

# Hepatitis B: An Overview & Update



## Learning Objectives

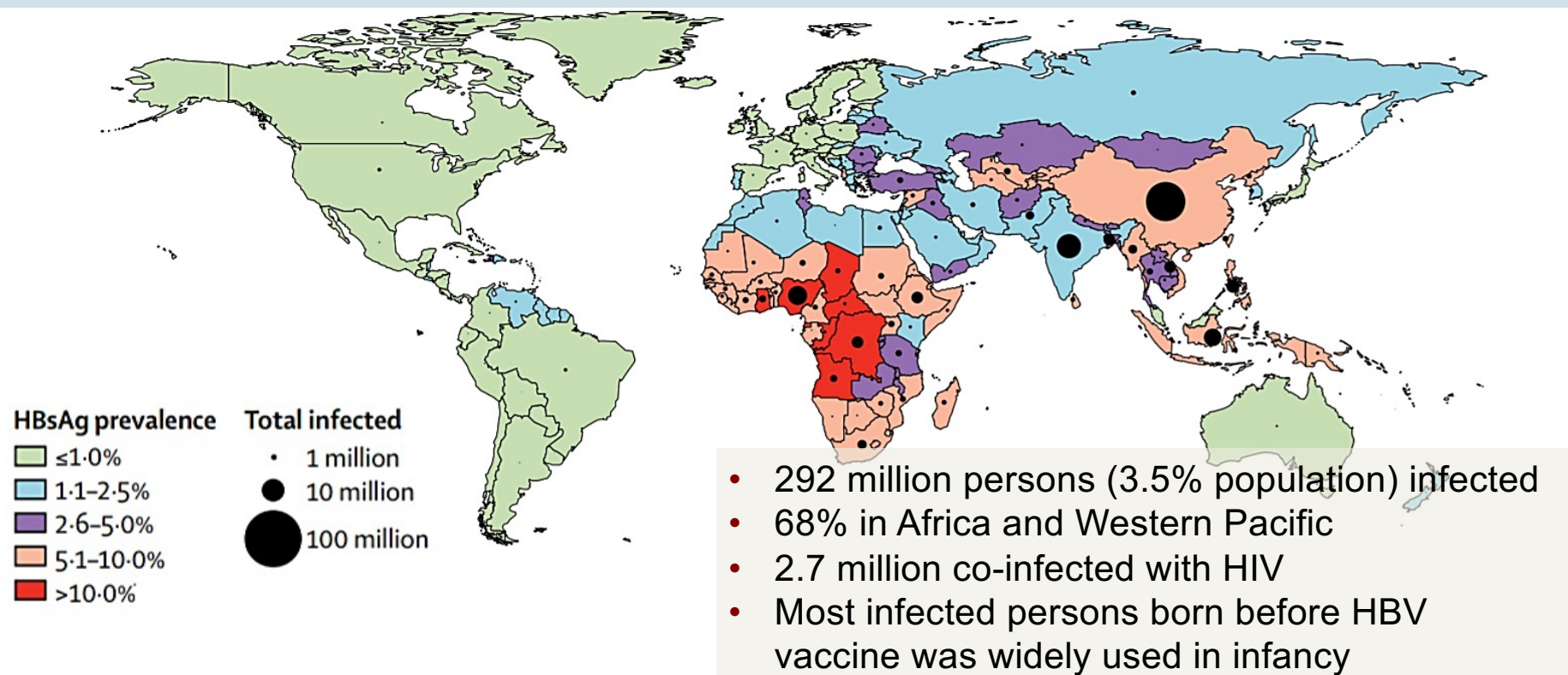
By the end of this presentation, participants will be able to:

- Describe the epidemiology of hepatitis B (HBV) infection
- Understand the natural history of HBV infection
- Identify candidates for HBV vaccination
- Identify patients who should be screened for HBV and interpret HBV serology
- Educate patients on preventing HBV transmission
- Define the goals of HBV therapy and how current therapies reduce disease progression
- Follow the key steps in HBV pretreatment evaluation and treatment algorithm
- Recall the role of the primary care provider (PCP) in HBV care

# Epidemiology

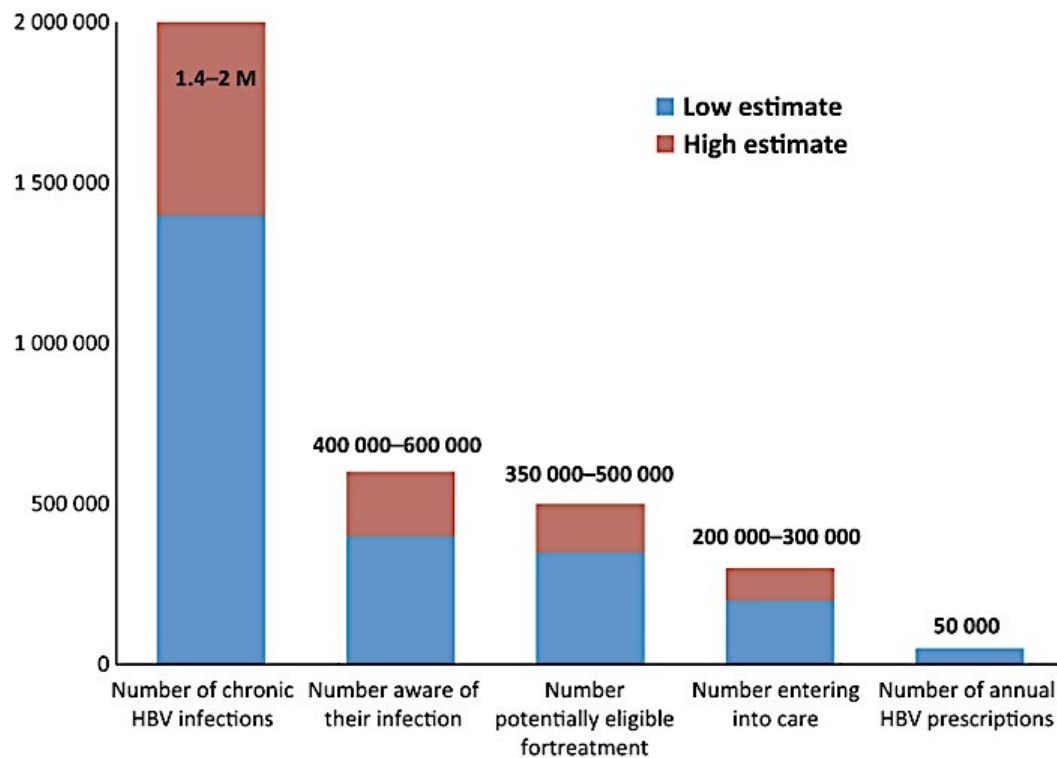
The background of the slide is composed of several overlapping geometric shapes. A large light blue rectangle occupies the left and bottom portions. A dark blue triangle is positioned in the bottom right corner. A maroon diagonal band runs from the top right towards the bottom right, separating a light grey area in the top right from the other colors.

