Hepatitis B:
An Overview & Update

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Empire Liver
FOUNDATION

Disclosures

- No Disclosures

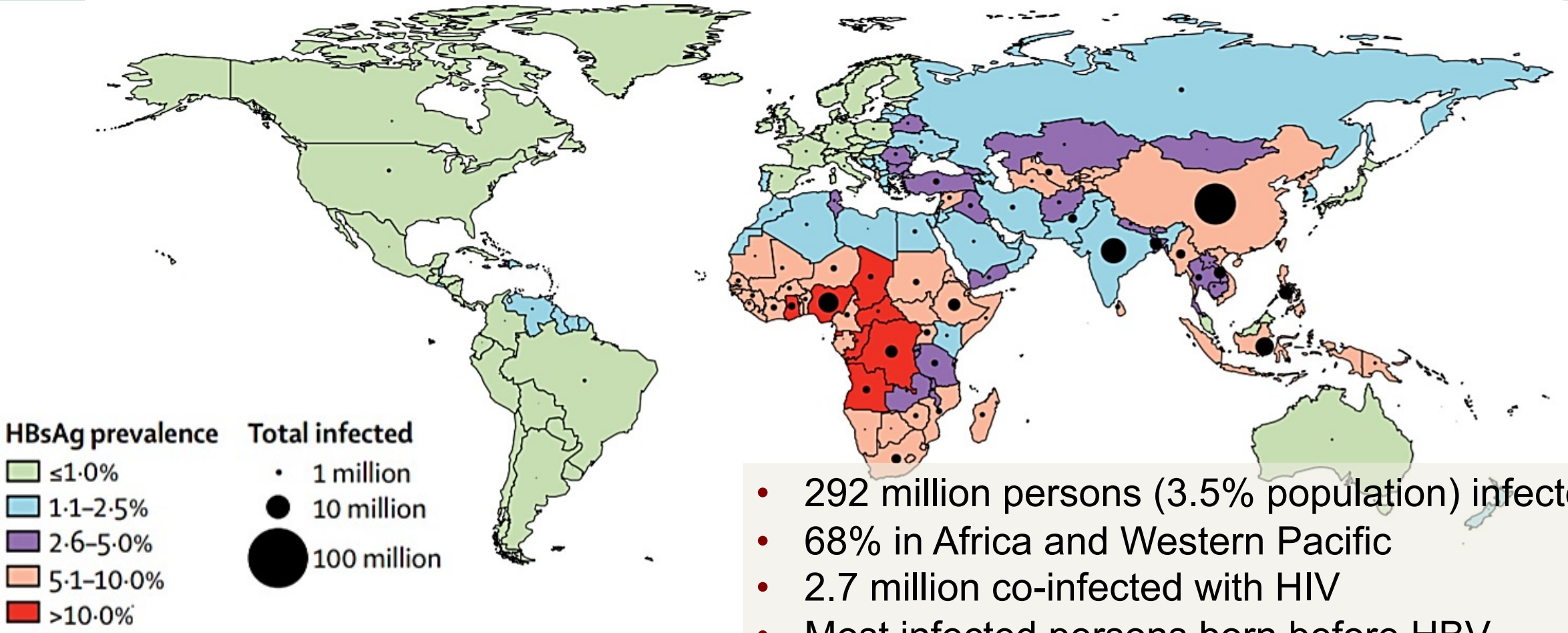
Learning Objectives

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

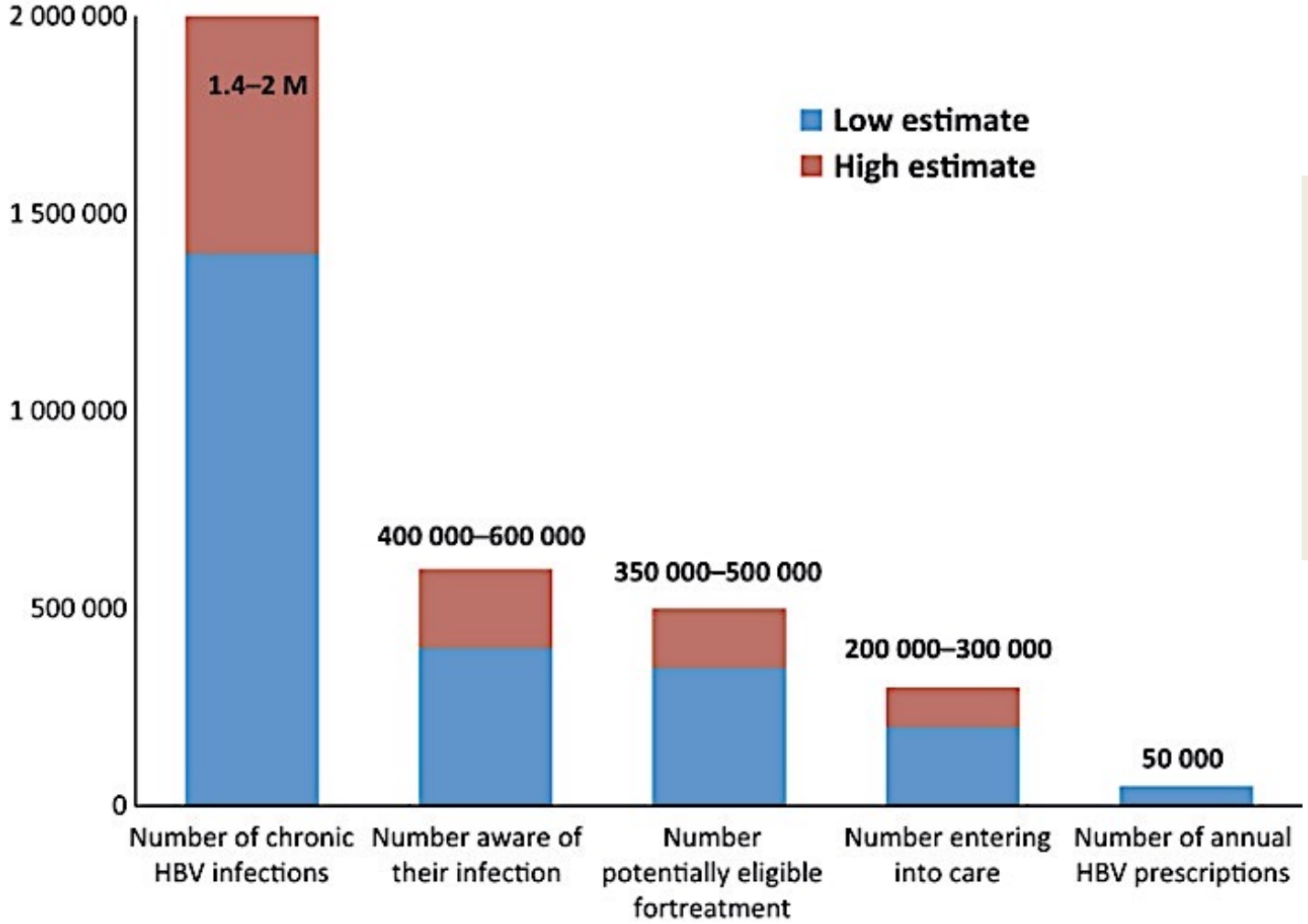
Global HBV Prevalence, 2016



- 292 million persons (3.5% population) infected
- 68% in Africa and Western Pacific
- 2.7 million co-infected with HIV
- Most infected persons born before HBV vaccine was widely used in infancy

