

Hepatitis B: Chronic Hepatitis and Inactive Carriers - Management

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Chronic HBV Infection

Epidemiology: United States

- **HBsAg seroprevalence: 0.2% - 1.0%**
- **HBsAg prevalence *highest* in Asians and Asian-Americans (3-20%)**
- **HBsAg prevalence intermediate in African-Americans**
- **Accounts for up to 15% of chronic liver disease**

Chronic HBV Infection

Morbidity and Mortality, U.S.

- **Previously infected individuals: ~10 million**
- **Actively infected individuals: ~1-1.25 million
(chronic hepatitis B and carriers)**
- **Annual cirrhosis deaths: ~4,000**
- **Annual HCC deaths: ~1,000-1,500**

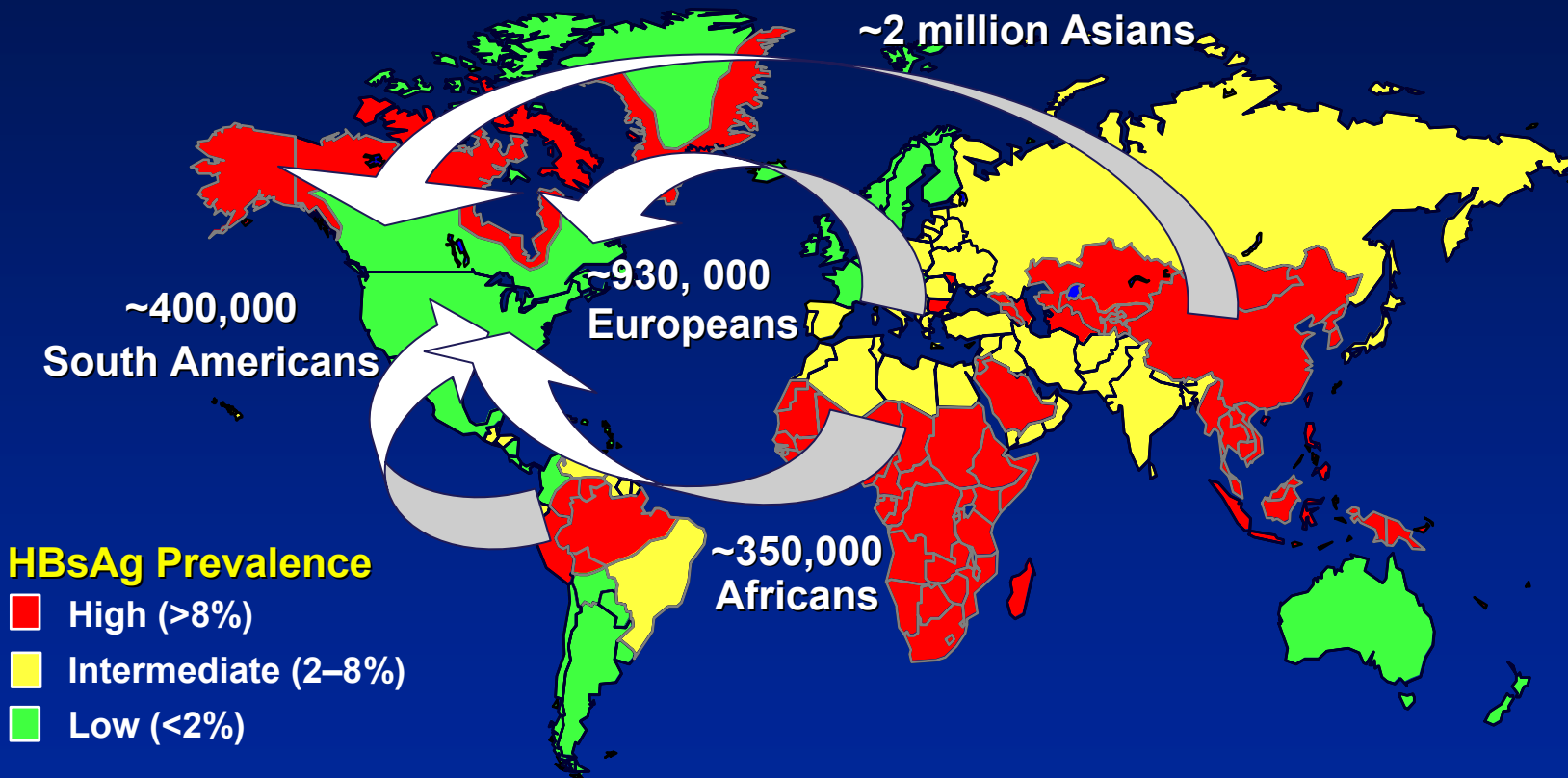
HBV - Epidemiology

Disease Burden of Hepatitis B Infection

	U.S.	Global
Estimated new infections per year	58,000	Uncertain
Number of persons with chronic infection	1.25 million	350 million
Deaths from chronic liver disease per year	5,000	500,000
Percent ever infected	<4.9%	30%

Geographic Prevalence of Chronic Hepatitis B May Be Impacted by Migration

Immigration Numbers Summed by Continent From 1996–2002



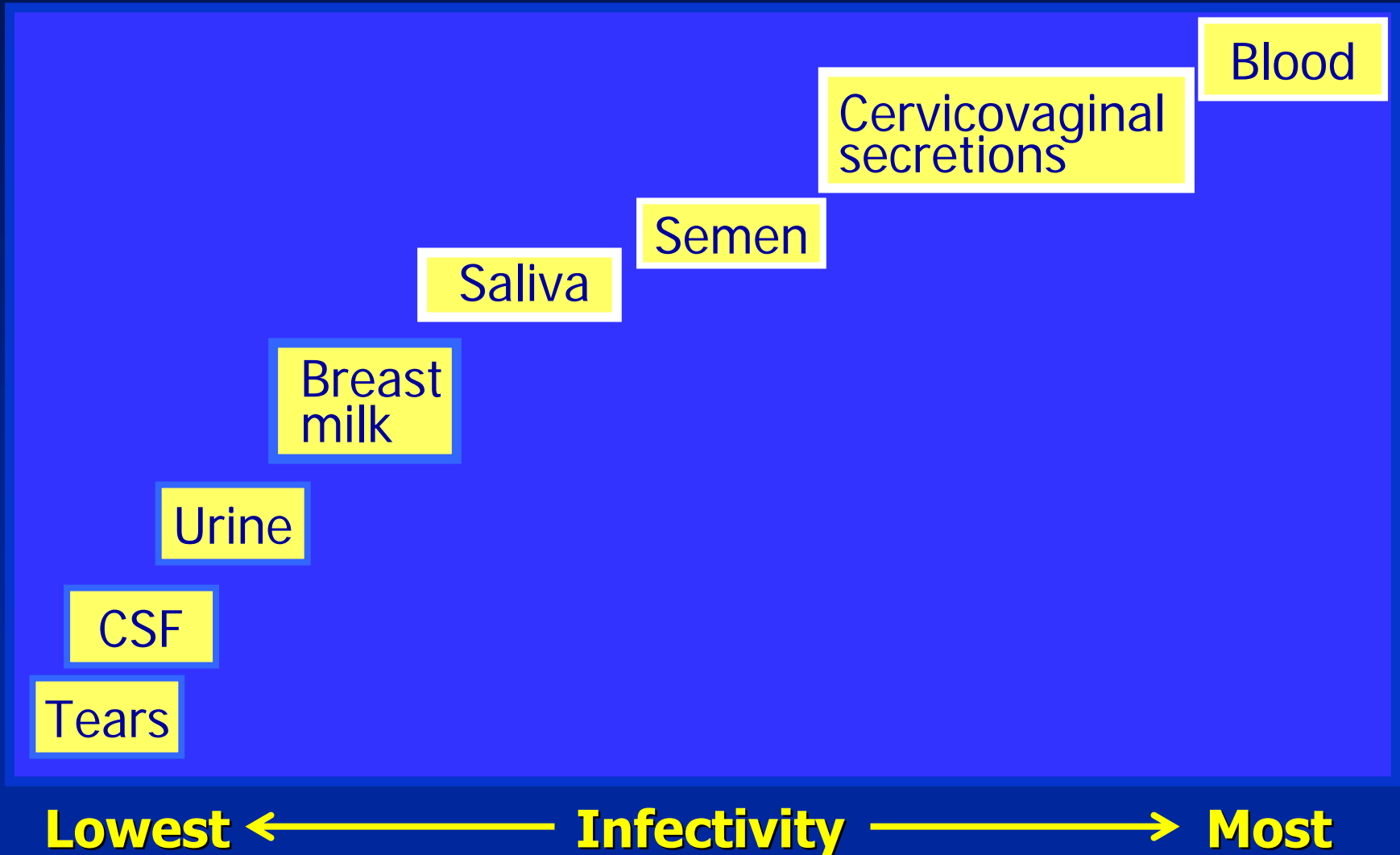
World Health Organization. Available at: <http://www.who.int/vaccines-surveillance/graphics/htmls/hepbprev.htm>. Accessed July 8, 2005.

