

# **Hepatitis B Update**

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# *Disclosures*

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- *Research Grants*
    - *BMS, Gilead, Merck*
  - *Advisory Board*
    - *BMS, Gilead, Merck, Roche*
  - *DSMB*
    - *GSK*
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# ***Hepatitis B Update***

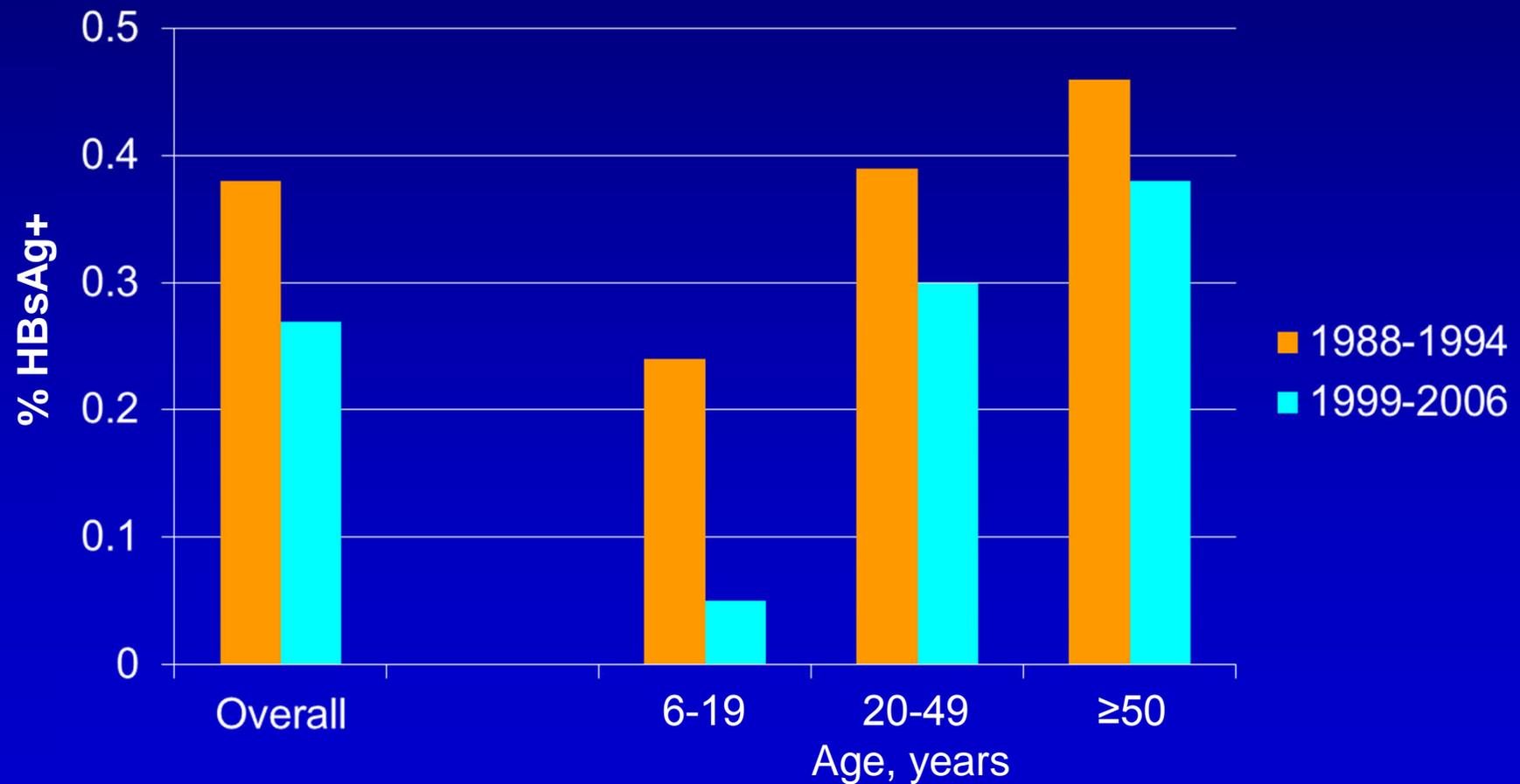
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- ***How common is hepatitis B in the US?***
  - ***Who should be screened for HBV, which tests to order and how to interpret those test results?***
  - ***Which patients are most likely to develop cirrhosis or hepatocellular carcinoma?***
  - ***How can hepatitis B be prevented?***
  - ***How effective is HBV treatment?***
  - ***Who should be considered for treatment?***
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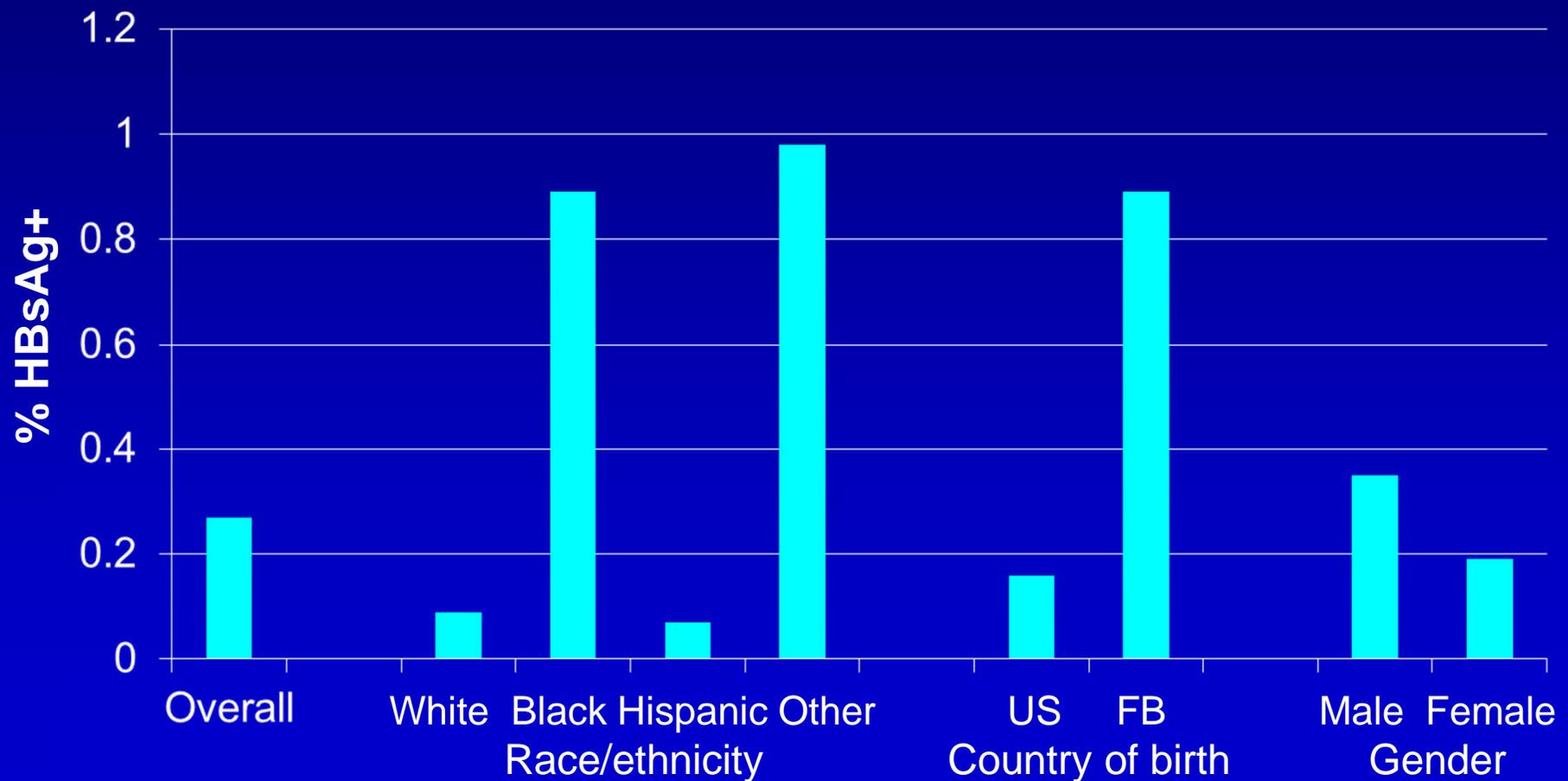
## ***HBV Infection - Disease Burden***

