GI Alliance

Advancing GI Patient Care 2021

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Chronic Hepatitis B: Screening and Treatments

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GI Alliance: TDDC Houston

Disclosures

- Gilead Sciences – Clinical Research/ Speaker Bureau

CME Objectives

- Able to interpret Hepatitis B screening test results
- Understand natural history of CHB
- Identify treatment candidates and goals of therapy
- Able to discuss future therapies of CHB

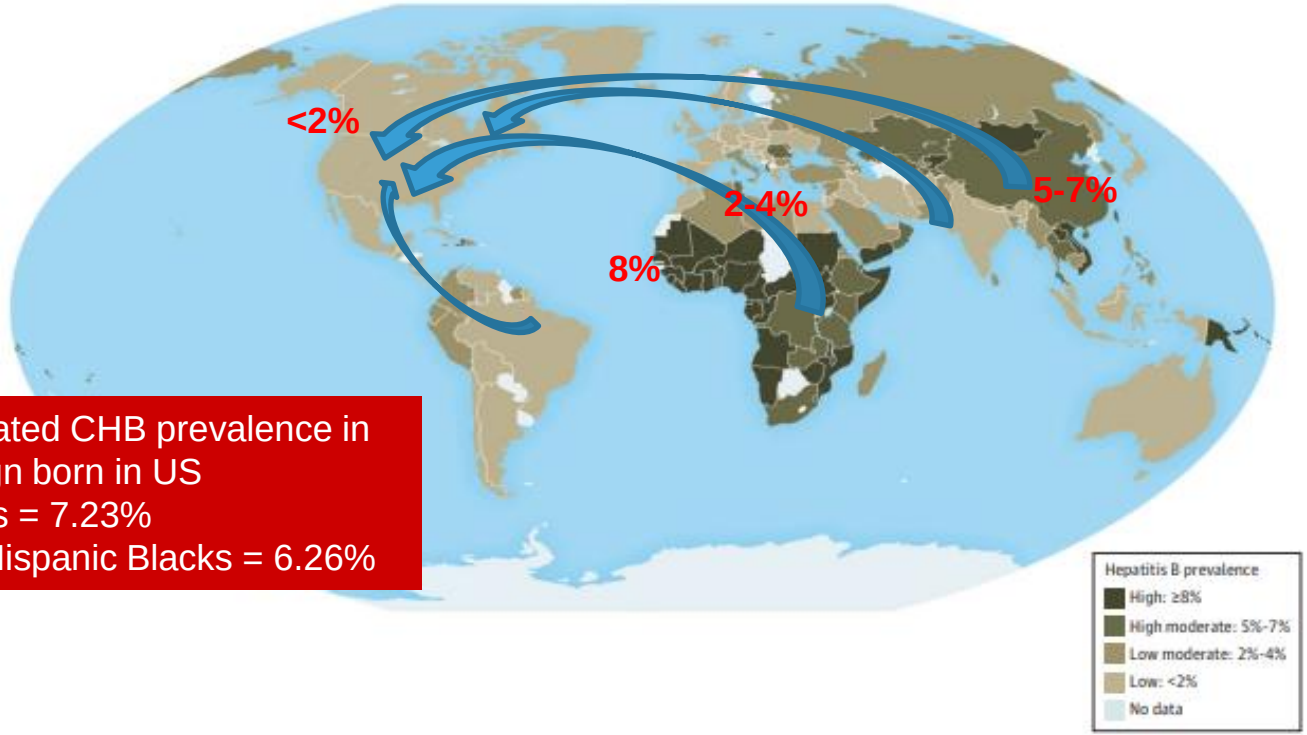

Tunisia:
Power is in the streets
Health Special:
Kids and concussions
Zodiac:
No really, what's your sign?
TIME
THE TRUTH ABOUT TIGER MOMS
A mother's memoir on tough-love parenting unleashed an international debate. Is that because she's onto something?
BY ANNIE MURPHY PAUL

HBV: A Global Problem

- 2 billion people worldwide have been infected with HBV[1]
- 257-291 million chronic carriers[2,6]
- 1.59 million persons with CHB in US(1.25-2.49)[6]
- Leading cause of cirrhosis and HCC worldwide[2]
- Causes 80% of all HCC in Asian Americans[3]
- 30% to 50% of HCC associated with HBV in the absence of cirrhosis[4]
- 15%-40% of persons with CHB develop cirrhosis, HCC or liver failure[6]
- Second only to tobacco in causing the most cancer deaths[5]
- HBV is 50-100 times more infectious than HIV[1]

1. World Health Organization. HBV fact sheet 2015; 2. M Nguyen, G Wong, et al. *Clin Micro Reviews.* 2020; 33(2) e00046-19: 1-38; 3. Stanford Asian Liver Center. For hepatitis B and liver cancer patients; 4. Bosch FX et al. *Clin Liver Dis*. 2005;9:191-211; 5. World Health Organization. Global alert and response: hepatitis B-Introduction; 6. JK Lim, MH Nguyen, et al. *AJG*. 2020;115(9):1429-1438.