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

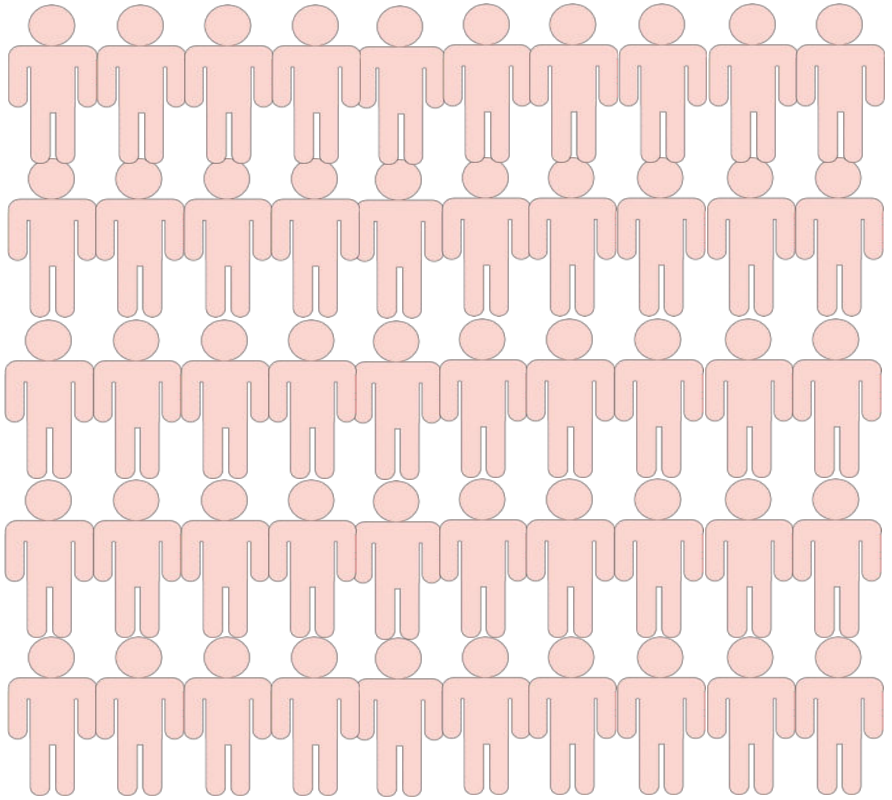
Gaps in HBV Care in the U.S.

- 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

Abara et al. Ann Intern Med. 2017 Nov 21.

Hepatitis B- Facts

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



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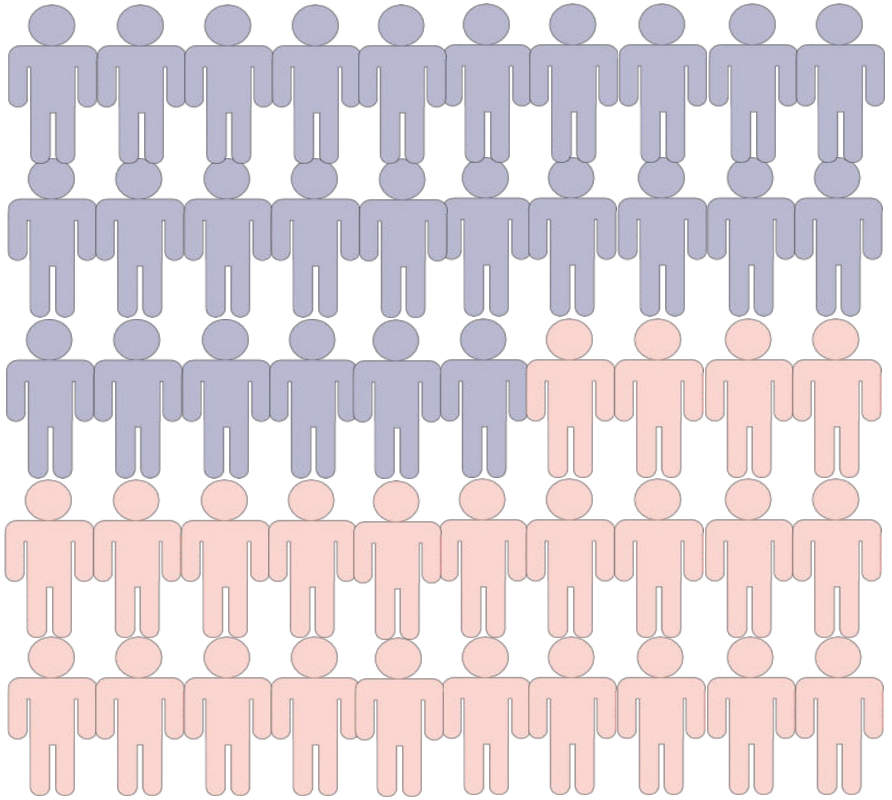
95,617 people are reported with Hepatitis B in NYC from 2016-2019 *(2019 Annual Report)*

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

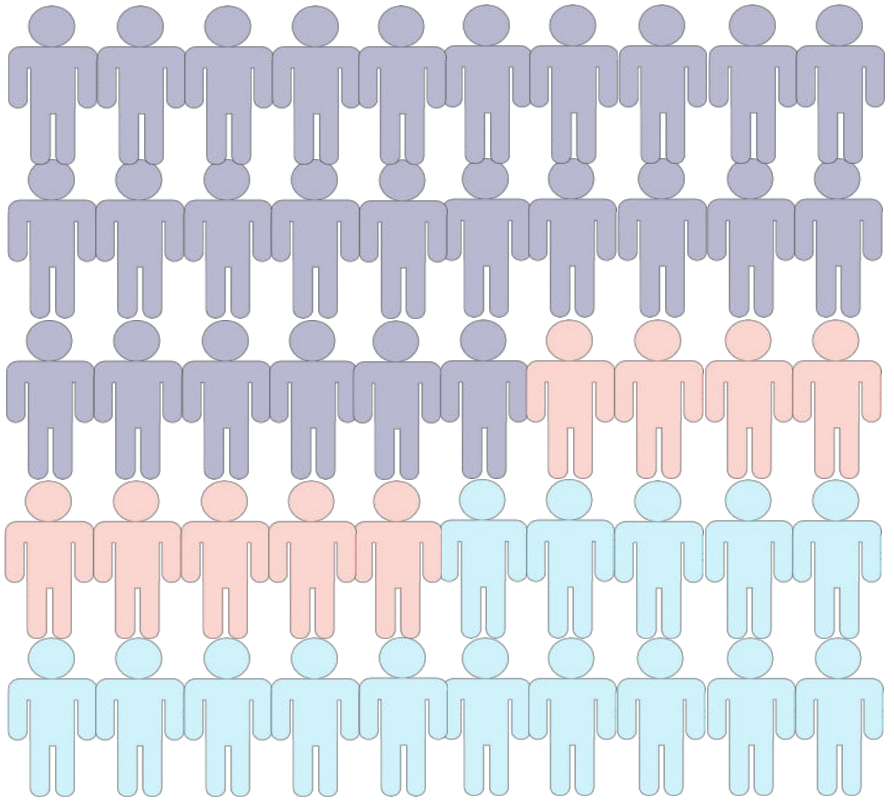


Hepatitis B- Facts

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)*



NYC Health

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%)

Wong, et al. *Hepatology.* 2021.