	<b><i>HBV</i></b>
<b><i>Worldwide</i></b>	
<b><i>Chronic infection</i></b>	<b><i>350 million</i></b>
<b><i>New infection/yr</i></b>	<b><i>21 million</i></b>
<b><i>Mortality/yr</i></b>	<b><i>600,000</i></b>
<b><i>U.S.</i></b>	
<b><i>Chronic infection</i></b>	<b><i>0.8-1.4 million</i></b> <b><i>(65% unaware of infection)</i></b>
<b><i>New infection/yr</i></b>	<b><i>43,000</i></b>
<b><i>Mortality/yr</i></b>	<b><i>3,000</i></b>

# Age Adjusted Prevalence of Chronic HBV Infection in the US, NHANES



# Age Adjusted Prevalence of Chronic HBV Infection in the US, NHANES 1999-2006



## ***Changing Epidemiology of HBV Infection in the US***

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- ***Incidence of acute HBV infection decreased***
  - ***Prevalence of chronic HBV infection decreased overall but remains high in some groups***
  - ***95% of new cases of chronic HBV infection are imported***
  - ***Approximately 2/3 of those chronically infected are not aware of the infection***
  - ***Efforts to improve awareness and diagnosis are needed***
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# ***Hepatitis B Update***

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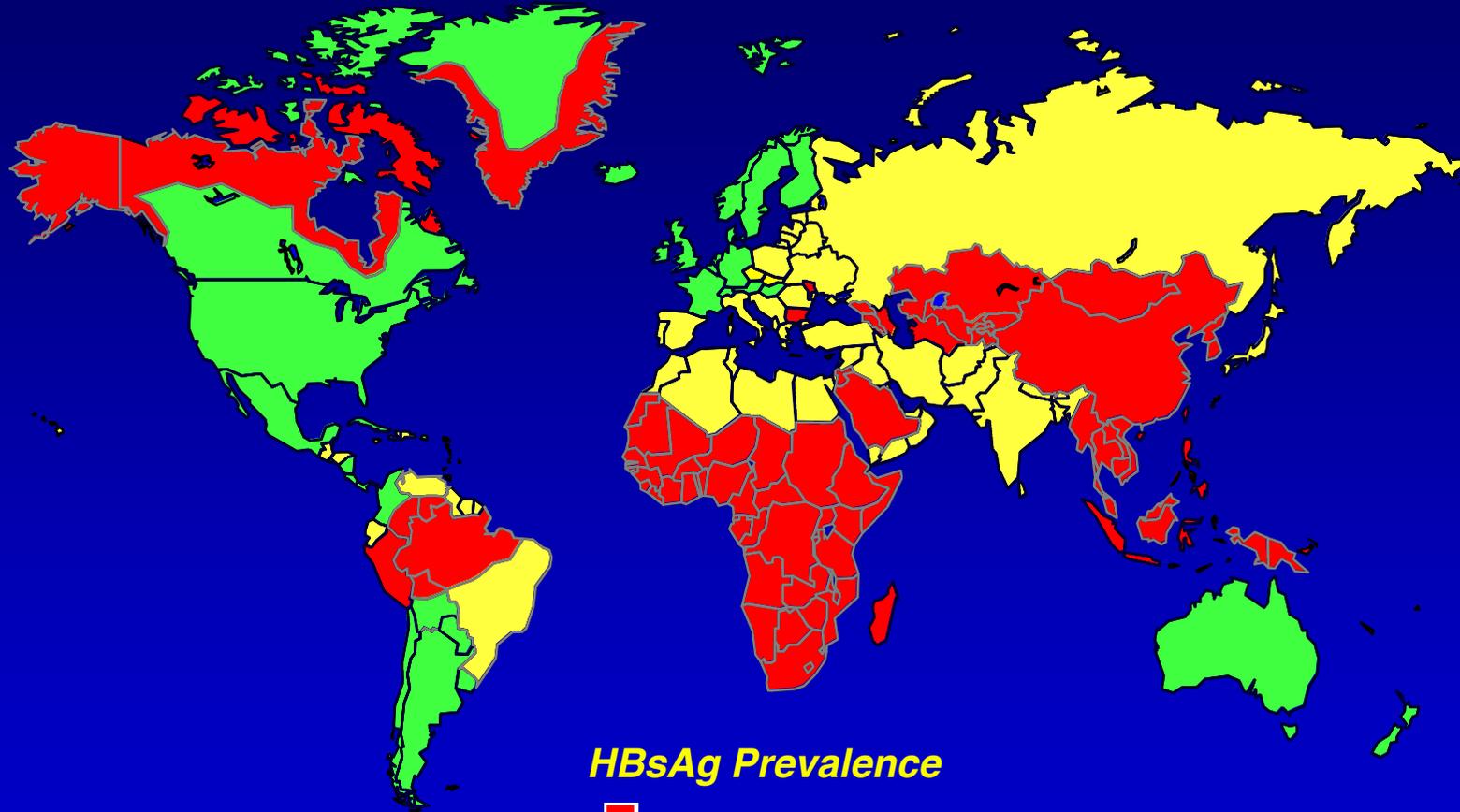
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  - *How effective is HBV treatment?*
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-

# ***Who Should be Screened for HBV?***

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- ***Persons born in geographical regions with HBsAg prevalence rate  $\geq 2\%$***
- ***Infants born to infected mothers***
- ***Household contact / sexual partners of infected persons***
- ***Persons with risk behaviors: IDU, MSM, multiple sex partners***
- ***Hemodialysis patients***
- ***Persons with HIV infection***
- ***Persons who have chronic liver disease***
- ***Persons who require long-term immunosuppressive therapy***

# *Geographic Distribution of Chronic HBV Infection*



## *HBsAg Prevalence*

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

## ***How can hepatitis B be diagnosed?***

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- ***The only way to know is to have a blood test***
  - ***Most people with hepatitis B have no symptoms until late stages of liver disease***
  - ***Tests for hepatitis B or liver enzymes are not included in most routine check-ups***
  - ***Hepatitis B may be present even if liver enzymes were tested and were normal***
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# ***Serological Markers of HBV Infection***

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<b><i>HBsAg</i></b>	<b><i>Acute/Chronic infection</i></b>
<b><i>Anti-HBc IgM</i></b>	<b><i>Recent infection</i></b>
<b><i>HBeAg</i></b>	<b><i>High infectivity</i></b>
<b><i>Anti-HBe</i></b>	<b><i>Low infectivity</i></b>
<b><i>Anti-HBs</i></b>	<b><i>Immunity</i></b>
<b><i>Anti-HBc IgG + HBsAg</i></b>	<b><i>Chronic infection</i></b>
<b><i>Anti-HBc IgG + anti-HBs</i></b>	<b><i>Resolved infection</i></b>

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# *Interpretation of HBV Serology*

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<b><i>HBsAg</i></b>	<b><i>Total anti-HBc</i></b>	<b><i>IgM anti-HBc</i></b>	<b><i>Anti-HBs</i></b>	<b><i>Interpretation</i></b>
-	-	-	-	<i>Not been exposed</i>

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-	-	-	-	<i>Not been exposed</i>
+	+	-	-	<i>Chronic infection</i>

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<b><i>-</i></b>	<b><i>-</i></b>	<b><i>-</i></b>	<b><i>-</i></b>	<b><i>Not been exposed</i></b>
<b><i>+</i></b>	<b><i>+</i></b>	<b><i>-</i></b>	<b><i>-</i></b>	<b><i>Chronic infection</i></b>
<b><i>+</i></b>	<b><i>+</i></b>	<b><i>+</i></b>	<b><i>-</i></b>	<b><i>Acute Infection</i></b>

# *Interpretation of HBV Serology*

<b>HBsAg</b>	<b>Total anti-HBc</b>	<b>IgM anti-HBc</b>	<b>Anti-HBs</b>	<b>Interpretation</b>
-	-	-	-	<i>Not been exposed</i>
+	+	-	-	<i>Chronic infection</i>
+	+	+	-	<i>Acute Infection</i>
-	+	-	+	<i>Immunity from past infection</i>

