Hepatitis B Management and Treatment

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HBV is a life long, dynamic disease

- Changes over time
- Risk of end stage liver disease and cancer increases with ongoing inflammation and viremia in adults
- Fibrosis can be reversible
- Drugs can decrease fibrosis progression
- HBV can be controlled but not cured
- Reactivation can occur even in those who have lost HBsAg

Who should be tested for HBV?new

- Blood and organs donors
- Hemodialysis patients
- Pregnant women
- Infants of HBsAg + mothers
- Behavioural contacts:
  - Household and sexual contacts
  - HIV+, MSM, IDU
- Individuals from countries where prevalence is ≥2%
- Patients receiving immunosuppressive therapy
- Abnormal ALT of unknown cause

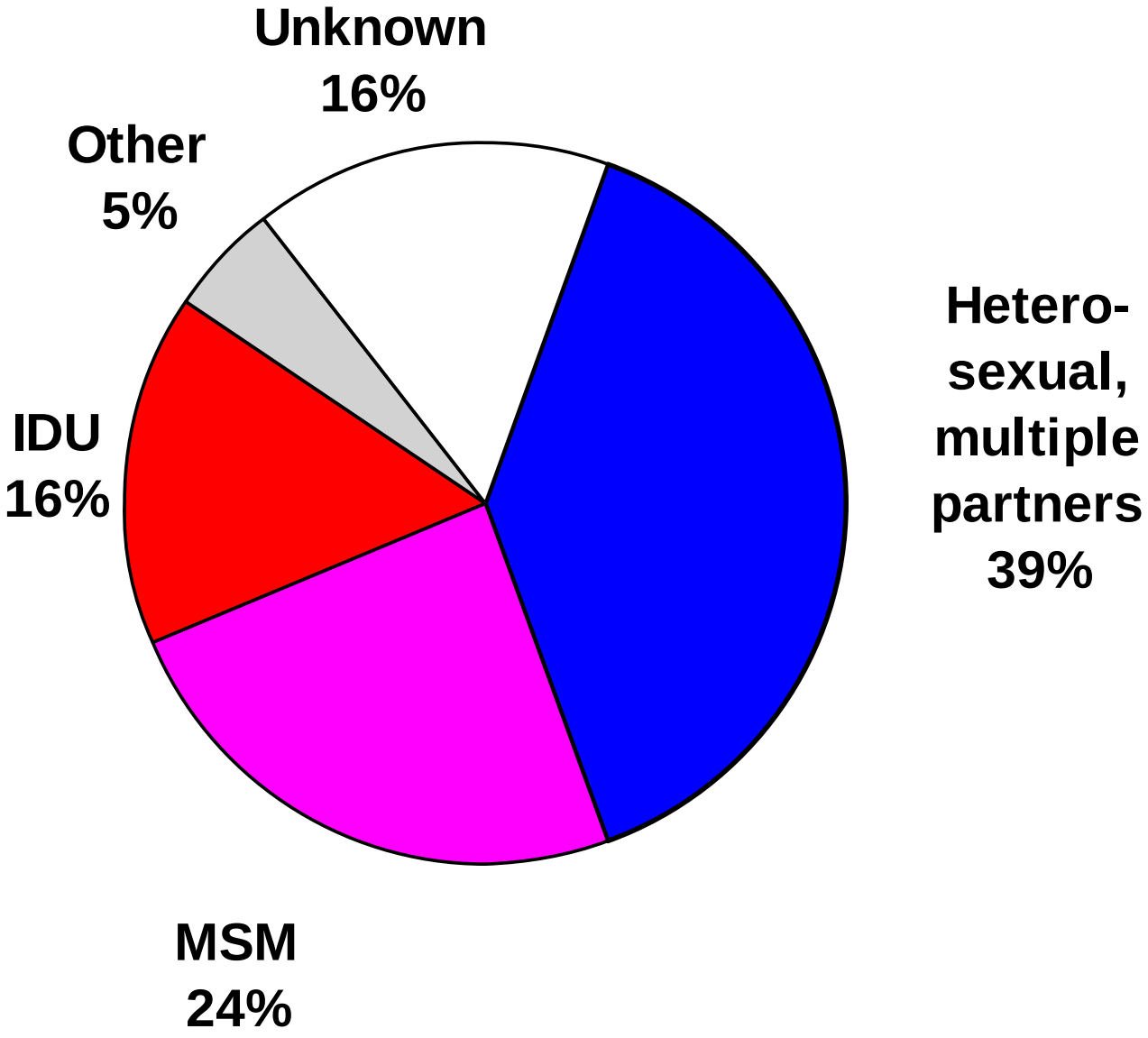
CDC 2008

Hepatitis B: Epidemiology

- HBV very common worldwide, ~350 million infected
- 3 million Turkish carrier (%5 population)
- %1 Cyprus citizen infected with HBV
- HBV is 10x more common in HIV+ than in general population

Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2006.
Nunez M, et al. *Lancet Infect Dis* 2005.

Risk Factors for Hepatitis B



Strategy to Eliminate Hepatitis B Virus Transmission

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
- Vaccination of adults in high-risk groups