Global Prevalence of CHB

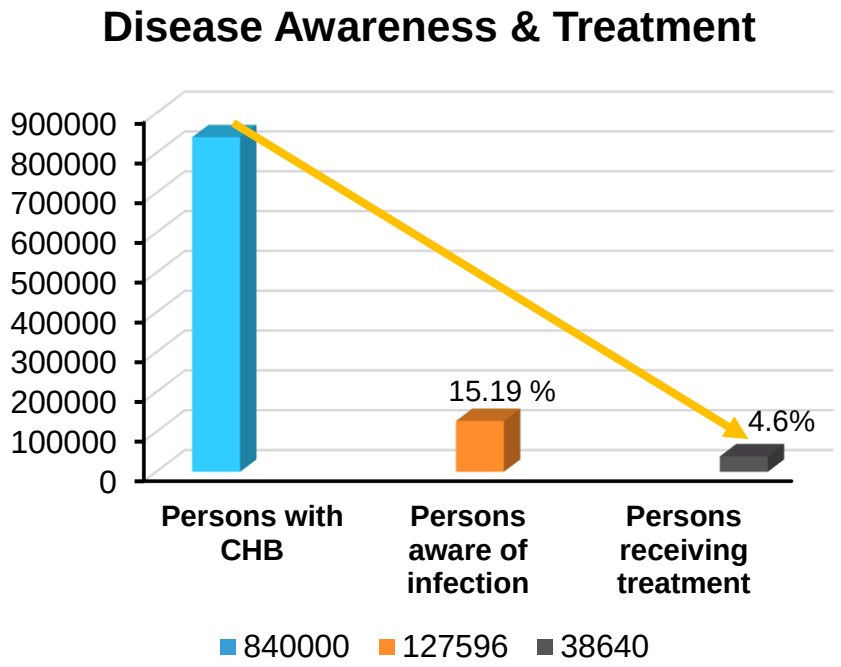


Estimated CHB prevalence in Foreign born in US
Asians = 7.23%
Non-Hispanic Blacks = 6.26%

US Preventive Services Task Force. *JAMA*. Dec 15, 2020. Vol 324, 23. 2415-2422;
JK Lim, MH Nguyen, et al. *AJG*. 2020;115(9):1429-1438.

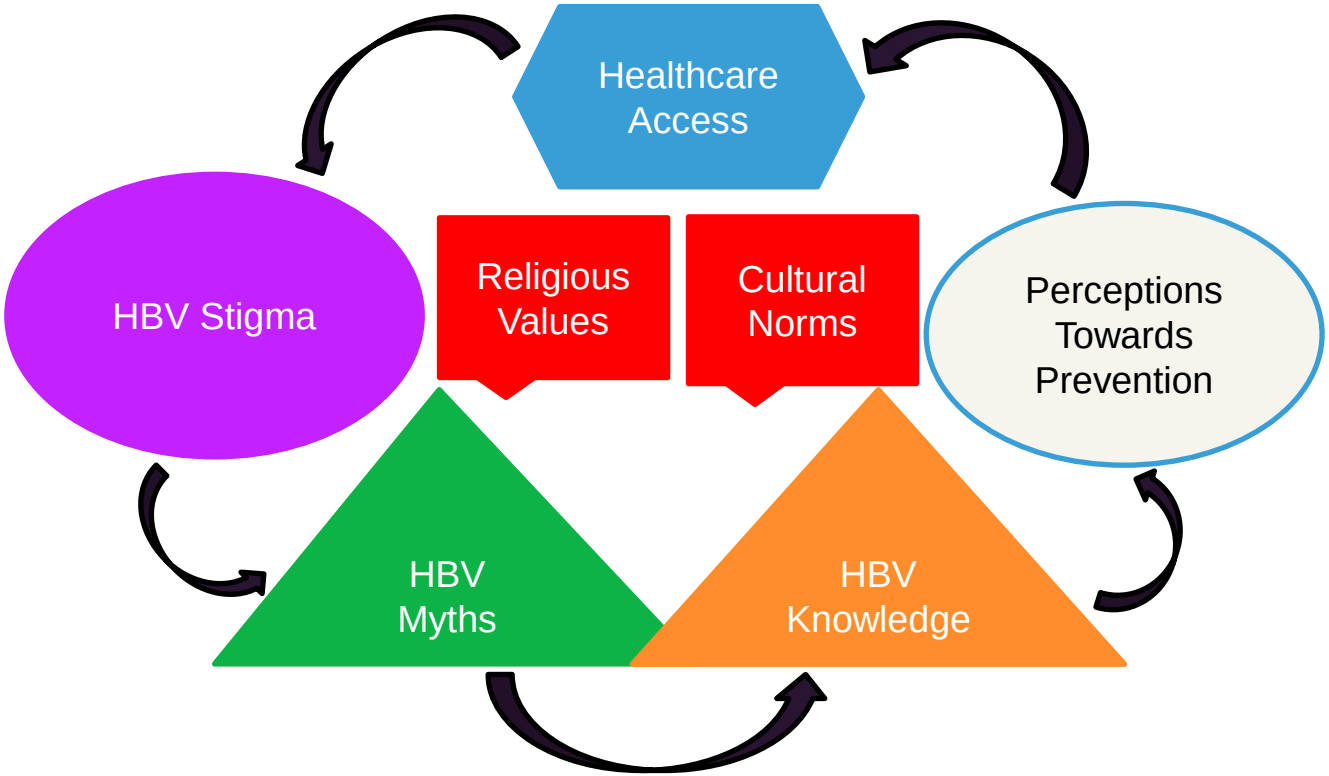
Chronic Hepatitis B Awareness in US 1999-2016

