Hepatitis B

Are we on the path to elimination?

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@swang8

May 23, 2018 NYC Viral Hepatitis Research Symposium





Let's be healthy together.







May 2016: WHO Adopts Goal to Eliminate HBV by 2030

https://www.youtube.com/watch?v=cVttqfgExL0



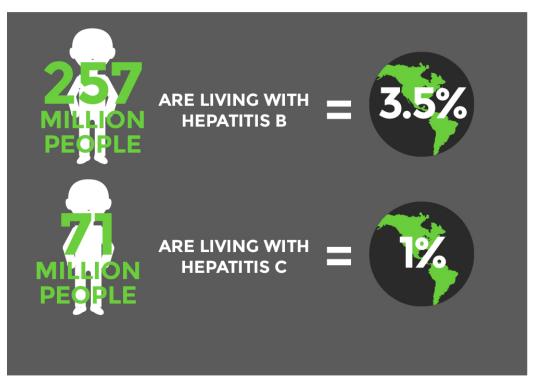






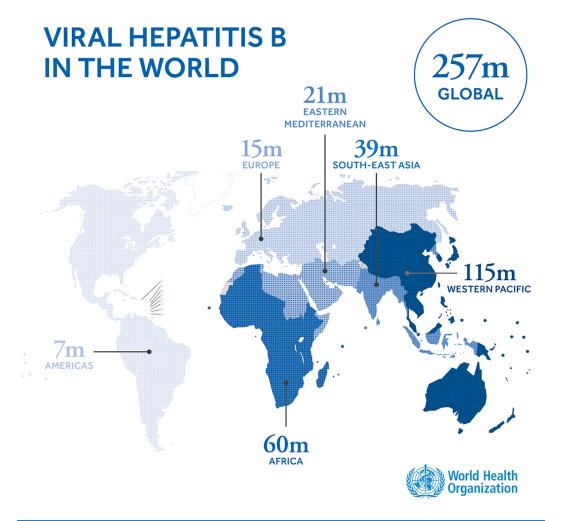
ELIMINATE HEPATITIS





#NOhep worldhepatitisday.org

#WorldHepatitisDay





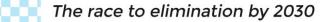
Worldwide Burden of Hepatitis B

- 260 Million with chronic hepatitis B (CHB) infection in the world¹
 - More prevalent than HIV (37M) and HCV (71M) globally
 - WPRO- 6.2% of adult infection has HBV
 - AFRO-6.1%
 - EMRO- 3.2%
 - Only 22 M (9%) know their diagnosis
- Chronic hepatitis B is #1 leading cause of primary liver cancer (hepatocellular carcinoma) worldwide²
 - 887,000 total deaths in 2015 due to Hep B, including HCC and cirrhosis
 - 1. IOM (Institute of Medicine). 2010. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Washington, DC: The National Academies Press
 - 2. El-Serag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med. 2000:160(21):3227-30



World Hepatitis ELIMINATE HEPATITIS







Commentary and Analysis

What is required to get us across the finish line:



Chronic Hepatitis B Infection

Active Hepatitis

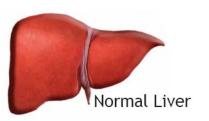
 Inflammation of liver from host immune response to virus presence in liver

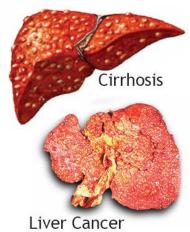
Cirrhosis

- Develops from chronic inflammation
- Fibrosis and cirrhotic nodules develop
- Leads to liver failure

Liver Cancer

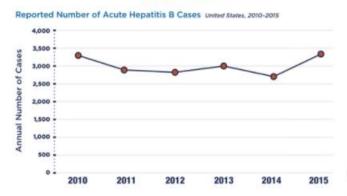
 Tumors can arise from cirrhotic or noncirrhotic livers





We are Losing Ground in the Fight Against New Viral Hepatitis Infections

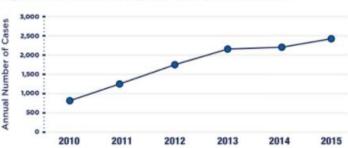
Reported Number of Acute Hepatitis B Cases 2010 - 2015

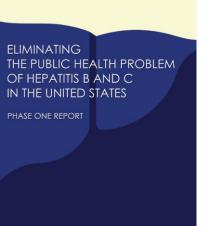


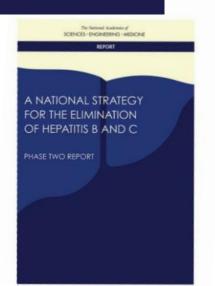
 New hepatitis C infections increased almost 300% from 2010 – 2015 National progress on hepatitis B prevention has stalled

Reported Number of Acute Hepatitis C Cases 2010 - 2015

Reported Number of Acute Hepatitis C Cases United States, 2010-2015







Viral Hepatitis Elimination in the US: The National Academy of Science Report Phase I (2016) Phase II (2017)

"We have the tools to eliminate, but will require significant resource allocation, commitment

Committee Chair, Dr. Brian Strom, Chancellor of Rutgers Medical School

and strategy"

The world has the tools to prevent hepatitis B and cure hepatitis C.

