HBV Is Not a Game: Or Is It?

Optimizing Your Approach to HBV Management

April 18, 2018
12:15 – 1:15 pm
Ernest Morial
Convention Center
Room 393-396
New Orleans, LA

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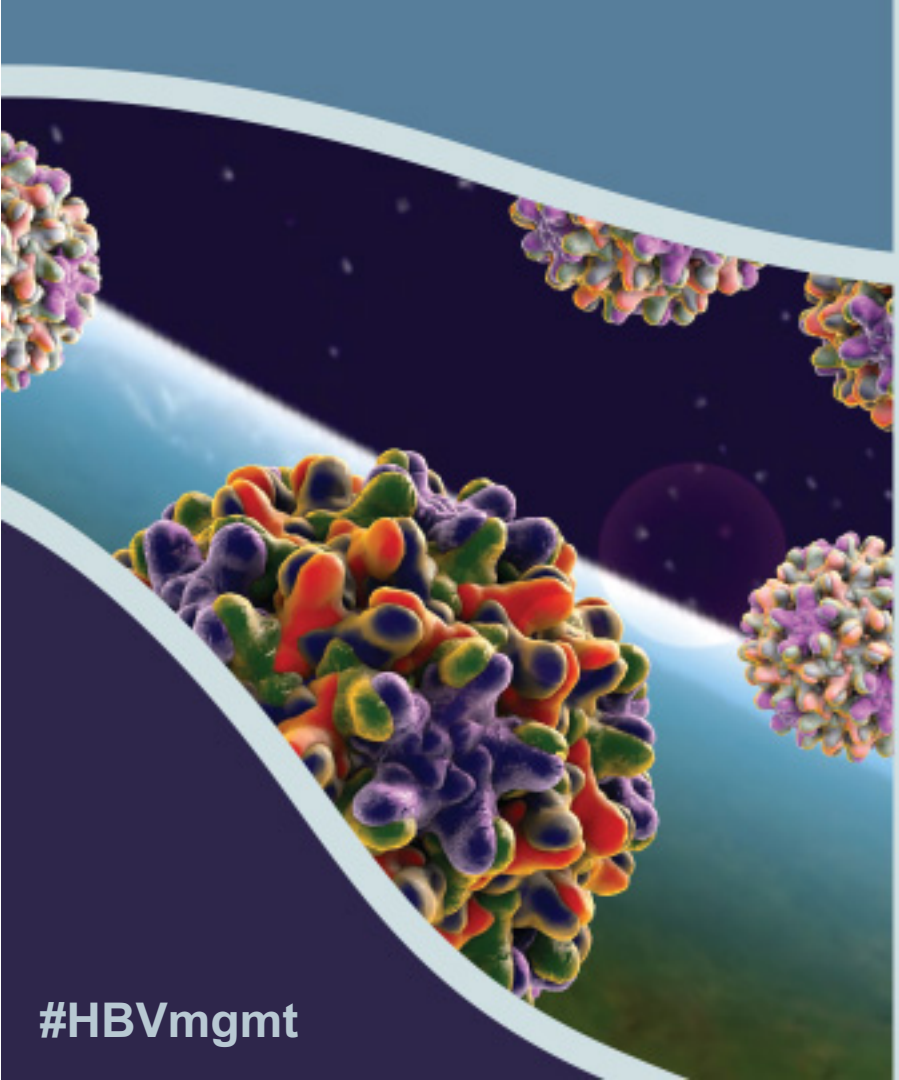