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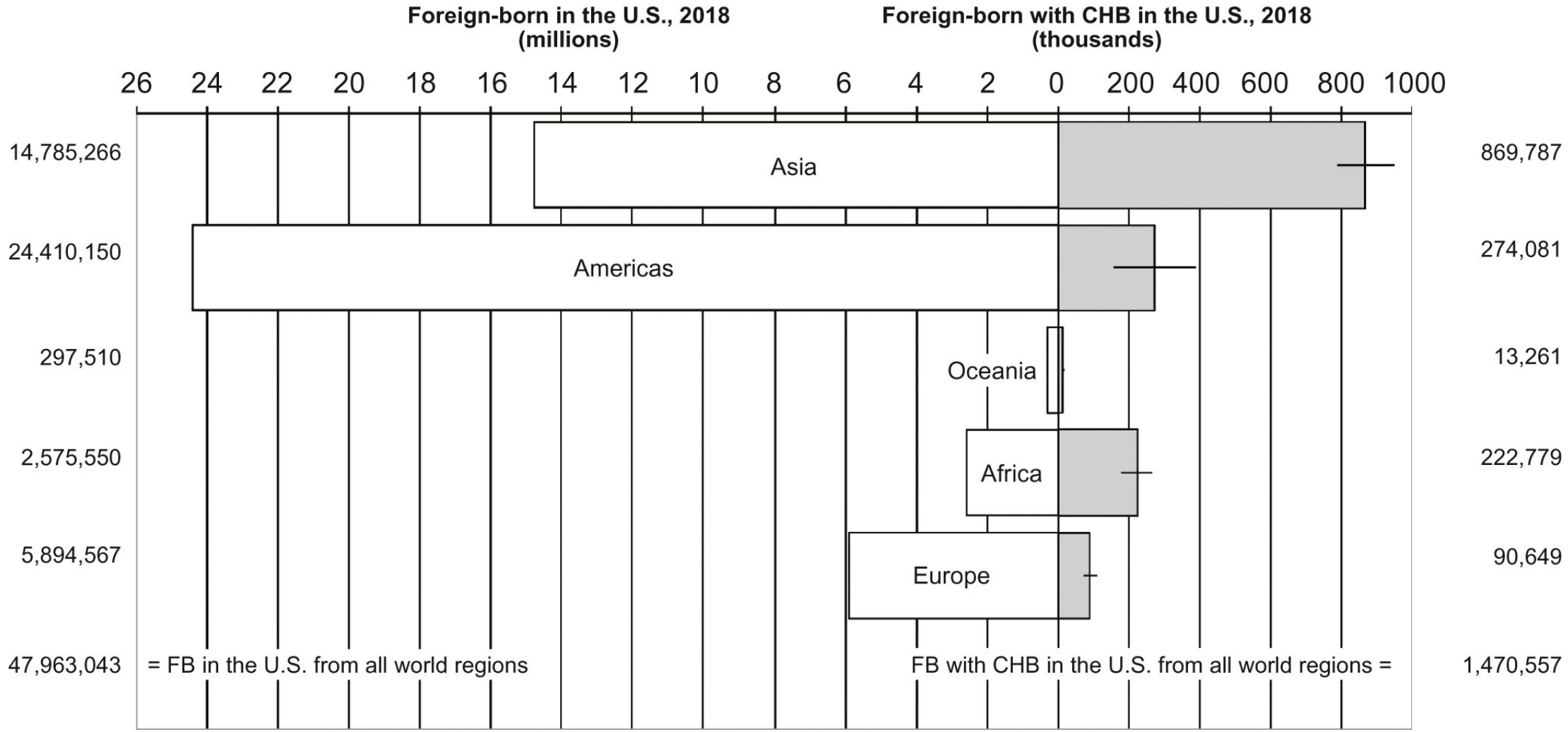


Wong, et al. *Hepatology.* 2021.

Viral Hepatitis is Underfunded

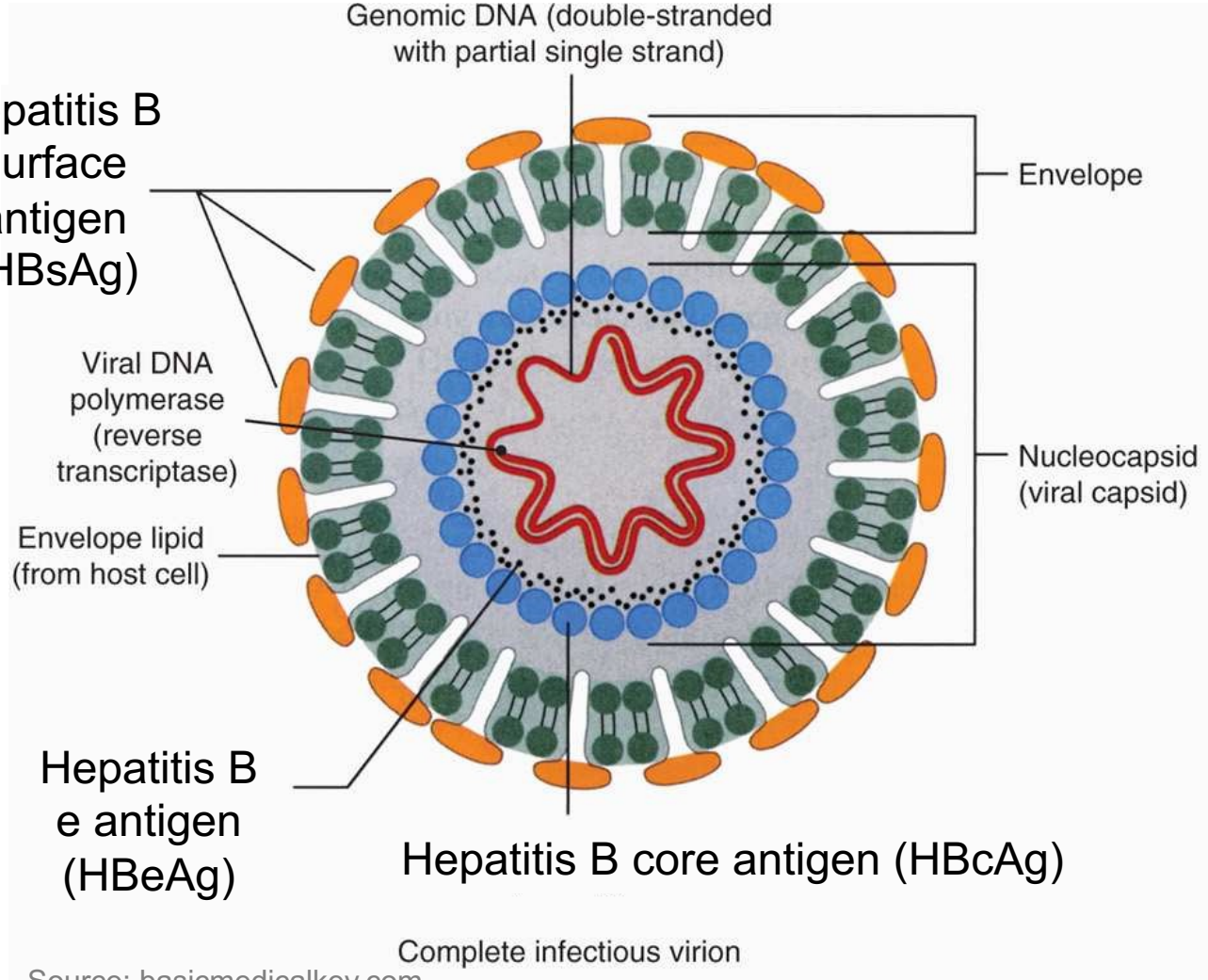
Virus	US population	% of CDC division budget
HBV **HCV**	0.8-2.2 million 2.7-3.9 million	**2%** (for both HBV/HCV domestic/international)
HIV	1.1 million	**69%** (domestic, not including international HIV work)