- National Health and Nutrition Examination Survey – NHANES
- 47,628 participants
- No significant change in prevalence between 1999 and 2016= 0.35% or 840,000 adults
- Prevalence was highest in non-Hispanic Asians in foreign born = 3.85% (95% CI 2.97-4.97), US born = 0.79% (95% CI 0.17-3.59) during 2011-2016
- Among infected persons, liver disease awareness = 15.19%, treatment rate 4.6%
- Up to 68% of people with CHB are unaware of their infection



M Le, Y H Yeo, R Cheung, L Henry, A S Lok, M H Nguyen. *Hepatology.* 2020 Feb;71(2):431-443;
US Preventive Services Task Force. *JAMA*. Dec 15, 2020. Vol 324, 23. 2415-2422.

Barriers to CHB Screening and Prevention in African Immigrants



Freeland C et al. *Viruses*. 2020;12(305);doi:10.3390/v12030305.

Screening Tests

HBsAg	Anti-HBs	Anti-HBc[a]	Interpretation	Recommended Follow-up
+	–	+	Acute or chronic infection[b]	**Contact patient for evaluation and further testing**
–	+	+	Patient has immunity from previous infection	**Follow up as appropriate[c,d]**
–	+	–	Patient has immunity from vaccination	**No further action required**
–	–	–	Patient is at-risk for HBV infection	**Vaccinate**

Consider screening for HAV and HCV also

[a]Anti-HBc refers to total anti-HBc.[2];[b]Patient is chronically infected if HBsAg+ for ≥6 months.[3]; [c]Patients who are anti-HBc positive should be monitored closely during and after the administration of cytotoxic chemotherapy for signs of HBV reactivation.[1]; [d]Patients with cirrhosis may need to be monitored for hepatocellular carcinoma per the AASLD guidelines.[4]

1. NA Terrault, ASF Lok, et al. Practice Guidance. *Hepatology*. 2018;vol 67, N0. 4:1560-1599; 2. Martin P et al. *Clin Gastroenterol Hepatol.* 2015 July 15; 3. CDC. *Morb Mortal Wkly Rep.* 2008;57:1-20; 4. Bruix J, Sherman M. *Hepatology.* 2011;53. www.aasld.org/sites/default/files/ guideline_documents/HCCUpdate2010.pdf. Accessed September 11, 2015.

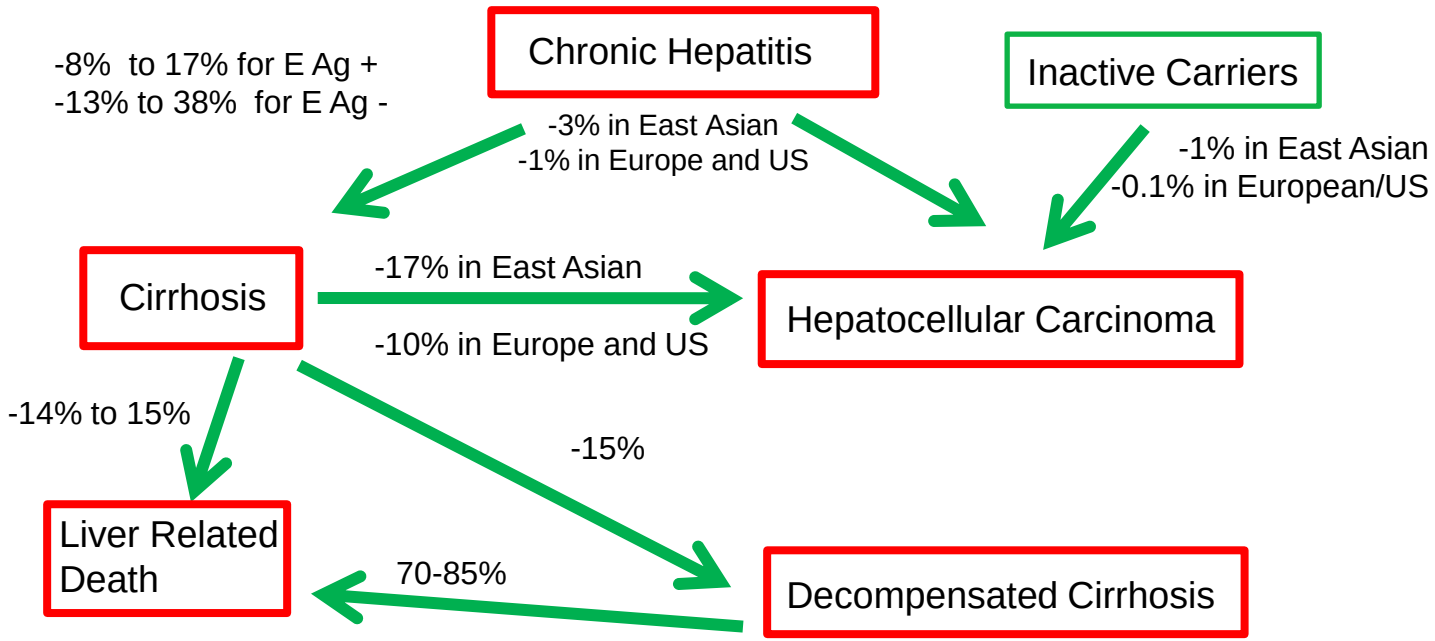
Screening Recommendations:

- People born in regions with prevalence of HBV infection of ≥2%[1-4]
- US-born people not vaccinated as infants whose parents were born in regions with prevalence of HBV infection of ≥8%[1-3]
- Household and sexual contacts of persons with HBV infection[1-3]
- All pregnant women[2-4]
- Men who have sex with men[1-3]
- Injection drug users[1-3]
- Individuals infected with human immunodeficiency virus (HIV)[1-3]
- People with certain medical conditions[2,3,5]
  - Needing immunosuppressive therapy
  - Undergoing hemodialysis

AASLD = American Association for the Study of Liver Diseases; CDC = Centers for Disease Control and Prevention; USPSTF = United States Preventive Services Task Force.

1. LeFevre ML. USPSTF. *Ann Intern Med.* 2014;161:58-66; 2. CDC. *Morb Mortal Wkly Rep.* 2008;57:1-20; 3. Lok ASF, McMahon BJ. *Hepatology.* 2009;50(3):1-36; 4. USPSTF. *JAMA*. 2020;324(23):2415-2422.

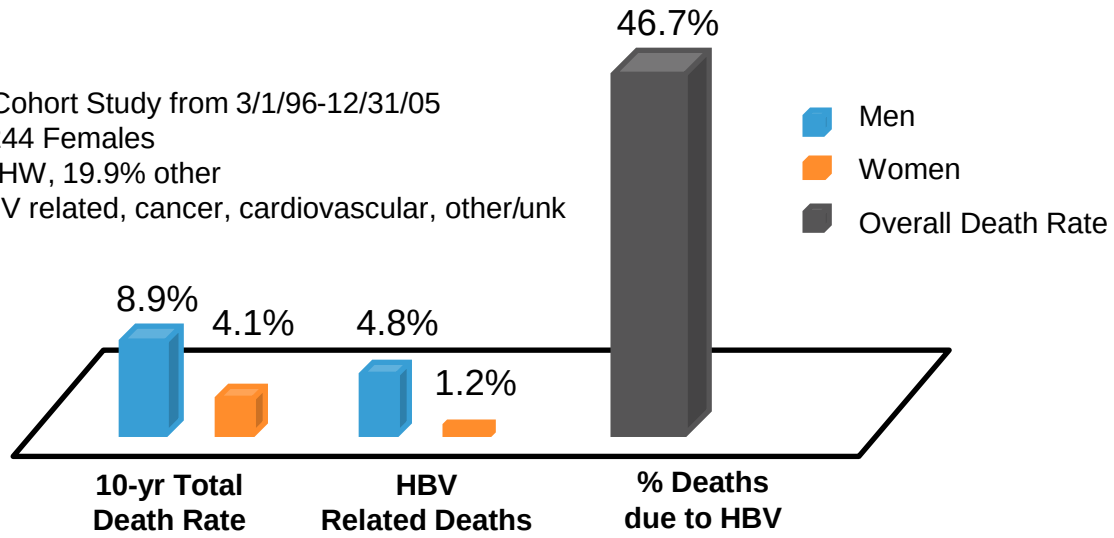
Natural History: Five-Year Rate of Progression of CHB



Fattovich G, Bortolotti F, Donato F. *J Hepatol*. 2008; 48:335;
Vlachogiannakos J, Papatheodoridis GV. *Liver International*. 2018;38(suppl 1):71-78.

