompensation, death, or urgent transplant
- Cross-resistance limits future treatment options
  - Subsequent requirement for dual therapy
- Transmission to treatment-naïve persons poses a potential public health problem
- Vaccine failure

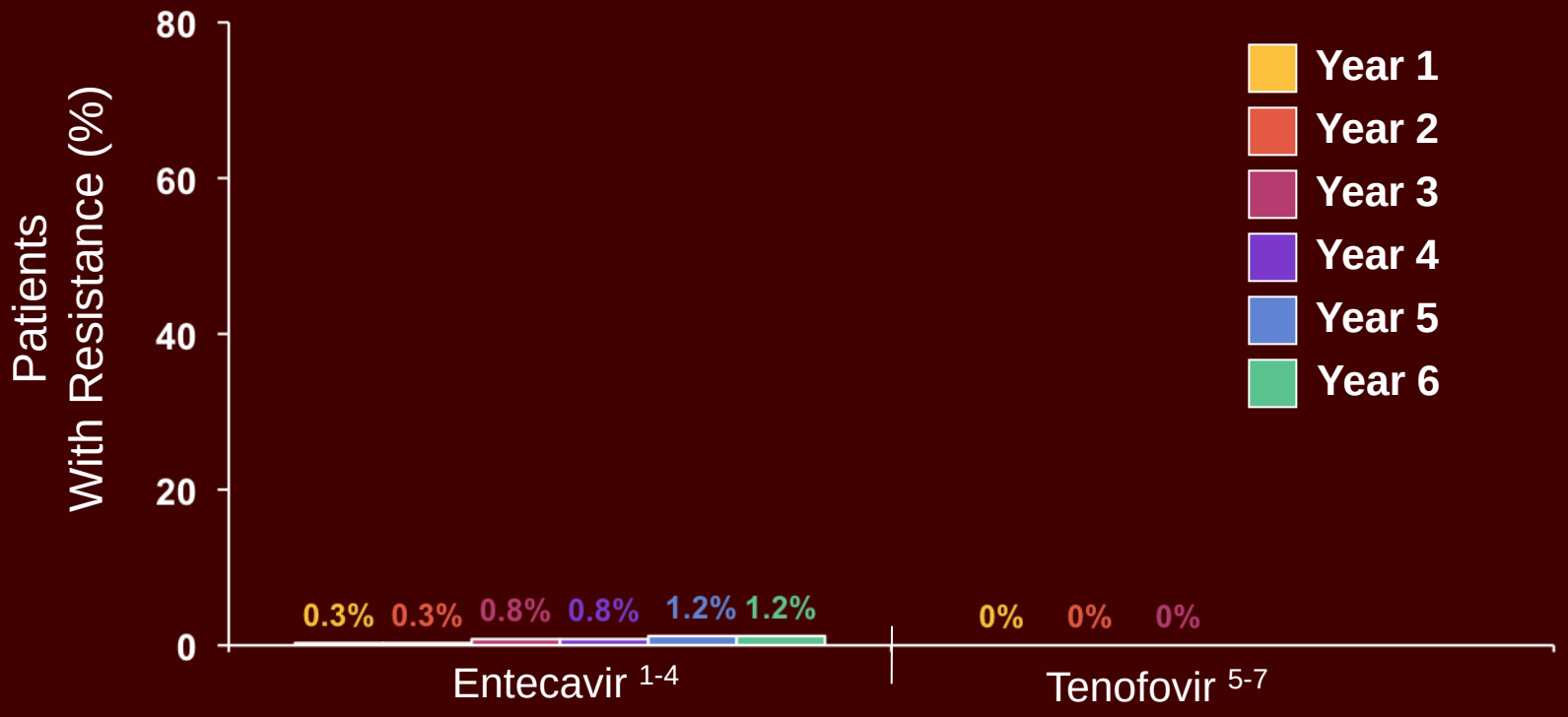
Adapted from Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

Increased Resistance With Long-Term Treatment in Nucleoside-Naïve Patients



1. Lok ASF et al. *Gastroenterology.* 2003;125:1714-1722.
2. Hadziyqnnis SJ et al. *Gastroenterology.* 2006;131:1743-1752.
3. Tyzeka® (telbivudine) Prescribing Information. Novartis Pharmaceuticals Corporation, East Hanover, NJ. April, 2009.