- 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

Source: Wang S, 2016

Natural History

HBV Structure



Source: basicmedicalkey.com

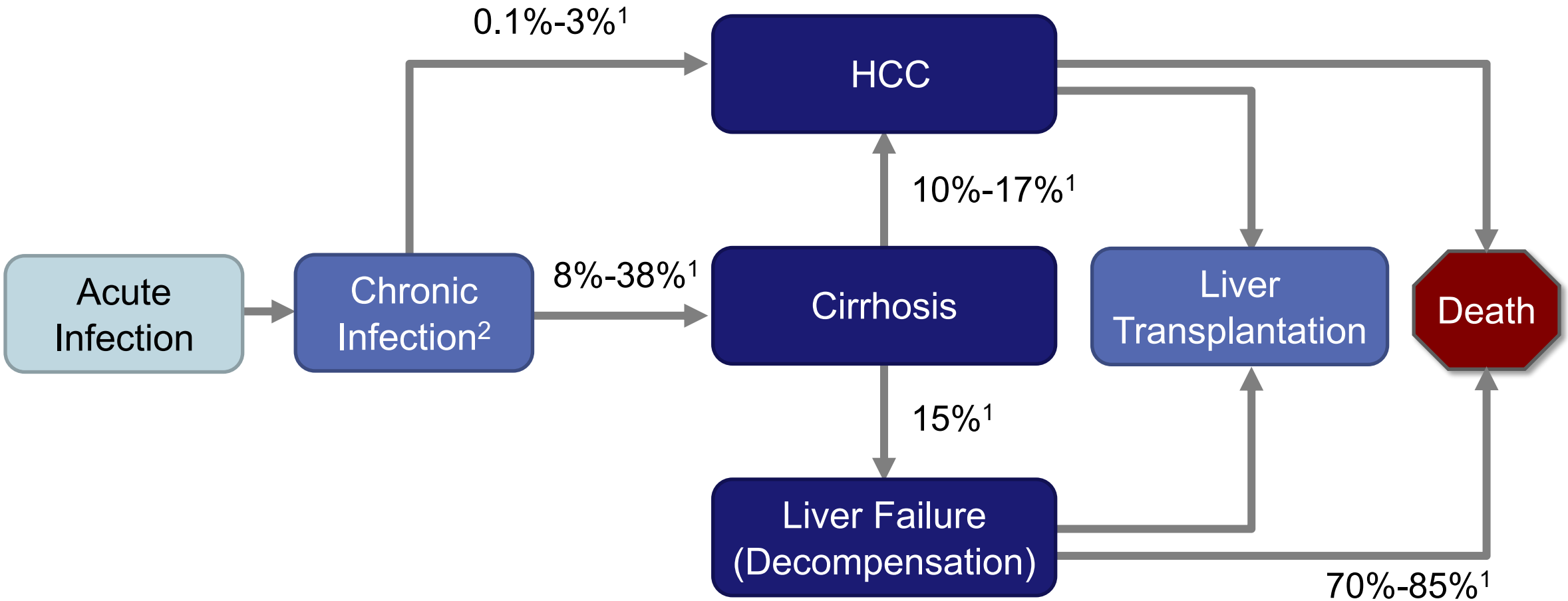
- DNA virus
- Ten genotypes, A to J
- HBV replicates through an RNA intermediate and can integrate into the host genome
- Virological and serological assays have been developed for diagnosis of various forms of HBV-associated disease

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
HBV test results	• HBsAg present for 6 months • HBeAg positive • HBV-DNA levels are very high (typically >1 million IU/mL)	• HBsAg present for 6 months • Serum HBV DNA >20,000 IU/mL in HBeAg-positive CHB • >2,000 IU/mL in HBeAg-negative CHB	• HBsAg present for 6 months • HBeAg negative, anti-HBe positive • Serum HBV DNA <2,000 IU/mL
ALT/AST levels	Normal or minimally elevated	Intermittently or persistently elevated	Persistently normal
Liver biopsy or noninvasive test results	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

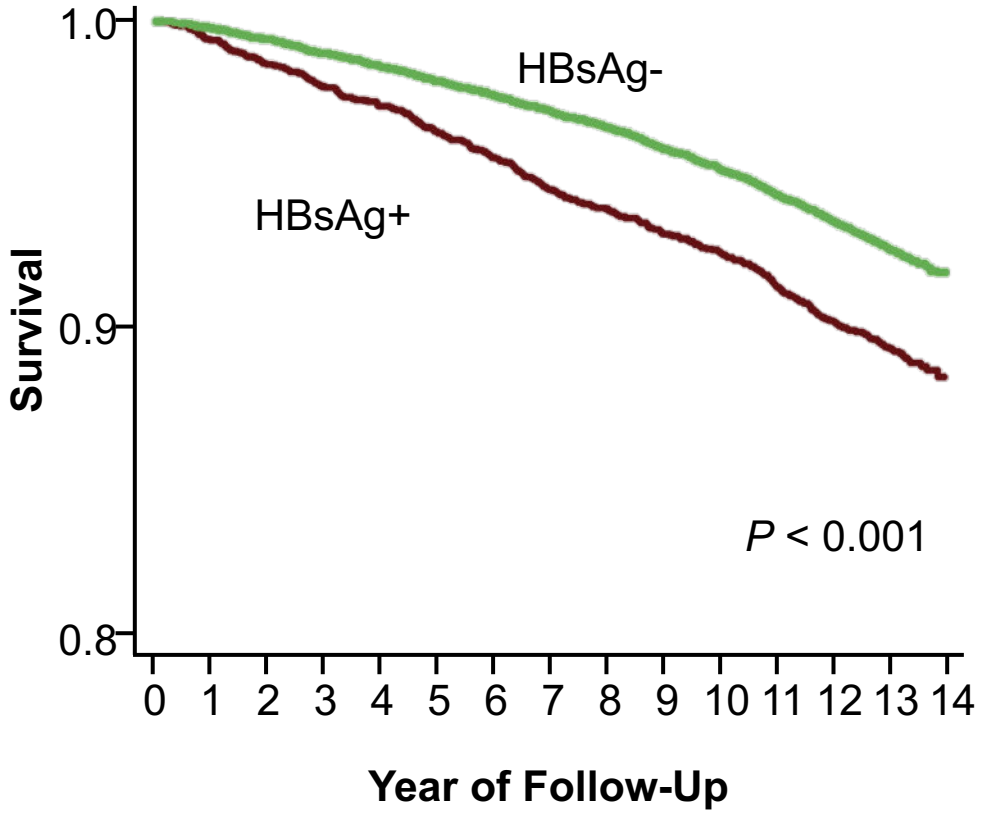
Disease Burden from HBV Infection: 5-Year Cumulative Incidence Rates of Development of Chronic HBV Complications