Hepatitis B Vaccine
Adolescent and Adult Schedule

Dose	Usual interval
Primary 1	0 month
Primary 2	1 month
Primary 3	5 month

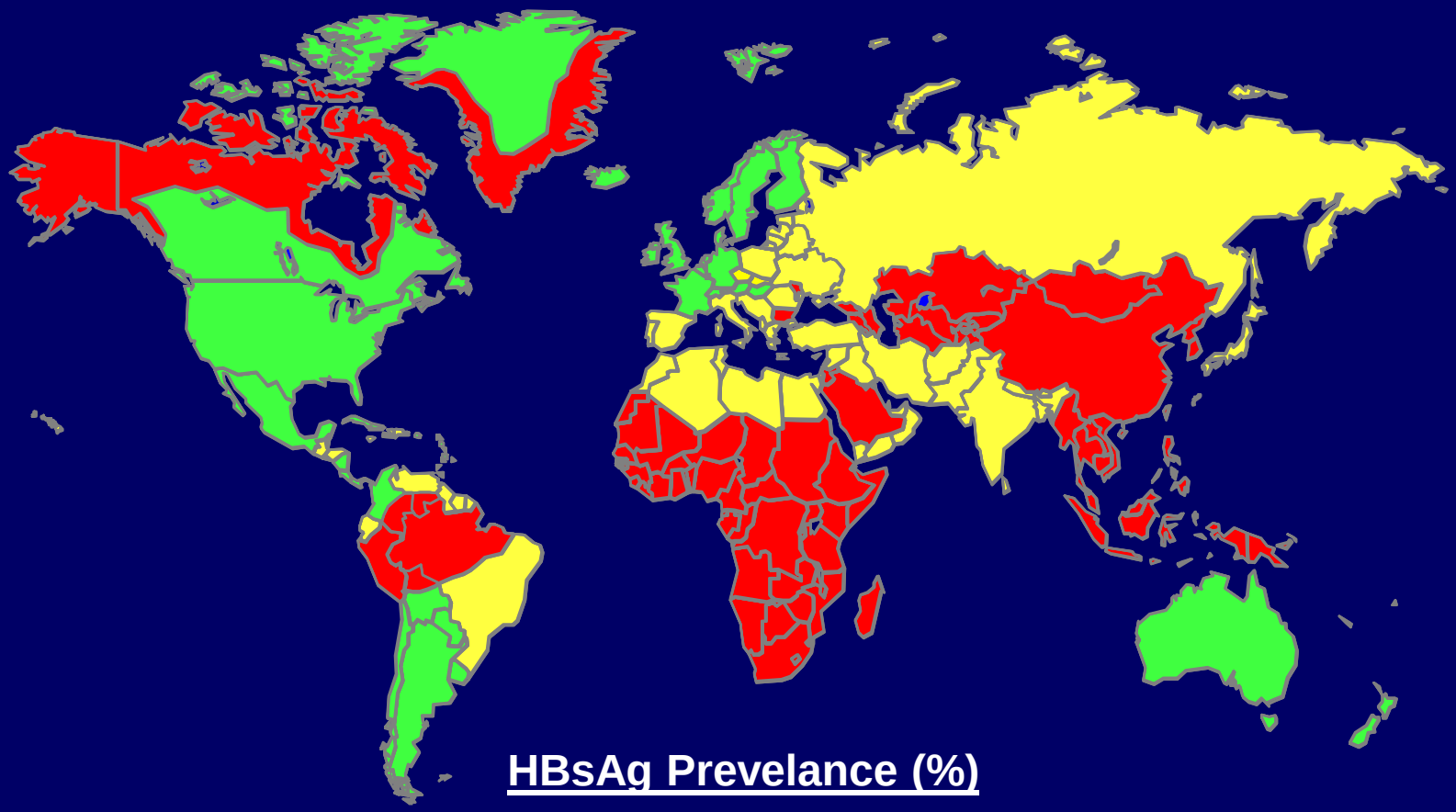
Hepatitis B Vaccine

- Routine booster doses are NOT routinely recommended for any group

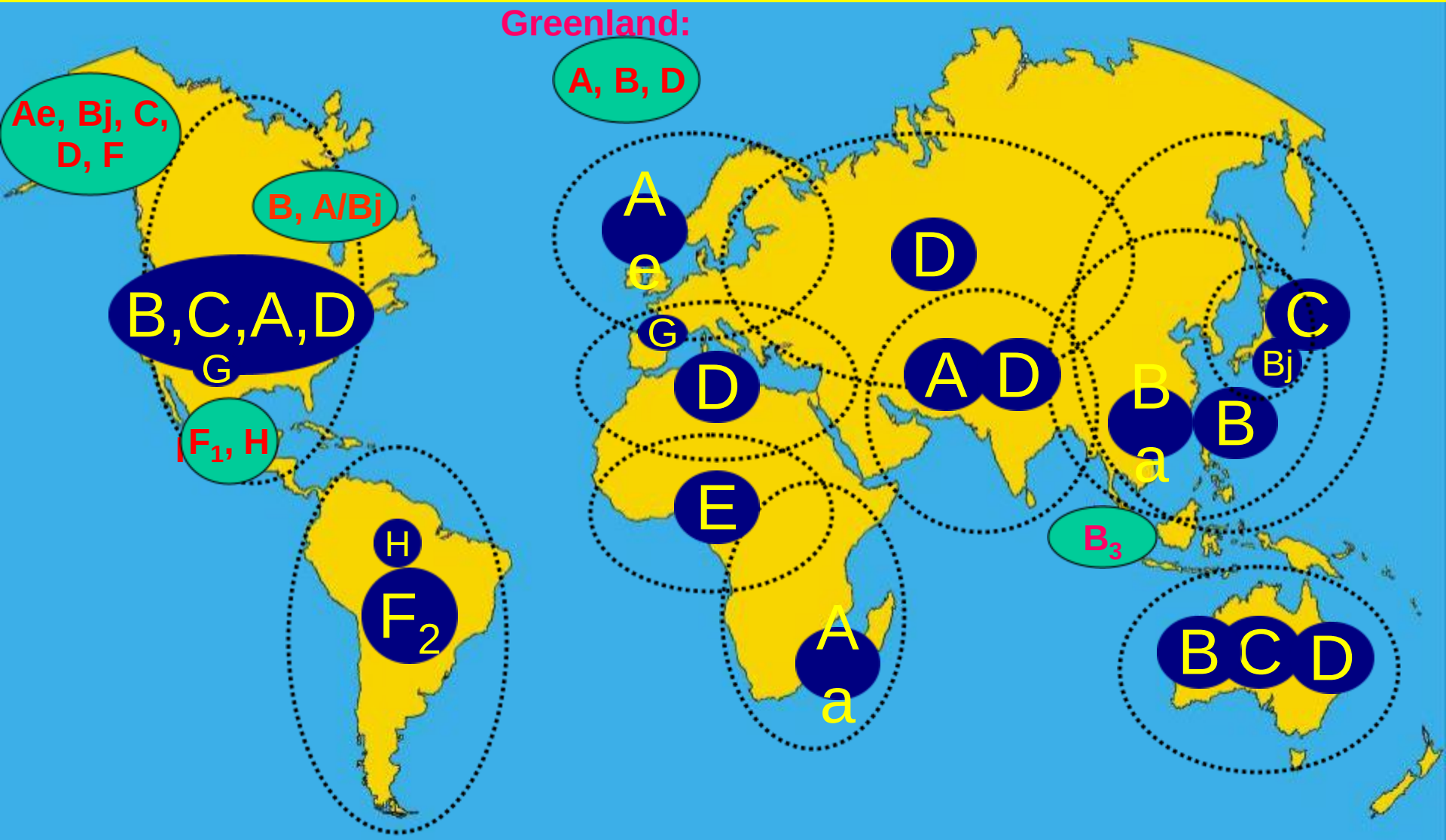
Global Patterns of Chronic HBV Infection

- High (≥8%): 45% of global population
  - lifetime risk of infection >60%
  - early childhood infections common
- Intermediate (2%-7%): 43% of global population
  - lifetime risk of infection 20%-60%
  - infections occur in all age groups
- Low (<2%): 12% of global population
  - lifetime risk of infection <20%
  - most infections occur in adult risk groups