2002 Yearbook of Immigration Statistics. Available at:

<http://uscis.gov/graphics/shared/aboutus/statistics/yearbook/2002.pdf>. Accessed July 8, 2005.

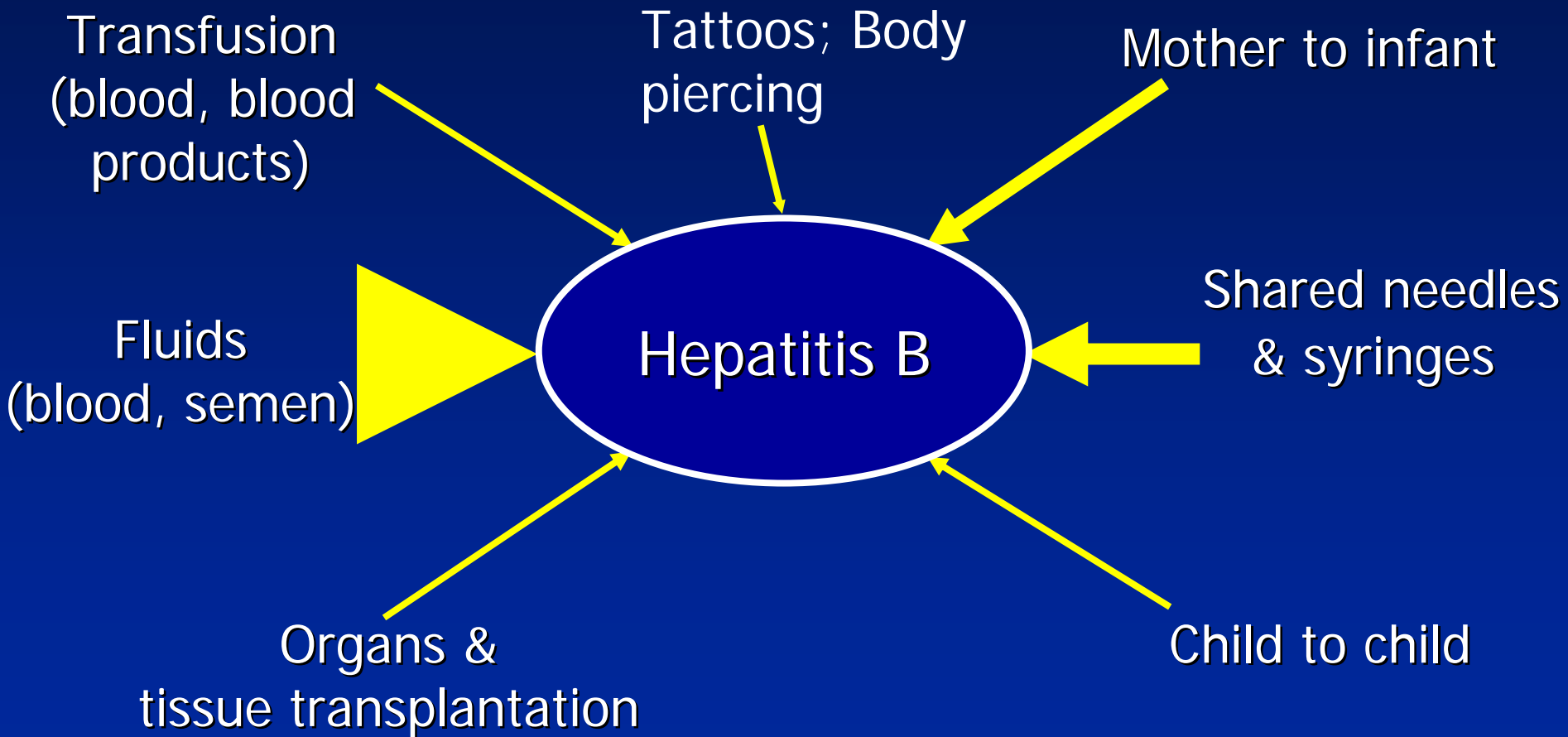
Mahoney FJ. *Clin Microbiol Rev.* 1999;12:351–366.

Estimates of HBV Infectivity in Body Fluids



HBV Infection

Modes of Transmission



Risk Factors for Hepatitis B Infection

Percutaneous

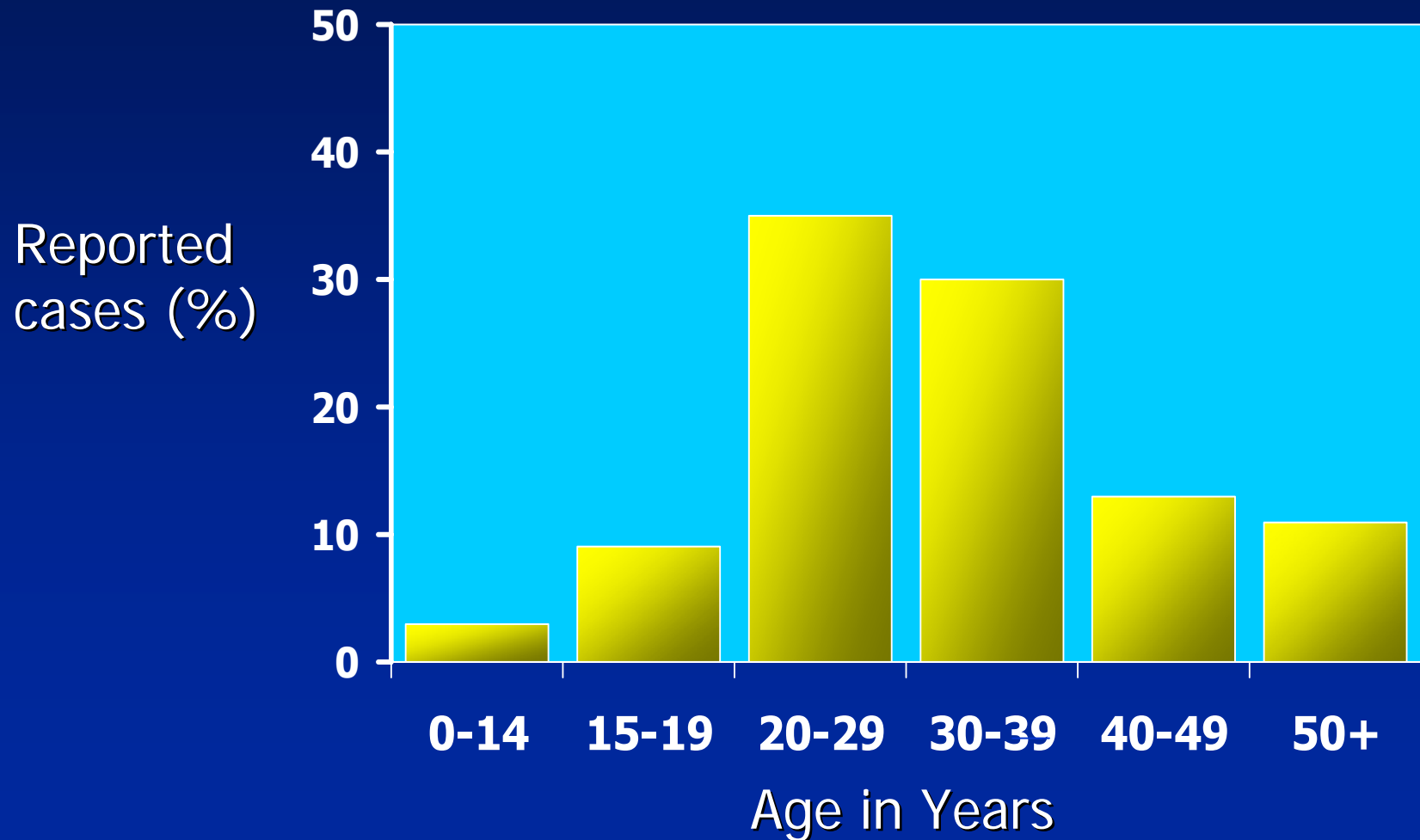
- Injection drug use
- Transfusion or transplant
- Occupational exposure
- Parenteral practices