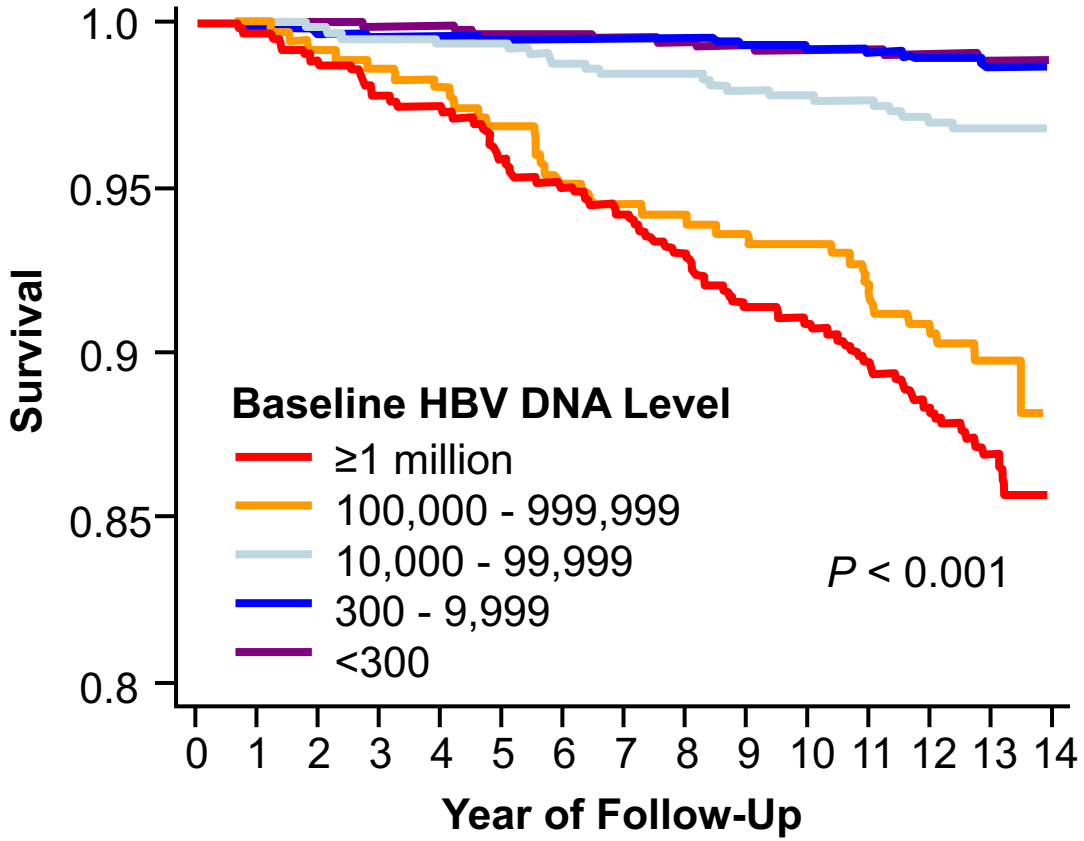
1. Fattovich G, et al. *J Hepatol.* 2008;48:335-352.
2. Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

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

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



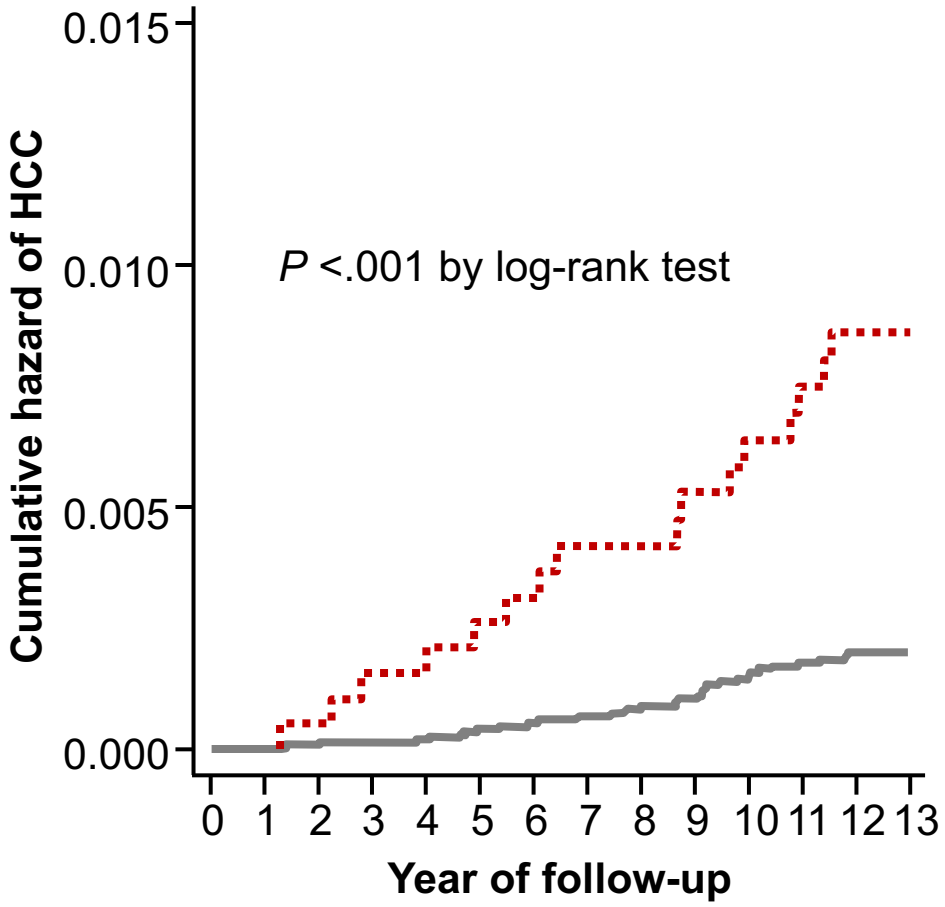
Liver-related mortality by baseline HBV DNA in HBsAg+ subjects without evidence of HCV infection (n=3,653)



Iloeje UH, et al. *Clin Gastroenterol Hepatol*. 2007;5(8):921-931.