Geographic Distribution of HBV Cases

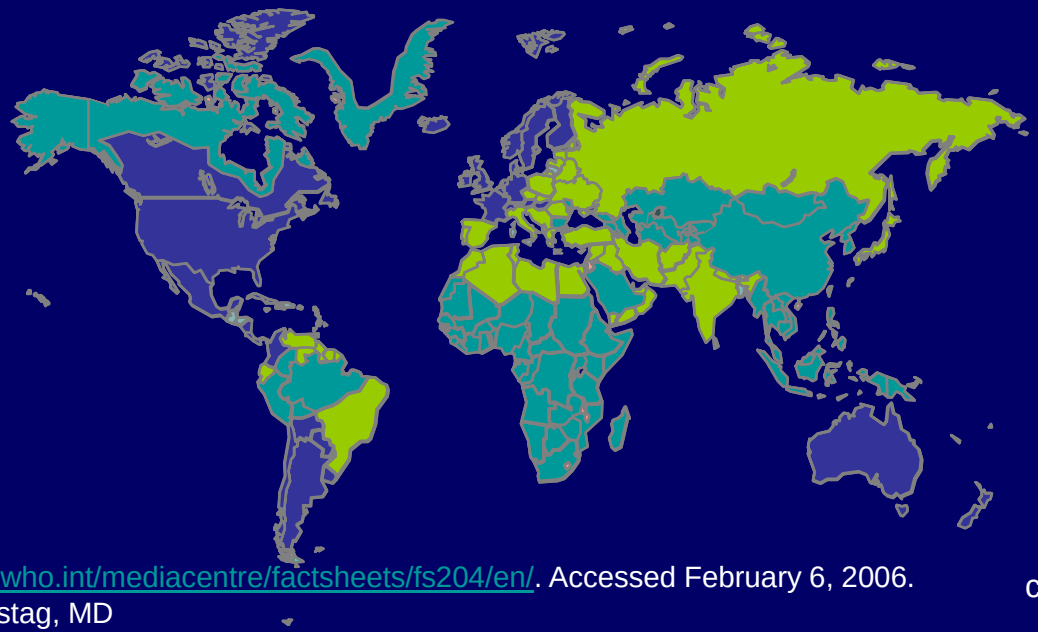


Geographic Distribution of HBV Genotypes



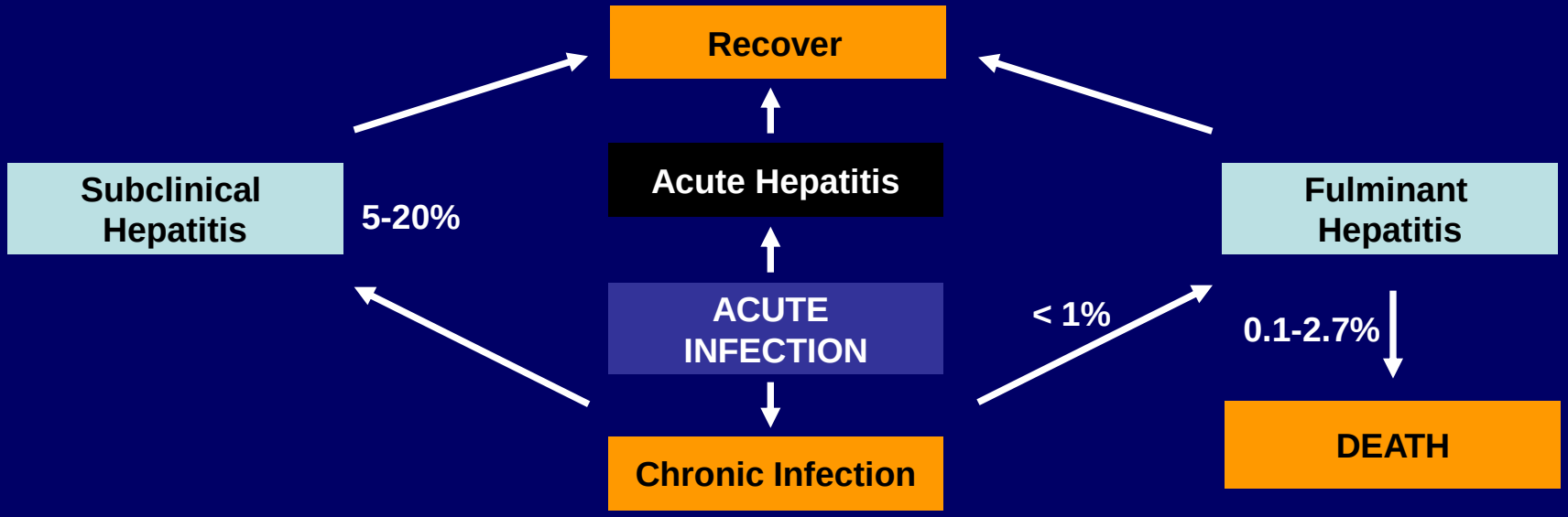
Clinical-Epidemiologic Correlations

HBV Endemicity	Location	Age of Infection	Mode of Transmission	Chronicity	HCC Risk
High 10-15%	Asia Sub-Sahara Africa	Birth Toddler	Perinatal Horizontal	Likely	High
Low < 2%	N. America W. Europe Scandinavia	Early Adulthood	Percutaneous Sexual	Rare	Low



Available at: http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed February 6, 2006.
Designed by Jules Dienstag, MD

Outcomes of Acute HBV Infection



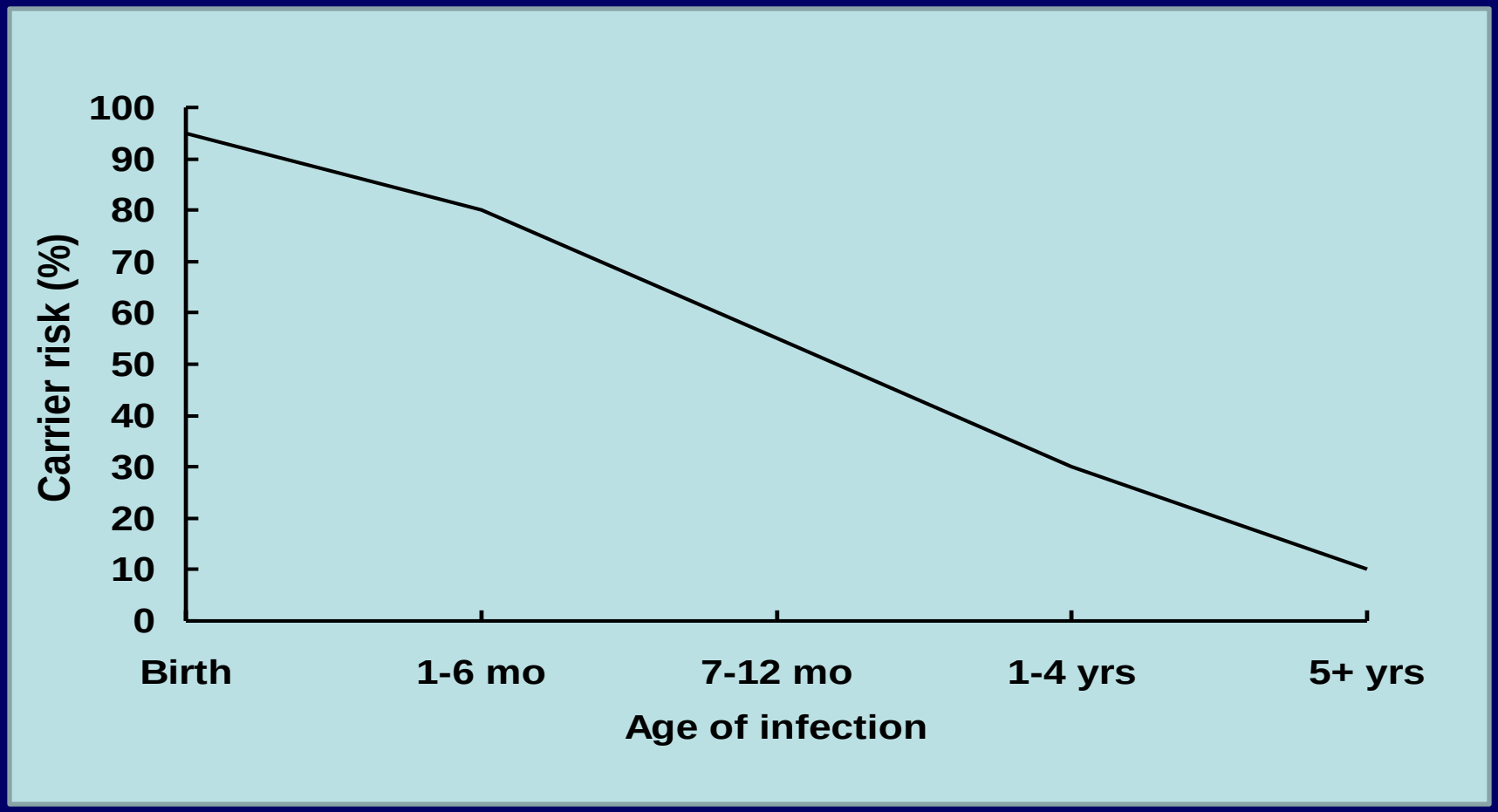
Risk is Related to Age at Infection			
Outcome	**Neonates, %**	**Children, %**	**Adults, %**
Chronic carrier	90	20	< 5
Recover	10	80	> 95

Juszczyk J. Vaccine. 2000;18(suppl 1):S23-S25.

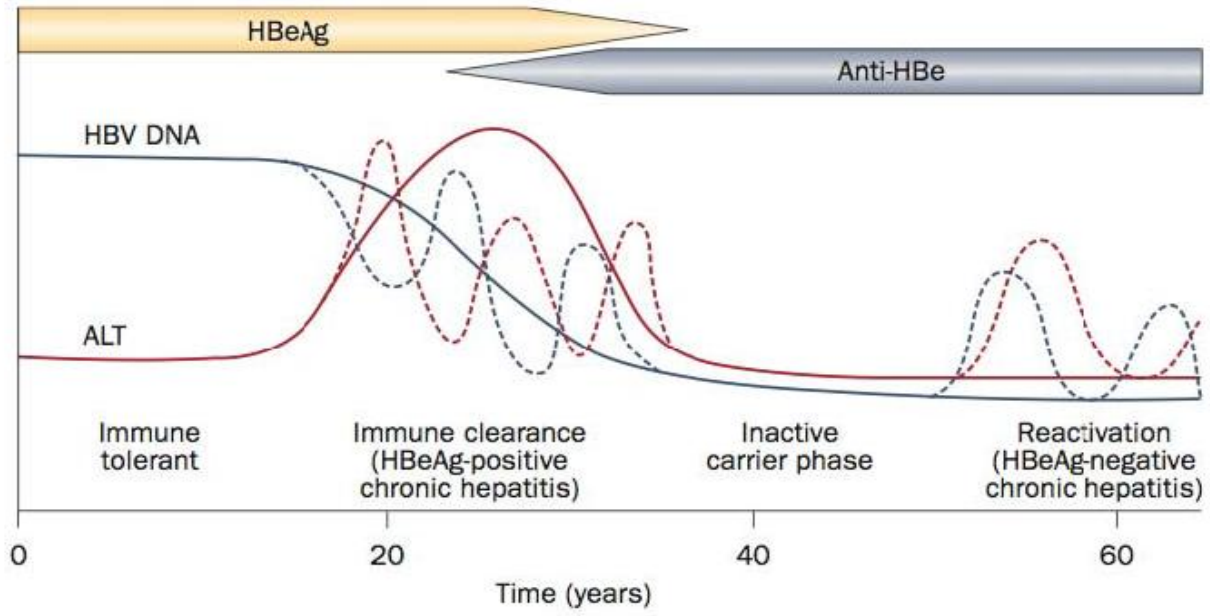
Hepatitis B Complications

- Fulminant hepatitis
- Hospitalization
- Cirrhosis
- Hepatocellular carcinoma
- Death