Per mucosal

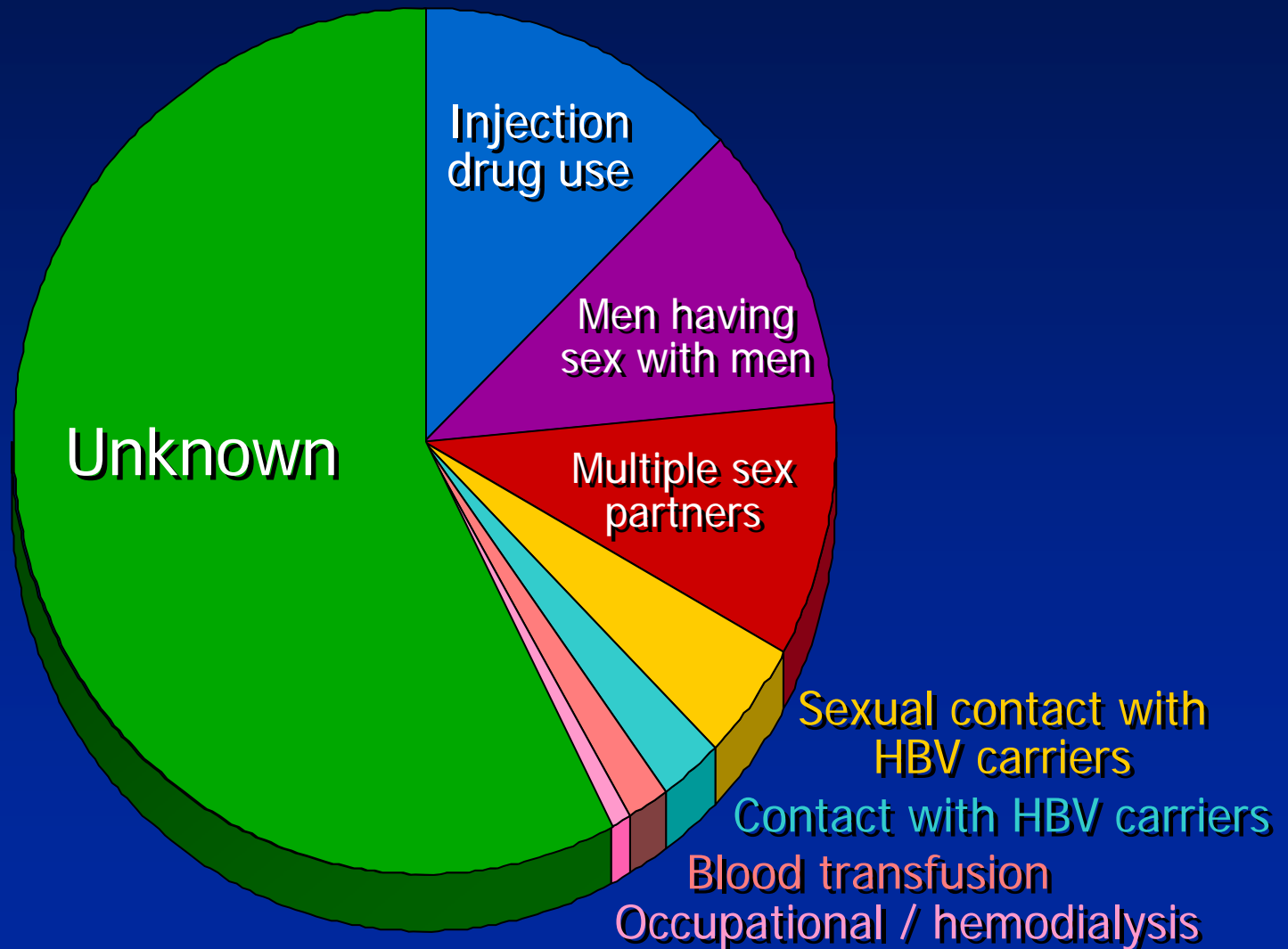
- Perinatal
- Sexual
- Household contact

Acute Hepatitis B

Age Distribution in the United States



Risk Factors for Acute HBV infection in the U.S.

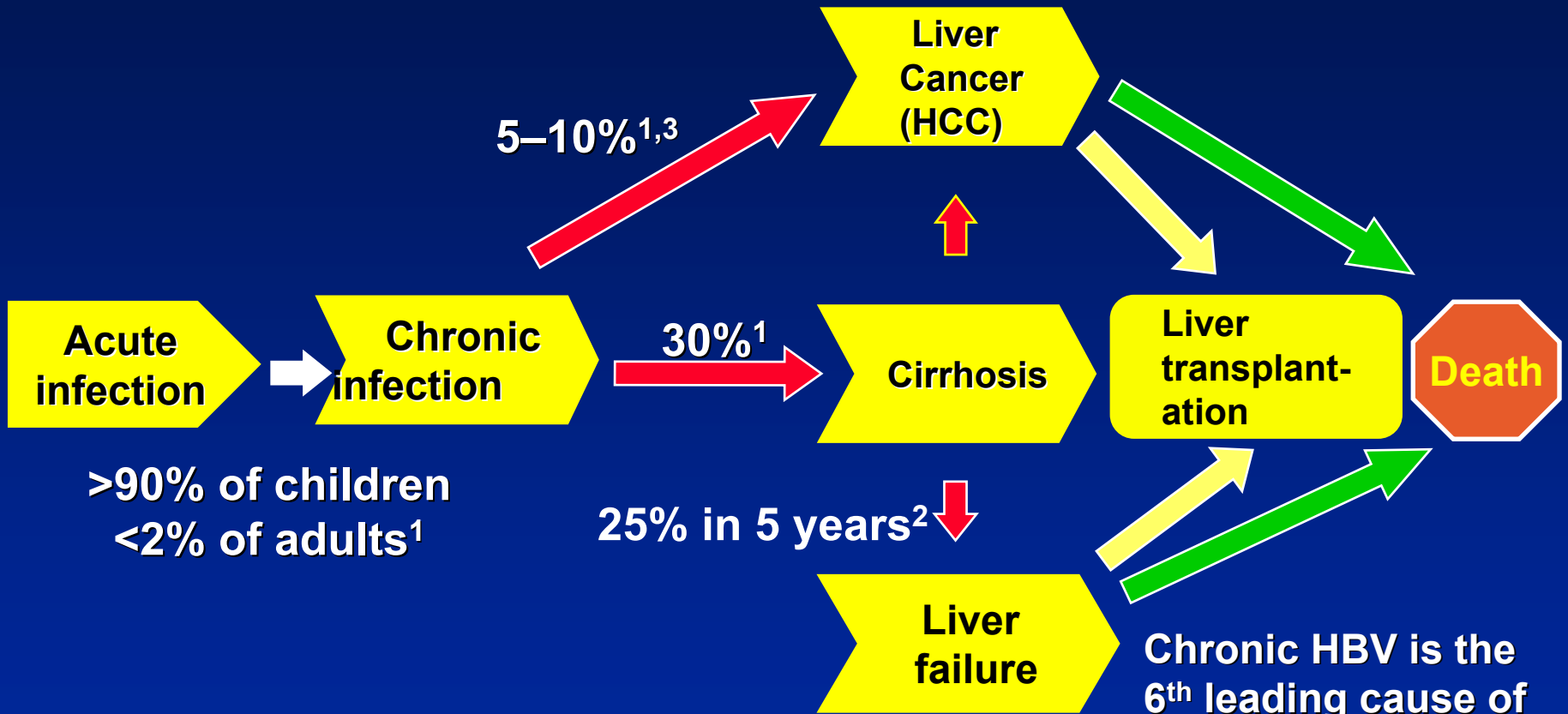


Chronic Hepatitis B

Natural History

- Ranges from mild infection (inactive carrier, with normal ALT) to severe chronic liver disease
- Fibrosis and subsequent cirrhosis
- Liver failure
- Hepatocellular carcinoma
- Premature death