Natural History of Untreated CHB

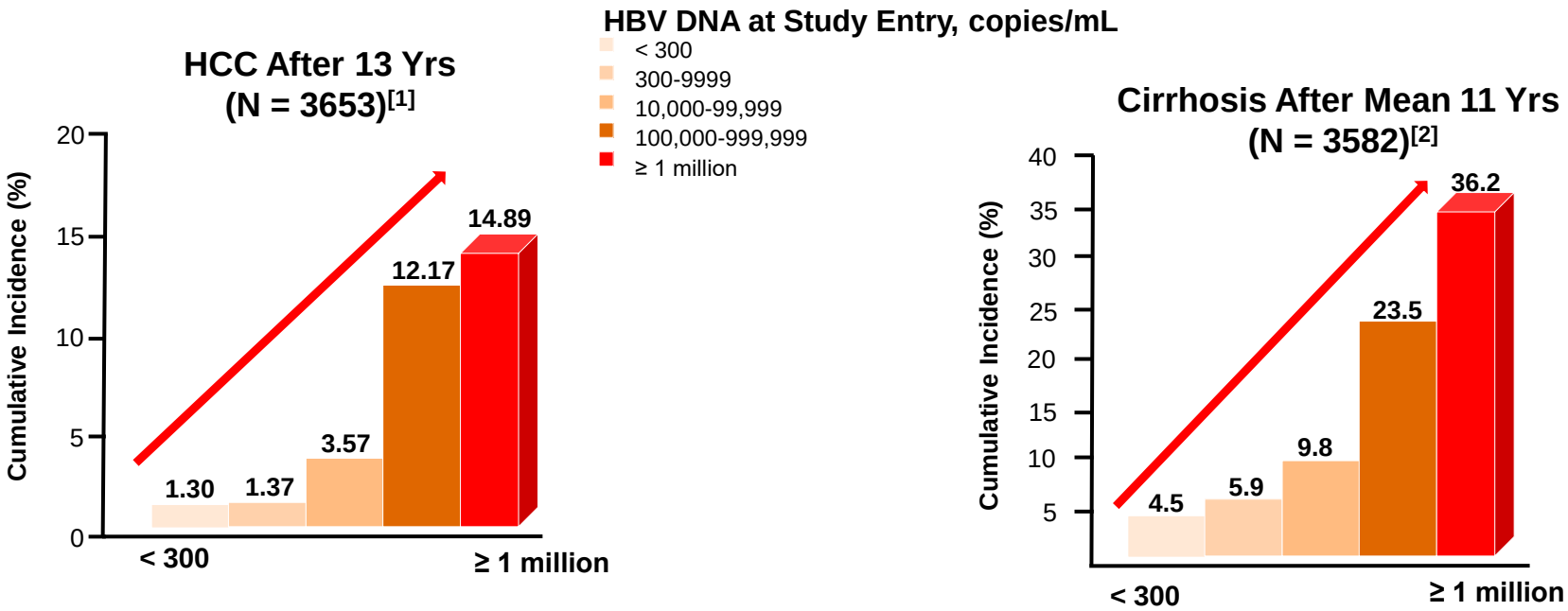
Kaiser Permanente Cohort Study from 3/1/96-12/31/05
N = 3,445 Males, 3,244 Females
68.3% API, 11.8% NHW, 19.9% other
Causes of death: HBV related, cancer, cardiovascular, other/unk



HCC deaths represented 70% of cancer death in males and 37% in females
HBV related deaths were 2X as common from HCC as from decompensated cirrhosis, 40% of death after age 40 were due to HBV
Mortality increased markedly in men >40 and women >50
Lifetime risk of dying from HBV related causes was 42.2%, with 27.6% risk for women and 48.7% risk for men

Szpakowski JL, Tucker LY. *Hepatology.* 2013 July;58(1):21-30.

REVEAL-HBV: HBV DNA Levels and Long-Term Outcomes



1. Chen. *JAMA*. 2006;295:65; 2. Iloeje. *Gastroenterology*. 2006;130:678.

Parameters Used to Determine Candidates for Treatment of HBV

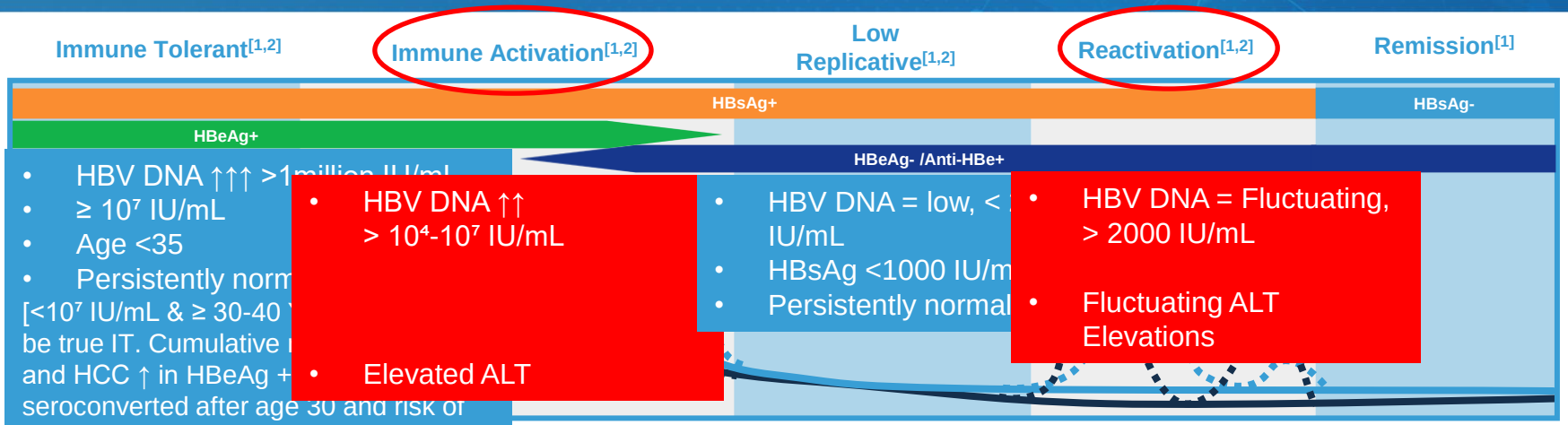
- Normal ALT levels in prospectively studied populations without identifiable risk factors for liver disease **range from 29-35 IU/L for males** and **19-25 IU/L for females**
  - Normal ALT level may not exclude significant liver disease
- There is a linear relationship between ALT level and BMI that should be assessed
- AST and ALT ULN ranges can vary between different labs
- Elevated ALT or AST above the ULN in a population without identifiable risk factors is associated with increased liver-related mortality