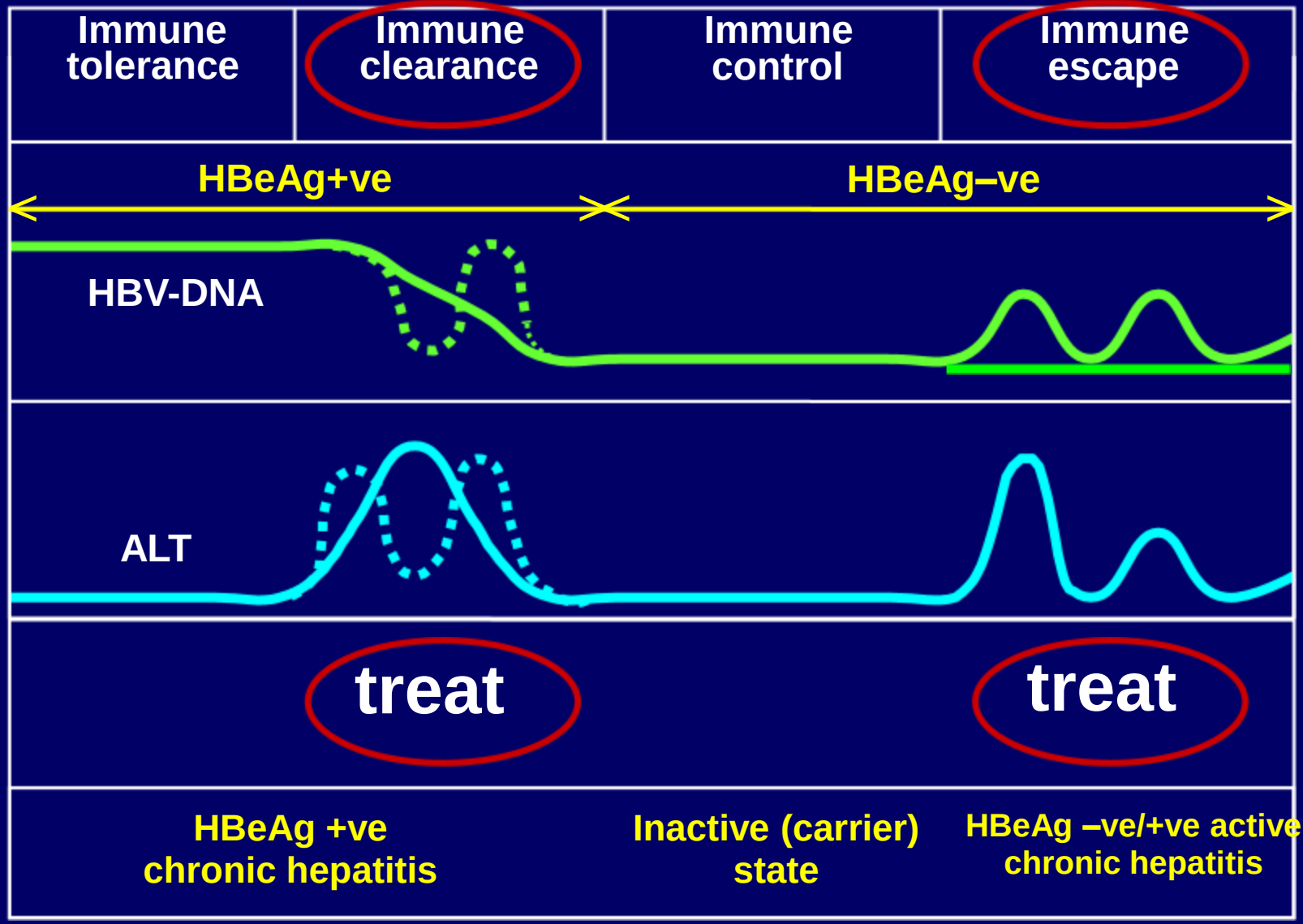
Risk of Chronic HBV Carriage by Age of Infection



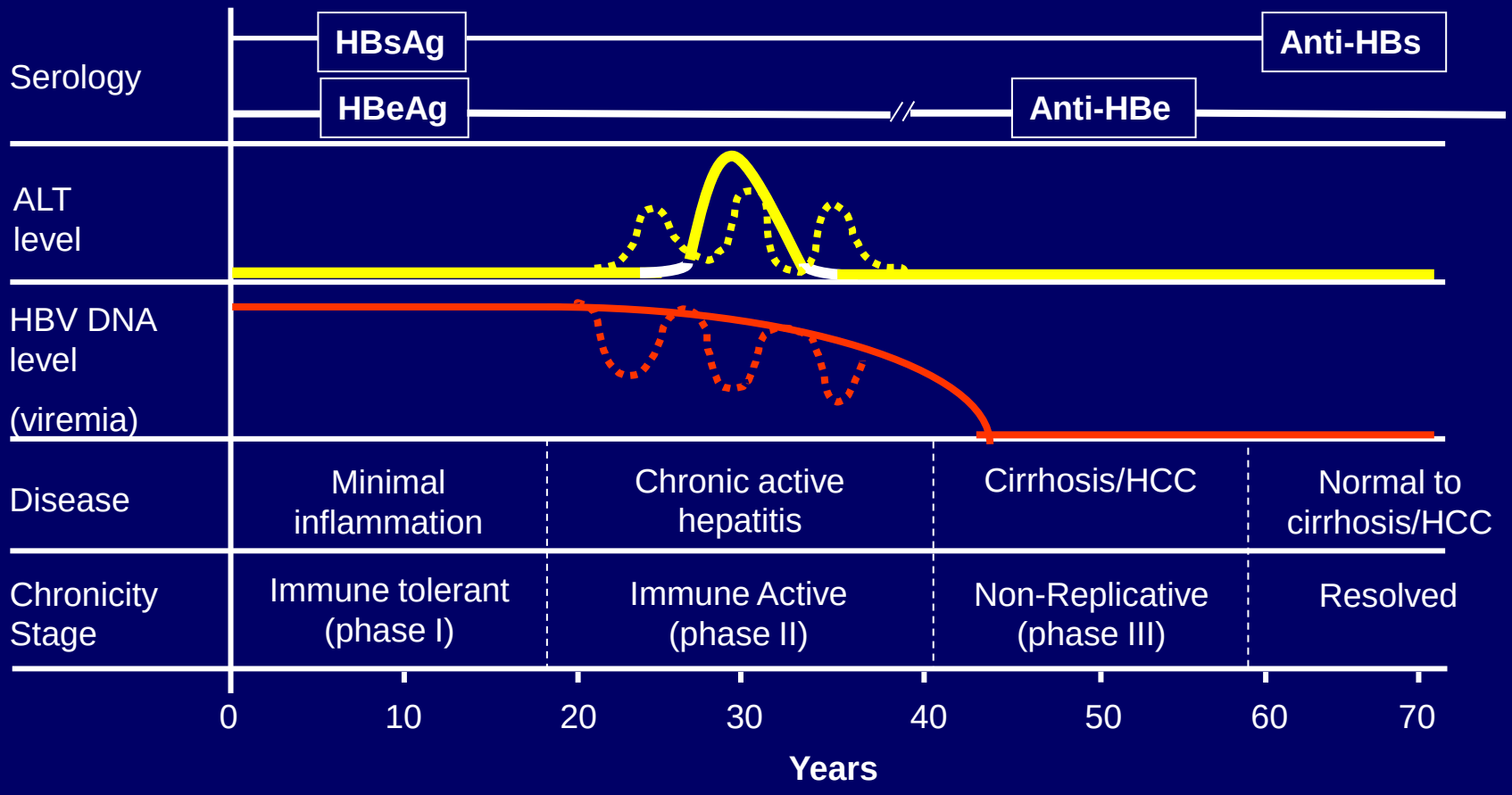
Natural History of Chronic HBV Infection



Who should be considered for treatment?