Learn more: nas.edu/HepatitisElimination

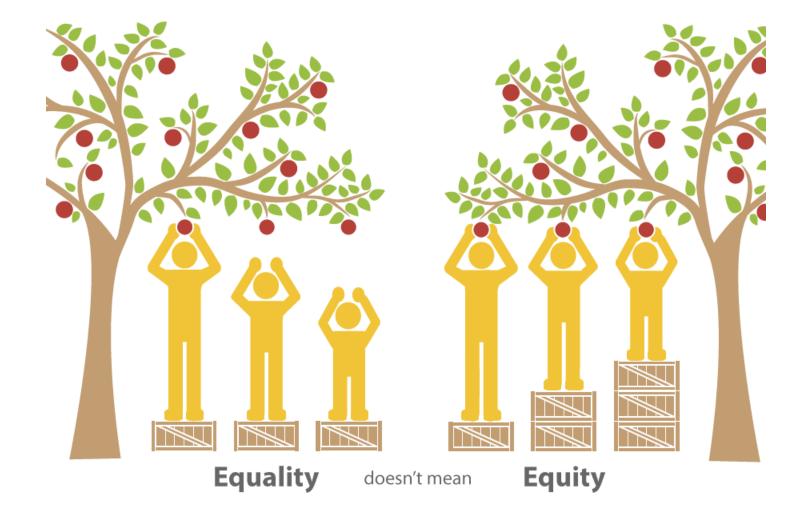
Hepatitis is Underfunded

Virus	US population	CDC NCHHSTP Budget '18 \$1,127,000,000
HBV HCV	0.8-2.2 million 2.7-3.5 million	Division of Viral Hepatitis- \$39 Million 3% (for all viral hepatitis, domestic/international)
HIV	1.1 million	HIV/AIDS- \$788 Million 69% (domestic, not including international HIV work)

- Those affected are often the silent minorities, may not have political representation
- Health Disparity/Equity Issue
 - We have the tools-vaccine, medications for cure/treatment, medical knowledge
 - Those most at-risk are falling through the system

My goal for this talk





Health Disparities







Health improves as advantage increases.

HBV SCREENING



Screening is the First Step

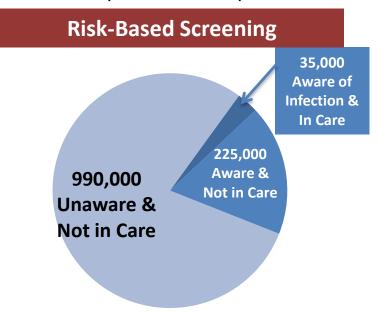


Only 9% of those with viral hepatitis have been identified worldwide

Impact of national screening strategies: HIV vs HBV Care Cascade

1,200,000 in US with HIV **Routine Screening** One time for all adults, as of 2006 168,000 **Unaware & Not** in Care 480,000 **Aware of** 552,000 Infection & In Care Aware & **Not in Care**

1,250,000 in US with Chronic HBV (low estimate)



HIV –CDC HIV Surveillance System & Monitoring Project, 2011 https://www.cdc.gov/vitalsigns/hiv-aids-medical-care/ HBV - Cohen, C. (2011) Is chronic hepatitis B being undertreated in the United States?. Journal of Viral Hepatitis, 18: 377–383

Hepatitis B Screening Covered



- 2015 USPSTF upgrades HBV screening to grade B (Grade B)
 - Recommends HBV screening for at-risk populations
 - Must be covered by insurance plans as a preventative service



 October 2016, Medicare begins covering HBV screening under part A & part B

HBV Vaccination, Screening and Linkage to Care Best Practice Advice from ACP (American College of Physicians) & CDC

December 2017



Hepatitis B Vaccination, Screening, and Linkage to Care: Best Practice Advice From the American College of Physicians and the Centers for Disease Control and Prevention

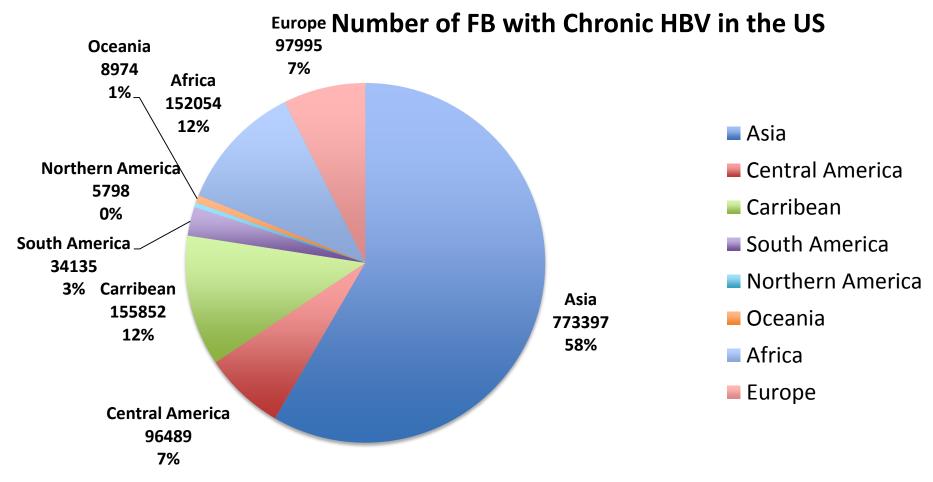
Winston E. Abara, MD, PhD; Amir Qaseem, MD, PhD, MHA; Sarah Schillie, MD, MPH, MBA; Brian J. McMahon, MD; Aaron M. Harris, MD, MPH *; for the High Value Care Task Force of the American College of Physicians and the Centers for Disease Control and Prevention

Article, Author, and Disclosure Information

FULL ARTICLE				
Abstract				
Methods				
Vaccination				
Screening				
Linkage to Care				
Harms of Vaccination,				
Screening, and Linkage				

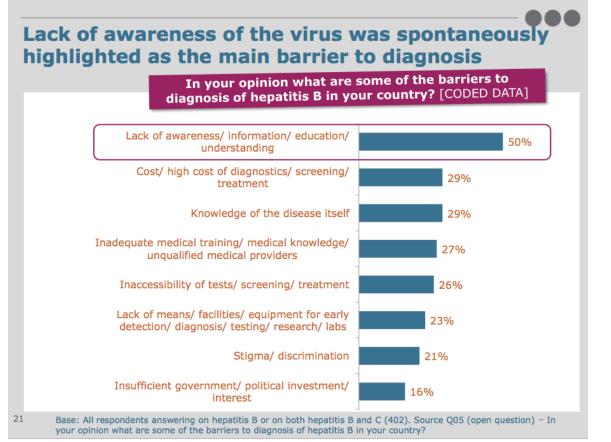
Abstract

Background: Vaccination, screening, and linkage to care can reduce the burden of chronic hepatitis B virus (HBV) infection. However, recommendations vary among organizations, and their implementation has been suboptimal. The American College of Physicians' High Value Care Task Force and the Centers for Disease Control and Prevention developed this article to present best practice statements for hepatitis B vaccination, screening, and linkage to care.