# Global HBV Prevalence, 2016



Source: Lancet Gastroenterology & Hepatology 2018

## HBV in the U.S.



- Up to 2.4 million infected
- 60% unaware of infection
- Only 50,000 HBV prescriptions a year

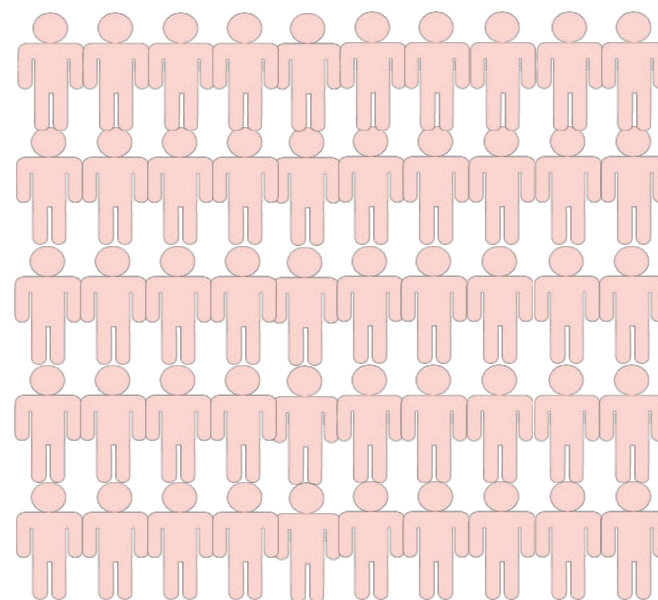
Figure from Cohen et al. Journal of Viral Hepatitis 2011; 18, 377-383  
Roberts et al. Hepatology 2016;63:388-397; Wong Gish Hepatology 2021 in press

## Gaps in HBV Care in the U.S.

- Up to 40% of HBV-infected persons develop cirrhosis, HCC, or liver failure
  - 25% die prematurely
  - Indirect/direct health care costs: \$1 billion
- Vaccination and screening can reduce this burden
  - Only 25% of U.S. adults have been completely vaccinated
  - 60% of infected persons are unaware of their infection
  - Only 10-15% of eligible patients have been treated

## Hepatitis B- Facts

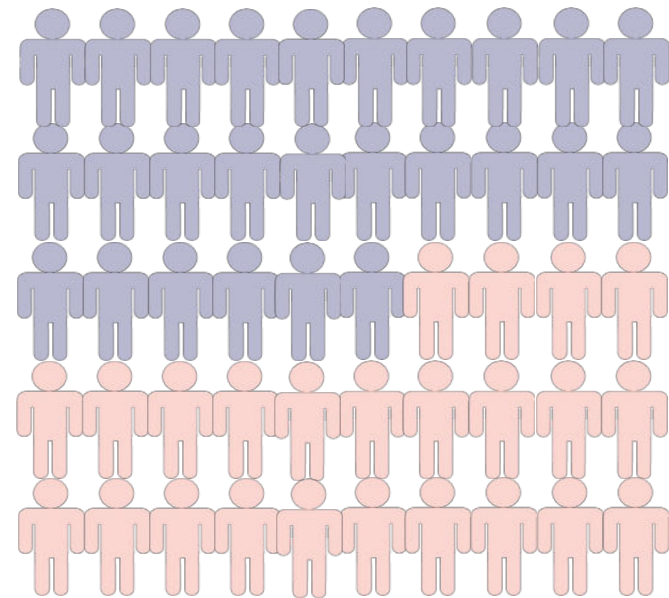
**95,617** people are reported  
with Hepatitis B in NYC from  
**2016-2019** *(2019 Annual Report)*



## Hepatitis B- Facts

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Only **54%** are aware of their  
**status** *(Moore, et al., Public Health Rep, 2019)*



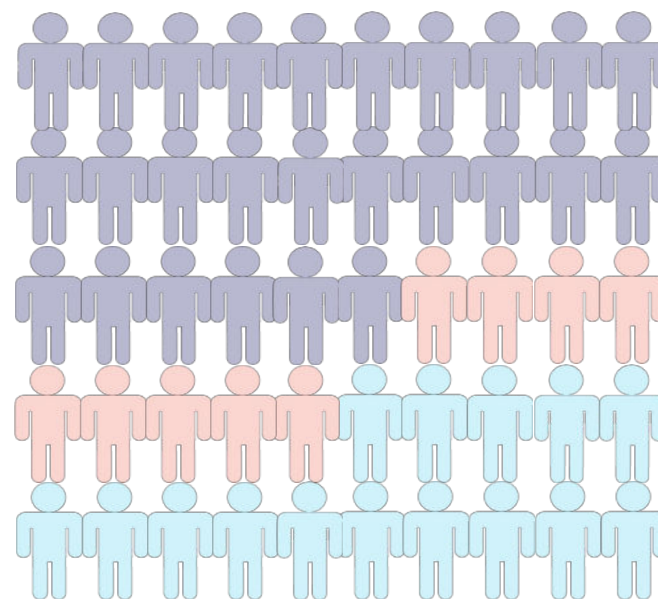


# Hepatitis B- Facts

**95,617** people are reported with  
**Hepatitis B in NYC from 2016-2019**  
*(2019 Annual Report)*

**Only 54%** are aware of their status  
*(Moore, et al., Public Health Rep, 2019)*

**Without treatment and monitoring**  
**15-25%** of people will die  
**prematurely from cirrhosis, liver**  
**failure, or liver cancer** *(Cohen, et al., Journal of*  
*Community Health, 2013)*



## HBV Infection in Foreign-Born Population, National

Foreign-born persons comprise 14% of the U.S. population but 60-90% of people living with chronic HBV.