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<b><i>+</i></b>	<b><i>+</i></b>	<b><i>-</i></b>	<b><i>-</i></b>	<b><i>Chronic infection</i></b>
<b><i>+</i></b>	<b><i>+</i></b>	<b><i>+</i></b>	<b><i>-</i></b>	<b><i>Acute Infection</i></b>
<b><i>-</i></b>	<b><i>+</i></b>	<b><i>-</i></b>	<b><i>+</i></b>	<b><i>Immunity from past infection</i></b>
<b><i>-</i></b>	<b><i>-</i></b>	<b><i>-</i></b>	<b><i>+</i></b>	<b><i>Immunity after vaccination</i></b>

# Interpretation of HBV Serology

<b>HBsAg</b>	<b>Total anti-HBc</b>	<b>IgM anti-HBc</b>	<b>Anti-HBs</b>	<b>Interpretation</b>
-	-	-	-	<i>E - Not been exposed</i>
+	+	-	-	<i>B - Chronic infection</i>
+	+	+	-	<i>A - Acute Infection</i>
-	+	-	+	<i>D - Immunity from past infection</i>
-	-	-	+	<i>C - Immunity after vaccination</i>
-	+	-	-	?

## ***Isolated Anti-HBc+: What does that mean? HBsAg-, anti-HBc+, anti-HBs-***

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- ***Previous chronic HBV infection with loss of HBsAg***
    - ***Most common, particularly in patients from HBV endemic areas or in patients with risk factors for HBV***
    - ***HBV persists in liver, reactivation may occur during immunosuppressive therapy***
  - ***Recovery from transient HBV infection with loss of anti-HBs***
  - ***Window phase of acute HBV infection***
  - ***False positive anti-HBc test result***
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## ***Evaluation of Patients with Isolated Anti-HBc***

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- ***Confirmation of test results***
    - ***Repeat test for HBsAg, IgG anti-HBc, anti-HBs***
      - ***Confirm isolated anti-HBc***
    - ***Consider testing for anti-HBe***
      - ***Confirm exposure to HBV, true positive anti-HBc***
    - ***Consider testing for HBV DNA***
      - ***Undetectable in most cases, worthwhile in patients who will be starting immunosuppressive therapy***
  - ***HBV vaccination***
    - ***Unnecessary in most cases***
  - ***Educate patient of risk of HBV reactivation during immunosuppressive therapy***
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## ***Importance of Monitoring Serum HBV DNA Levels***

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- **Direct measurement of HBV replication**
  - **Determine phase of chronic HBV infection, indications for treatment and treatment response**
  - **Fluctuating levels, serial tests important for clinical assessment**
  - **HBV DNA levels do not always correlate with ALT levels or histologic activity of liver disease**
  - **Persistently high serum HBV DNA levels are associated with increased risk of cirrhosis and HCC**
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# ***Initial Evaluation of Patients with Hepatitis B***

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- ***Clinical evaluation***
  - ***Lab tests***
    - ***HBeAg, anti-HBe, HBV DNA***
    - ***Tests to r/o HCV, HDV, HIV, other causes of liver disease if indicated***
    - ***Tests to assess liver disease severity – liver chemistry, CBC+P, PT***
  - ***+/- Abdominal ultrasound – assess cirrhosis, surveillance for liver cancer***
  - ***+/- Liver biopsy***
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## ***Initial Evaluation of Patients with Hepatitis B***

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- ***Vaccination against hepatitis A***
  - ***Counseling on precautions to prevent transmission of infection, limit alcohol use, and healthy lifestyle***
  - ***Emphasize importance of long-term follow-up***
  - ***Screening of household and sexual contacts for HBV and vaccination of those who test negative for both HBsAg and anti-HBs***
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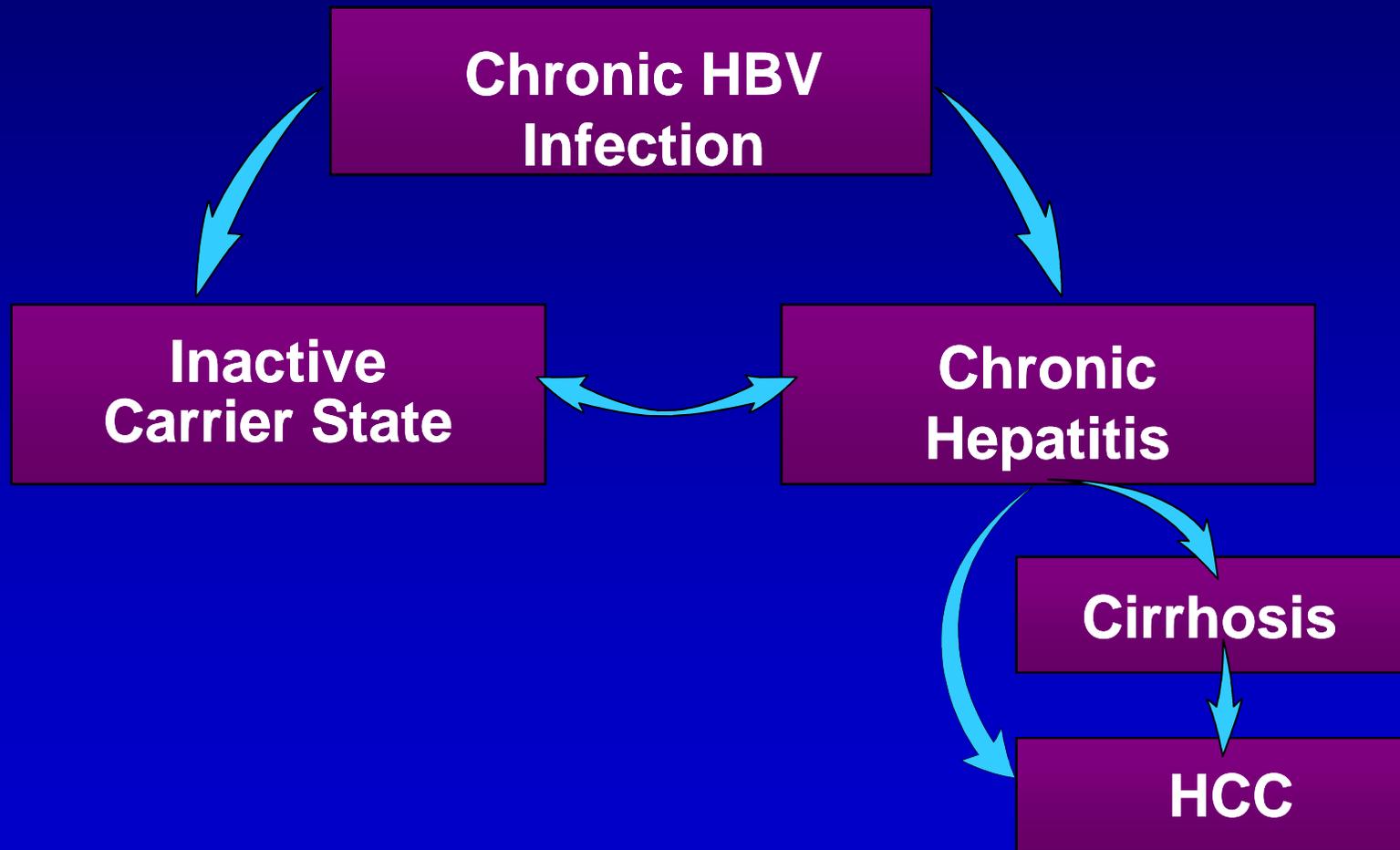
# ***Hepatitis B Update***