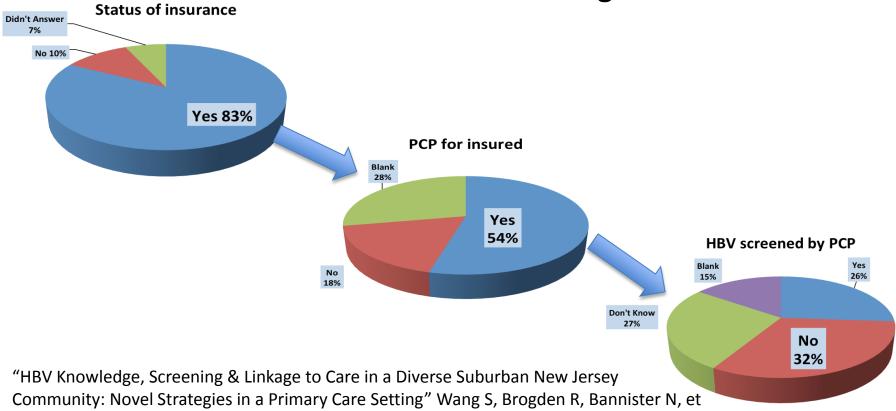
Kowdley KV, et al. *Hepatology*. 2012;56(2):422-433.

World Hepatitis Alliance Survey on Barriers to Diagnosis: Finding the Missing Millions





Insurance, Primary Care Physician Status & Previous HBV Testing



al. AASLD Liver Meeting, Washington, DC October 23, 2017

At-Risk Groups Include

- ✓ Persons born in HBV endemic regions of the world: Asia, Africa, Pacific Islands, Middle East, Eastern Europe, Mexico, Central America, and the Caribbean
- ✓ Injection drug users
- ✓ Men who have sex with men
- Persons with condition that may require immune-modifying therapy

- Persons with elevated ALT/AST of unknown etiology
- ✓ Blood or tissue donors
- ✓ Pregnant women
- ✓ Infants born to HBV-infected mothers
- ✓ Hemodialysis patients
- ✓ Household and sexual contacts of HBV-infected individuals
- ✓ HIV-positive individuals

HBV screening <u>must be covered by insurance plans</u> under ACA rules (As a preventative service with no cost sharing to patient)

Interpretation of Serologic Test Results for HBV

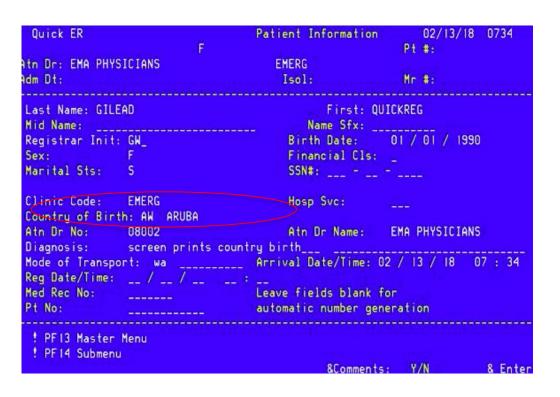
HBsAg	Total Anti-HBc	Anti-HBs	Interpretation
-	-	-	Susceptible to HBV, not infected/not immune -> vaccinate
+	+	-	Infected
-	+	+	Recovered from past infection and immune
-	-	+	Immune from immunization
-	+	-	Immune but HbsAb waned or occult HBV infection or false positive

Weinbaum CM, et al. MMWR Recomm Rep. 2008;57(RR-8):1-20.

Novel Screening Approaches

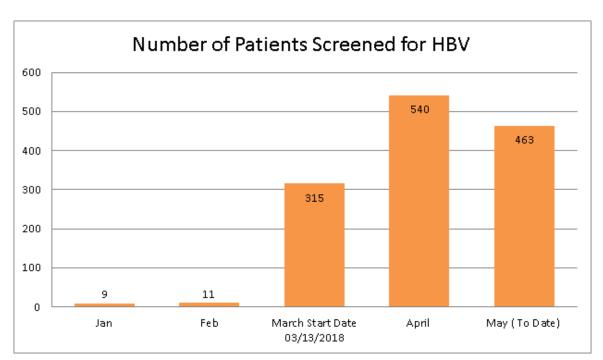
Automated HBV Test based on Country of Birth

Saint Barnabas Medical Center ED (~100,000 visits/year)



- Collect Country of Birth (COB) at Registration
- EMR Protocol
 - If bloodwork ordered by provider and COB is HBV endemic
 - Automatic HBsAg test added
 - Nurse alerted, pt informed, opt out