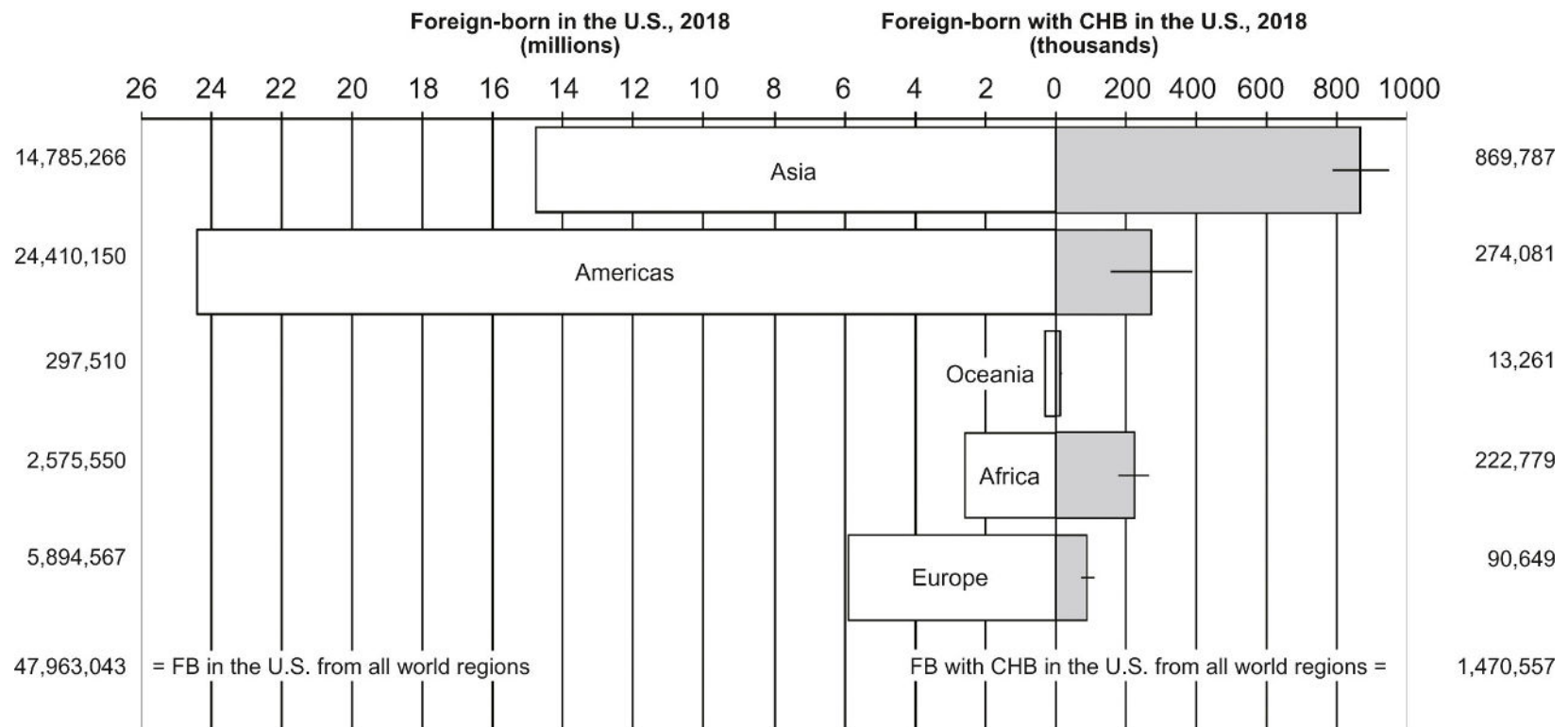
Top countries of origin of foreign-born persons with HBV (by number of people):

1. China
2. Vietnam
3. Philippines
4. India
5. Dominican Republic
6. Taiwan

HBV prevalence rate among foreign-born persons by region of birth (2012):

- Africa (8.7%)
  - Liberia (16.5%)
  - Guinea (14.9%)
- Asia (5.9%)
  - Taiwan (13.0%)
  - Vietnam (11.7%)
- Oceania (4.5%)
  - Micronesia (14.28%)
  - Tonga (12.0%)

# HBV Infection in Foreign-Born Population, National



Wong, et al. *Hepatology*. 2021.

## Viral Hepatitis is Underfunded

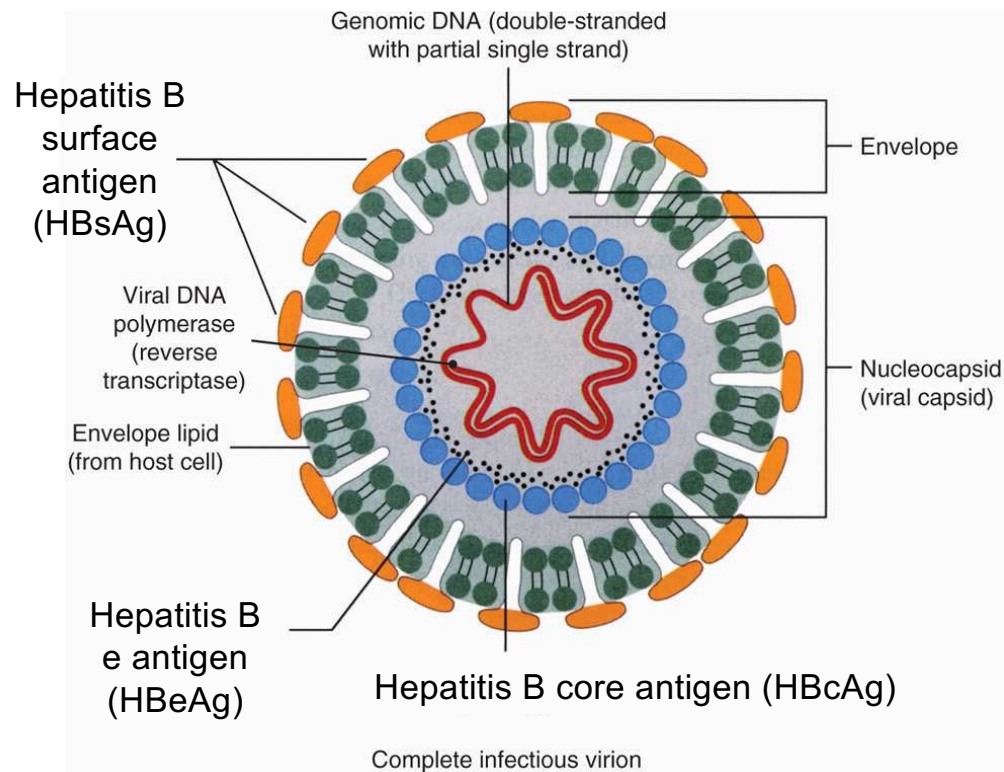
<b>Virus</b>	<b>US population</b>	<b>% of CDC division budget</b>
<b>HBV</b>	0.8-2.2 million	<b>2%</b> (for both HBV/HCV domestic/international)
<b>HCV</b>	2.7-3.9 million	
<b>HIV</b>	1.1 million	<b>69%</b> (domestic, not including international HIV work)

- Those affected are the silent minorities, no political voice
- Health disparity/equity issue
  - We have the tools – vaccine, medications for cure/treatment, medical knowledge
  - Those most at-risk are falling through the system

# Natural History

The background features a light blue rectangular area on the left. To its right, a dark blue triangular shape is partially visible, with a maroon diagonal band crossing over it. The top right corner is a light gray area.