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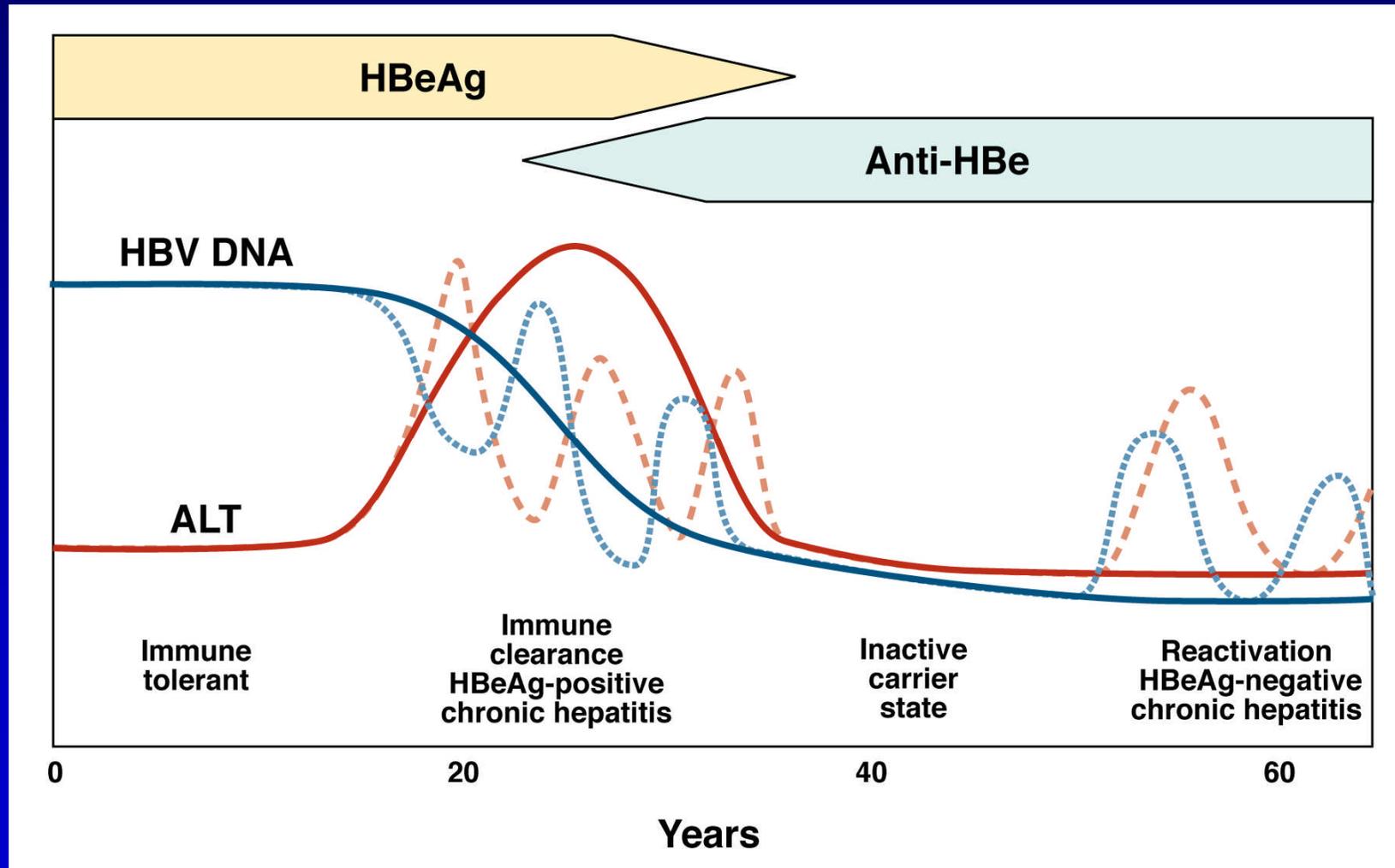
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# Outcome of Chronic HBV Infection

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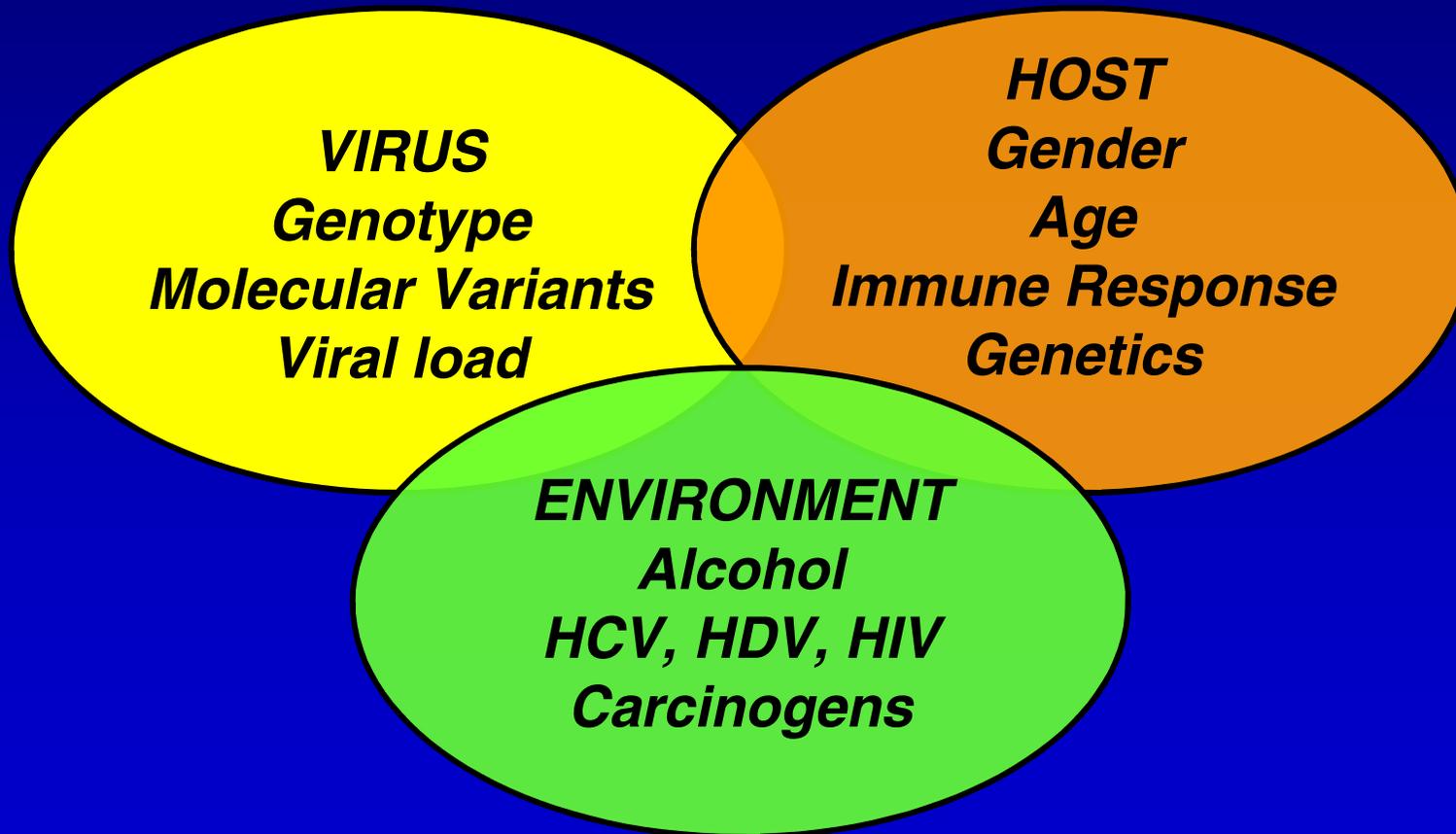
# Natural Course of Chronic HBV Infection