Dramatic increase in screening



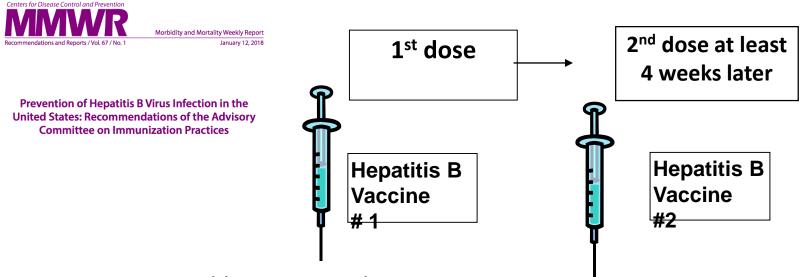
Top 10 countries represe	nted
Haiti	258
Jamaica	111
Ecuador	81
Guyana	59
Dominican Republic	58
Peru	51
Brazil	50
Portugal	50
Puerto Rico	46
India	45

VACCINATION

New Adult Vaccine- Heplisav-B Hepatitis B Birth Dose



New Adult Hepatitis B Vaccination: Heplisav-B



- Approved by ACIP April 18
- 2 doses in shorter time frame is opportunity to improve vaccine completion rate
- Interchangeability: can start with 3 shot series (Engerix or Recombivax)
 and with this

Give HBV Birth Dose within 24 hours

Pediatrics September 2017, VOLUME 140 / ISSUE 3 From the American Academy of Pediatrics Policy Statement



Elimination of Perinatal Hepatitis B: Providing the First Vaccine Dose Within 24 Hours of Birth

COMMITTEE ON INFECTIOUS DISEASES, COMMITTEE ON FETUS AND NEWBORN

The AAP statement recommends that all medically stable newborns with a minimum birth weight of 2000 grams (about 4 lbs., 6 oz.) receive the vaccine within 24 hours of birth. This AAP statement follows the practice now recommended by the Advisory Committee on Immunization Practices (ACIP), part of the Centers for Disease Control and Prevention.

The previous policy statement included an option to delay the first dose of Hepatitis B vaccine until the first newborn pediatric checkup. In the updated statement, the AAP recommends the first dose be given within the first 24 hours because this timing maximizes the effectiveness of the vaccine in preventing newborn infection.

US Health and Human Services has set a goal of **0 perinatal HBV transmissions** by 2020

HBV is a vaccine success story, but there are gaps Low Coverage of Universal Birth Dose

Institute of Medicine Report (2010):

"The goal of eliminating perinatal HBV transmission has not been achieved largely because of incomplete coverage of newborns with a birth dose of hepatitis B vaccine"

HBV Birth Dose in the Americas

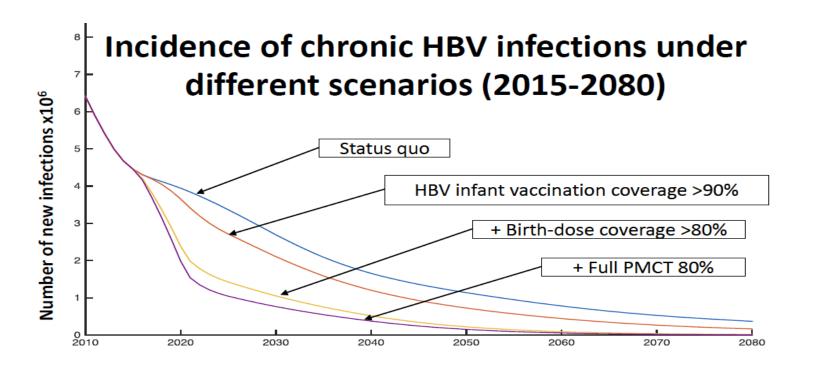
- US: 69%*Dominican Republic 82%
- Mexico 89%
- _*@mpared_tox%6% receive vit K at birth

New Jersey (48) & NY rank at the bottom of US states for HBV Birth Dose

^{*}http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6245a4.htm?s_cid=mm6245a4_w

[^] http://www.iom.edu/Reports/2010/Hepatitis-and-Liver-Cancer-A-National-Strategy-for-Prevention-and-Control-of-Hepatitis-B-and-C.aspx

Modeling of PMTCT intervention impact



Razavi, Homie "Presentation to PAHO Technical Advisory Group", Center for Disease Analysis, Polaris Observatory, http://polarisobservatory.org



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DATA.NY.GOV DEVELOPERS ▼ HELP ▼ ABOUT ▼ HEALTH DATA NY ▼



Hepatitis B Birth Dose Percent Vaccinated by Hospital: 2016

Based on Hepatitis B Birth Dose Vaccination Rates: Beginning 2012 This dataset contains an annual summary of the number of infants receiving a dose of hepatitis B vaccine within 3 days of birth at hospitals around the