# HBV Structure



Source: basicmedicalkey.com

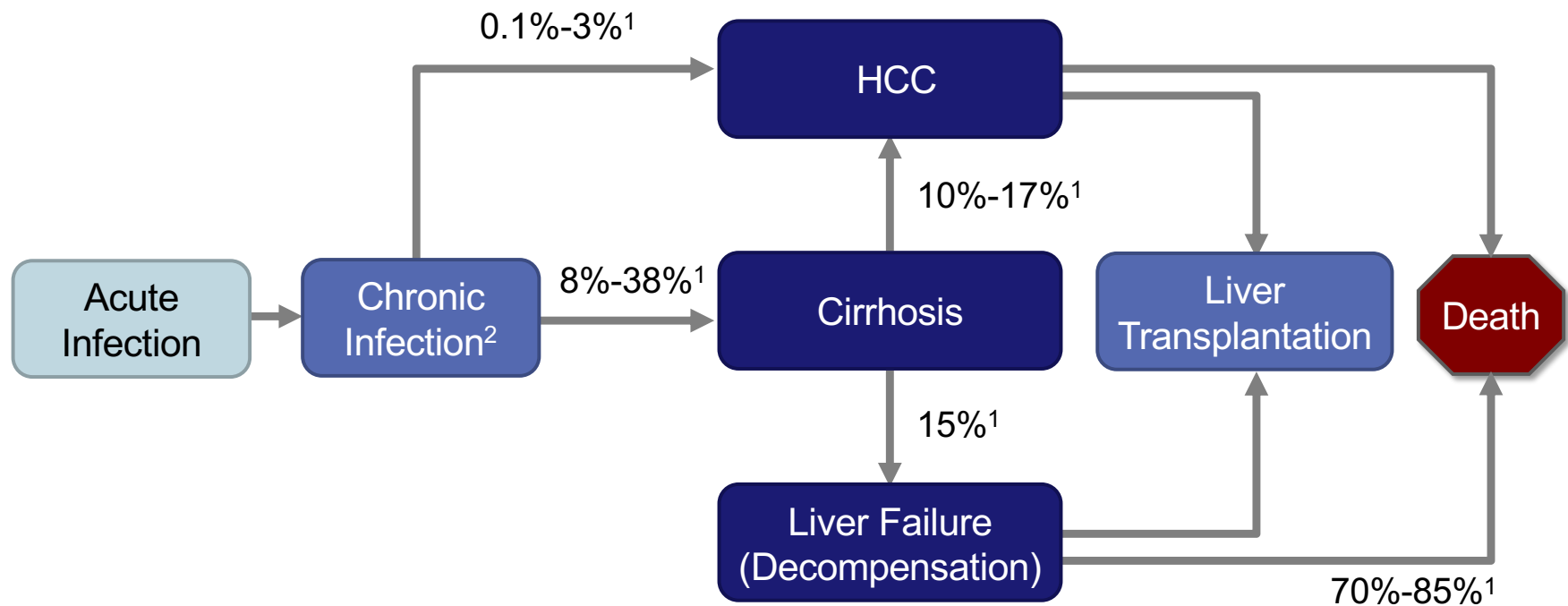
- DNA virus
- Ten genotypes, A to J
- HBV replicates through an RNA intermediate and can integrate into the host genome
- Virological and serological assays have been developed for diagnosis of various forms of HBV-associated disease

Liang JT, Hepatology. 2009 May ; 49(5 Suppl): S13–S21

## AASLD Guidelines: Diagnostic Criteria and Definitions for Chronic HBV

	Immune-Tolerant CHB	Immune-Active CHB	Inactive CHB
<b>HBV test results</b>	<ul style="list-style-type: none"> <li>• HBsAg present for 6 months</li> <li>• HBeAg positive</li> <li>• HBV-DNA levels are very high (typically &gt;1 million IU/mL)</li> </ul>	<ul style="list-style-type: none"> <li>• HBsAg present for 6 months</li> <li>• Serum HBV DNA &gt;20,000 IU/mL in HBeAg-positive CHB</li> <li>• &gt;2,000 IU/mL in HBeAg-negative CHB</li> </ul>	<ul style="list-style-type: none"> <li>• HBsAg present for 6 months</li> <li>• HBeAg negative, anti-HBe positive</li> <li>• Serum HBV DNA &lt;2,000 IU/mL</li> </ul>
<b>ALT/AST levels</b>	Normal or minimally elevated	Intermittently or persistently elevated	Persistently normal
<b>Liver biopsy or noninvasive test results</b>	no fibrosis and minimal inflammation	chronic hepatitis with moderate or severe necroinflammation and with or without fibrosis	absence of significant necroinflammation (biopsy); variable levels of fibrosis

## Disease Burden from HBV Infection: 5-Year Cumulative Incidence Rates of Development of Chronic HBV Complications



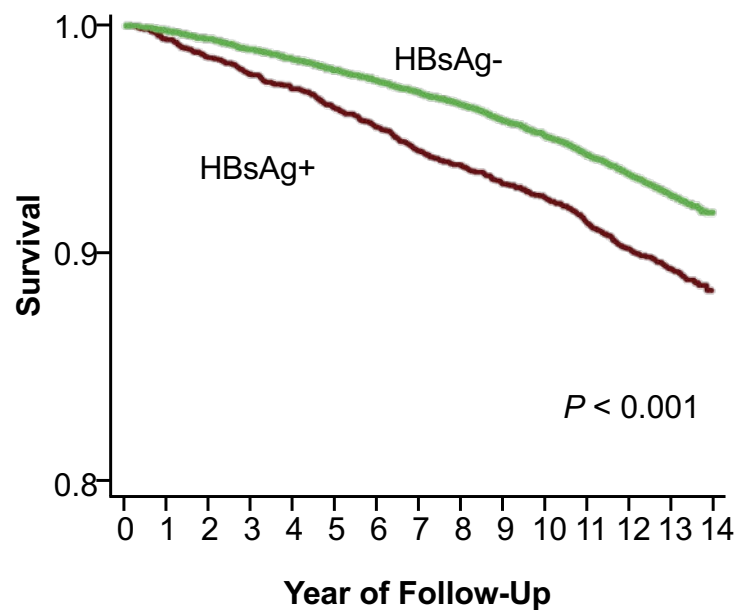
1. Fattovich G, et al. *J Hepatol.* 2008;48:335-352.