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

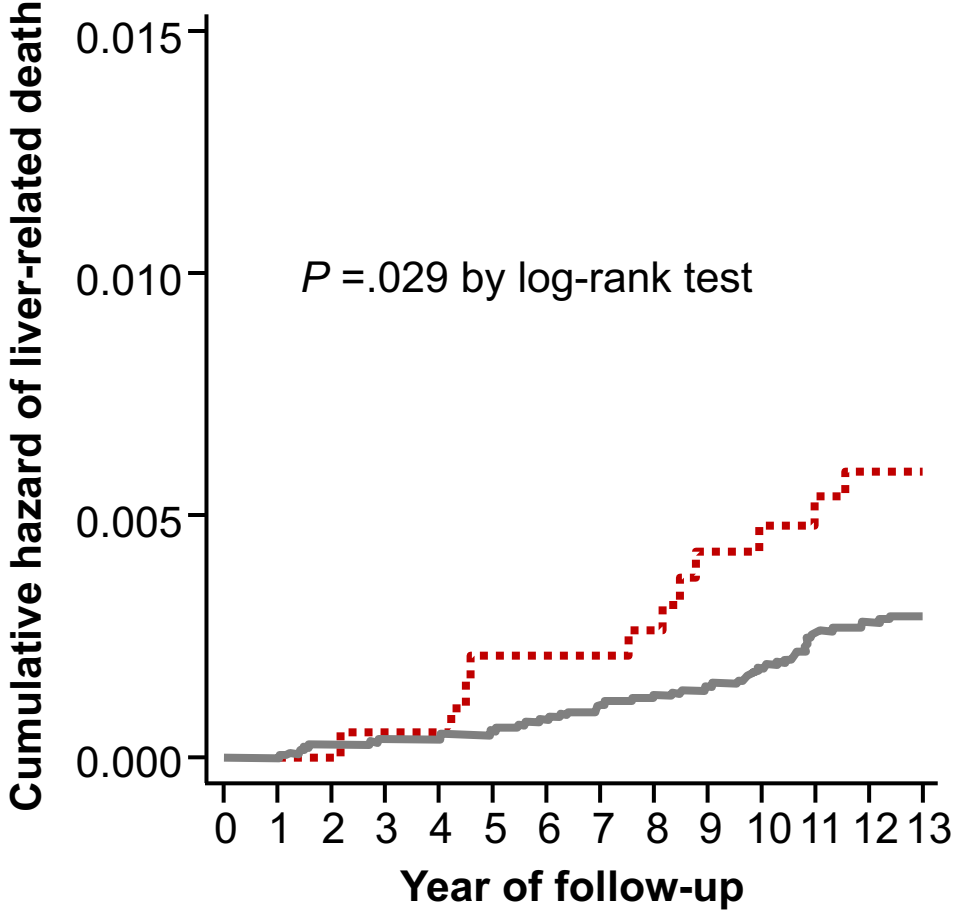
Cumulative hazard of progression to HCC



Control

HBeAg Negative Chronic Infection (HBV DNA <10,000 copies/mL and ALT <45 U/L)

Cumulative hazard of progression to liver-related death



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

Abara WE et al, Ann Intern Med. 2017;167(11):794-804

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/

Source: HBV Immunizations. Hepatitis B Online. https://www.hepatitisb.uw.edu/go/prevention-hbv/hbv-immunizations/core-concept/all#background

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

Source: NYC Health Department

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
Chronic infection	+	-	+	Evaluate for treatment
Acute infection	+	-	+ (IgM anti-HBc)	Link to HBV directed care
Resolved infection	-	+	+	Counseling, reassurance
Immune (immunization)	-	+	-	Reassurance
Susceptible (never infected or immunized)	-	-	-	Vaccinate
Exposed	-	-	+	Depends on situation

www.cdc.gov/hepatitis

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 (≥19 IU/L for women and ≥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.

Abara WE et al, Ann Intern Med. 2017;167(11):794-804

Additional High-Risk Groups for HBV Screening

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

- Persons born in countries and regions with a high prevalence of HBV infection (≥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 (≥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%)

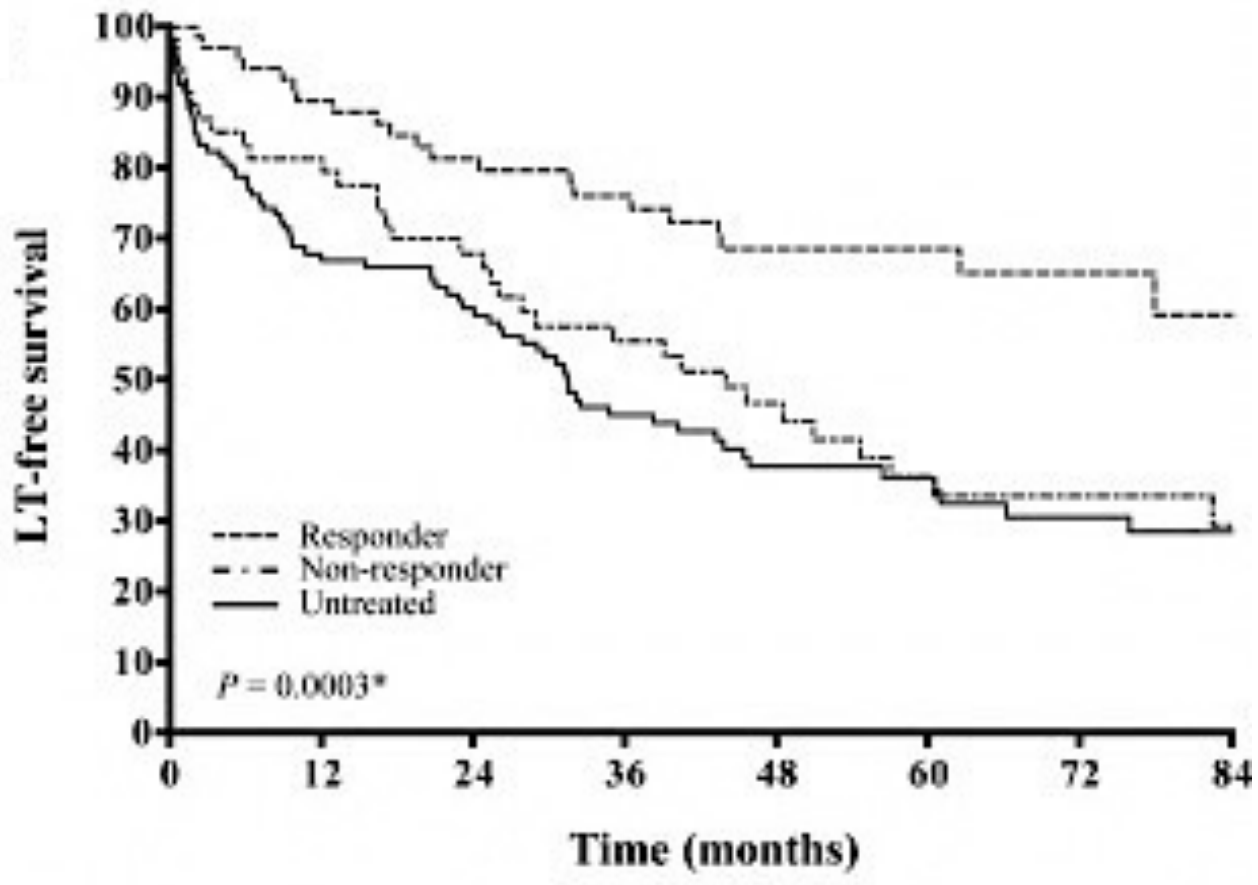
Chu D et al, Gut Liver. 2013; 7(4):450-457

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)