# ***Hepatitis B***

## ***Factors affecting disease activity and progression***

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# ***REVEAL-HBV Study***

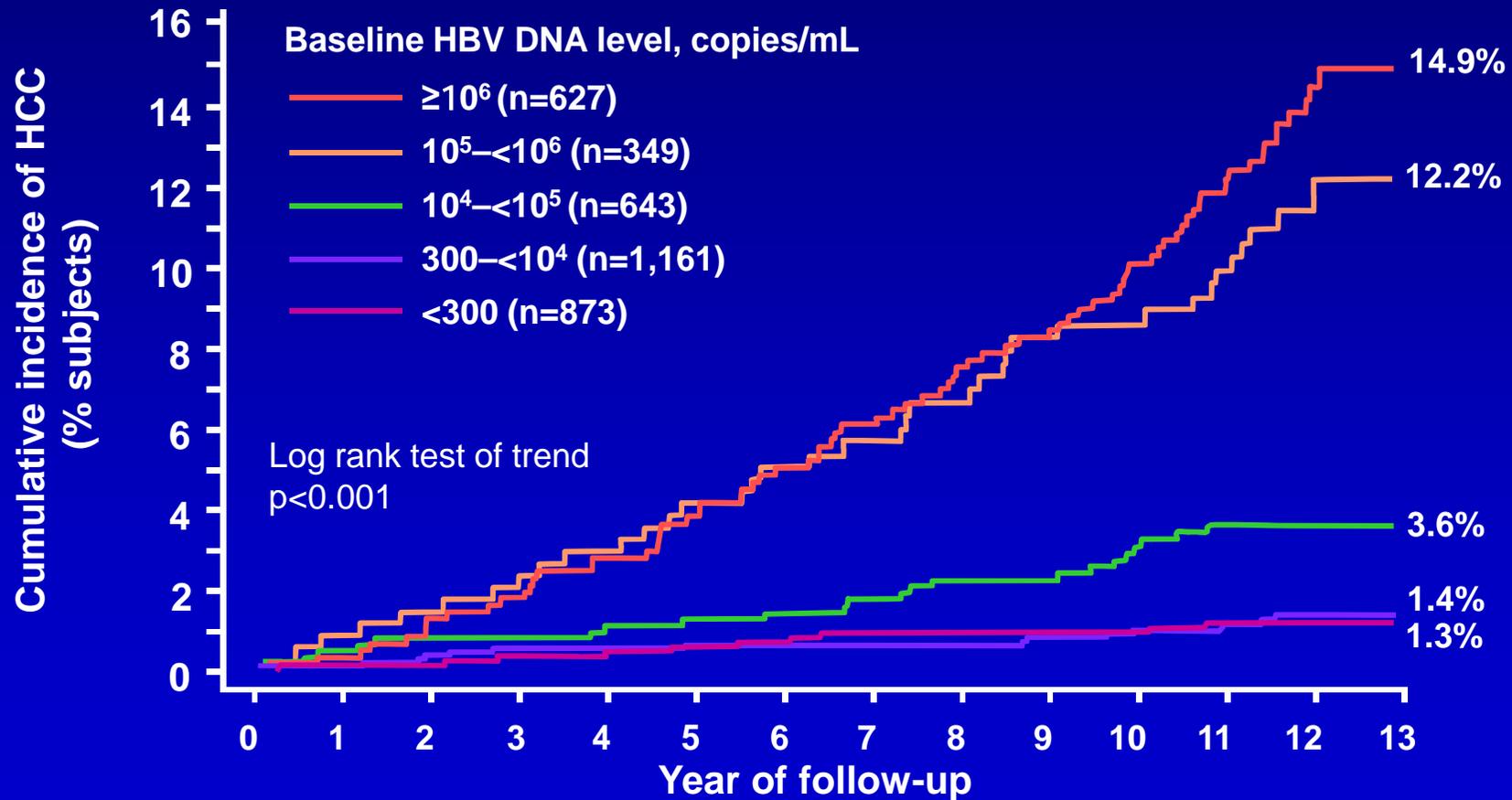
## ***Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer***

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- ***Community based cohort study in Taiwan***
- ***3,653 HBsAg+, anti-HCV-, mean age 43 (range 30-65)***
- ***At enrollment, 38% women, 15% HBeAg+, 94% normal ALT, 2% cirrhosis***
- ***Prospective follow-up q 6-12 months until June 2004***

# High Viral Load is Associated with Increased Incidence of HCC

## REVEAL Study (n=3,653)



# Nomogram for Predicting Risks of HCC

	<i>Model</i>	<i>Case 1</i>	<i>Case 2</i>	<i>Case 3</i>
<b>Gender</b>	<b>0/2</b>	<b>F (0)</b>	<b>M (2)</b>	<b>M (2)</b>
<b>Age</b>	<b>0-6</b>	<b>29 (0)</b>	<b>62 (6)</b>	<b>46 (3)</b>
<b>ALT</b>	<b>0-2</b>	<b>22 (1)</b>	<b>40 (1)</b>	<b>36 (1)</b>
<b>HBeAg</b>	<b>0/2</b>	<b>Pos (2)</b>	<b>Neg (0)</b>	<b>Pos (2)</b>
<b>HBV DNA (c/mL)</b>	<b>0-5</b>	<b>9.2 log (4)</b>	<b>2.7 log (0)</b>	<b>5.3 (5)</b>
<b>Total score</b>	<b>0-17</b>	<b>7</b>	<b>9</b>	<b>13</b>
<b>10 year risk of HCC</b>		<b>1.2%</b>	<b>3.2%</b>	<b>21%</b>

Initial model developed with data from REVEAL study, validated with data from 3 cohorts of patients seen in liver centers in Hong Kong and Korea

# ***Hepatitis B Update***

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# ***Prevention of Hepatitis B***

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- ***HBV vaccination : universal vaccination of all newborns and at risk adults***
  - ***Universal precaution***
  - ***Counseling of infected patients on precautions to prevent transmission, screening and vaccinating household and sexual contacts***
  - ***Education of health care providers***
  - ***Education of the public***
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# ***Hepatitis B Vaccines***

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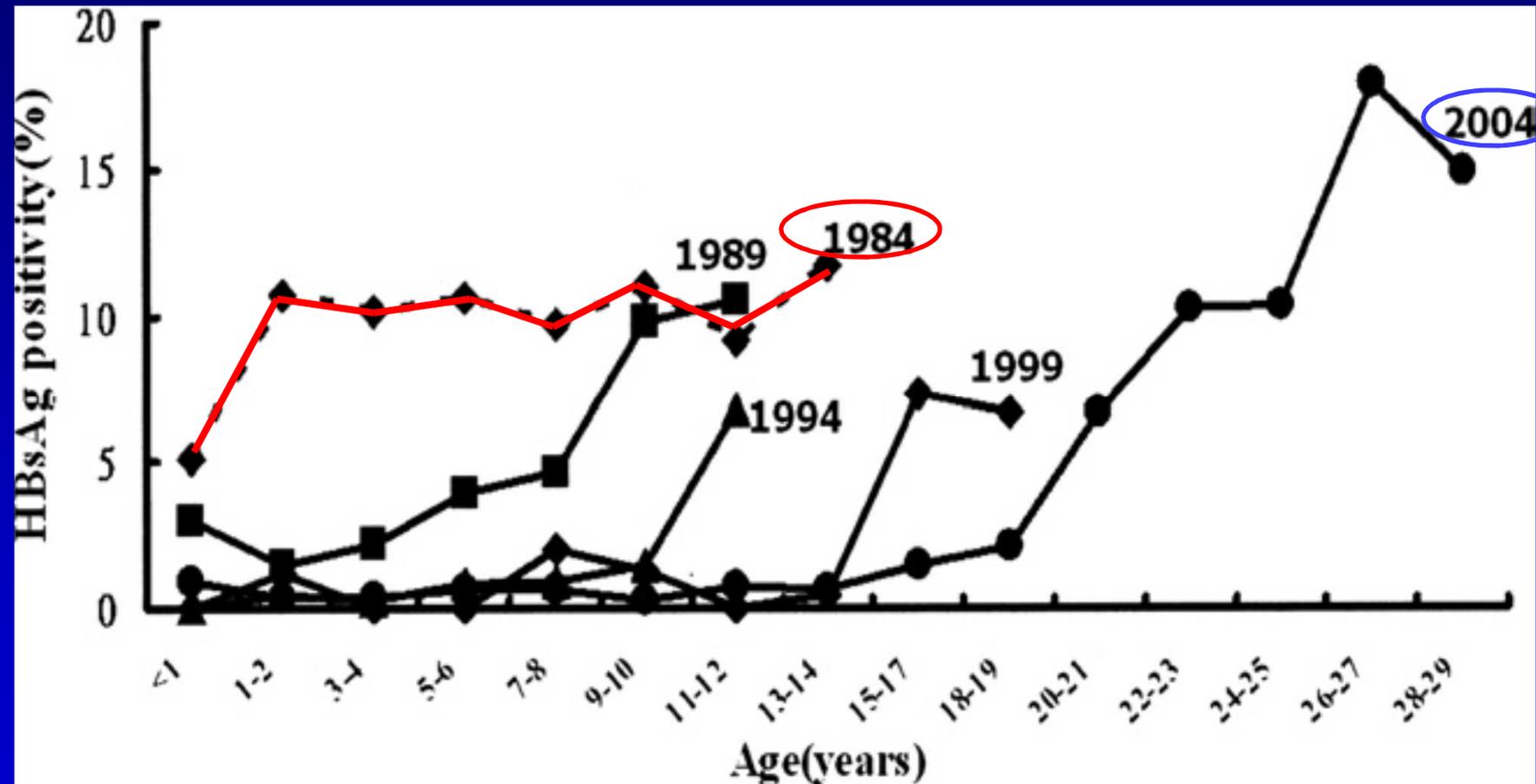
- **Genetically engineered hepatitis B surface antigen alone or in combination with hepatitis A vaccine**
  - **3 doses: month 0, 1, 6**
  - **Immune response: 50% after 1 dose  
95% after 3 doses**
  - **Duration of protection: >15 years, dependent on initial antibody response**
  - **Factors associated with poor response: older age, chronic medical illness (cirrhosis, kidney failure, diabetes), decreased immune response, smoking, obesity, genetics**
-