HBV Disease Progression



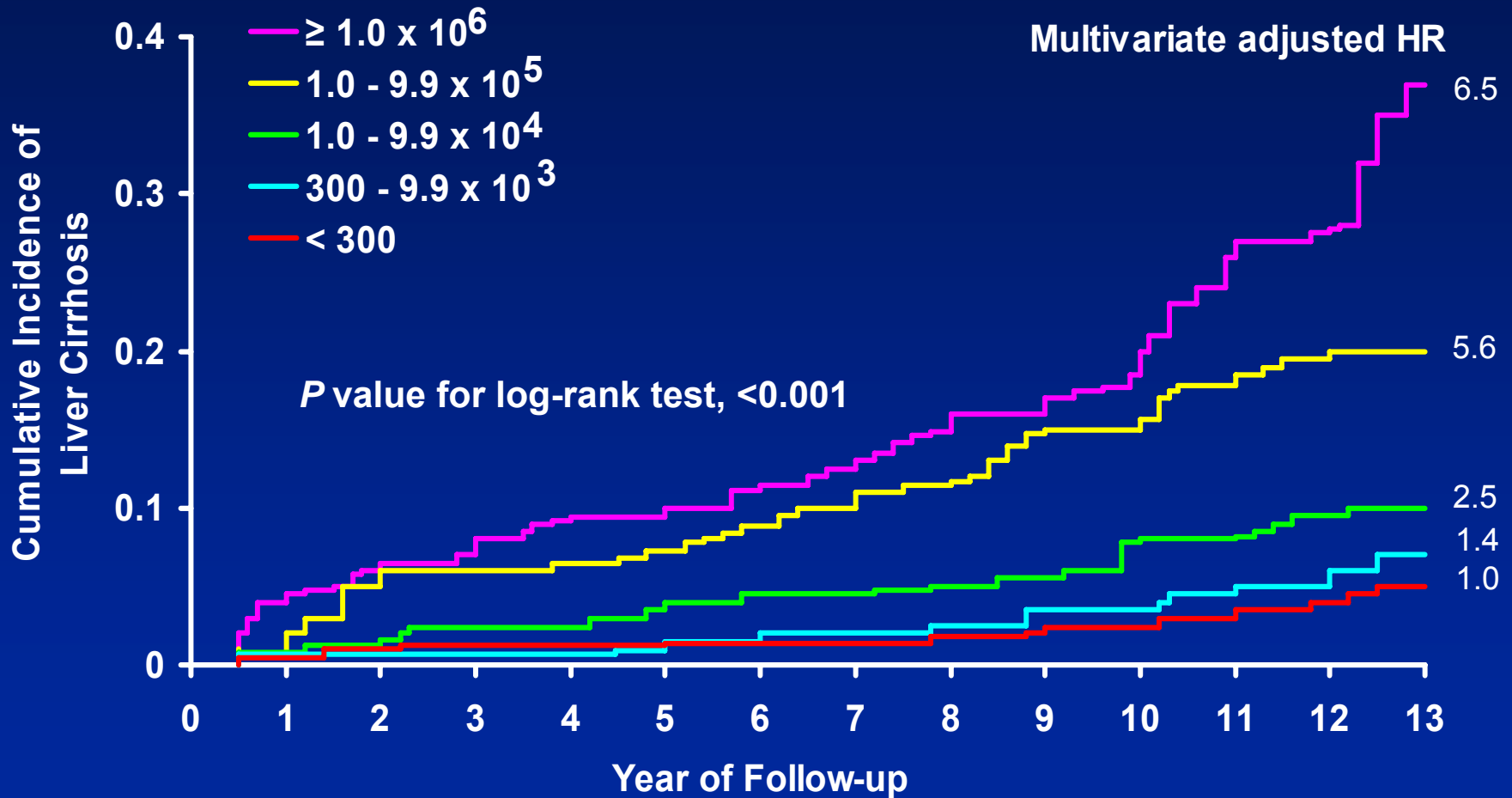
1. Torresi J. *Gastroenterology*. 2000;118(2 suppl 1):S83–S103.
2. Fattovich G. *Hepatology*. 1995;21:77–82.
3. Moyer LA. *Am J Prev Med*. 1994;10:45–55.
4. Perrillo R. *Hepatology*. 2001;33:424–432.

Chronic Hepatitis B

Factors Influencing Risk of Cirrhosis

- **Higher HBV DNA levels ($>10^4$ copies/mL)**
- **HBeAg-positivity**
- **Persistent ALT elevation**
- **HIV, alcohol, immunosuppression**

Cumulative Incidence of Cirrhosis for Five HBV DNA Categories (n=3,774)



HBV DNA Levels and Risk of Hepatocellular Carcinoma: The Taiwan Natural History Study*

Serum HBV DNA (copies/mL)	Incidence (per 100,000)	Adj. Rel Risk	<i>p</i>
$\geq 1.0 \times 10^6$	1150	11.6	<.001
$\geq 1.0 \times 10^5 - < 1.0 \times 10^6$	952	7.2	<.001
$\geq 1.0 \times 10^4 - < 1.0 \times 10^5$	315	2.4	<.008
$> 300 - < 1.0 \times 10^4$	112	0.9	NS
< 300	145	1.0	---

* Chen C-J et al. JAMA, 2006

Hepatocellular Carcinoma

- Among solid tumors, 5th highest incidence worldwide and 3rd most common cause of cancer deaths
- In the U.S. in 2007, 13th most common cancer and **increasing faster** than all others from 1995 to 2004; 8th most common cause of cancer deaths
- Despite advancing technology and available treatments, 5-year survival rates are generally less than 5%

Strategies for Eliminating HBV Transmission in the U.S.