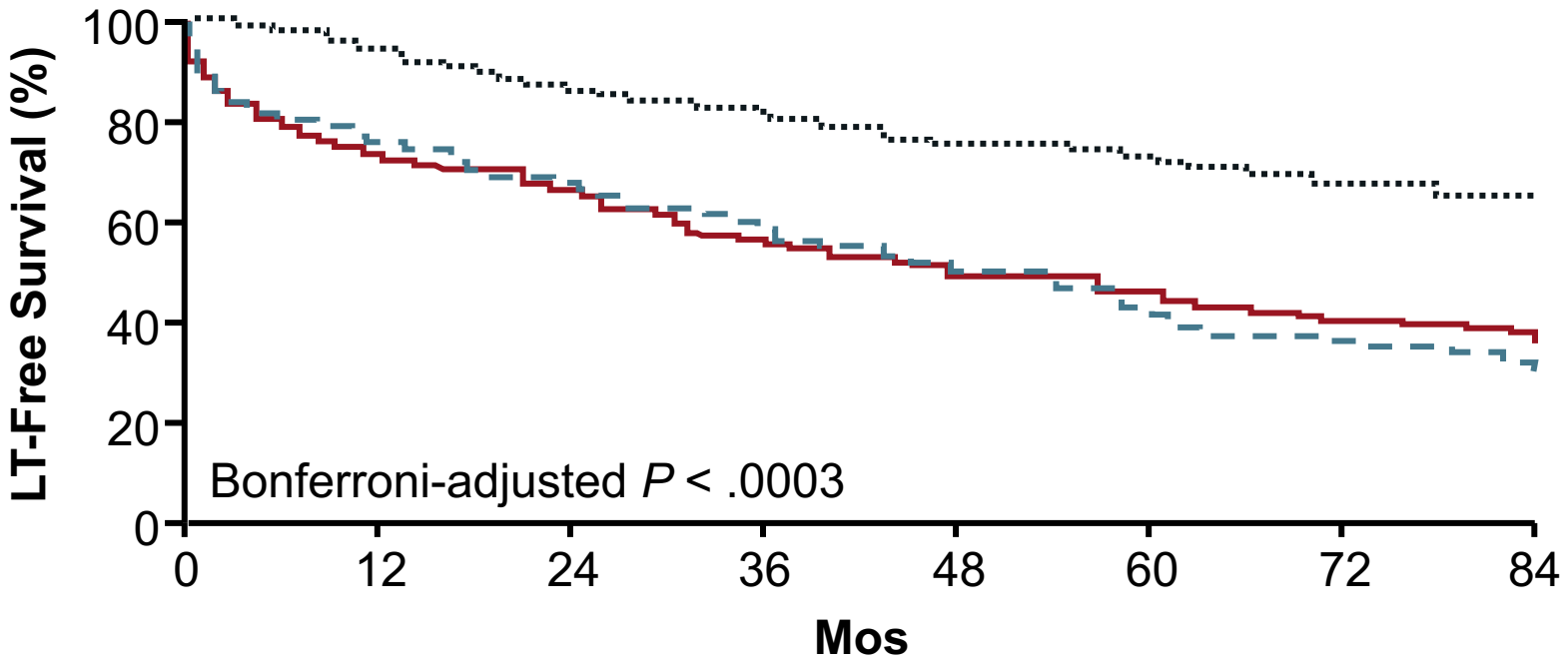


*Nonresponders included pts with HBV rebound or genotypic resistance, primary nonresponse, Not evaluable due to early event (death, LT, LTFU).

Jang JW, et al. Hepatology. 2015;61:1809-1820.

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)

Jang JW, et al. Hepatology. 2015;61:1809-1820.

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

Martin P et al, Clinical Gastroenterology and Hepatology 2015;13:2071–2087

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

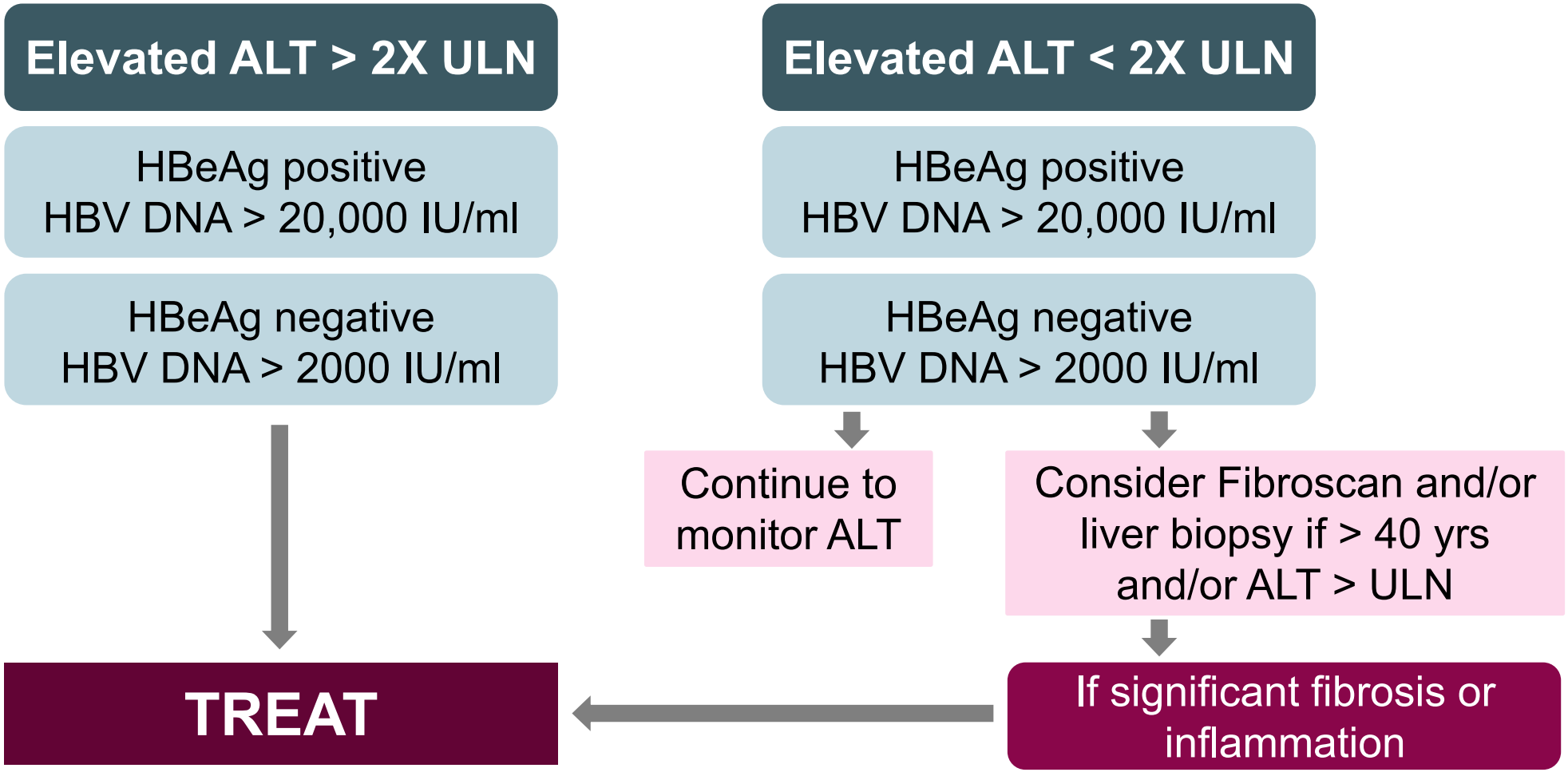
- **Inactive state**
  - Sustained, off drug
    - No inflammation – Normal ALT and liver biopsy
    - HBVDNA low or undetectable
    - HBsAg positive
- **Functional Cure (Clinical Resolution)**
  - Sustained, off drug
    - No inflammation – Normal ALT and liver biopsy
    - HBsAg loss
    - Anti-HBs 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

Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

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



Terrault NA, et al. Hepatology. 2016;63:261-283, Sarin et al. Hep Int 2016

AASLD HBV Treatment Recommendations

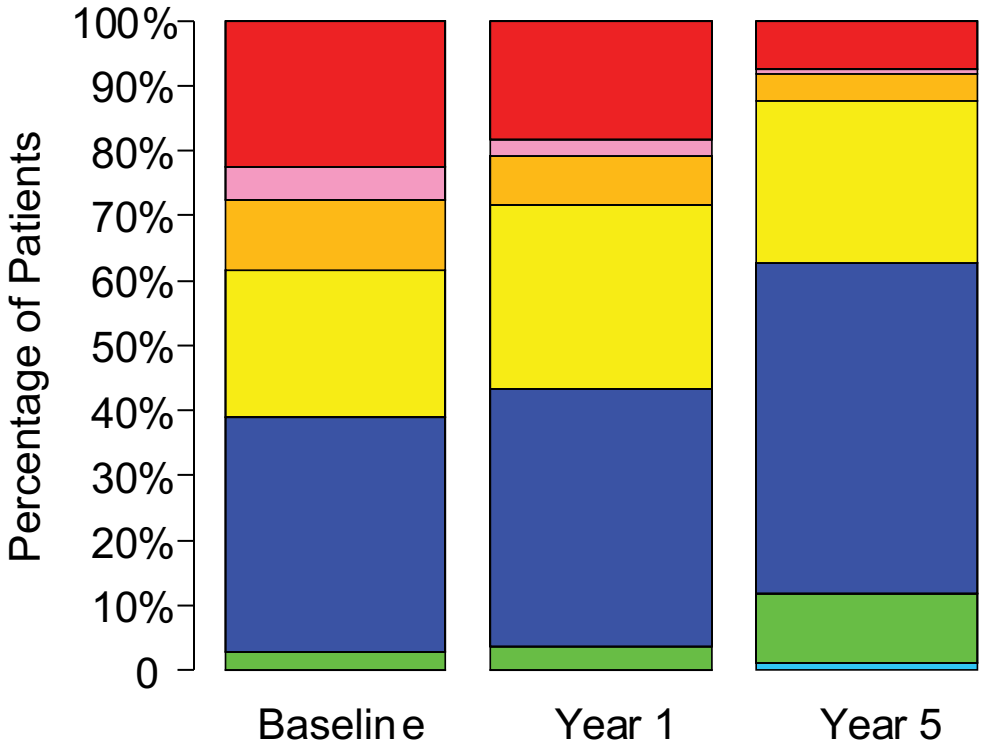
- Patients with cirrhosis, regardless of e antigen status or ALT level with detectable HBV DNA should be treated
- Patients with normal ALT and HBV DNA > 1,000,000 IU/ml, regardless of E antigen status, should be treated if there is moderate to severe inflammation/fibrosis and/or > 40 years of age

Terrault NA, et al. Hepatology. 2016;63:261-283

Anti-Viral Treatment Options for HBV

Name	Anti-viral Potency	Side effects	Risk of resistance	Caveats
Peg-IFN alfa 2a	++	Fatigue, cytopenias, depression	None	Not recommended in cirrhosis, cardiopulmonary disease, psychiatric disease, uncontrolled seizures, pregnancy
Entecavir	+++	Lactic acidosis	Very low	Not recommended if prior nucleoside analogue treatment Dose adjustment if Cr cl < 50 ml/min
TDF	+++	Renal and bone toxicity	Very low	Dose adjustment if Cr cl < 50 ml/min
TAF	+++	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 ≥5) at baseline no longer had cirrhosis at Year 5

Marcellin, P, Lancet 2013; 381: 468

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

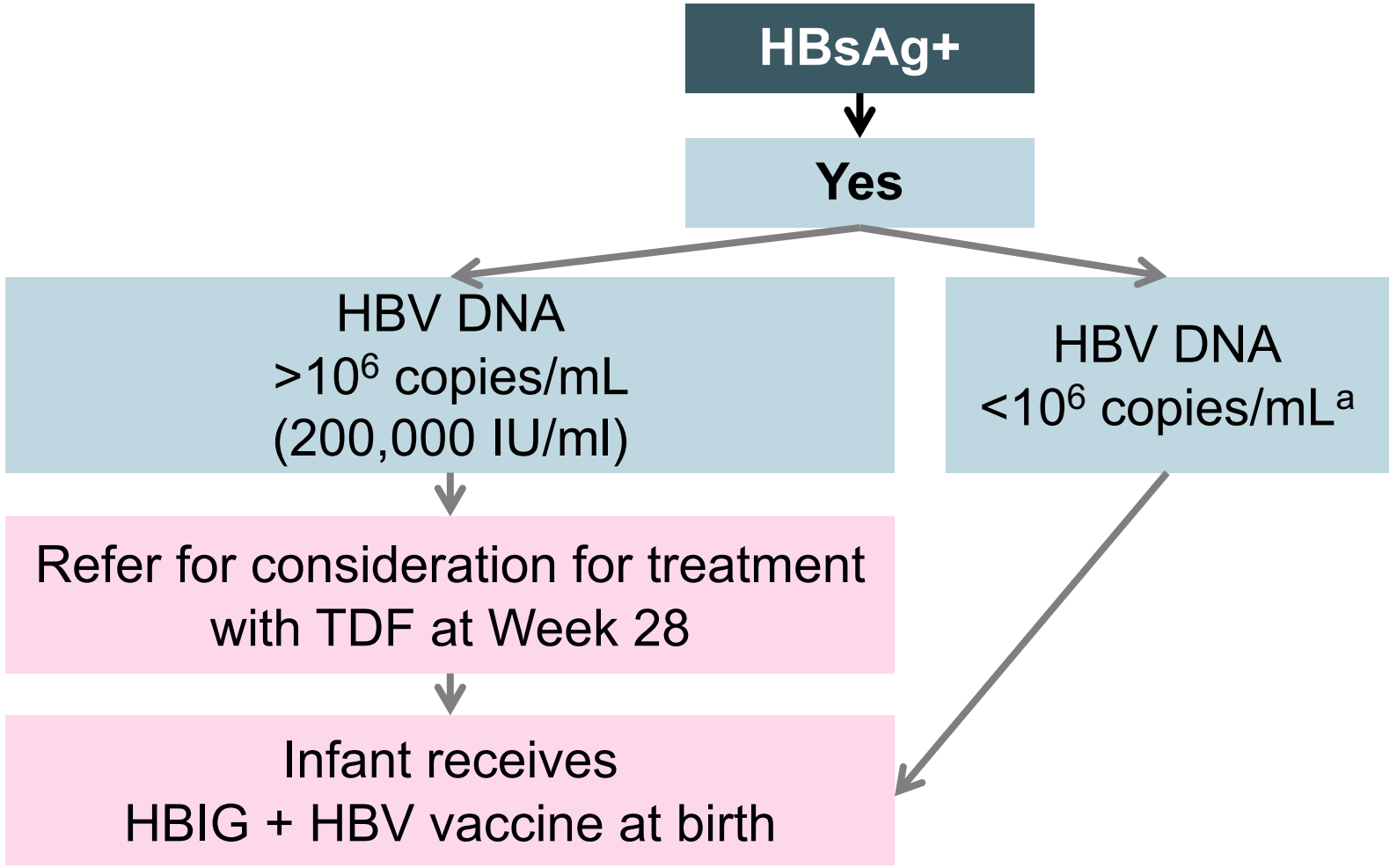
Sample Case

- 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



*May consider treatment if previous child HBV+.

Terrault et. al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2015.

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

Abara et al. Ann Intern Med. 2017 Nov 21.