## ***Indications for HBV Vaccines***

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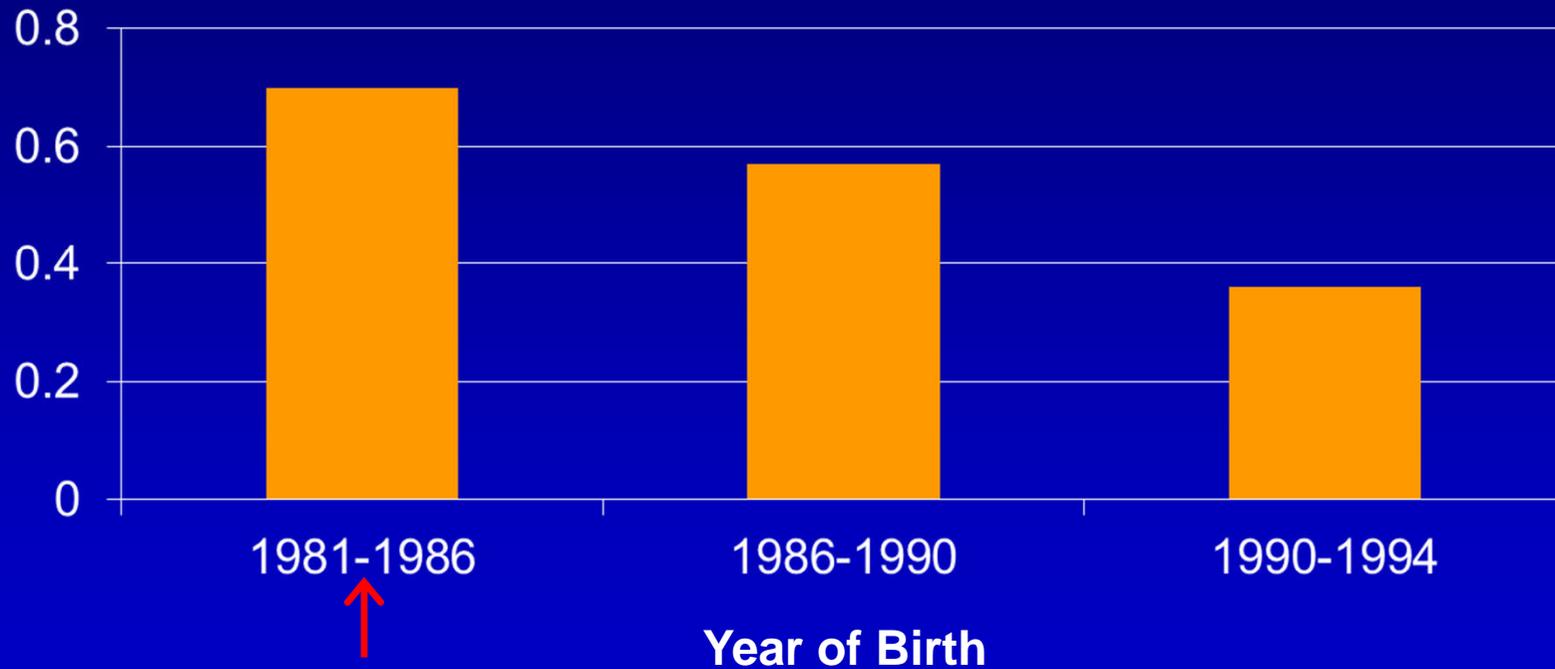
- All infants (+HBIG for infants of HBsAg+ mothers)
  - All children and adolescents who were not vaccinated at birth
  - Vaccination of adults at risk of infection
    - Occupational
    - Sexual / household contacts
    - Persons with high risk behaviors, e.g. injection drug users, men who have sex with men, persons with multiple sexual partners
    - Persons born in endemic areas or persons born to parents from endemic areas
    - Dialysis patients
    - Patients with chronic liver disease
-

# Impact of HBV Vaccination on Prevalence of HBsAg in Taiwanese Children and Young Adults



# ***HBV Vaccine Prevents HCC***

**Incidence of HCC per 100,000 children**



**20 yr follow-up, adjusted RR of HCC among those vaccinated at birth: 0.31**

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## ***Goals of HBV Treatment***

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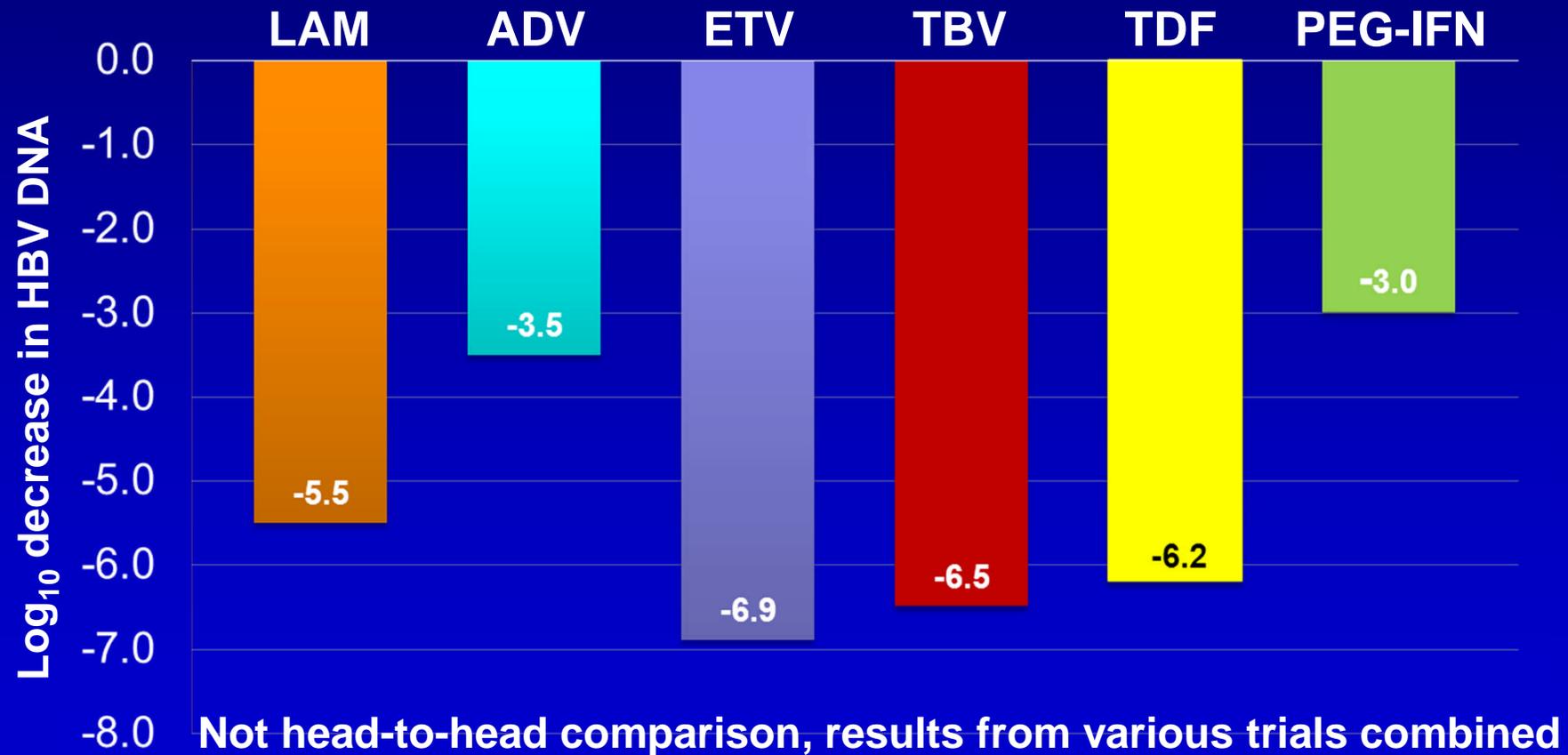
- ***Suppress HBV replication***
  - ***Decrease necroinflammation***
  - ***Reverse fibrosis***
  - ***Prevent progression to cirrhosis, liver failure, and hepatocellular carcinoma***
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# ***Responses to HBV Treatment***