Natural History of Chronic HBV Infection

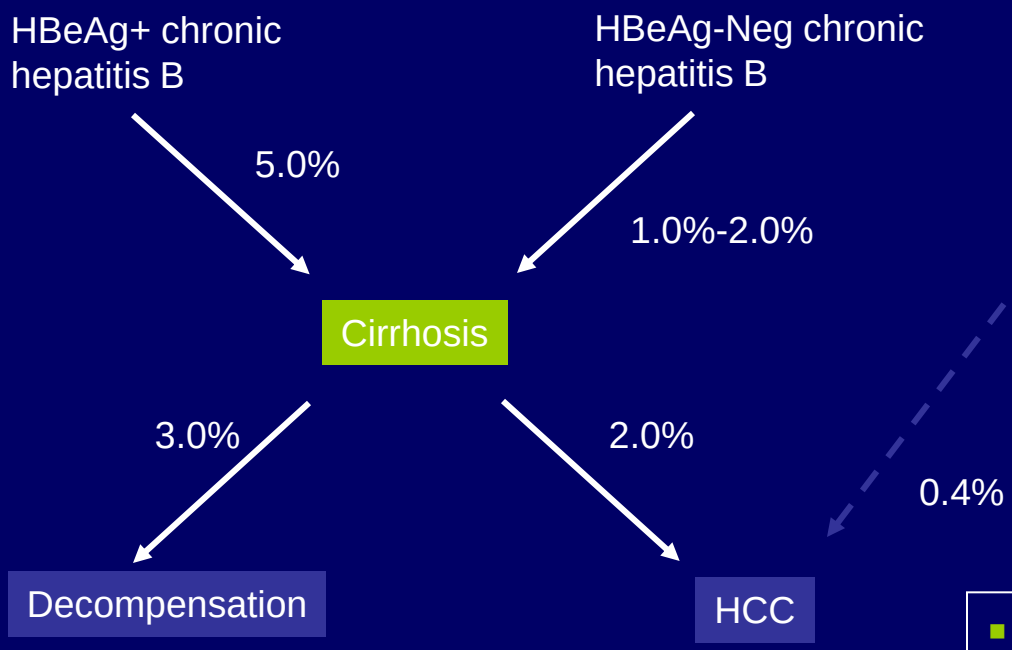


Possible Outcomes of HBeAg+ Chronic HBV Infection

Patient Populations in Chronic Hepatitis B				
Marker	**Immune Tolerant**	**HBeAg+ CHB**	**Inactive HBsAg Carrier**	**HBeAg– CHB (Precore Mutant)**
HBsAg	+	+	+	+
HBeAg	+	+	–	–
Anti-HBe	–	–	+	+
ALT	Normal	↑	Normal	↑
HBV DNA (copies/mL)	$> 10^5$	$> 10^5$	$< 10^3$	$> 10^4$
Histology	Normal/Mild	Active	Normal	Active

Lai CL, et al. Lancet. 2003:362:2089-2094. Lok AS, et al. Gastroenterology. 2001;120:1828-1853.

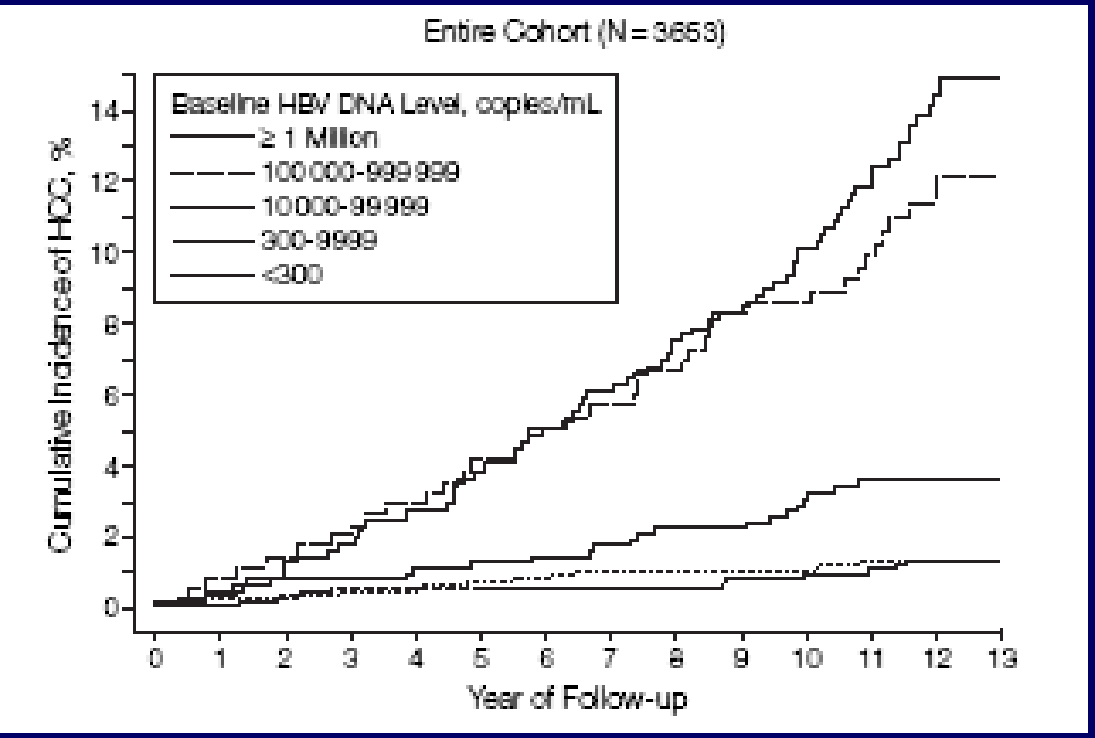
Annual Risk of HBV Progression



- Factors linked with progression
  - Duration of “active”disease
  - Heavy alcohol use
  - Immune suppression (HIV)

Juszczyk J. Vaccine. 2000;18(suppl 1):S23-S25.