#HBVmgmt

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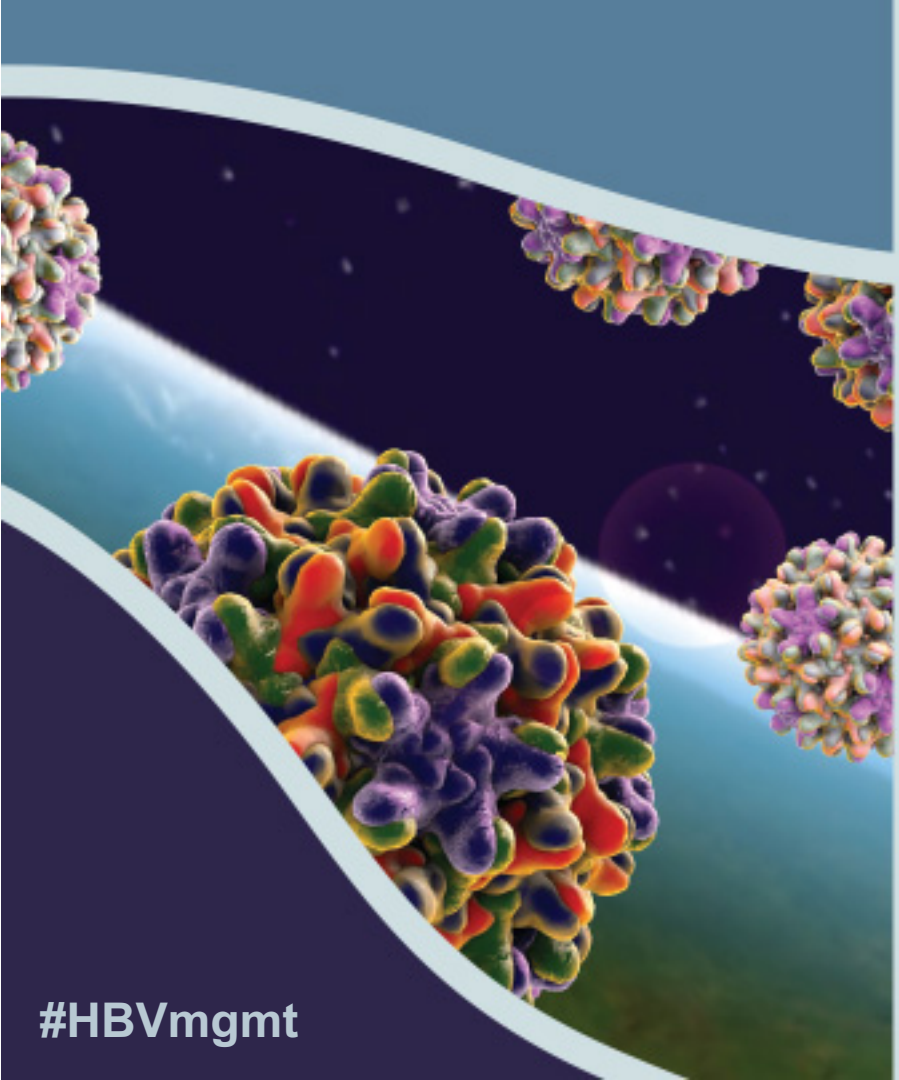