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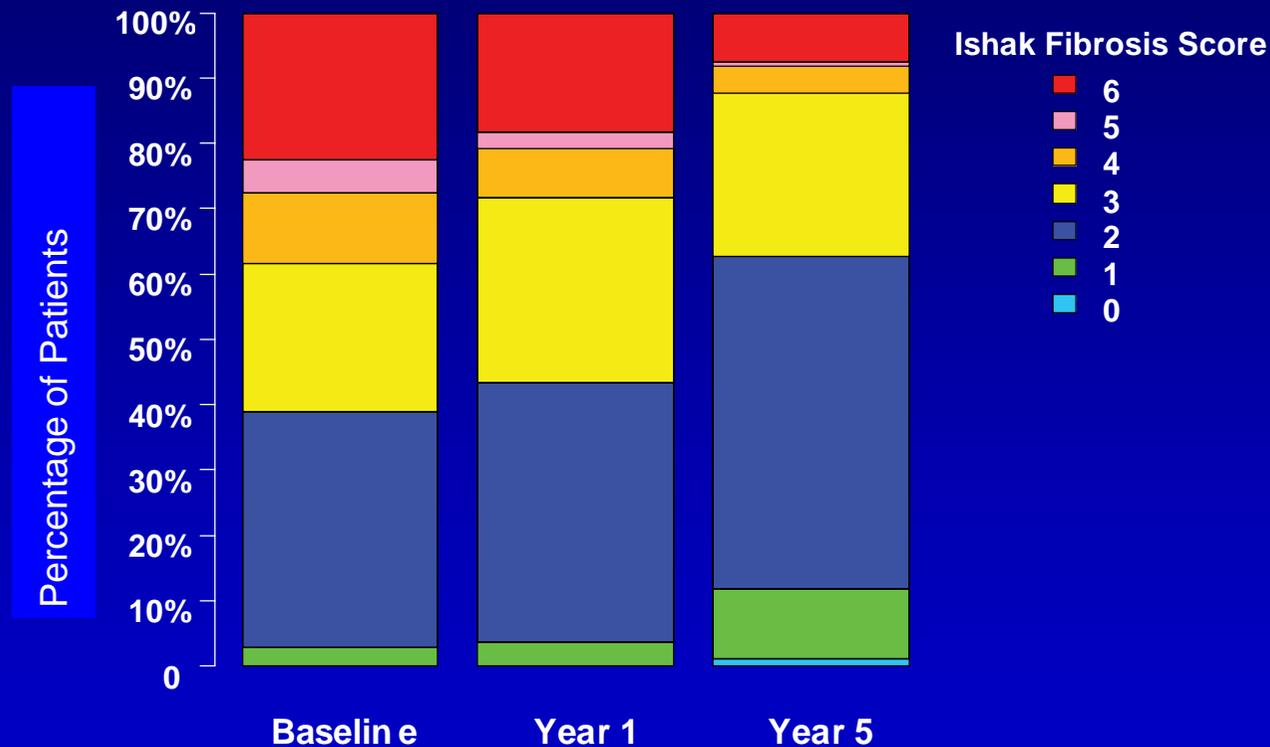
- ***Virologic Response***
    - ***Decrease in serum HBV DNA: preferably to undetectable by PCR***
    - ***HBeAg loss / seroconversion: applicable to HBeAg+ patients only***
    - ***HBsAg loss: Ultimate goal***
  - ***Biochemical Response***
    - ***ALT normalization***
  - ***Histological Response***
  - ***Clinical Response***
-

# *Decrease in Serum HBV DNA after 1 Year of Treatment*



LAM=lamivudine, ADV=adefovir, ETV=entecavir, TBV=telbivudine, TDF=tenofovir, PEG-IFN=peginterferon

# Reversal of Fibrosis and Cirrhosis Tenofovir Phase III Trial: Biopsies at Year 0, 1 & 5



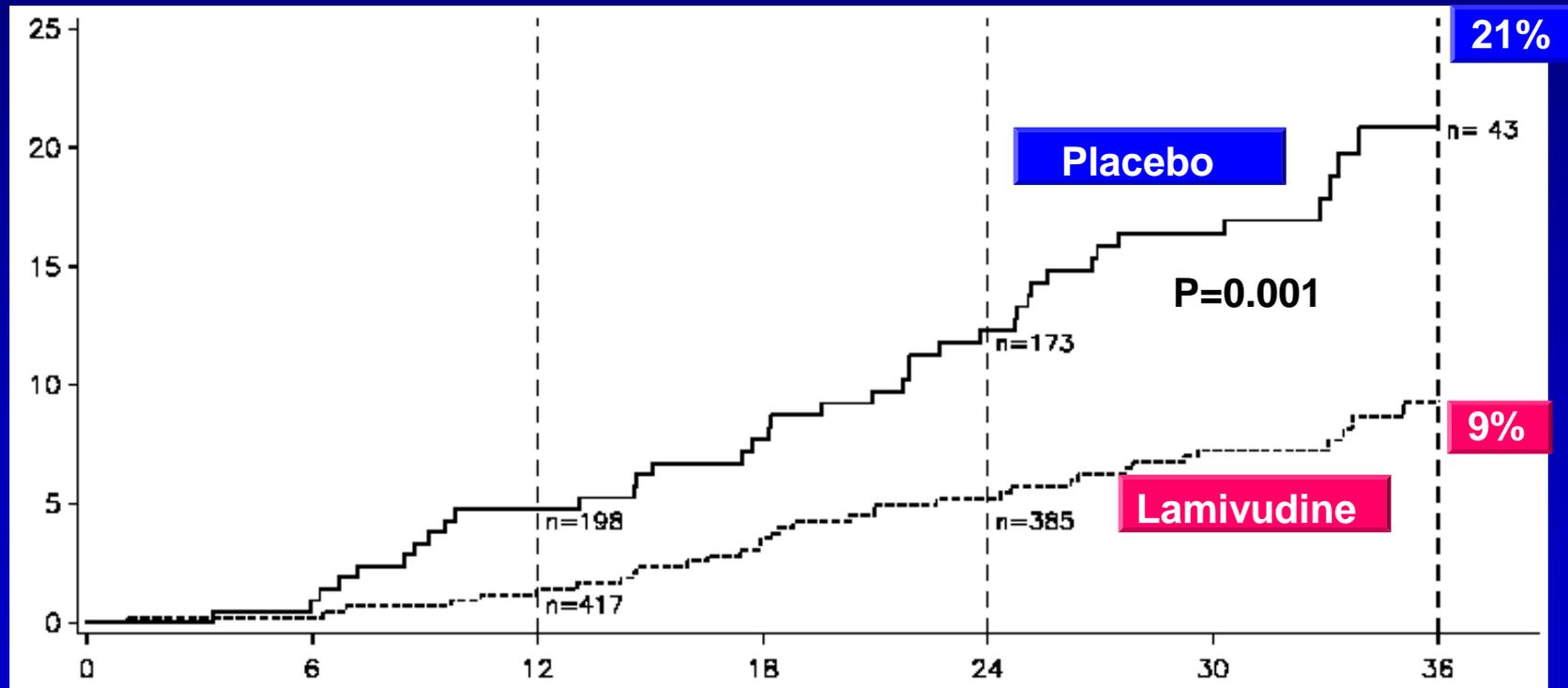
- **348/641 (54%) had liver biopsy at baseline and Year 5**
- **71/96 (74%) with cirrhosis (Ishak Score  $\geq 5$ ) at baseline no longer had cirrhosis at Year 5**
- **3/252 (1%) with no cirrhosis at baseline progressed to cirrhosis at Year 5**