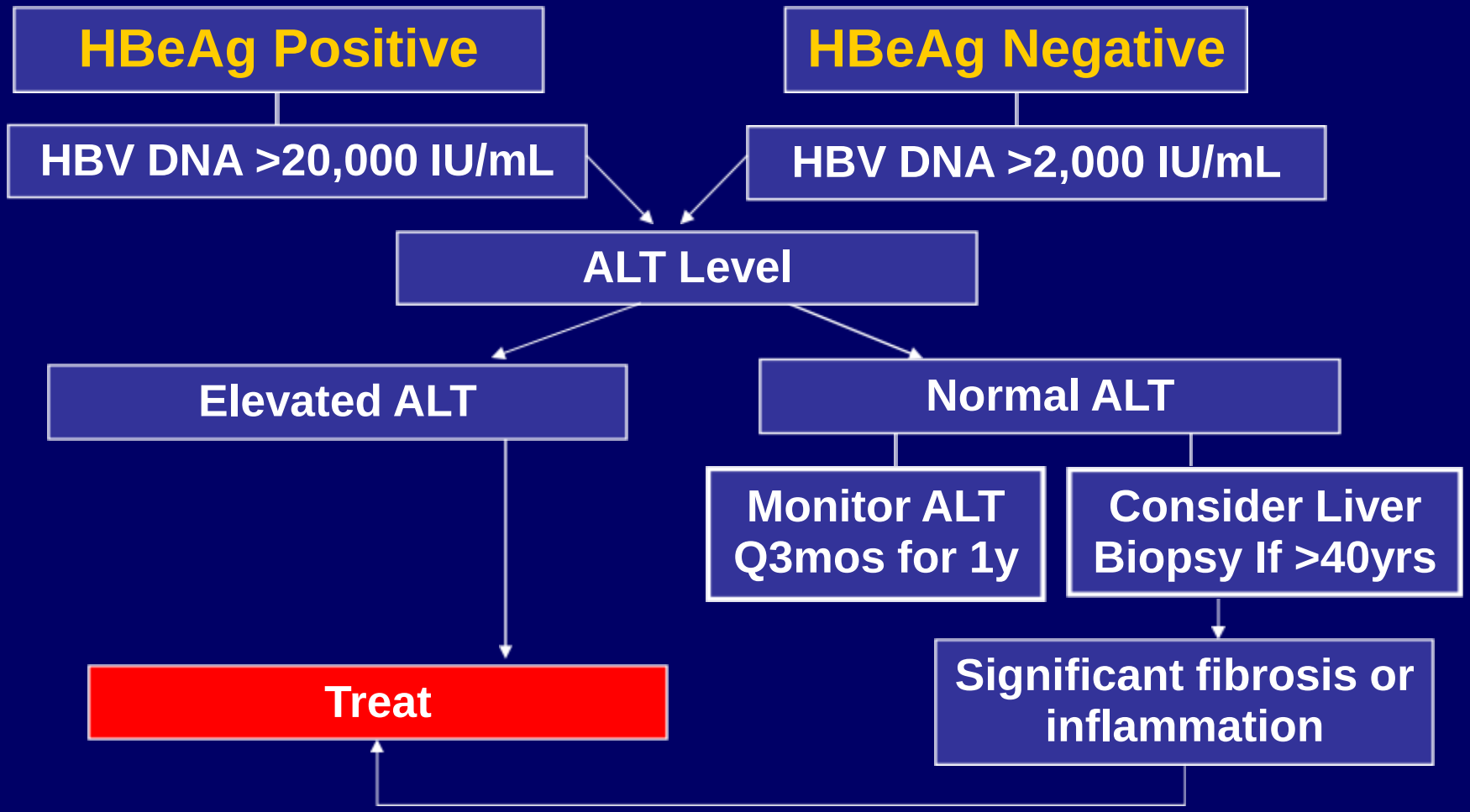
HBV DNA Level and Risk of HCC



HBV DNA (copies/ml)	Cumulative incidence of HCC
<300	1.30
300-9999	1.37
10,000-99,999	3.57
100,000-999,999	12.17
>1 million	14.89

Chen C-J. *JAMA* 2006; 295:67-73.

Overview of Algorithm Used to Determine Need for Treatment of HBV



Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2008
Lok AS et al Hepatology, 2009

HBV Treatment Guidelines

HBeAg	HBV DNA (IU/ml)*	ALT	Management
+	< 20,000	Normal[#]	Follow, no treatment
+	≥ 20,000	Normal	Consider biopsy; treat if diseased
+	≥ 20,000	Elevated	Treat
–	< 2,000	Normal	Follow, no treatment
–	≥ 2,000	Normal	Consider biopsy; treat if diseased
–	≥ 2,000	Elevated	Treat

*1 IU = 5.6 copies; [#]Normal ALT for men = 30 U/ml and for women = 19 U/ml
Keeffe EB, et al. *Clin Gastroenterol Hepatol.*2006.

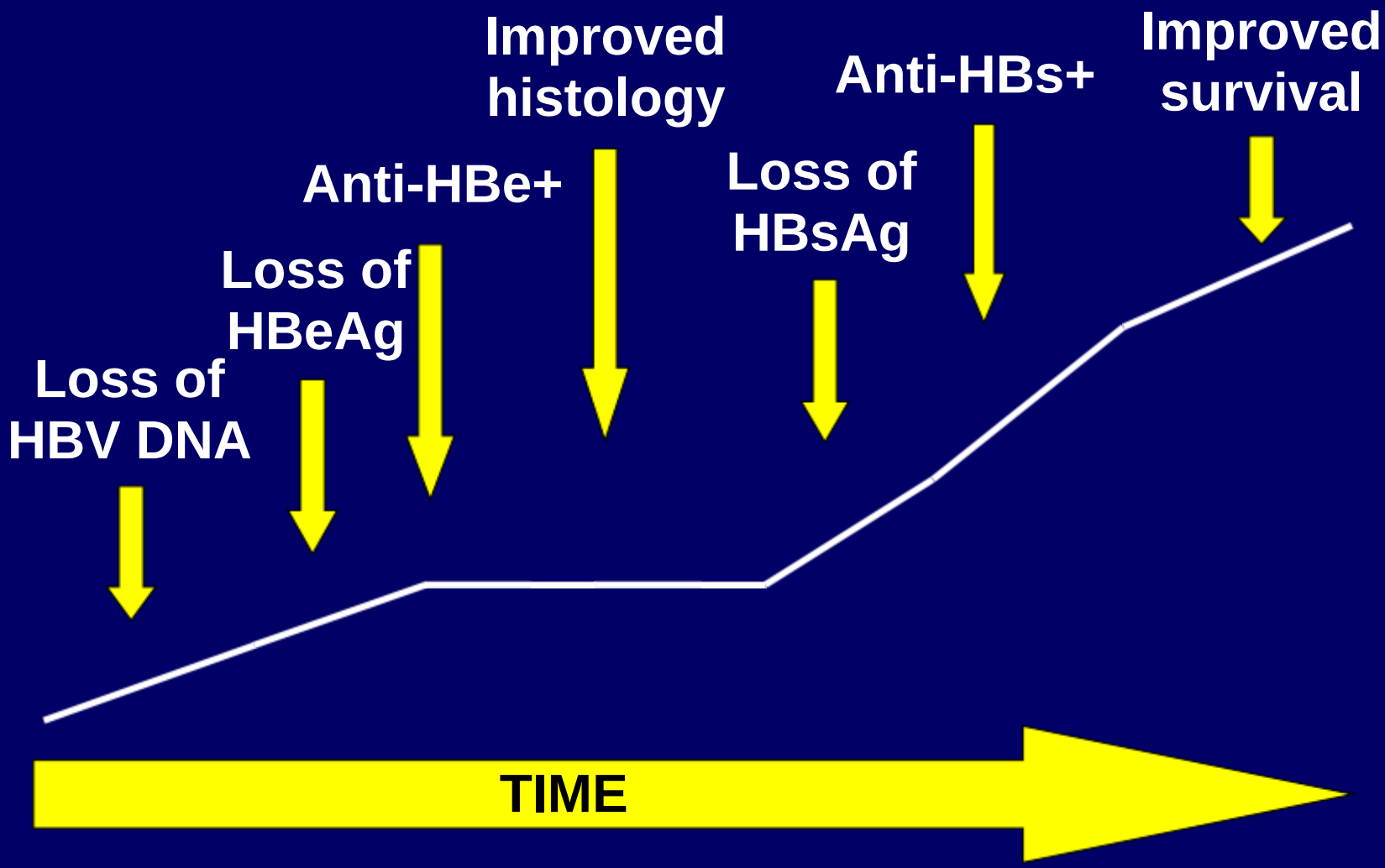
Goals of Therapy in Patients With Chronic HBV Infection

- Eradication of infection
  - HBsAg seroconversion
  - Undetectable HBV DNA
- Prevent complications of liver disease
  - Histologic progression to cirrhosis
  - Decompensated liver disease
  - Liver cancer

Therapeutic Endpoints

- HBeAg-positive patients (wild type)
  - HBeAg seroconversion is **KEY**
  - Sustained suppression of HBV DNA to low or undetectable levels
  - ALT normalization
  - Reduced necroinflammation on biopsy
- HBeAg-negative patients (precore and core promoter mutants)
  - HBeAg seroconversion not an endpoint
  - Sustained suppression of HBV DNA to low or undetectable levels
  - ALT normalization
  - Reduced necroinflammation on biopsy