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

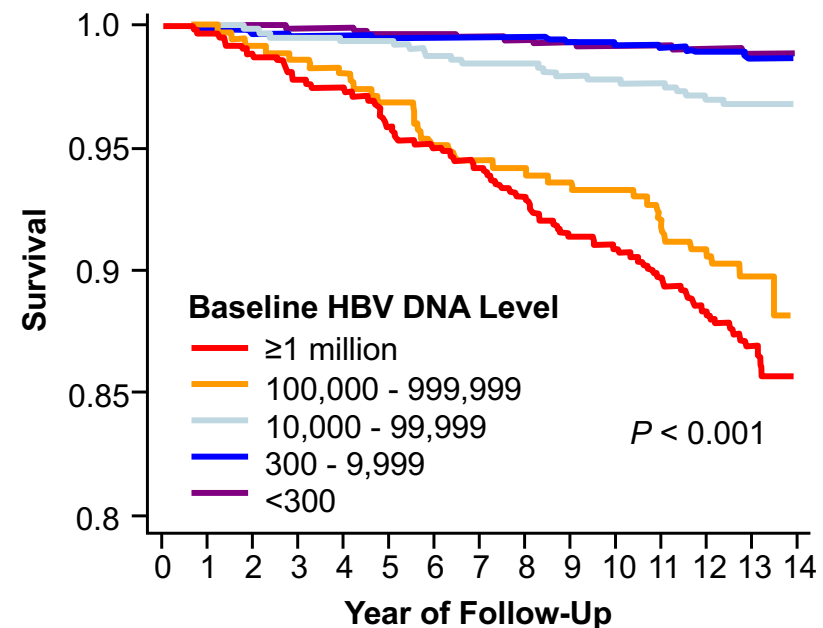


## REVEAL Study: All-Cause and Liver-Related Mortality in Patients with HBV

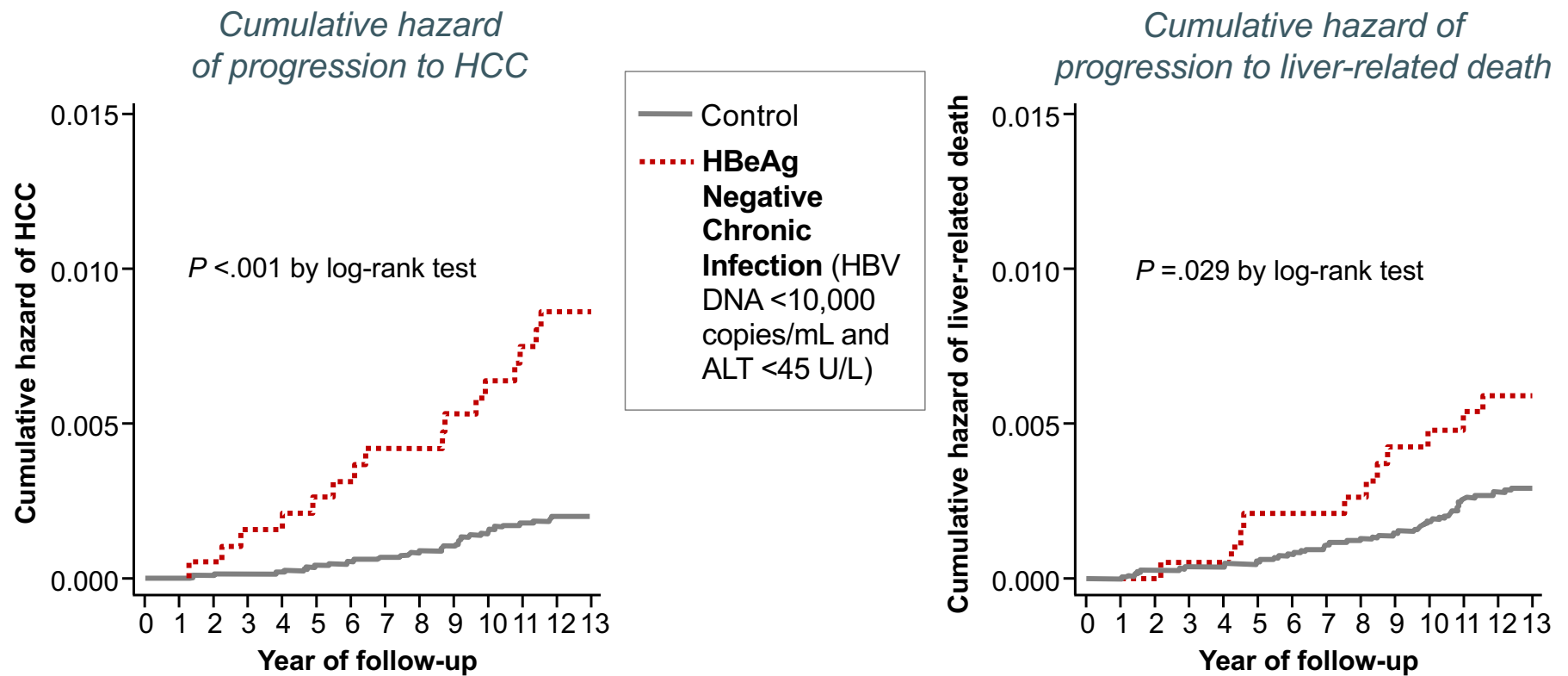
Total mortality according to HBsAg status (n=22,472)



Liver-related mortality by baseline HBV DNA in HBsAg+ subjects without evidence of HCV infection (n=3,653)



## REVEAL Study: Progression to HCC and Liver-Related Death in HBeAg Negative Chronic Infection



Chen JD, et al. *Gastroenterology*. 2010;138(5):1747-1754.



**Prevention**

## HBV Vaccination: Infants and Children

- Infants:
  - First dose of HBV vaccine at birth
  - Complete the series at 6 months of age
- Unvaccinated children <19 years

## HBV Vaccination: At Risk Adults

- Adults at risk by **sexual exposure**
  - sex partners of HBsAg+ persons
  - persons with multiple sex partners
  - persons seeking STI treatment
  - men who have sex with men
- Adults at risk by **percutaneous or mucosal exposure**
  - injection drug users
  - household contacts of HBsAg+ persons
  - incarcerated, health care and public safety workers
- Adults with chronic liver disease, end-stage renal disease (incl. hemodialysis patients), or HIV infection
- Pregnant women at risk for infection
- Travelers to HBV endemic regions
- Adults seeking protection from HBV infection

## Gaps in HBV Vaccination

- Adult HBV vaccine coverage is low.
- Only 31% of primary care physicians reported routinely assessing for and vaccinating adults with HBV risk factors.
- Similarly, among men who have sex with men (MSM) surveyed in the Young Men's Health Study, only 17% had received hepatitis B vaccine.
- \*11/2021: An updated recommendation from the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) calls for universal [hepatitis B](#) vaccination of all adults aged 59 and younger

\*<https://www.cdc.gov/vaccines/acip/>

# Preventing HBV Transmission: Educating Patients

Tell patients:

- Use condoms during sex until partners is fully vaccinated against Hep B.
- Use only new or sterile equipment for injection (e.g. drugs, insulin, steroids), tattooing, or acupuncture
- Ensure household and sexual contacts are tested and vaccinated
- Avoid sharing toothbrushes, razors, needles, nail clippers, nail scissors or washcloths
- Cover cuts and sores, wash hands after touching your blood or body fluids
- Clean blood spills with bleach solution
- Do not donate blood, organs or sperm

HBV-infected children and adults:

- **Can** participate in all activities including contact sports
- **Should not** be excluded from daycare or school participation and should not be isolated from other children
- **Can** share food, utensils, or kiss others



# Screening & Diagnosis



## HBV Tests Part I:

### All Patients Need this “Triple Panel” When Evaluating for HBV

- +HBsAg = infection (Test all patients for HDV)
- +Anti-HBc = exposure = cccDNA = persistence
  - Eval for Occult HBV if HBsAg (-)
  - Reactivation risk
  - No vaccine boosting
- +Anti-HBs = immunity, **if anti-HBc is negative**
- Note:
  - HBV is incurable
  - There is no “natural immunity”