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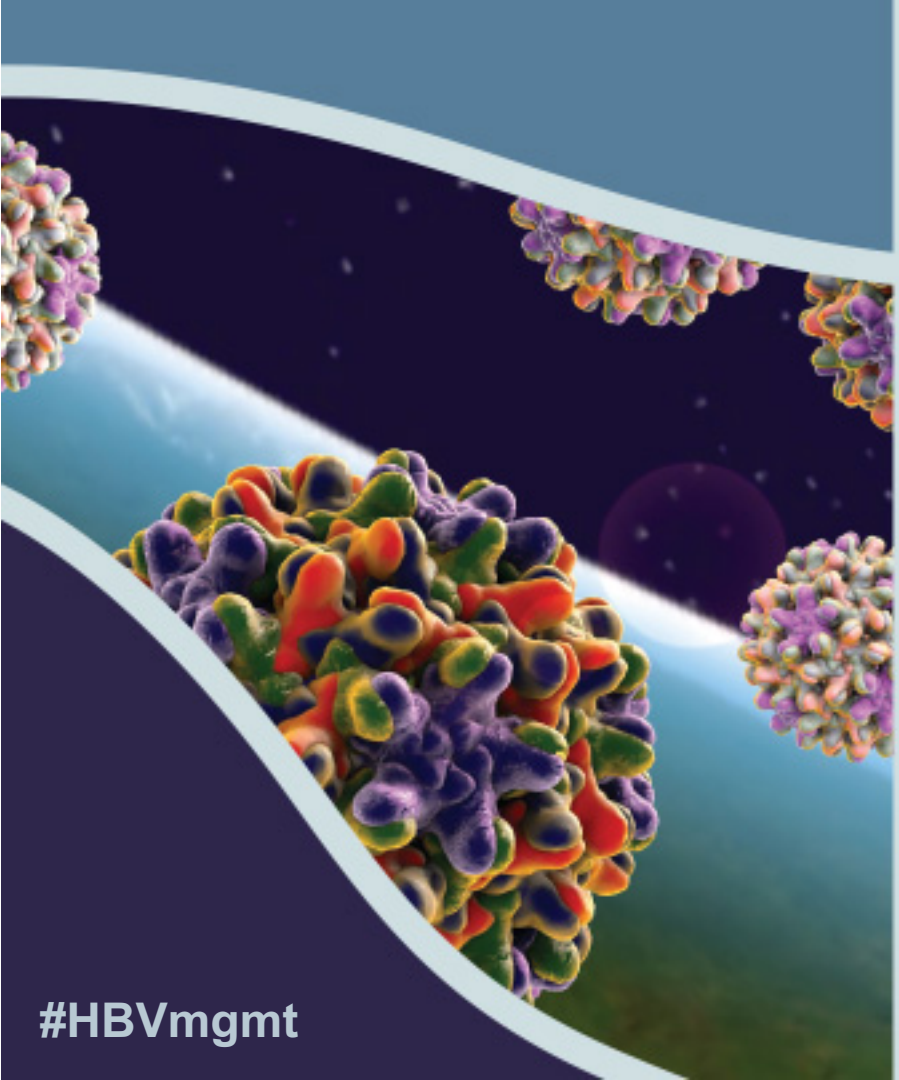

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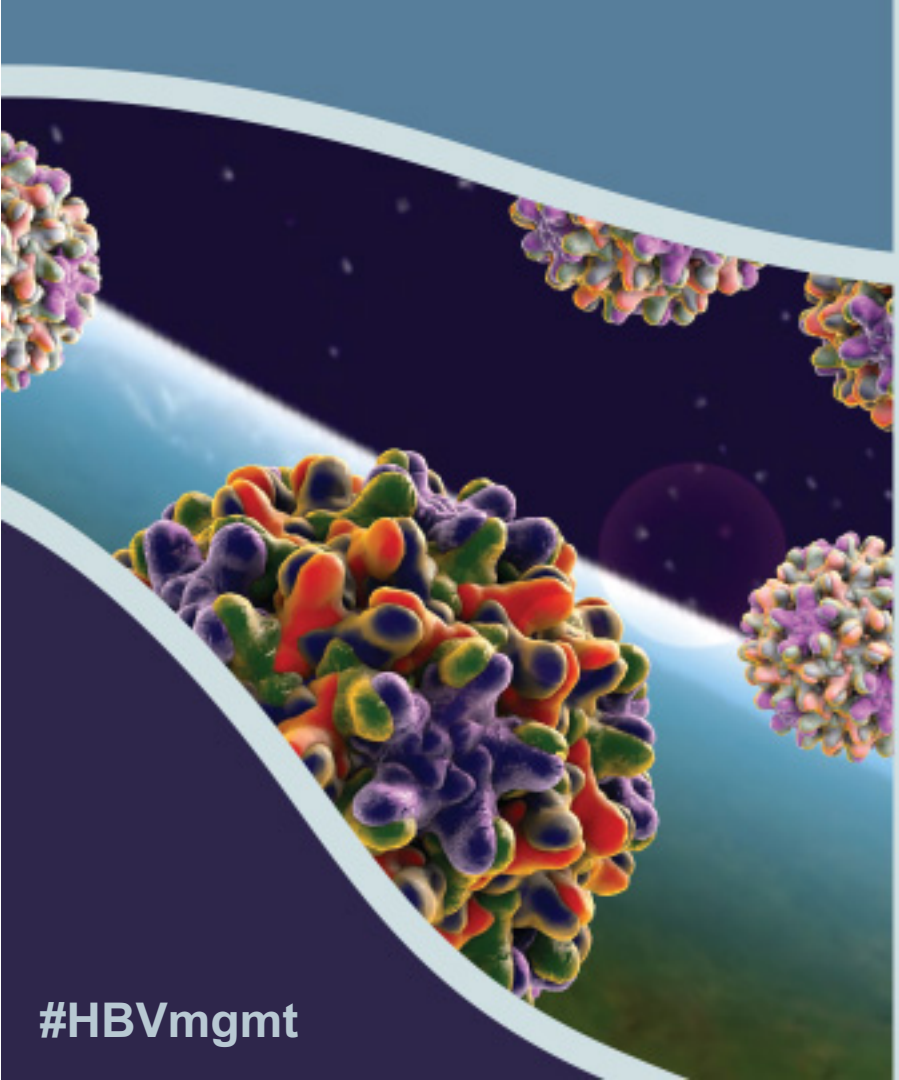
Learning Objective 1