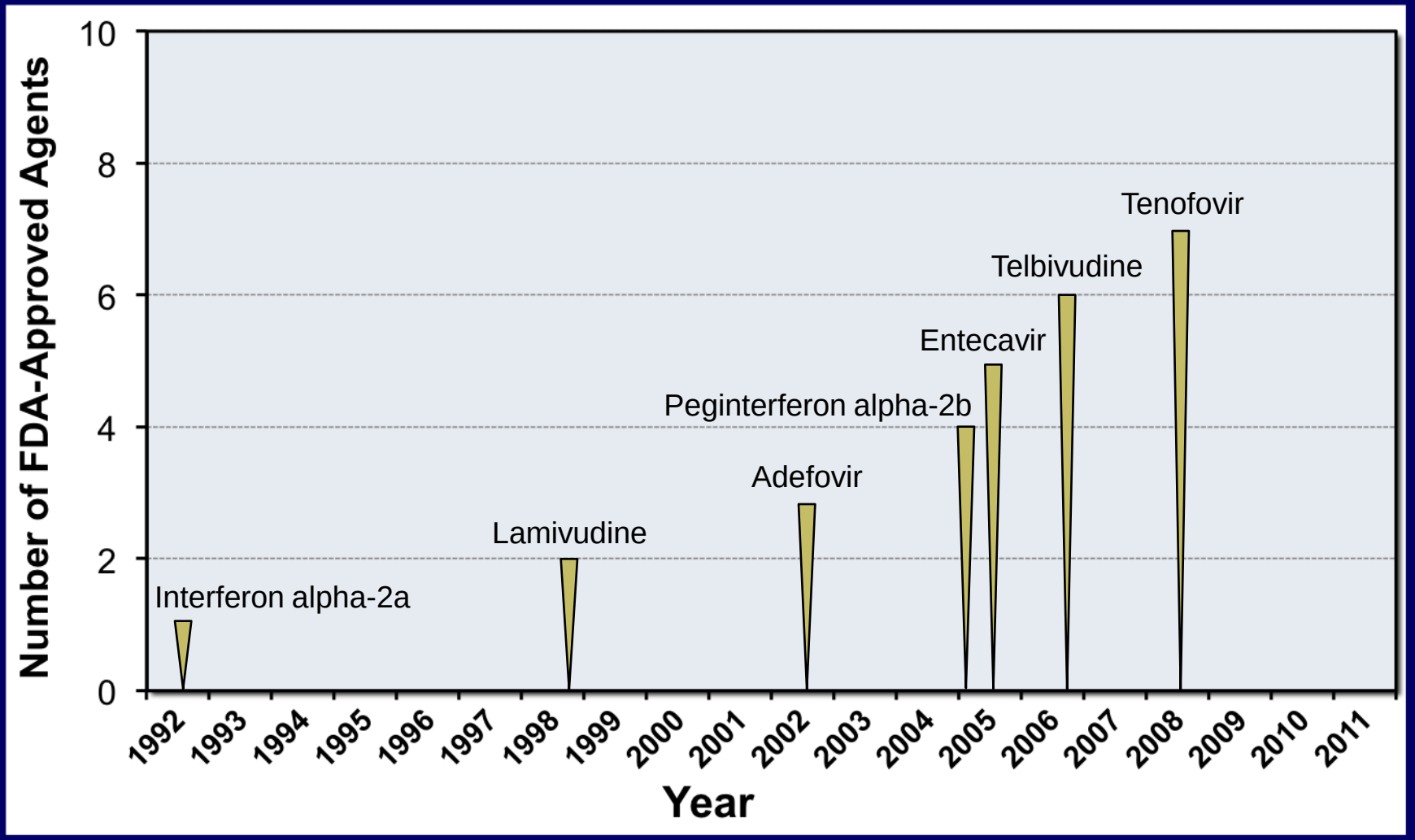
Therapeutic endpoints over time



HBV Control

- Inflammatory: normalize serum ALT, biopsy
- Virologic: decrease HBV DNA
- Immune: seroconversion
  - HBeAg to HBeAb
  - HBsAg to HBsAb
- HBV never “cured” but controlled

Timeline for FDA-Approved Agents used to Treat HBV



Timeline for FDA-Approved Agents used to Treat HBV

Medication	Trade Name	Dose
Interferon alfa-2b	*Intron A*	5 million IU sq once daily or 10 million IU sq 3x/week
Peginterferon alfa-2a	*Pegasys*	180 mcg sq once weekly
Lamivudine (3TC)	*Zeffix,HBV* (100 mg) *Epivir*	100 mg PO once daily 300 mg PO once daily for HIV-infected
Adefovir (ADV)	*Hepsera*	10 mg PO once daily
Entecavir (ETV)	*Baraclude*	0.5 mg PO once daily: treatment-naïve 1 mg PO once daily: lamivudine resistance
Telbivudine (LdT)	*Tyzeka*	600 mg PO once daily
Tenofovir (TDF)	*Viread*	300 mg PO once daily

Abbreviations: IU = international units; sq = subcutaneously qd = once daily bid = twice daily

Lamivudine (3TC, Zeffix,Epivir)

- Nucleoside analog
- Different dose for HBV (100 mg) monotherapy
- Well-tolerated and cheap
- HBeAg conversion rate b/t 21-28%
- High rates of resistance!
  - 47% develop YMDD mutation at 2 yrs, 90% at 4 yrs

Adefovir (Hepsera)

- Nucleotide analog
- At 10 mg/d dose
- Effective for LAM resistant HBV, no cross-resistance
- Side effects: renal toxicity, Fanconi's Syndrome

Tenofovir (Viread)

- Nucleotide analog for HBV
- Perhaps more potent than Adefovir
  - 48 wk mean decline in HBV DNA (log10) 4.4 vs 3.2
- 63% had HBV suppression by wk 48, 15% had anti-HBe seroconversion
- Rare cases of ADV resistance but TDF sensitivity

Schildgen O. 2006 N Engl J Med 354:1807-12
Peters M. CROI 2005; Abstract 124.

Entecavir (Baraclude)

- Nucleoside analog
- Good for LAM failures
  - 84% of patients had 2 log decline or <400 copies/ml after 24 wks
- Cross-resistance can occur w/ LAM
- Start w/ higher dose (1.0 mg/d) Entecavir in HIV/HBV patients

Peg-interferon alfa 2a/2b (Pegasys,Pegintron)

- Long acting form of IFN, once weekly
- Pros: defined duration (48 wks), low resistance
- Cons: Many side effects, expensive, not for decompensated cirrhosis

Pegintron used for Chronic HBV: Adverse Effects

Adverse Effects

Systemic
- Fever (low grade)
- Myalgias/Arthralgias
- Fatigue

Mood Disturbances
- Depression
- Irritability
- Insomnia

Hematologic
- Neutropenia
- Anemia
- Thrombocytopenia

Endocrine
- Hypothyroidism
- Hyperthyroidism

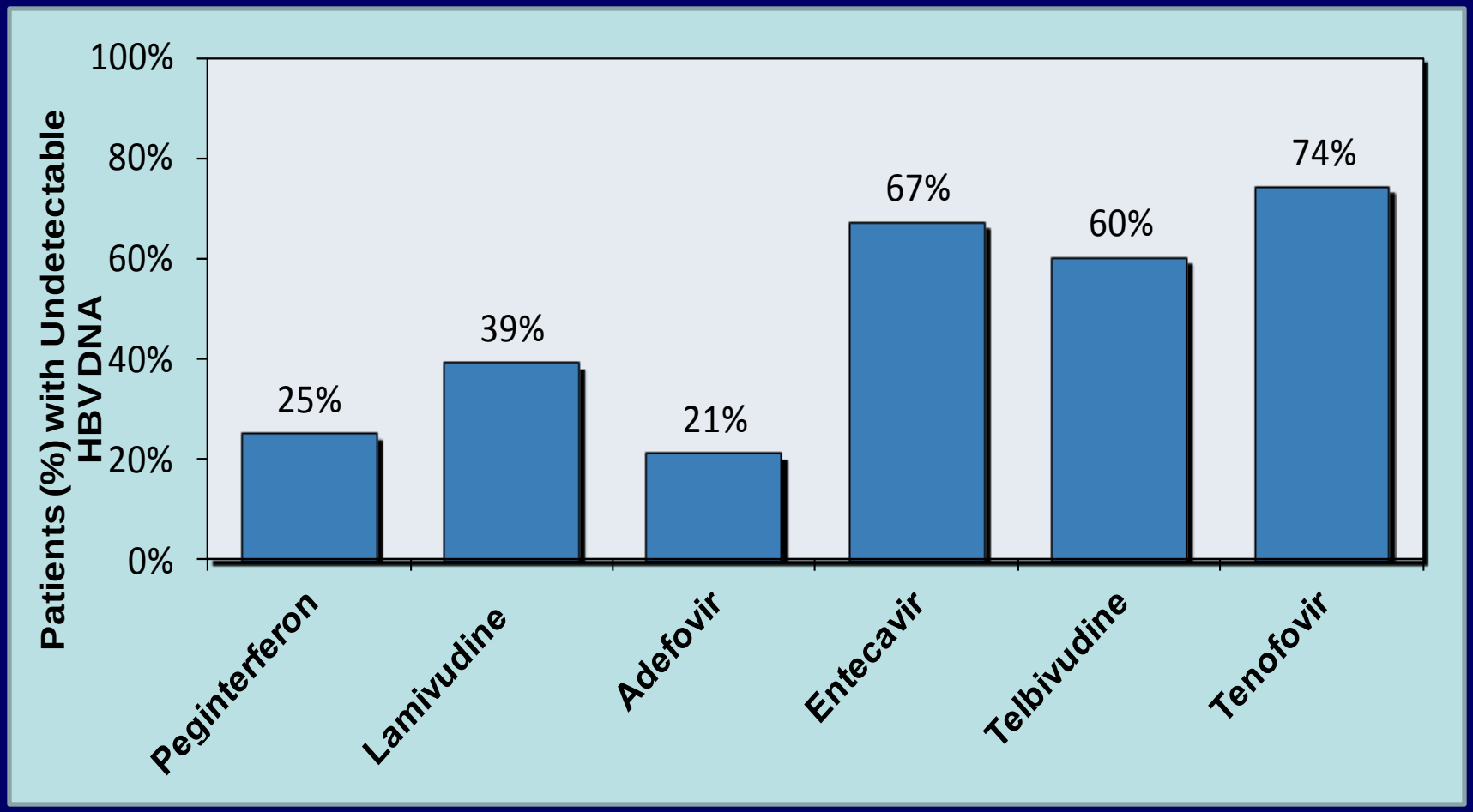
Dermatologic
- Rash
- Dry skin
- Pruritis
- Thinning of Hair