Minimal Resistance With Long-Term Treatment in Nucleoside-Naïve Patients



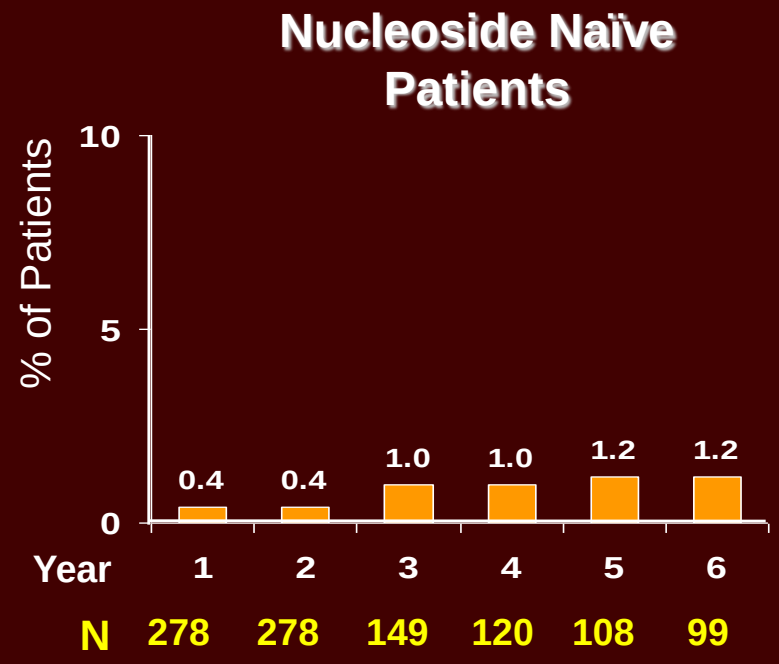
1. Colonno RJ et al. *Hepatology.* 2006;44:1656-1665.
2. Colonno et al. *Hepatology.* 2006;44(suppl 1):229A.
3. Colonno RJ et al. *J Hepatol.* 2007;46(suppl 1):S294.
4. Tenney DJ et al. *Gastroenterology.* 2009;136(suppl 1):A-865.
5. Viread® (Tenofovir) Prescribing Information. Gilead Sciences, Foster City, CA. May, 2009.
6. Snow-Lampart A et al. *Hepatology.* 2008;48(suppl 1):745A.
7. Snow-Lampart A et al. *Hepatology.* 2009;50(suppl 4):732A.

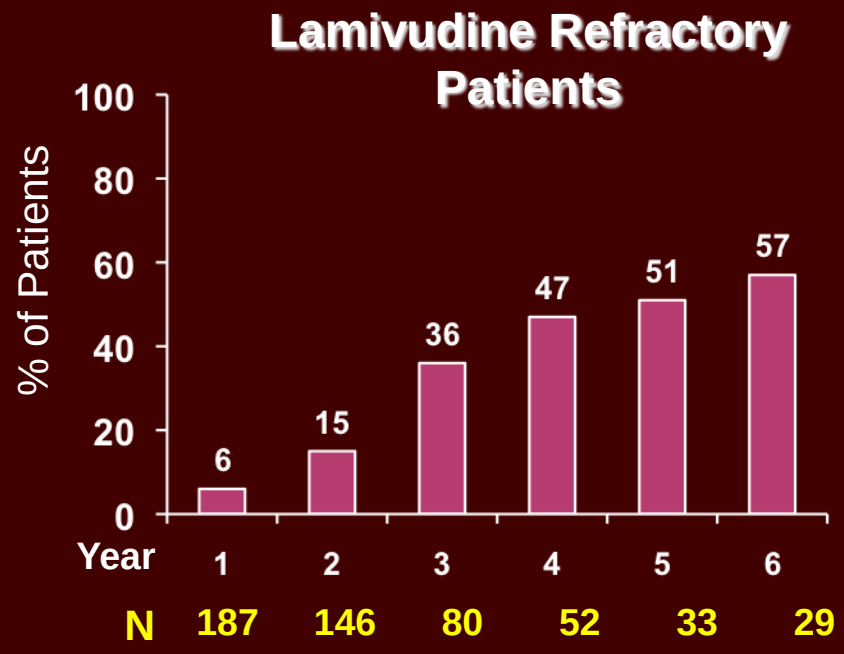
Antiviral-Resistant HBV: Treatment

Lamivudine-resistance →	Add adefovir or tenofovir Stop lamivudine, switch to Truvada Use tenofovir with entecavir
Adefovir-resistance →	Add lamivudine Stop adefovir, switch to Truvada Switch to or add entecavir
Entecavir-resistance →	Switch to or add tenofovir or Truvada
Telbivudine-resistance →	Add adefovir or tenofovir Stop telbivudine, switch to Truvada

Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

Entecavir Resistance in Nucleoside Naïve and Lamivudine Refractory CHB Patients





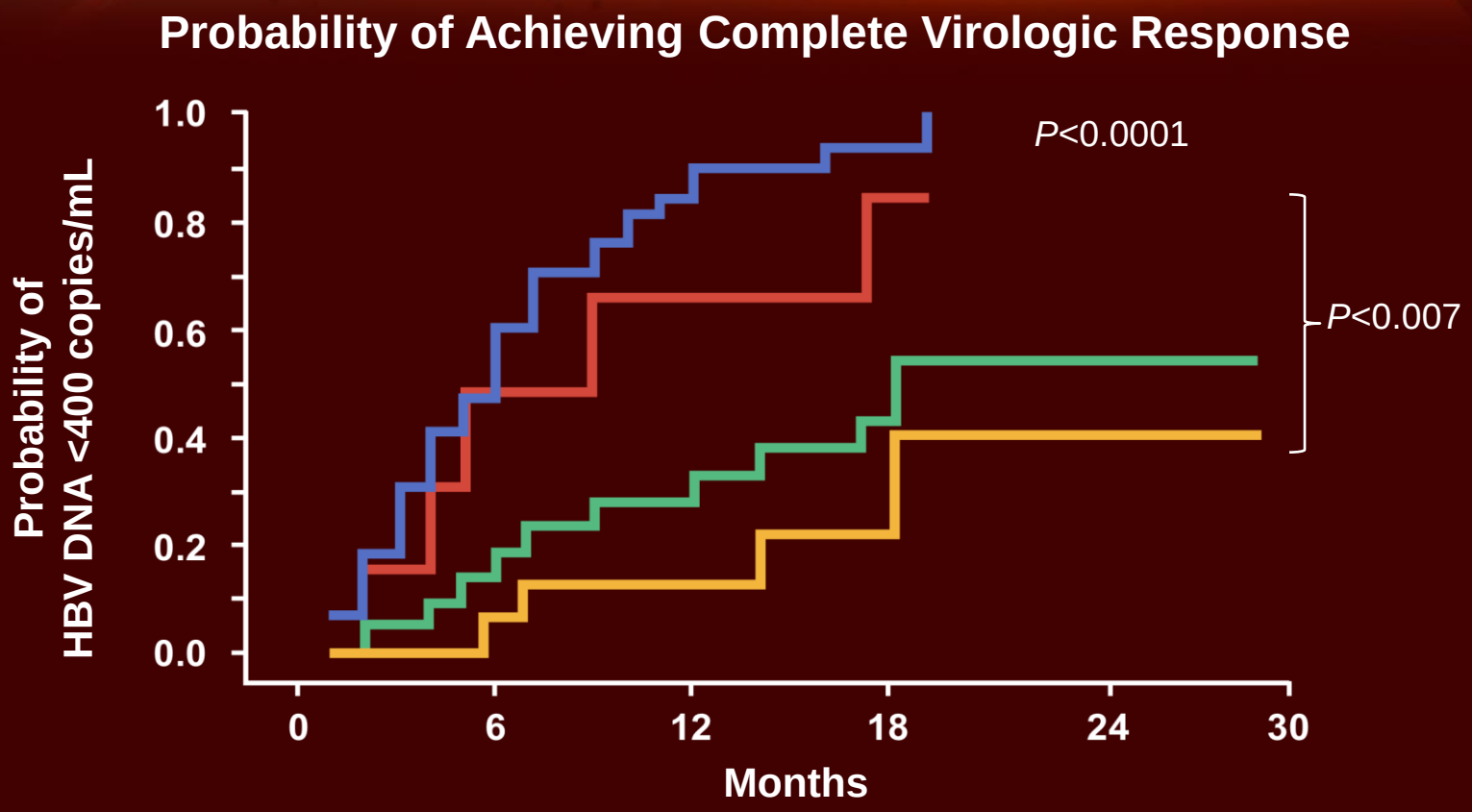
Colonno RJ et al. *Hepatology.* 2006;44:1656-1665.
Colonno et al. *Hepatology.* 2006;44(suppl 1):229A.
Colonno RJ et al. *J Hepatol.* 2007;46(suppl 1):S294.
Tenney DJ et al. *Gastroenterology.* 2009;136(suppl 1):A-865.

Entecavir in Patients With Prior Adefovir Treatment Failure

- Since no cross-resistance *in vitro*, Entecavir therapy is recommended in patients not responding to Adefovir
- Entecavir therapy (1.0 mg/day) administered to 18 patients previously treated with Adefovir (10 mg/day x 48 wks) with incomplete response on-treatment or relapse off-treatment
  - Treatment gap ranged from 1 to 128 days for relapse patients
- Median exposure to Entecavir: 46 weeks
  - Week 24: 8/16 (50%) achieved HBV DNA <300 copies/mL
  - 9 patients had reached week 48; 8/9 had HBV DNA <300 copies/mL

Lai CL et al. *J Hepatol.* 2009;50(suppl 1):S334.

Tenofovir Monotherapy in Patients With Prior Adefovir Failure: Response According to Presence of Absence of Genotypic Resistance



Patients under observation (n):			
ADV resistance	21	15	3
– HBV DNA <10^7 at BL	6	3	-
– HBV DNA >10^7 at BL	15	12	3
ADV experienced, no ADV resistance	89	35	-

Van Bömmel F et al. *Hepatology.* 2010;51:73-80.

Linkage to Care

- All chronic hepatitis B patients should be monitored according to AASLD guidelines
- Those meeting AASLD guidelines for treatment should receive appropriate therapy
- Those meeting AASLD guidelines for HCC surveillance should be monitored
- While chronic hepatitis B cannot be cured, careful monitoring and appropriate treatment can decrease progression to cirrhosis, decompensated liver disease, transplant, and death

– CLDF Advisory Board

Summary

Maximal suppression of HBV replication is the most effective way to improve long-term outcomes in chronic hepatitis B

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