In at-risk populations, document that appropriate patients have been screened for HBV in alignment with the best practice advice of the new ACP clinical guidelines.



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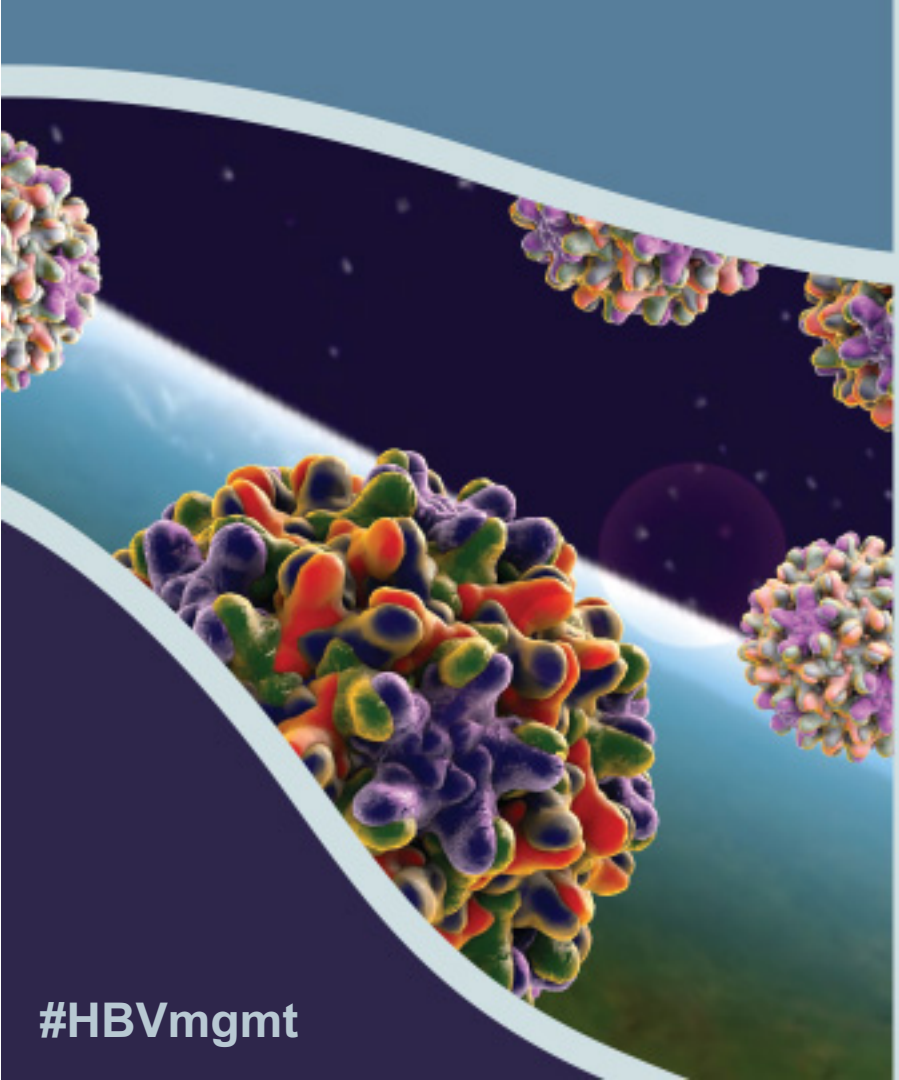
Learning Objective 2