- HBV DNA
  - Predicts development of cirrhosis and HCC[2,3]
  - Interpret in conjunction with ALT and/or histology
- Liver biopsy/noninvasive fibrosis assessment
  - Useful in situations where ALT or HBV DNA do not provide clear guidelines for treatment[1]

ALT ULN	AASLD 2018[1]	EASL 2017[2]
Males	35 U/L	40 IU/L
Females	25 U/L	40 IU/L

1. Lok AS et al. *Hepatology*. 2009;50:661-662; 2. Iloeje UH et al. *Gastroenterology*. 2006;130:678-686;
3. Chen CJ et al. *JAMA*. 2006;295:65-73; 4. NA Terrault, ASF Lok et al. Practice Guidance. *Hepatology.* 2018;vol 67, N0. 4:1560-1599; 5. EASL. *J Hepatol*. 2017;67:370.

Course of HBV Infection



CHB follows a nonlinear clinical course; not all patients will go through each phase.

1. Tong. *Dig Dis Sci*. 2011;56:3143; 2. Yim. *Hepatology*. 2006;43:S173; 3. EASL. *J Hepatol*. 2017;67:370; 4. WJ Jeng, AS Lok. *Clinical Gastroenterology and Hepatology*. 2020 in press;https://doi.org/10.1016/j.cgh.2020.04.091; 5. HW Lee, H LY Chan. *J Gastroenterol.* 2020;55:383-389; 6. Terrault NA et al. *Hepatology.* 2018;63(4):1560-1599.

Overview of Existing CHB Treatment Guidelines and Algorithms

HBeAg+	
HBV DNA (IU/mL)	**ALT (U/L)**
AASLD 2018[1] >20,000	**AASLD 2018**[1] >2x ULN (Men 35; Women 25) or noninvasive test/biopsy (+)
EASL 2017[2] ≥2000	**EASL 2017**[2] >ULN[a] (40) &/or TE*/biopsy (+)
APASL 2015[3] >20000	**APASL 2015**[3] >2x ULN (40)

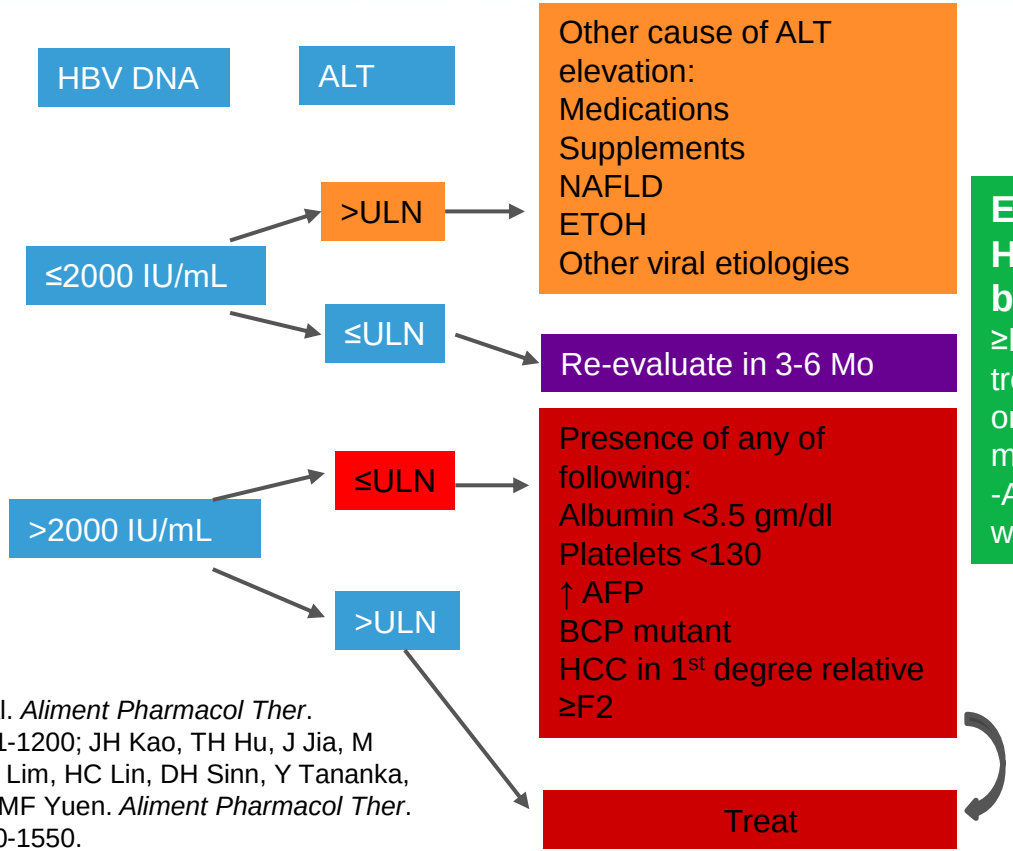
HBeAg–	
HBV DNA (IU/mL)	**ALT (U/L)**
AASLD 2018[1] >2000	**AASLD 2018**[1] >2x ULN (Men 35; Women 25) or noninvasive test/biopsy (+)
EASL 2017[2] ≥2000	**EASL 2017**[2] >ULN[a] (40) &/or TE*/biopsy (+)
APASL 2015[3] >2000	**APASL 2015**[3] >2x ULN (40)