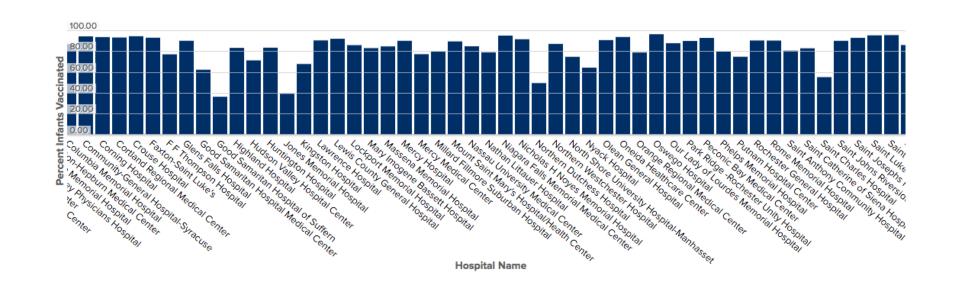






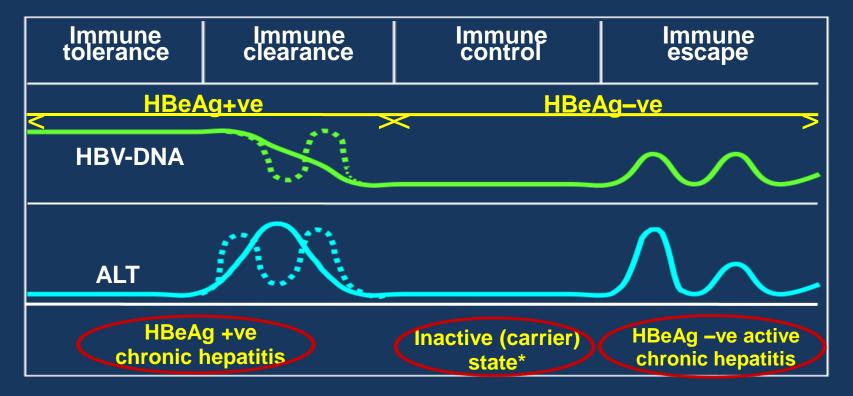






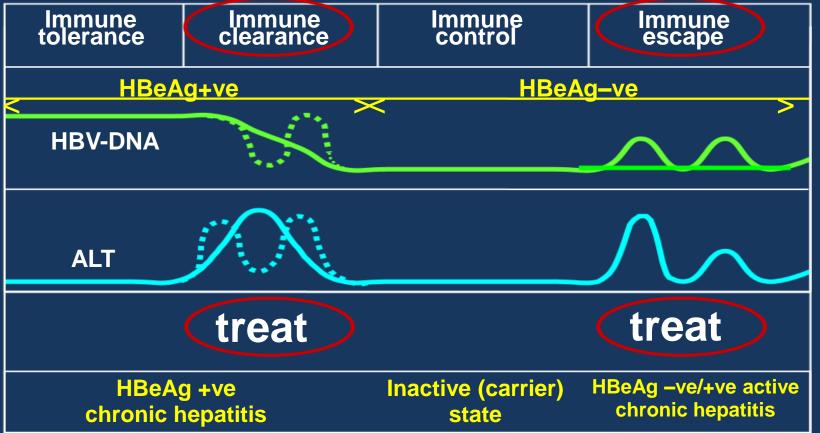
HBV CARE & TREATMENT RECENT RECOMMENDATIONS

The phases of chronic hepatitis B



^{*}Previously considered to be 'healthy carriers'

Who should be considered for treatment?



AASLD Hep B Guidelines for Treatment of CHB August 2015

https://www.aasld.org/sites/default/files/guideline_documents/hep28156.pdf





PRACTICE GUIDELINE

AASLD Guidelines for Treatment of Chronic Hepatitis B

Norah A. Terrault, ¹ Natalie H. Bzowej, ² Kyong-Mi Chang, ³ Jessica P. Hwang, ⁴ Maureen M. Jonas, ⁵ and M. Hassan Murad ⁶

Objectives and Guiding Principles

Guiding Principles

This document presents official recommendations of the American Association for the Study of Liver Diseases (AASLD) on the treatment of chronic hepatitis B (CHB) virus (HBV) infection in adults and children. Unlike previous AASLD practice guidelines, this guideline was developed in compliance with the Institute of Medicine standards for trustworthy practice guidelines and uses the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. ¹ Multiple systematic reviews of the literature were conducted to support the recommendations in this practice guideline. An enhanced understanding of this guideline will be obtained by reading the applicable portions of the systematic reviews.

This guideline focuses on using antiviral therapy in chronic HBV infection and does not address other related and important issues, such as screening, prevention, and

- Should adults with immune-tolerant infection be treated with antiviral therapy to decrease liverrelated complications?
- Should antiviral therapy be discontinued in hepatitis B e antigen (HBeAg)-positive persons who have developed HBeAg seroconversion on therapy?
- Should antiviral therapy be discontinued in persons with HBeAg-negative infection with sustained HBV DNA suppression on therapy?
- 5. In HBV-monoinfected persons, does entecavir therapy, when compared to tenofovir therapy, have a different impact on renal and bone health?
- 6. Is there a benefit to adding a second antiviral agent in persons with persistent low levels of viremia while being treated with either tenofovir or entecavir?
- 7. Should persons with compensated cirrhosis and low levels of viremia be treated with antiviral agents?
- 9 Charld hummant manna mha ana hakatitis R am

AASLD 2018 Hepatitis B Guidance February 2018

https://www.aasld.org/sites/default/files/HBVGuidance_Terrault_et_al-2018-Hepatology.pdf

HEPATOLOGY



PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 4, 2018

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance

Norah A. Terrault, Anna S.F. Lok, Brian J. McMahon, Kyong-Mi Chang, Jessica P. Hwang, Maureen M. Jonas, Robert S. Brown Jr., Natalie H. Bzowej, and John B. Wong

Purpose and Scope of the Guidance

This AASLD 2018 Hepatitis B Guidance is intended to complement the AASLD 2016 Practice Guidelines for Treatment of Chronic Hepatitis $B^{(1)}$

hepatitis B. It differs from the published 2016 AASLD *guidelines*, which conducted systematic reviews and used a multidisciplinary panel of experts to rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development and Evaluation system in support of guideline recommendations.⁽¹⁻⁴⁾

2018 AASLD Practice Guidelines – an Update to those published in 2016

HBV Screening	 Updated screening, counseling, and prevention of hepatitis B recommendations Selected diagnostic tests used in the screening (HBsAg, Anti-HBs, and Anti-HBc)
Disease Monitoring	 New ULN for ALT 35 U/L for males and 25 U/L for females Management of chronic hepatitis B (eg, qHBsAg, resistance testing, genotyping)
Treatment	 TAF joins the list of preferred HBV therapies, along with ETV, TDF and Peg-IFN Update on management of CHB in special populations including: acute hepatitis B, pregnancy, coinfected patients, recipients of immunosuppressive therapy, and transplant recipients