# Antiviral Therapy Prevents Disease Progression

Bridging fibrosis or cirrhosis, HBeAg+ / HBV DNA >700,000 GEq/ml

% with disease progression

Increase CTP score, liver failure or HCC



Time to disease progression (months)

— Placebo (n=215) ITT population  
..... Lamivudine (n=436) p=0.001

## ***How Efficacious is Currently Available HBV Therapies?***

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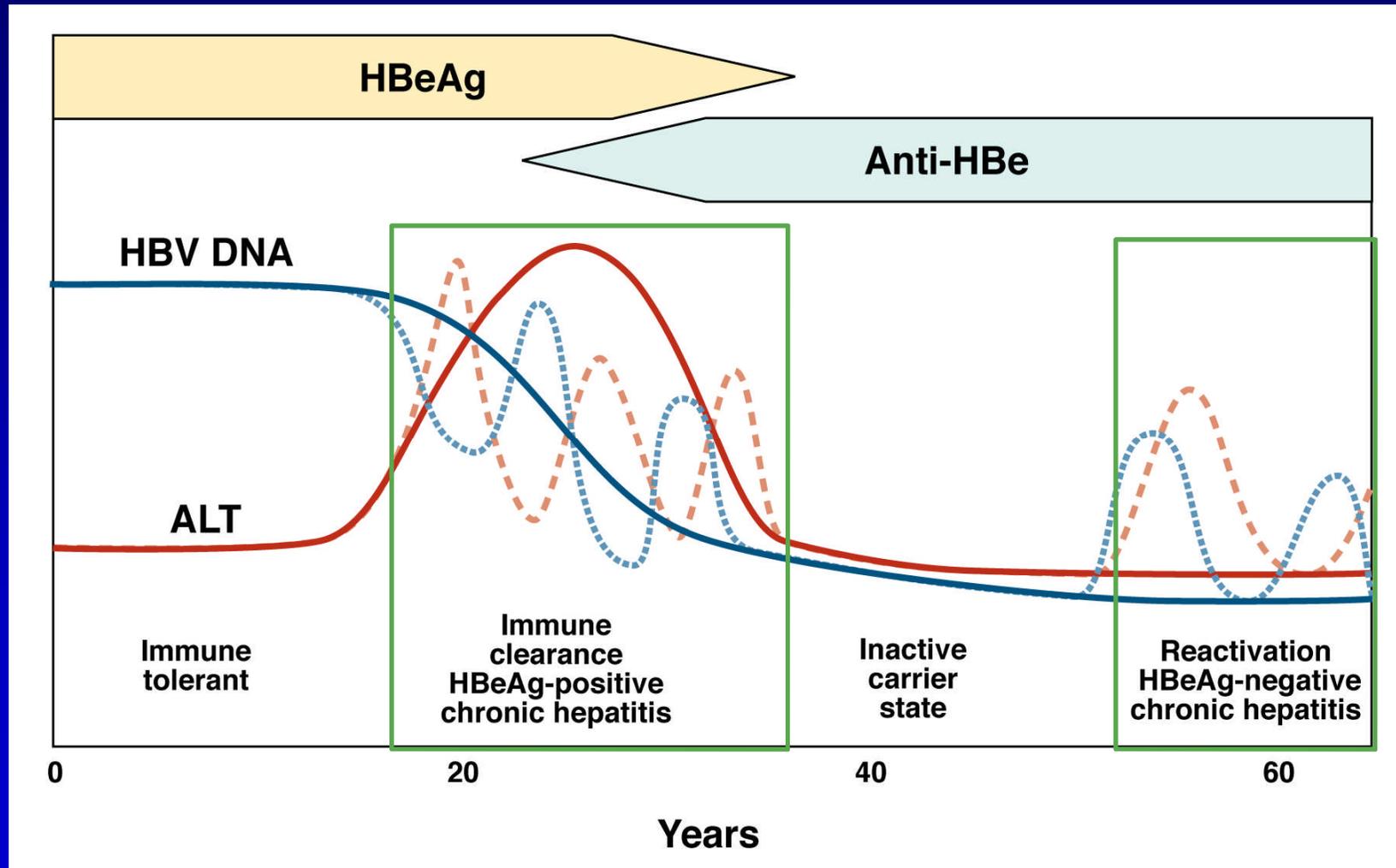
- ***Potent viral suppression***
  - ***Low rate of HBeAg and HBsAg loss***
    - ***HBeAg loss ~20% after 1 year and 40-50% after 5 years of nucleos(t)ide analogues***
    - ***HBsAg loss ~1-5% after 5 years of nucleos(t)ide analogues***
    - ***Higher rate of HBeAg and HBsAg loss after interferon therapy***
  - ***Reverse hepatic fibrosis and cirrhosis***
  - ***Prevent progression to liver failure (and HCC)***
-

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# When to Initiate Treatment in Non-Cirrhotics?



## ***When to Initiate Treatment in Non-Cirrhotics?***

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- ***Active liver disease and high level HBV DNA***
- ***HBeAg+/HBeAg-***
  - ***ALT >2x ULN and HBV DNA >20,000 IU/mL***
  - ***Lower threshold in patients >40, liver histology showing moderate-severe inflammation / fibrosis***
  - ***HBeAg+ patients: can observe for 3-6 months to allow time for spontaneous seroconversion***

# Which Is the Best Initial Treatment?

<b><i>Treatment</i></b>	<b><i>Interferon</i></b>	<b><i>Nucleos(t)ide Analogues</i></b>
<b><i>Route</i></b>	<b><i>Parenteral</i></b>	<b><i>Oral</i></b>
<b><i>Duration of treatment</i></b>	<b><i>Finite duration ~ 12 mos</i></b>	<b><i>Long duration, yrs to life long</i></b>
<b><i>Antiviral activity</i></b>	<b><i>Modest, additional immunomodulatory effects</i></b>	<b><i>Stronger antiviral activity</i></b>
<b><i>HBsAg loss</i></b>	<b><i>1-3% after 1 yr</i></b>	<b><i>Rare, 0-1% after 1 yr</i></b>
<b><i>Resistance mutations</i></b>	<b><i>None</i></b>	<b><i>0-25% after 1 yr</i></b>
<b><i>Side effects</i></b>	<b><i>Frequent</i></b>	<b><i>Rare</i></b>

## ***Which Should be the Initial Oral Drug?***

	<b>LAM</b>	<b>ADV</b>	<b>ETV</b>	<b>LdT</b>	<b>TDF</b>
<b><i>Antiviral activity</i></b>	<b>++</b>	<b>+</b>	<b>+++</b>	<b>+++</b>	<b>+++</b>
<b><i>Safety</i></b>	<b>+++</b>	<b>++</b>	<b>+++</b>	<b>++</b>	<b>++</b>
<b><i>Risk of drug resistance</i></b>	<b>++++</b>	<b>++</b>	<b>1% after 5 yr</b>	<b>+++</b>	<b>0% after 5 yr</b>

LAM = lamivudine, ADV = adefovir, ETV = entecavir, LdT = telbivudine, TDF = tenofovir

# **Treatment**

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- ***When to start?***
    - ***Life-threatening liver disease***
    - ***High risk of cirrhosis or HCC***
    - ***High levels of HBV DNA and ALT***
    - ***Lower threshold in older patients, cirrhosis***
  - ***Which drug?***
    - ***First line treatment: Peg-IFN, Entecavir or Tenofovir***
  - ***When to stop?***
-