Gray Zone: HBV DNA > 2000 IU/mL; ALT < ULN;
HBV DNA < 2000 IU/mL; ALT >ULN.

AASLD: Other factors to consider treatment include age >40, FH of HCC and extra hepatic manifestations;
EASL: Other factors to consider treatment include HBeAg+, high HBV DNA, age >30, FH of HCC or cirrhosis and extra hepatic manifestations.

1. NA Terrault, AS F Lok, et al. *Hepatology.* 2018;67(4):1560-1599; 2. EASL Clinical Practice Guidelines. *J Hepatol.* 2017;67(2):370-398; 3. SK Sarin et al. *Hepatol Int.* 2016;10:1-98; 4. MH Nguyen et al. *Clinical Microbiology Reviews.* 2020;33(2):1-38.

Expert Consensus for Management of CHB in Asians From US, Taiwan, China, Japan, South Korea



East Asian Expert Consensus- HBeAg +/- , HBV DNA ≥2000IU/mL but ALT<1xULN: treat if significant fibrosis ≥F2 and/or significant inflammation ≥A2; treatment can be considered in FH of cirrhosis or HCC in 1st degree relative, extrahepatic manifestation or age >40
-ALT normal: 30 U/L for men; 19 U/L for women

MJ Tong et al. *Aliment Pharmacol Ther*. 2018;47:1181-1200; JH Kao, TH Hu, J Jia, M Kurosaki, YS Lim, HC Lin, DH Sinn, Y Tananka, VWS Wong, MF Yuen. *Aliment Pharmacol Ther*. 2020:52:1540-1550.

Antiviral Therapies in CHB

GOALS of THERAPY IN CHB

- To decrease CHB related morbidity and mortality: Prevent progression to cirrhosis and the development of liver cancer
- Sustained viral suppression
- Normalization of ALT
- Loss of HBe Ag +/- HBe Ab
- Improvement in liver histology

- Cure = HBS Ag loss[+/- surface Ab], sustained HBV DNA suppression off therapy, negative cccDNA, eradication of integrated HBV DNA?

1. Emmet B, Keeffe et al. *Clinical Gastroenterology and Hepatology.* 2008;6:1315-1341;
2. Anna SF Lok, Brian J McMahon. *Hepatology*. Sept. 2009; 3. Terrault NA et al. *Hepatology.* 2016;63:261-283.

Antiviral Therapy for CHB Viral Infection: Systematic Review and Meta-Analysis

- 59 studies: 15 randomized control trials, 44 observational studies reviewing the effectiveness of antiviral therapy in CHB[1]
- 43 randomized control trials evaluating the effectiveness of antiviral therapies in terms of virologic response, normalization of ALT, HBeAg loss, HBeAg seroconversion, HBsAg loss[2]
- 15 non-randomized comparative studies with 61,787 chronic hepatitis B patients, reviewing the effectiveness of Tenofovir DF versus Entecavir in reducing the incidence of HCC among patients with CHB[3]
- Antiviral therapy in patient with immune active CHB is beneficial in reducing progression to cirrhosis, liver decompensation, risk of HCC and all cause mortality[1]
- For virologic response, ALT normalization, HBeAg loss, HBeAg seroconversion, HBsAg loss comparing PEG-IFN, ADV, LAM, ETV, TBV, TDF, TAF: TAF is effective across all outcomes[2]
- Both TDF & ETV are effective in reducing the risk of HCC
- TDF is associated 20% lower risk of HCC than with ETV[3]. RCT are needed for direct comparison

1. ASF Lok et al. *Hepatology.* 2016;63(1):284-306; 2. WWL Wong et al. *Systematic Reviews.* 2019;8(207):1-15;
3. WM Choi et al. *Clinical Gastroenterology and Hepatology.* 2021;19:246-258.