- **Maternal screening for HBsAg and providing post-exposure prophylaxis to infants of HBsAg-positive women**
- **Routine vaccination of all infants**
- **Catch-up vaccination for children aged <19 yrs**
- **Targeting high risk children, adolescents, adults**

Natural History of Chronic Hepatitis B

Phase of disease

Annual risk of cirrhosis

- **Chronic hepatitis B:**

HBeAg-positive

~2-6 %

HBeAg-negative

~8-10%

- **Inactive carrier:**

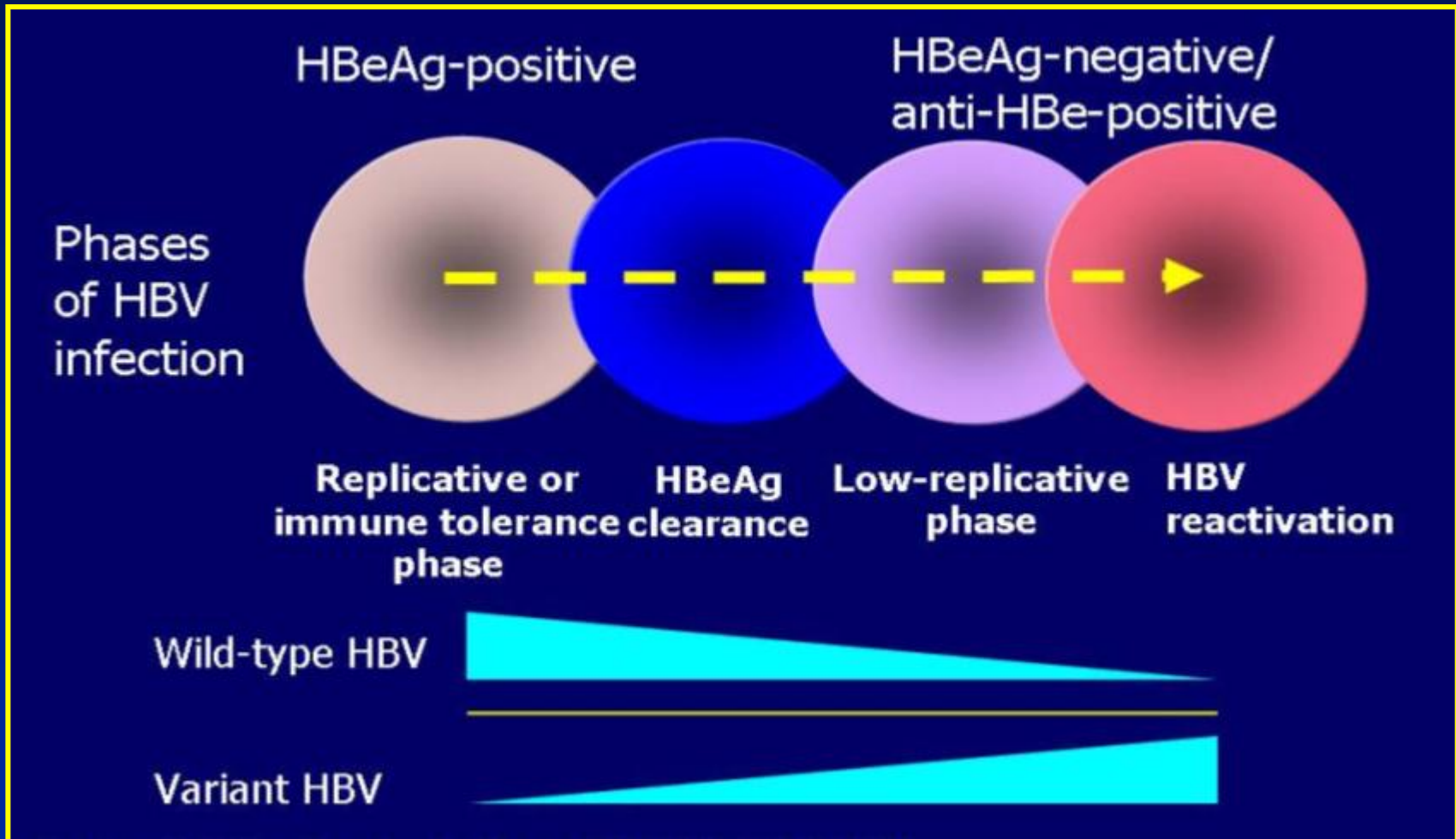
~0.5%

Chronic HBV Infection

Inactive HBsAg Carriers





- **HBsAg-positive/HBeAg-negative**
- **Normal serum ALT levels**
- **$<10^4$ copies/mL by PCR**
- **Generally mild histology**
- **Absence of evidence of effective therapy**
- **Very low risk of progression**

Natural History of HBV: Development of HBeAg-Negative Chronic HBV



Chronic Hepatitis B

Natural History of HBeAg-positive Disease

<i>Change in Status</i>	<i>Annual Probability</i>
• Chronic hepatitis B  cirrhosis	~ 2-6 %
• Cirrhosis  decompensation	~ 6 %
• Cirrhosis  hepatocellular carcinoma	~ 2.5 %
• Hepatocellular carcinoma  death	~ 85%

Chronic Hepatitis B

Natural History of HBeAg-negative Disease

- Older than HBeAg-positive patients
- Lower circulating HBV DNA levels
- More extensive hepatic injury
- Lower rates of spontaneous remission
- Pre-core and/or core promoter mutants in 90%

HBsAg Present?

Yes

Is IgM anti-HBc present?

No

Chronic hepatitis

Yes

Acute hepatitis

Is HBeAg or HBV DNA present?

Yes

Replicative HBV infection

No

Nonreplicative HBV infection (carrier)

No

Is anti-HBs present?

Yes

**Recovered/vaccinated
± anti-HBc**

No

No HBV infection

Evaluation of the HBsAg-positive Patient

- HBV DNA level
- HBeAg/anti-HBe status
- Serum ALT
- Clinical/laboratory/imaging evidence of cirrhosis or HCC
- Testing for viral resistance/genotype
- ?Histology

Treatment of Chronic HBV

Chronic Hepatitis B

Candidates for Treatment

Elevated or Normal ALT levels and:

- **HBeAg-positive and HBV DNA $\geq 10^5$ copies/mL by PCR**
- **HBeAg-negative and HBV DNA $\geq 10^4$ copies/mL by PCR**

Cirrhosis with detectable HBV DNA

Goals of Therapy

- **HBeAg-positive**

- **Suppression of HBV DNA to low or undetectable levels**
- **HBeAg loss \pm seroconversion**
- **Sustained response after seroconversion**
- **ALT normalization**
- **HBsAg loss \pm seroconversion**

- **HBeAg-negative**

- **Suppression of HBV DNA to low or undetectable levels and ALT normalization**
- **HBeAg seroconversion not an endpoint**
- **HBsAg loss \pm seroconversion**

HBV Treatment Options in 2008

- **Pegylated interferon alfa-2a**
- **Interferon alfa-2b**
- **Nucleoside analogs**
 - **Entecavir**
 - **Lamivudine**
 - **Telbivudine**
- **Nucleotide analog**
 - **Adefovir**
 - **Tenofovir**

Chronic Hepatitis B

Comparing Oral Antivirals and Interferon

	Orals	IFN
Oral administration:	Yes	No
Side effects:	minimal	frequent
Duration of treatment:	prolonged	finite
Flares during treatment:	rare	yes
Resistant mutant:	yes	no
Impact of genotype:	no	yes
Rate of HBsAg clearance:	low	higher

Interferon Therapy for HBeAg-positive HBV: Long-term Follow-up*

- Meta-analysis of 12 studies (n=1975)
- 765 interferon treated/1210 untreated
- Follow-up range: 2.1–8.9 yrs (mean 6.1)[†]

Distribution of probabilities:

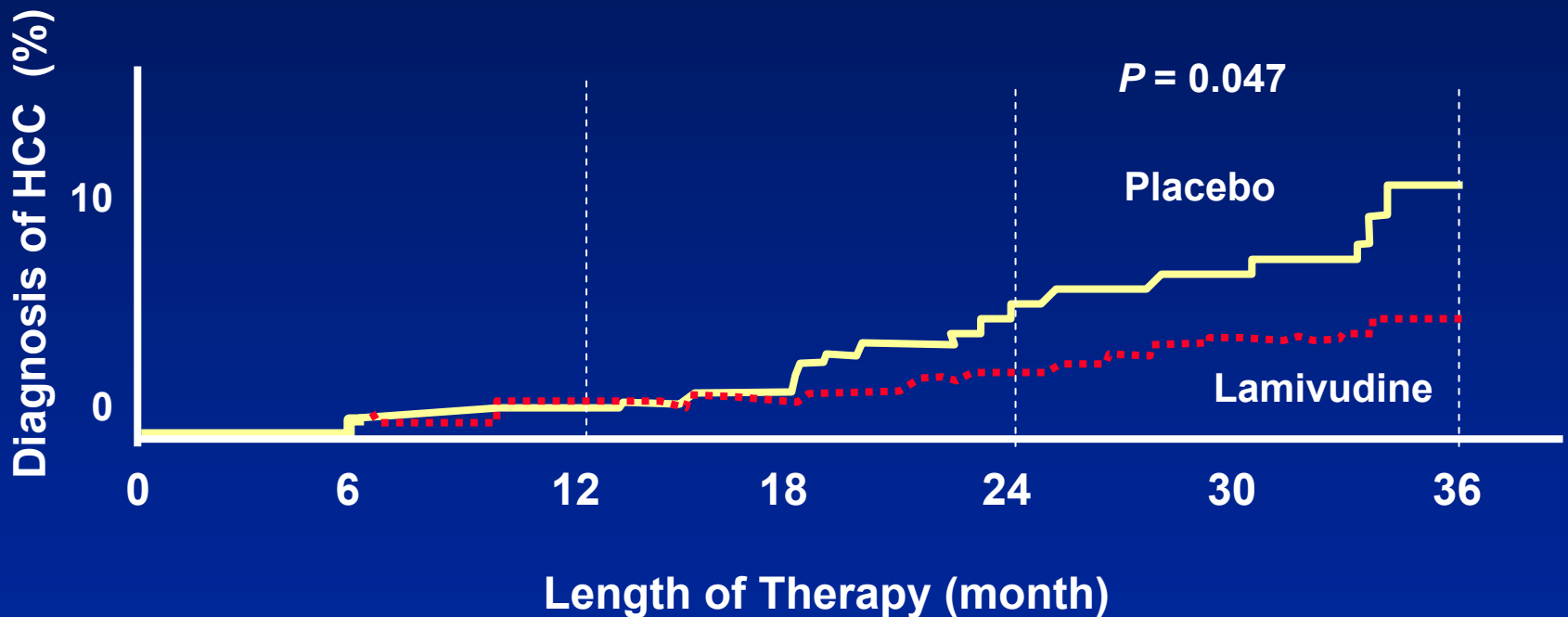
	Interferon	Untreated
Loss of HBsAg	11.4%	2.6%
Disease decompensation	9.9%	13.3%
Development of HCC	1.9%	3.2%
Liver-related death	4.9%	8.7%

*Long term response in treatment-free follow-up

[†]Treatment duration: 4–6 months

Craxi et al. *EASL* 2002.

Effect of Lamivudine on Incidence of HCC in Chronic HBV and Advanced Fibrosis



Chronic Hepatitis B, HBeAg-Positive

Comparing Oral Agents and Peg-IFN alfa-2a

1-year of Treatment	Seroconversion	
	HBeAg	HBsAg
Lamivudine:	18%	0%
Telbivudine:	22%	0%
Adefovir:	12%	0%
Entecavir:	21%	0%
Tenofovir:	21%	3%
Peg-IFN alfa-2a:	32%	3%