Summary of Treatment Recommendations for CHB

Guideline	HBeAg+		HBeAg-	
	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL	ALT U/L
AASLD 2018	>20,000	>2 x ULN [‡] or significant histological disease	>2,000	>2 x ULN [‡] or significant histological disease
AATA 2018	>2,000	>ULN	>2,000	>ULN
EASL 2017	≥2000	>ULN and/or at least moderate liver necroinflammation or fibrosis	≥2,000	>ULN and/or at least moderate liver necroinflammation or fibrosis
	≥20,000	>2 x ULN irrespective of fibrosis	≥20,000	>2 x ULN irrespective of fibrosis
JSH 2017	≥2,000	>ULN^	≥2,000	>ULN^
APASL 2015	≥20,000	Varies	≥2,000	Varies
US Algorithm 2015 [†]	≥2000	>ULN	≥2,000	>ULN

[†] If patients with HBV DNA ≥ 2000 IU/mL and elevated ALT without fibrosis do not undergo treatment, monitor HBV DNA and ALT every 3–6 months.

AASLD: American Association for the Study of Liver Diseases; AATA: Asian American Treatment Algorithm; ALT: alanine aminotransferase; APASL: Asian Pacific Association for the Study of the Liver; CHB: chronic hepatitis B; EASL: European Association for the Study of the Liver; HBeAg: hepatitis B e antigen; ULN: upper limit of normal; JSH, Japan Society of Hepatology

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800

Tong MJ, Pan CQ, Han SB, et al. An expert consensus for the management of chronic hepatitis B in Asian Americans. Aliment Pharmacol Ther. 2018

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; doi: 10.1016/j.jhep.2017.03.021

JSH Guidelines for the Management of Hepatitis B Virus Infection. 2017

Sarin SK, et al. Hepatol Int 2015; doi 10.1007/s12072-015-9675-4; Martin P, et al. Clin Gastroenterol Hepatol 2015;13: 2071–87

Martin P, et al. Clin Gastroenterol Hepatol 2015; Published online July 15, 2015: http://dx.doi.org/10.1016/j.cgh.2015.07.007

^{*}Liver biopsy Stages 1–3, Grade 1–3; and/or Risk Impact Score ≥3;

[‡] ALT ULN: Males 35 U/L, females 25 U/L ^ ALT ULN: 31 U/L

Real World Settings & Guidelines:

CDCs Chronic Hepatitis Cohort Study (CHeCS)

- 2338 patients, 2006-13
- 4 sites
 - Geisinger Health System (PA)
 - Henry Ford Health System (MI)
 - Kaiser-Permanente- Northwest (OR)
 - Kaiser-Permanente-Honolulu (HI)
- ALT testing
 - 78% had ≥ 1 ALT done per year
- Overall 32% prescribed antiviral therapy
 - 41% with cirrhosis
 - 62% with HBV DNA >2000 IU/ml and elevated ALT before initiating
 - 17% with biopsy of F2-F4

- 37% had ≥ 1 HBV DNA per year follow up
- 44% had < annual testing,
- 18% never had HBV DNA
- 57% elevated ALT results had subsequent HBV DNA done within 60 days

Cirrhotics

- 54% with HBV DNA done annually, 35% less than annually,
- 11% never had HBV DNA done
- 53% had at least 1 hepatic imaging but only
 27% had annual imaging
- 56% prescribed antiviral therapy

HBV DNA

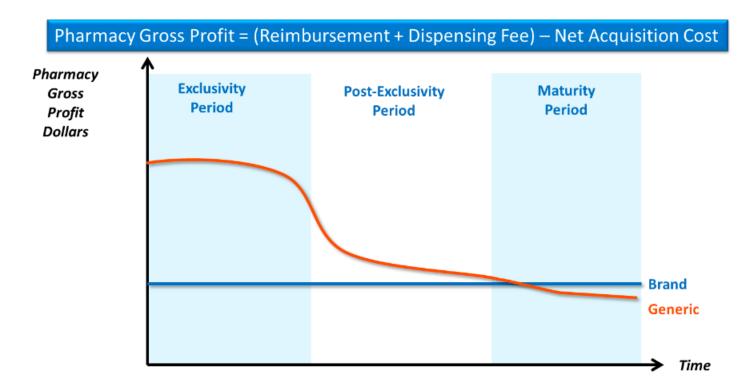
Spradling, PR, et al. "Infrequent Clinical Assessment of Chronic Hepatitis B Patients in United States General Healthcare Settings". Clin Infect Dis. 2016 Nov 1;63(9):1205-1208. Epub 2016 Aug 2.

FDA Approved Hepatitis B Therapies

Generic	Brand Name	Dose	Approved	Comments
First Line				
Entecavir (ETV)	Baraclude	0.5mg/1.0 mg po qd	2005	Generic
Tenofovir (TDF)	Viread	300 mg po qd	2008	Generic in US 2018
Tenofovir alafenamide (TAF)	Vemlidy	25 mg po qd	2016	Less bone, renal toxicity
Peginterferon alfa- 2a	Pegasys	180 ug SQ q week	2005	Finite tx, 48 weeks
Second Line				
Adefovir (ADV)	Hepsera	10 mg po qd	2002	Low potency, high rate of resistance
Telbivudine (LDT)	Tyzeka	600 mg po qd	2006	High potency, high rate of resistance
Third Line				
Lamivudine (LAM)	Epivir	100 mg po qd	1998	Low potency, high rate of resistance

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

Typical Lifecycle Path of Pharmacy Gross Profits, Brand vs. Multi-Source Generic



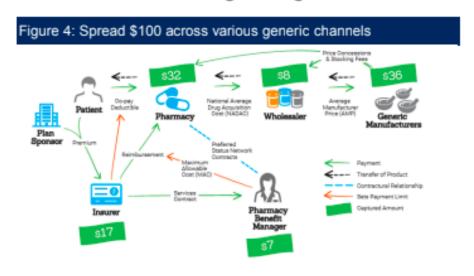
Source: 2012-13 Economic Report on Retail, Mail and Specialty Pharmacies, Drug Channels Institute, January 2013. (http://drugchannelsinstitute.com/products/industry_report/pharmacy/)

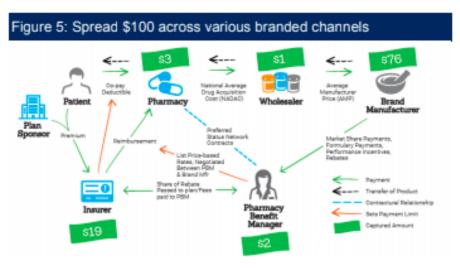
Published on Drug Channels (www.DrugChannels.net) on December 13, 2012.