## Interpreting HBV Test Results

Clinical state	HBsAg	anti-HBs	anti-HBc	Action
<b>Chronic infection</b>	+	-	+	Evaluate for treatment
<b>Acute infection</b>	+	-	+	Link to HBV directed care
			(IgM anti-HBc)	
<b>Resolved infection</b>	-	+	+	Counseling, reassurance
<b>Immune</b> (immunization)	-	+	-	Reassurance
<b>Susceptible</b> (never infected or immunized)	-	-	-	Vaccinate
<b>Exposed</b>	-	-	+	Depends on situation

## Other Recommended Testing With HBV Diagnosis

- Test for coinfection:
  - Hepatitis Delta virus (HDV) in HbsAg-positive persons
    - Especially HbsAg positive patient with low HBV DNA and high ALT
    - → Consider treatment with Peg-IFN-a for 12 months
  - HIV
    - Initiation of ART
  - Hepatitis C virus (HCV)
    - Treat HCV with antiviral therapy once on HBV treatment

## High-Risk Groups for HBV Screening

- Persons requiring immunosuppressive therapy
- Persons with end-stage renal disease (including hemodialysis patients)
- HCV infected persons
- Persons with elevated ALT ( $\geq 19$  IU/L for women and  $\geq 30$  IU/L for men)
- Persons who have been incarcerated
- Pregnant women\*
- Infants born to HBV infected people

\*The 1990 NYS Public Health Law Article 25, Section 2500-e (Appendix A) mandates HBsAg testing of all pregnant women.

## Additional High-Risk Groups for HBV Screening

Important risk groups for HBV infection with a prevalence of  $\geq 2\%$  that should be screened include

- Persons born in countries and regions with a high prevalence of HBV infection ( $\geq 2\%$ ), such as Asia, Africa, the Pacific Islands, and parts of South America
- US-born persons not vaccinated as infants whose parents were born in regions with a very high prevalence of HBV infection ( $\geq 8\%$ )
- HIV-positive persons
- Persons with injection drug use
- Men who have sex with men
- Household contacts or sexual partners of persons with HBV infection

## Underscreening of HBV

- Even among Asian-American PCPs with a large percentage of Asian patients, only 50% routinely screen their Asian patients for HBV
- Stated reasons for not ordering a screening test in Asian patients included:
  - **Patients not considered to be at risk for HBV (23%)**
  - **No symptoms (16%)**
  - Patient has received vaccination series (15%)
  - Lack of insurance (13%)

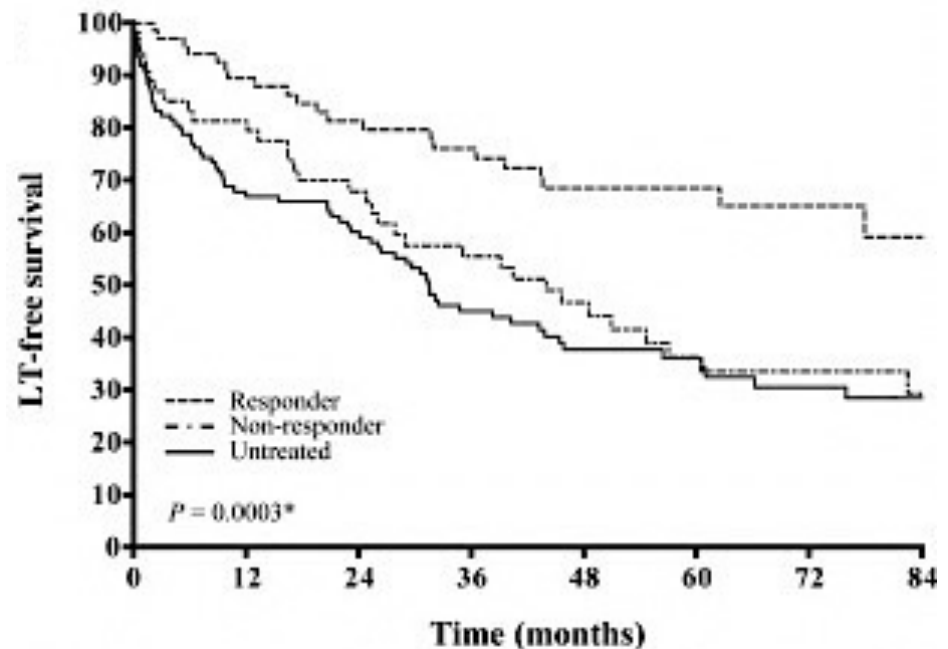


**Treatment**

# HBV Therapy Reduces Risk of Disease Progression

Prospective cohort study in HBV pts with first-onset complications of decompensated cirrhosis (n = 707) treated predominantly with lamivudine (n = 203) or entecavir (n = 19)

**Antiviral therapy improved transplant-free survival over mean follow-up of 49 mos ( $p = .0098$  vs untreated)**

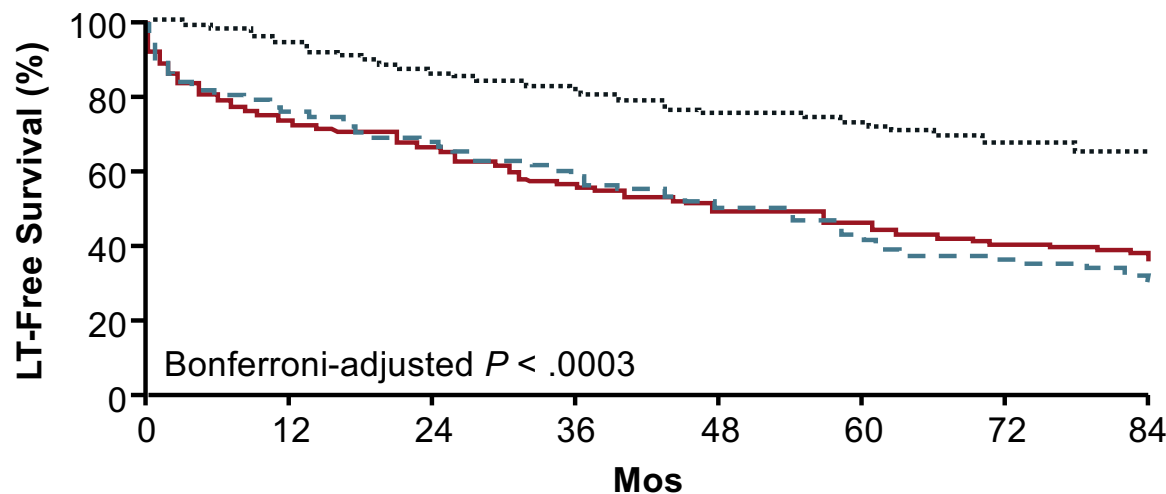


\*Nonresponders included pts with HBV rebound or genotypic resistance, primary nonresponse, Not evaluable due to early event (death, LT, LTFU).