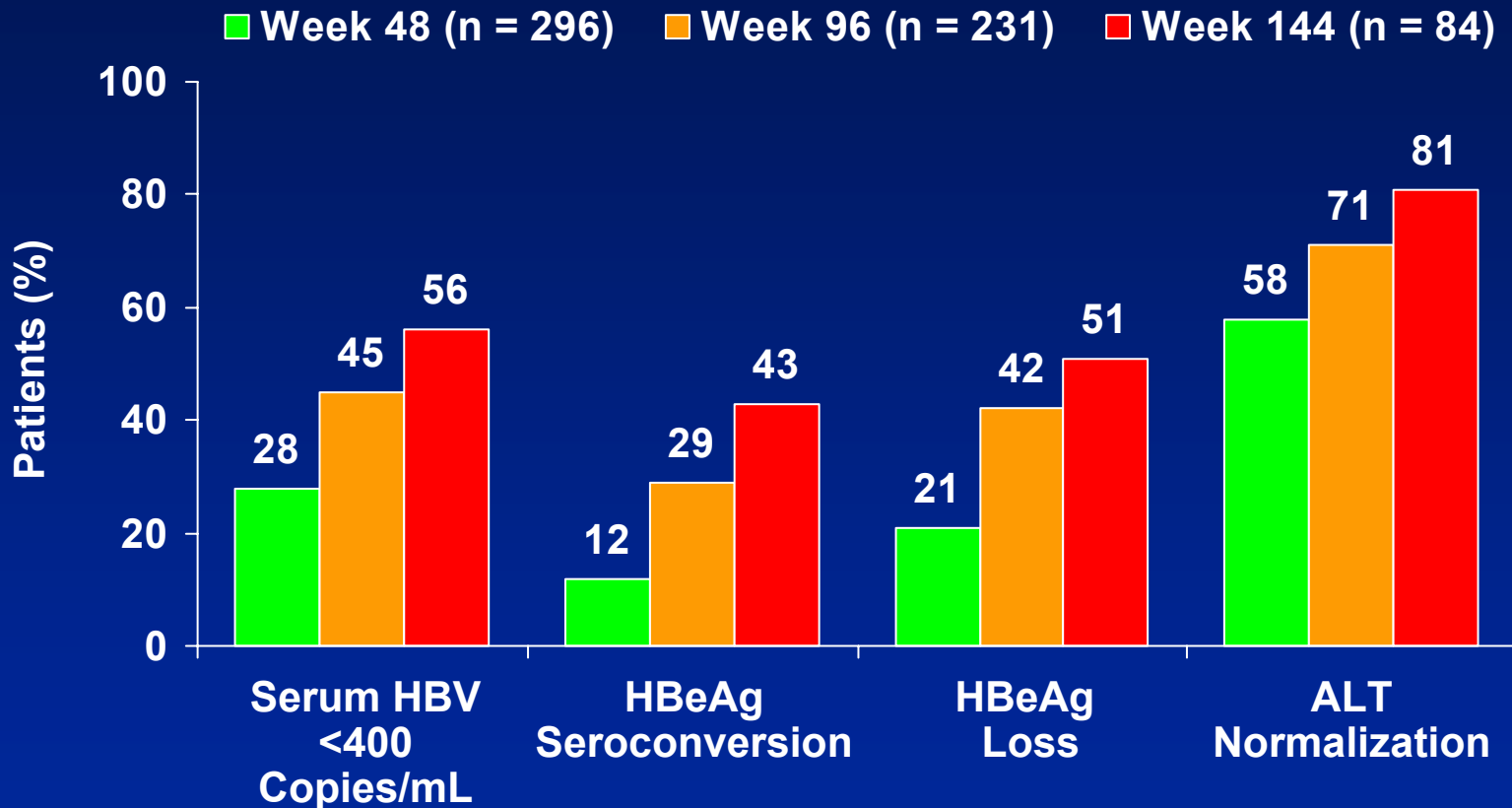
Chronic Hepatitis B

Comparing Oral Agents and Peg-IFN alfa-2a

**1-year of Treatment HBV DNA <300-400
cp/mL at end of Rx**

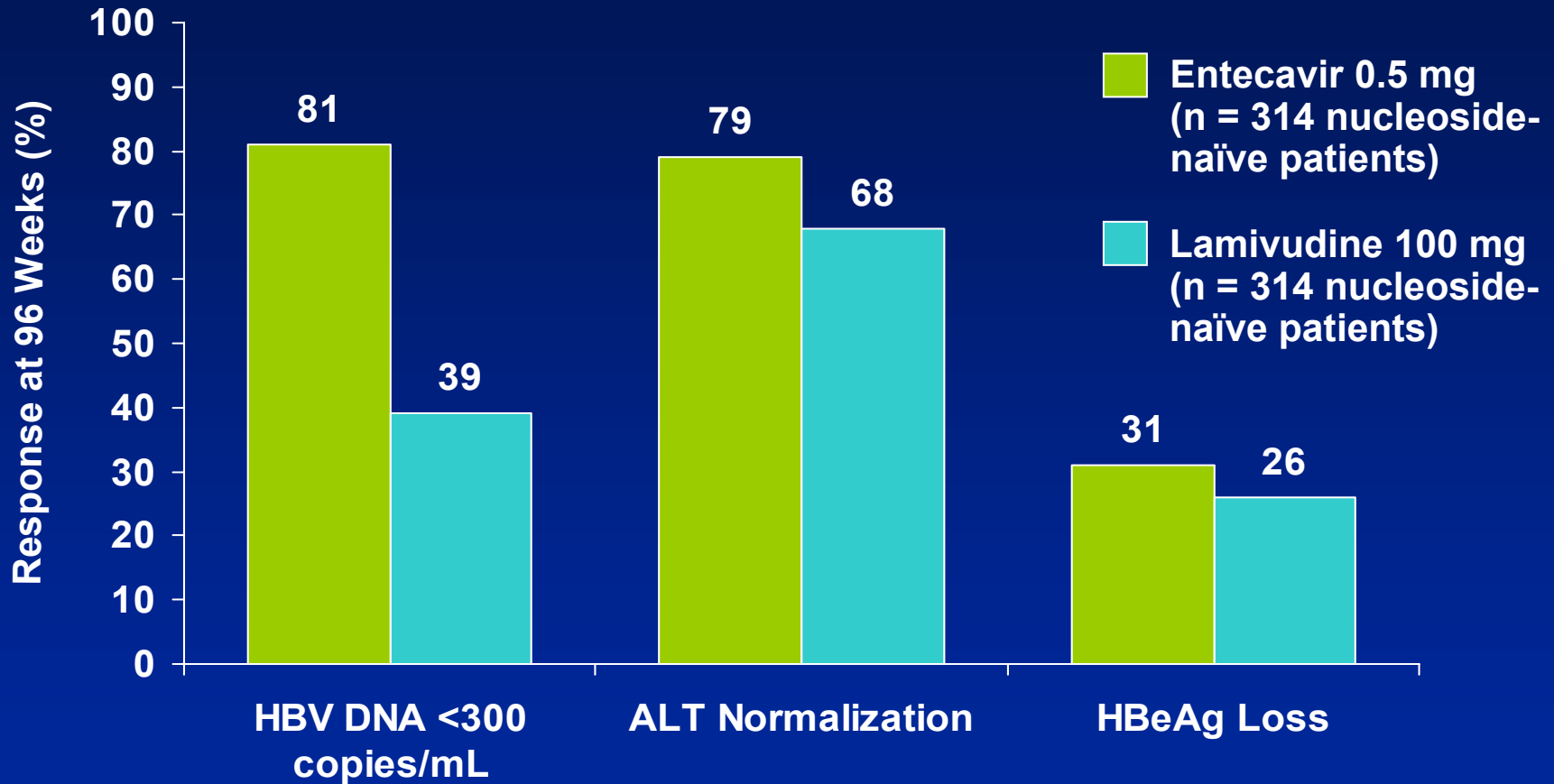
Lamivudine:	38%
Telbivudine:	60%
Adefovir:	21%
Entecavir:	69%
Tenofovir:	80%
Peg-IFN alfa-2a:	25-63%

Adefovir: Long-Term Efficacy in HBeAg-positive Patients



Two patients (3.1%) developed resistance (N236T, 1; A181V, 1) through week 144.
Kaplan Meier estimates of time to confirmed event.
Marcellin P, Asselah T. *J Hepatol.* 2005;43:920–923.

Entecavir: Average Response Rates in Chronic Hepatitis B (HBeAg Positive) at 2 years of Treatment



HBsAg loss was 5% at 96 weeks for entecavir.

Current Treatment Strategies

Clinical Form

Drug Therapy

Chronic hepatitis B:

PEG-IFN alfa-2a or
tenofovir, entecavir,
adefovir, telbivudine,
lamivudine or ?combinations

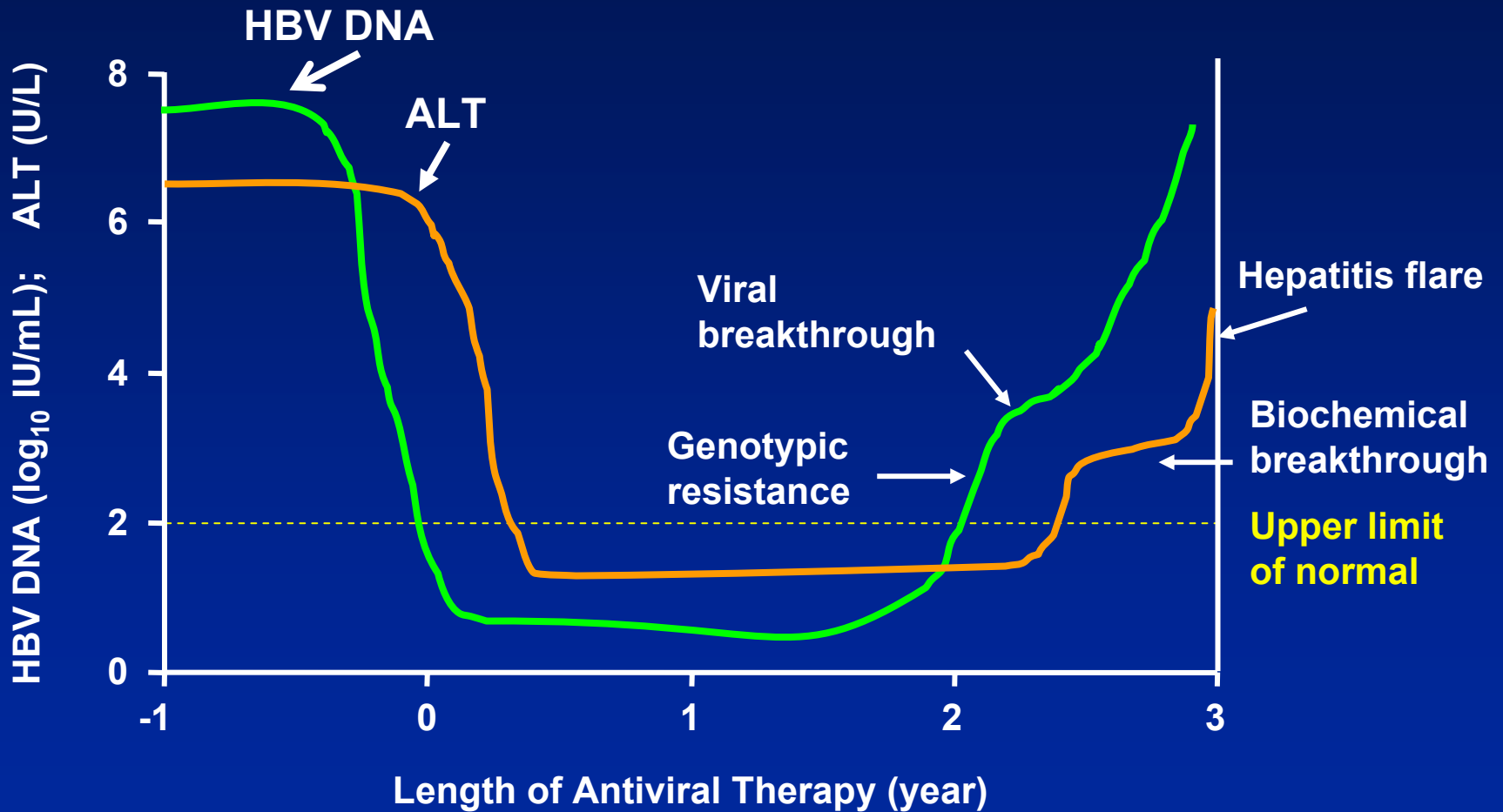
HBV-cirrhosis

- **Compensated:** same as above
- ***Decompensated:*** *tenofovir, entecavir, adefovir, telbivudine, lamivudine, or transplantation*

Key Issues in HBV Therapy

- **Efficacy**
- **Duration of therapy**
- **Resistance**
- **Combination therapy**
- **Genotyping**