Tenofovir newly generic in 2018, but patients can still pay high prices (copay \$300-1000/month)

Working Through the Mechanics of the Generic Supply Chain





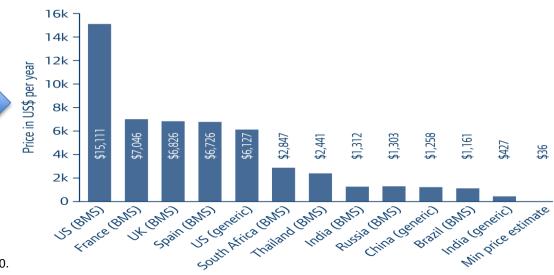
Source: AAM Source: AAM

Access to the recommended regimens: HBV

Global and USA price overview for HBV drugs

Drug	USA price (originator) (per patient per year)	Global lowest price (per patient per year)
Entecavir	\$15,111	\$427
Tenofovir (TDF)	\$10,718	\$38
Lamivudine	\$2,627	\$10

The lowest price for **entecavir** 0.5 mg in selected countries (per patient per year)

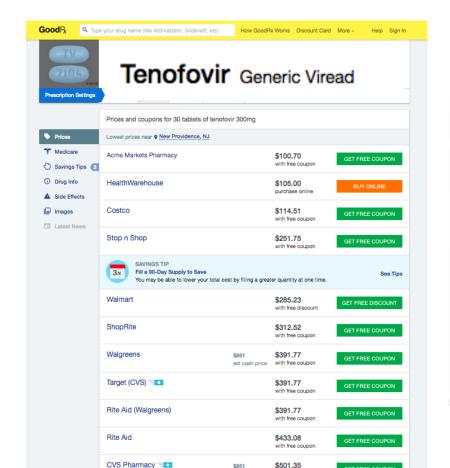


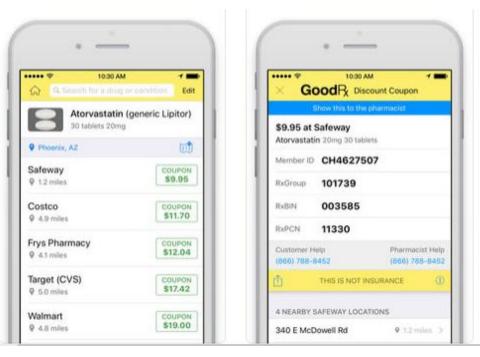
Source: Hill A, 2015 Journal of Virus Eradication. 2015;1(2):103-110.

Rx assistance options for patients

- Use 340B pharmacy if you are able
- Patient assistance programs (PAP) with pharmaceutical companies
- Foundations to help with copays
- Good Rx app- finds nearest pharmacy with the best price under insurance or without insurance
 - Drugs can be cheaper when you pay out of pocket not using your insurance

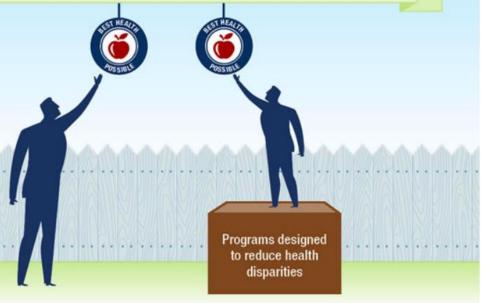
GoodRx: Collates Prices & Discounts at Local Pharmacies





— REACHING FOR— Health Equity

Reducing health disparities brings us closer to reaching health equity.





http://www.cdc.gov/minorityhealth/strategies2016/

REACTIVATION & CURE

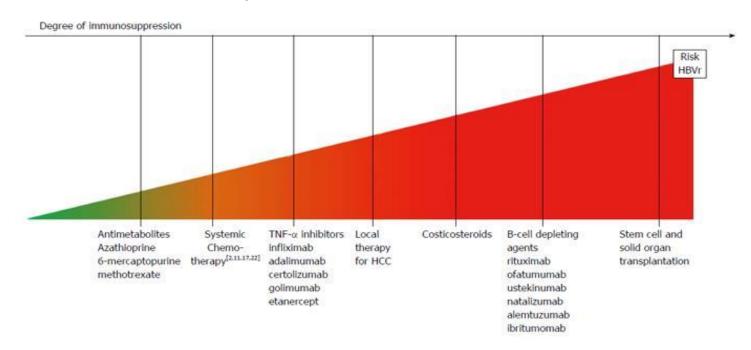


Hep B Reactivation



- 66 yr old healthy Chinese-American man dx with Primary Central Nervous System Lymphoma
- Treated with Temozolomide & Methotrexate
- 2/15 Routine Labwork
 - HBsAg negative
 - HBcAb IGM neg
 - (IgM only positive if acute infection- would not screen for previous exposure to HBV)
 - Should have tested with HBcAb, IgG or Total
- 4/16 starting 6th cycle of methotrexate, ALT became abnormal (from 26/55-->384/664)
- HBV retested- HBsAg+,
 - Oncologist recommendation: treat HBV after chemo completed
- HBV DNA 95,000,000 IU/ml
 - Pt symptomatic with Nausea, vomiting and diarrhea
 - Admitted to ICU with fulminant, liver failure and admitted in ICU (too late to start antivirals)
- Late April passed away

Immunosuppressing agents and related risk of hepatitis B reactivation



Bessone F, Dirchwolf M. Management of hepatitis B reactivation in immunosuppressed patients: An update on current recommendations. *World Journal of Hepatology*. 2016;8(8):385-394. doi:10.4254/wjh.v8.i8.385.