When to Stop Therapy

	EASL 2017	AASLD 2018	APASL 2015
HBeAg +	• HBsAg loss or • HBeAg loss & seroconversion • HBV DNA undetectable • 12 months consolidation	• HBsAg loss or • HBeAg loss & seroconversion • 12 months consolidation	• HBsAg loss or • HBeAg loss & seroconversion • HBV DNA undetectable • 12-36 months consolidation
HBeAg -	• HBsAg loss w/w/o seroconversion-or HBV DNA undetectable ≥ 3 years of NA Rx	• HBsAg loss or indefinite	• HBsAg loss or • HBV DNA undetectable ≥ 2 years on 3 separate occasions 6 months apart
Cirrhosis	• Indefinite	• Indefinite	• Indefinite

- Monitor q3 months for at least one year after discontinuation of therapy for recurrent viremia, ALT flares, clinical decompensation

1. NA Terrault, ASF Lok et al. *Hepatology.* 2018;67(4):1560-1599; 2. EASL Clinical Practice Guidelines. *J Hepatol.* 2017;67(2):370-398; 3. SK Sarin et al. *Hepatol Int.* 2016;10:1-98; 4. MH Nguyen et al. *Clinical Microbiology Reviews.* 2020;33(2):1-38.

Working Toward a Cure in CHB

HBV DNA

- Replicating HBV DNA
- Covalently closed circular DNA (cccDNA)
- Integrated HBV DNA

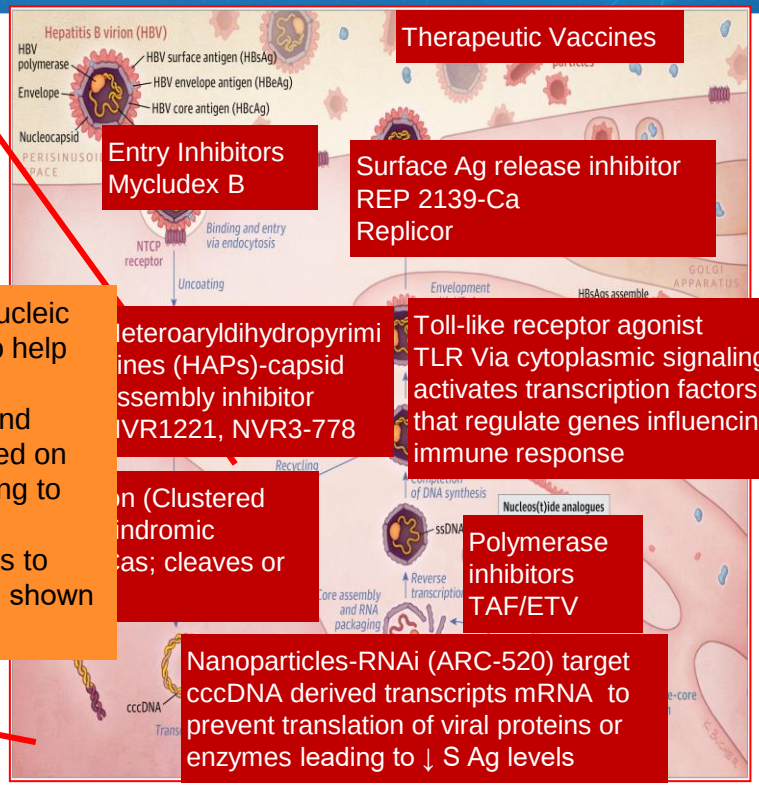
Limitations of Current Therapies

- Adequate biochemical virologic suppression
- Satisfactory histologic response
- None/minimal effect on cccDNA
- None on integrated HBV DNA
- Modest effect on HCC prevention

HBV Life Cycle

Activation of STING-stimulator of IFN gene, Activation of RIG-1(retinoic acid inducible protein) resulting in IFN mediated antiviral immune response [Preclinical development]

- siRNA/LNA small interfering RNA/locked nucleic acid approach knocks down HBV protein to help reconstitute weakened immune response
- PD-1/PD-L1 program cell death protein 1 and ligand 1: inhibitory receptors, over expressed on HBV specific T cells and hepatocytes leading to ineffective immune response. Monoclonal antibody blockade with therapeutic vaccines to ↑ T cell activity to control viremia, has been shown to reduce production of HBsAg



Tang. *JAMA*. 2018;319:1802; Nguyen MH et al. *Clin Microbiol Rev.* 33(2):1-38:e00046-19.https://doi.org/10.1128/CMR.00046-19; Rehermann and Nascimbeni: From Bhattacharya D, Thio CL. *Clin Infec Dis*. 2010 November 15;51(10): 1201-1208; Block TM et al. *Gastroenterology & Hepatology*. 2016;12(11):679-689; Soriano V, Barreiro P et al. *Expert Opin Investig Drugs*. 2017 Jul:26(7):843-851.

What Percentage of Patients With Chronic Hepatitis B Develop Liver Related Complications?

A. 10 – 20%

B. 15 – 40%

C. 50 – 60%

D. >70%

E. None of the above

Which of the Following Laboratory Test Combinations Are Most Useful for Screening of CHB in the US?

A. HB Surface antigen, HB Surface antibody

B. HB Core antibody total, HB Surface antibody, Hepatitis B Surface antigen

C. HB Surface antigen, HB Core IgM, HB Surface antibody

D. HB Surface antigen, HB Core antibody total, HBV DNA quantification

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Thank you for your attention