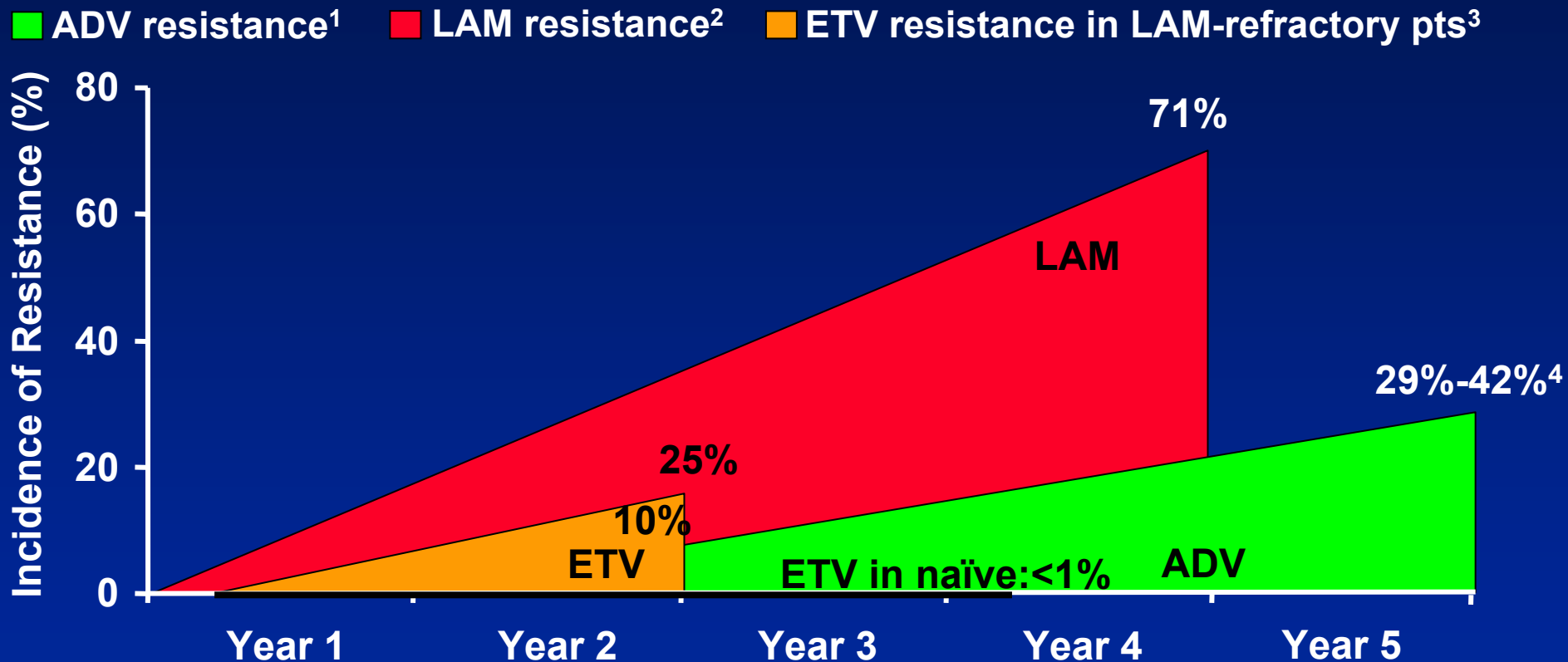
Manifestations of Antiviral Resistance



The Risk of Resistance

- **Antiviral potency**: the emergence of resistant mutants is reduced when viral replication is highly suppressed – **no virus, no resistance**
- **Genetic barrier**: the number of mutations required to decrease susceptibility to an antiviral drug
- **Viral fitness**: the ability of a mutant virus to replicate

Cumulative Incidence of HBV Genotypic Resistance



1. Qi YL, et al. *EASL*. 2005. Abstract 57.

2. Lai CL, et al. *Clin Infect Dis*. 2003;36:687–696.

3. Tenney DJ, et al. *AASLD*. 2004. Abstract 184.

4. In HBeAg-negative pts; higher resistance in HBeAg-positives

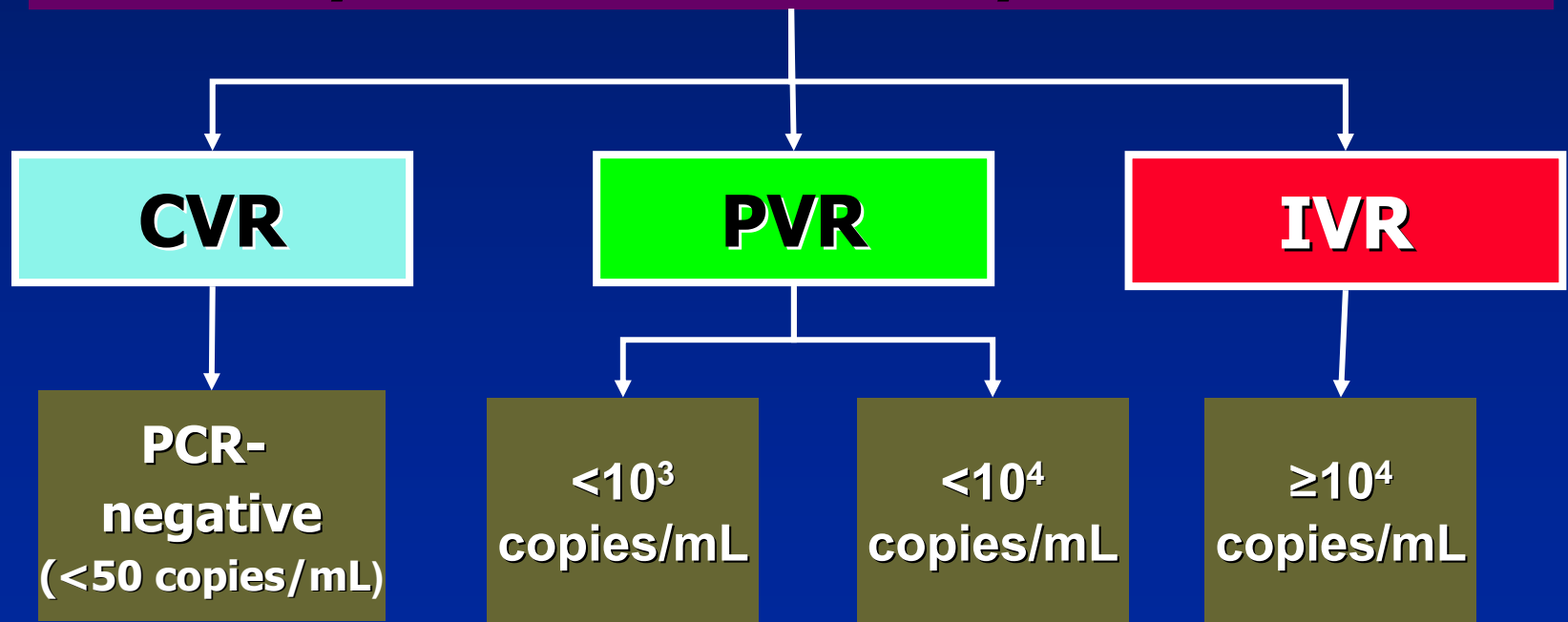
Antiviral-Resistant HBV: Treatment Recommendations

Resistant Drug	Rescue Therapy
Lamivudine-R	Add adefovir (may be preferred over switch) Switch to entecavir (risk of entecavir-R) Add tenofovir or switch to FTC/tenofovir
Adefovir-R	Add lamivudine (may be preferred over switch) Switch to entecavir (if no prior lamivudine-R) Switch to FTC/tenofovir
Entecavir-R	Add or switch to adefovir or tenofovir

HBV Roadmap Schema

Assessment of Primary Non-Response at week 12

Early Predictors of Efficacy at week 24



Current and Future Treatment of HBV Patients

- Focus on HBV DNA suppression
- Treatment decisions based on HBV DNA levels, disease severity, drug efficacy and resistance patterns (for oral agents)
- Combination oral therapy emerging
- New agents with prolonged activity after end-of-treatment, e.g. clevudine, may become available