# HBV Treatment Reduces Risk of Liver Transplant

*Prospective cohort study in pts with HBV and first-onset complications of decompensated cirrhosis (n = 707)*



**Antiviral therapy improved transplant-free survival over 5 years ( $p = .0098$  vs untreated)**

..... Treated,\* responder (n = 245)  
- - - Treated,\* nonresponder (n = 178)  
— Untreated (n = 284)

\*Treated predominantly with lamivudine (n = 203) or entecavir (n = 198).

## Pretreatment Evaluation: History and Physical Examination

- Risk factors for viral hepatitis
- Duration of infection
- Route of transmission
- Risk factors for HIV co-infection
- Alcohol history
- Presence of comorbid diseases
- Family history of liver cancer
- HBV testing of family members
- General counseling regarding transmission
- Vaccination of at-risk household and sexual contacts
- Family planning

## Goals of HBV Therapy



Improve liver histology



Decrease serum HBV DNA levels



Seroconversion  
(loss of HBeAg,  
development of anti-HBe,  
loss of HBsAg,  
development of anti-HBs)



ALT normalization



- Prevention of death, cirrhosis, and HCC
- Reduce infectivity and stigma

# What About a Cure?

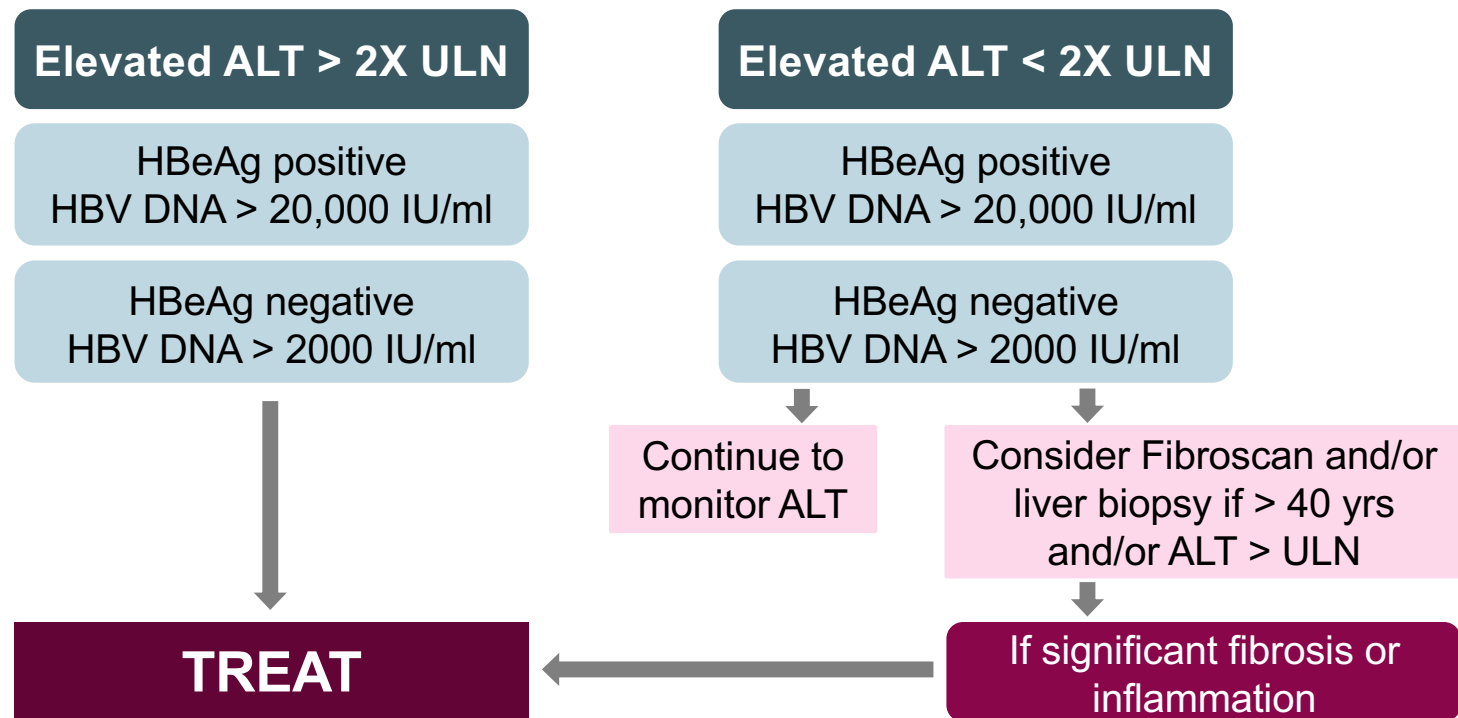
## Types of HBV Cure

- **Inactive state**
  - Sustained, off drug
    - No inflammation – Normal ALT and liver biopsy
    - HBVDNA low or undetectable
    - HBsAg positive
- **Functional Cure (Clinical Resolution)**
  - Sustained, off drug
    - No inflammation – Normal ALT and liver biopsy
    - HBsAg loss
    - Anti-HBs gain
- **Complete Cure (Virologic Cure)**
  - All of the above plus
  - Loss of cccDNA in the liver

## FDA Approved Therapies

- **First line therapy**
  - 2005: Peg interferon alfa-2a (PEGASYS®) Roche
  - 2005: Entecavir (BARACLUDE™), Bristol-Myers Squibb
  - 2008: Tenofovir disoproxil fumarate (VIREAD®), Gilead
  - 2016: Tenofovir alafenamide (VEMLIDY®), Gilead
- **Second line therapy**
  - 2002: Adefovir dipivoxil (HEPSERA™), Gilead
  - 2006: Telbivudine (TYZEKA™), Idenix and Novartis
- **Third line therapy**
  - 1998: Lamivudine (EPIVIR-HBV®), GlaxoSmithKline

# American Association for the Study of Liver Diseases Algorithm for Treatment Decisions in HBV



## AASLD HBV Treatment Recommendations

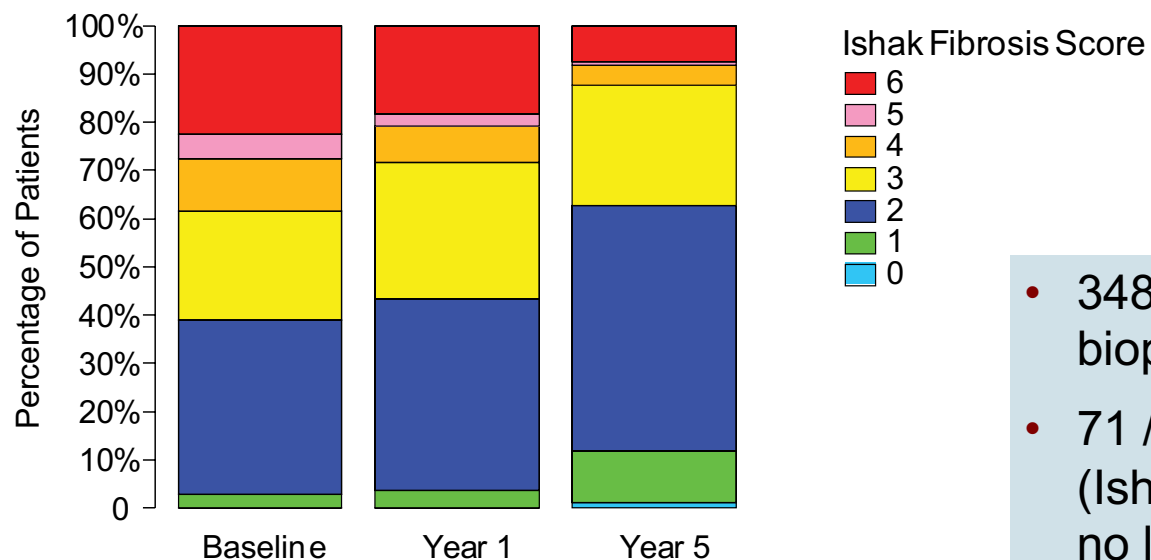
- Patients with cirrhosis, regardless of e antigen status or ALT level with detectable HBV DNA should be treated
- Patients with normal ALT and HBV DNA > 1,000,000 IU/ml, regardless of E antigen status, should be treated if there is moderate to severe inflammation/fibrosis and/or > 40 years of age