AGA and ASCO Guidelines for HBV Reactivation (HBVr)

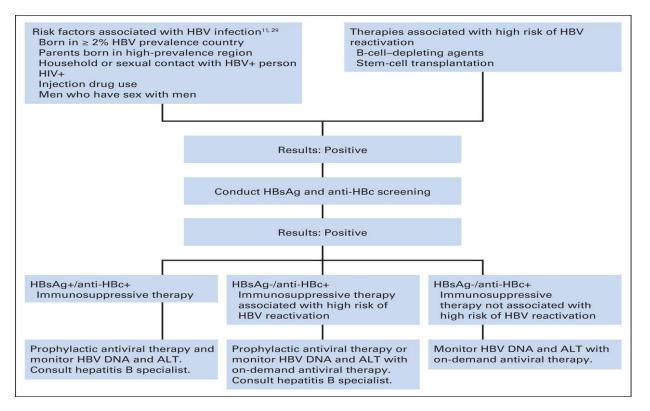
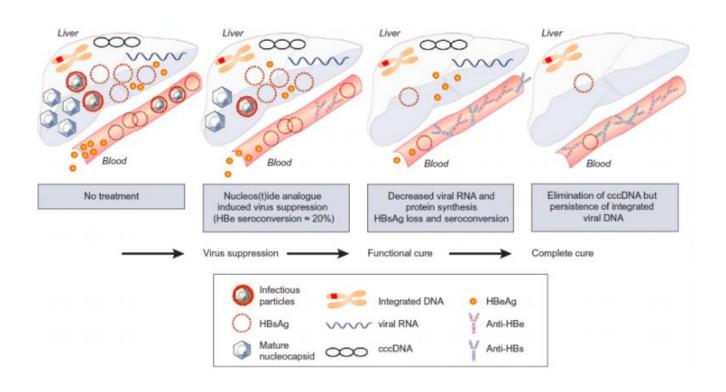


Fig 2. Risk-adaptive hepatitis B virus (HBV) screening and management decision-making algorithm for patients with cancer before immunosuppressive therapy. anti-HBc, antihepatitis B core antibody (either total or immunoglobulin G); HBsAg, hepatitis B surface antigen.

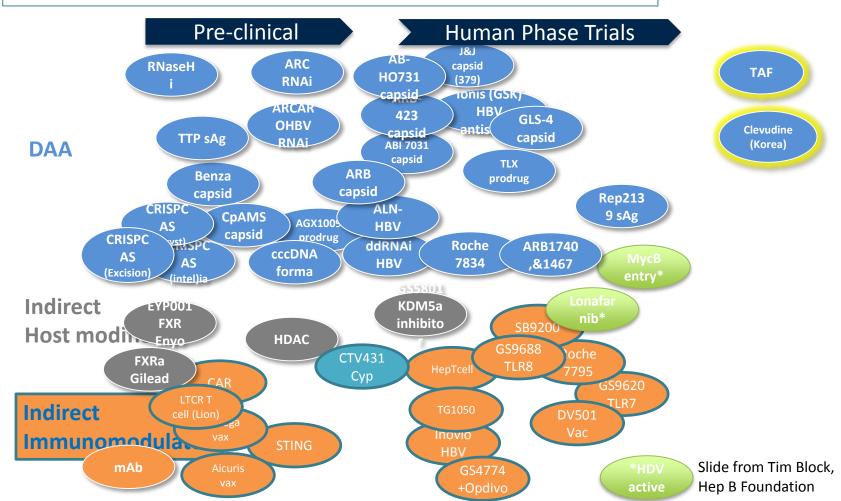
Published in: Jessica P. Hwang; Mark R. Somerfield; Devena E. Alston-Johnson; Donna R. Cryer; Jordan J. Feld; Barnett S. Kramer; Anita L. Sabichi; Sandra L. Wong; Andrew S. Artz; JCO 2015. 33. 2212-2220.

What does HBV Cure look like?

Viral suppression vs Functional Cure vs Sterilizing Cure



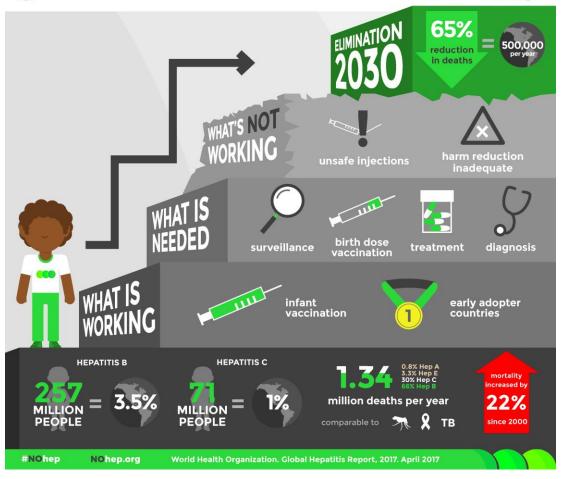
The HBV Therapeutic Development Landscape as of 12. 2017





World Hepatitis ELIMINATE HEPATITIS







Harnessing the Power of the Medical Community

We have the tools, but it will take a global movement to eliminate viral hepatitis.



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