Gastrointestinal
- Anorexia
- Nausea
- Weight loss

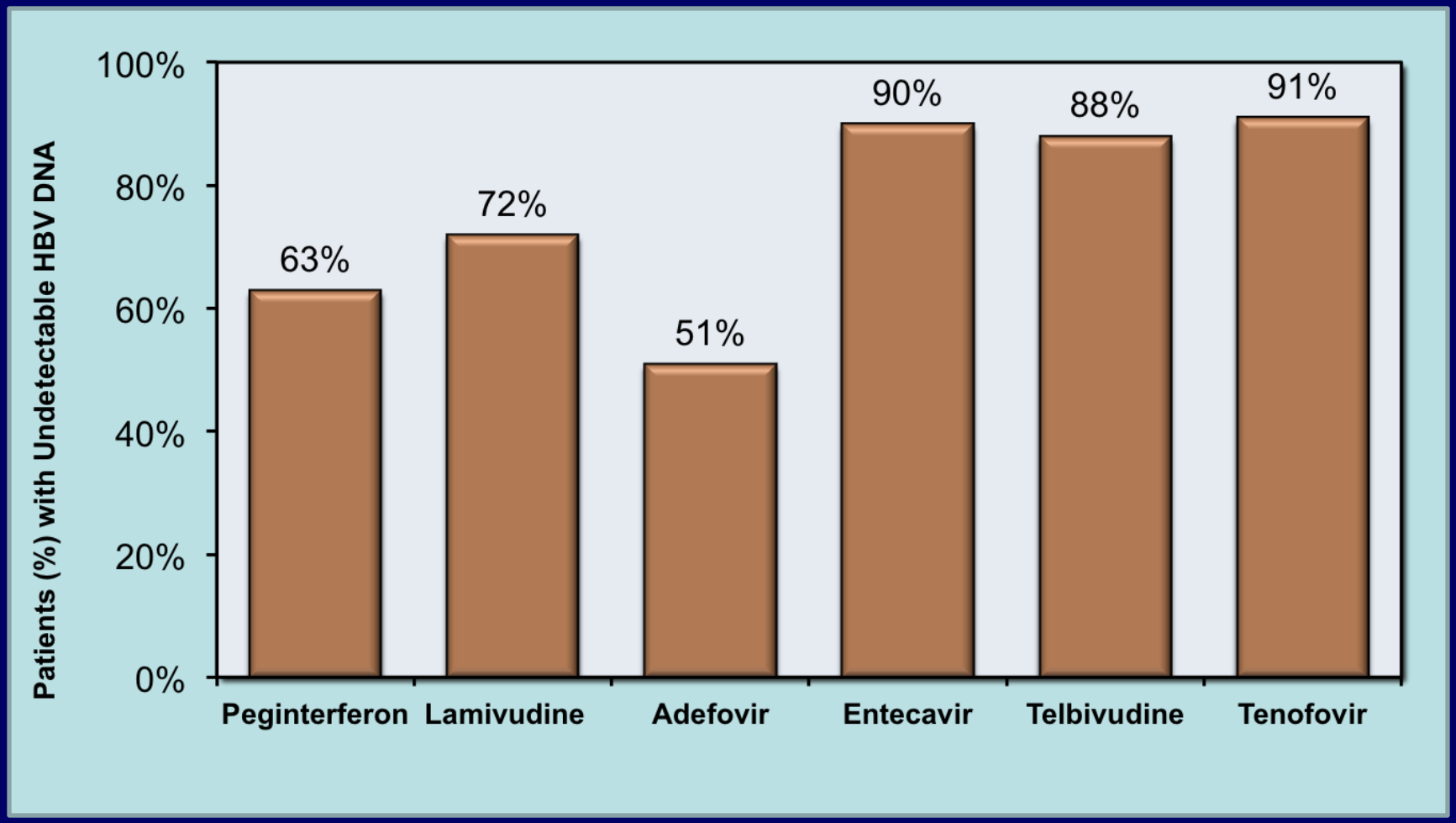
Agents used for Chronic HBV: Cautionary Notes

Medication	Cautionary Note
Interferon alfa-2b and Peginterferon alfa-2a	Contraindicated in patients with: • Uncontrolled major depression (especially with past suicide attempts) • Autoimmune hepatitis or other autoimmune diseases • Severe cardiovascular disease (e.g. uncontrolled hypertension, coronary artery disease, congestive heart failure) • Decompensated cirrhosis or hepatocellular carcinoma • Uncontrolled seizure disorder
Lamivudine (3TC)	Not recommended for first-line anti-HBV therapy because of high resistance rates
Adefovir (ADV)	Caution in patients with baseline renal insufficiency
Entecavir (ETV)	Taken on empty stomach (>2 hours before or after a meal); should not use without HIV therapy in HIV-HBV co-infected patients
Tenofovir (TDF)	Caution in patients with baseline renal insufficiency

Undetectable HBV DNA Levels after 1 Year of Therapy (HBeAg Positive)



Undetectable HBV DNA Levels after 1 Year of Therapy (HBeAg Negative)



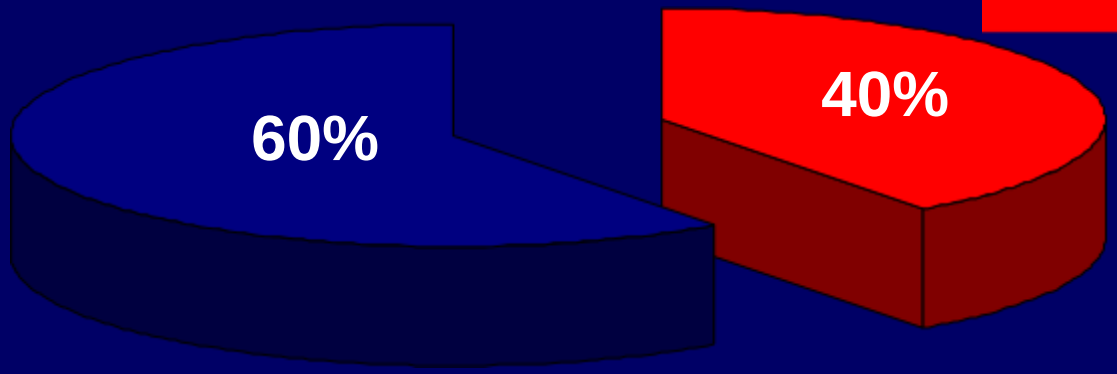
HBV is a dynamic disease

- Diagnose
- Initial evaluation includes education
  - Family and sexual contacts should be tested
- Monitor as status changes over time
- Selection of patients to treat
  - Individualize treatment decisions
  - Change if no/ poor response
- Long term monitoring
  - HCC, special populations, reactivation

HBV: The importance of monitoring

HBV is a dynamic disease!!!

Require treatment



Require monitoring…

- Inactive disease may not remain inactive
- Liver damage may occur if HBV reactivates

HBV can be controlled but not cured