## Anti-Viral Treatment Options for HBV

Name	Anti-viral Potency	Side effects	Risk of resistance	Caveats
<b>Peg-IFN alfa 2a</b>	++	Fatigue, cytopenias, depression	None	Not recommended in cirrhosis, cardiopulmonary disease, psychiatric disease, uncontrolled seizures, pregnancy
<b>Entecavir</b>	+++	Lactic acidosis	Very low	Not recommended if prior nucleoside analogue treatment Dose adjustment if Cr cl < 50 ml/min
<b>TDF</b>	+++	Renal and bone toxicity	Very low	Dose adjustment if Cr cl < 50 ml/min
<b>TAF</b>	+++	Minimal renal and bone toxicity	Very low	Dose adjustment if Cr cl < 15 ml/min



## 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

## Sample Case

- 36 year old Asian women
- History of hepatitis B with risk factor pre-natal transmission
- Feels well
- ALT 55
- HBVDNA 120,000 IU
- Platelet count 185,000
- HBsAg +
- HBeAg+
- F1 on transient elastography
- What do you do now?
  - Screen for HCC q 6months
- Initiate HBV anti-viral therapy

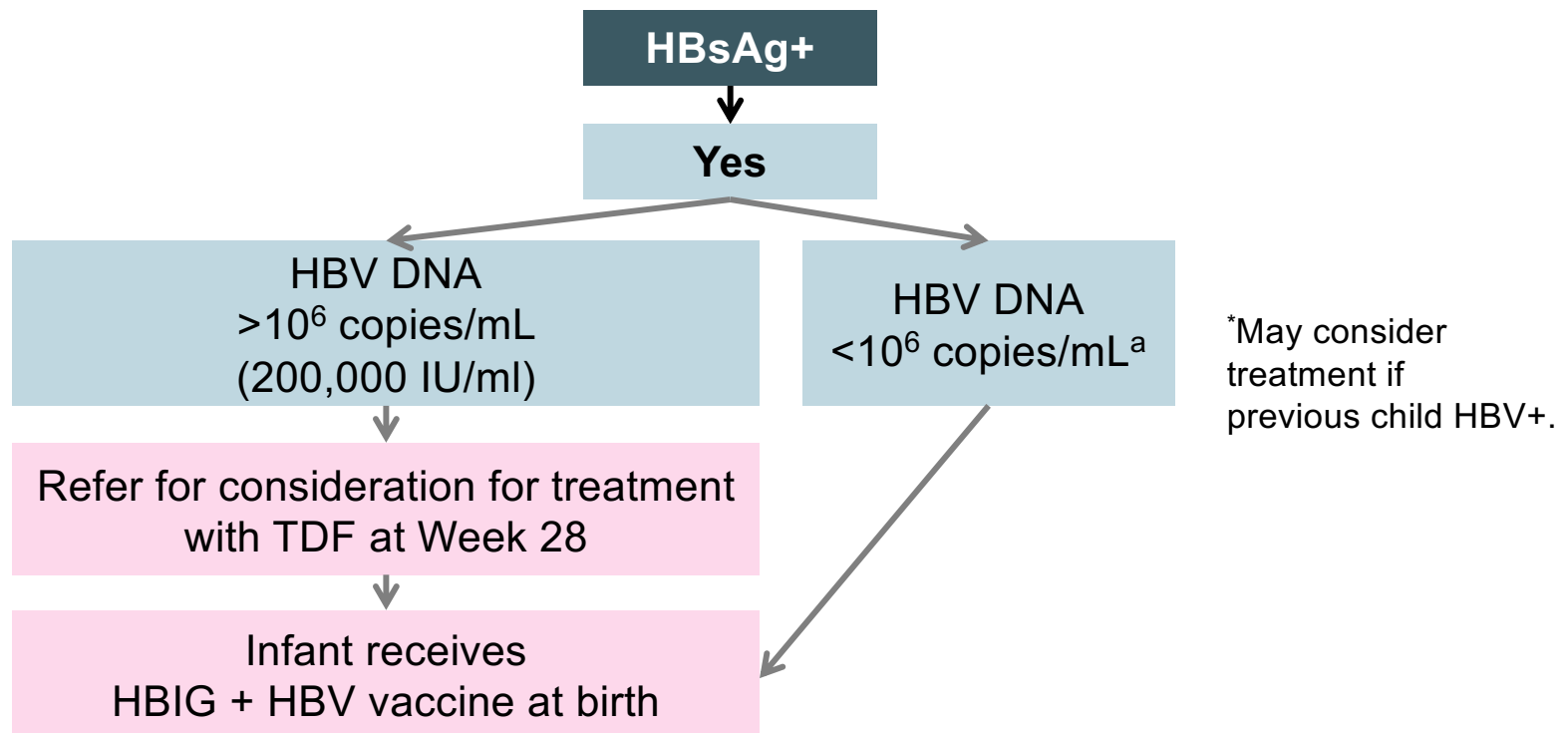
## Sample Case

- 39 year old Asian man
- History of hepatitis B with risk factor pre-natal transmission
- Feels well
- ALT 30
- HBVDNA 1200 IU
- Platelet count 285,000
- HBsAg +
- HBeAg-
- F1 on transient elastography
- What do you do now?
  - Screen for HCC q 6months
- Do not start HBV anti-viral therapy
  - Follow with ALT, HBVDNA every 3-6 months



# HBV and Pregnancy

## Suggested Management of HBV Infection During Pregnancy



## Role of PCP in HBV Care

- Link HBV infected patients to treatment centers
- Follow patients on therapy every 3-6 months with:
  - Liver enzymes
  - HBV DNA
- HCC surveillance every 6 months with U/S and AFP regardless of whether patient is on treatment or not
- Discuss modes of transmission and prevention
- Discuss HBV testing and vaccination for close contacts
- Vaccinate for hepatitis A if susceptible
- Screen for HCV