Initiate antiviral therapy in patients with immune-active chronic hepatitis B (CHB) aligned to AASLD and EASL recommendations.



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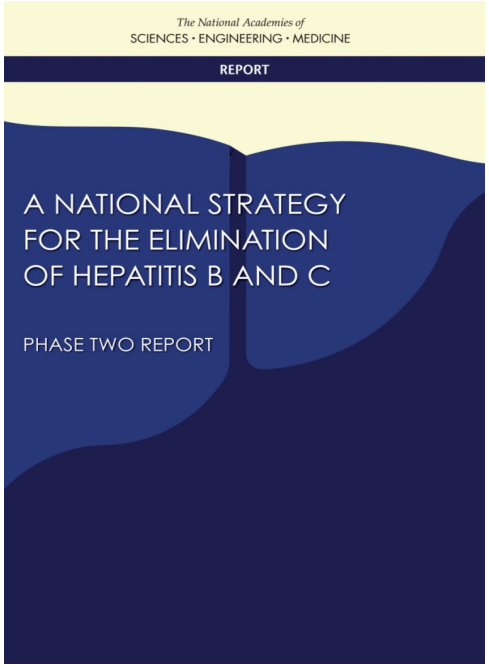
Learning Objective 3

Establish regular monitoring protocols for patients with CHB infection to prevent reactivation and surveil for HCC.

Hepatitis B Targets

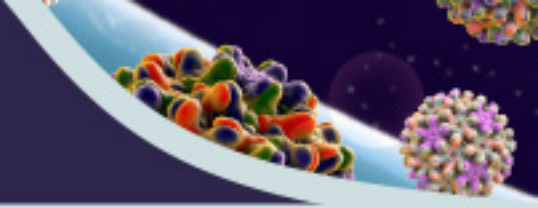


- A **50% reduction** in mortality from chronic HBV is possible in the US by **2030**. This would avert over 60,000 deaths.
- Meeting this goal will require
  - Diagnosing 90% of chronic hepatitis B cases
  - Bringing 90% of those to care
  - Treating 80% of those for whom treatment is indicated
- The same level of diagnosis, care, and treatment will **reduce new cases of HBV-related HCC by ~1/3 and new cases of HBV-related cirrhosis by ~ 45%**
- **Elimination of HBV infection in neonates and children under 5 is possible**, as demonstrated in Alaska Natives.

HCC = hepatocellular carcinoma.

National Academies of Sciences, Engineering, and Medicine. Available at http://nationalacademies.org/hmd/Reports/2017/national-strategy-for-the-elimination-of-hepatitis-b-and-c.aspx.

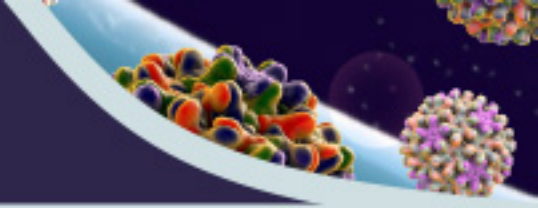
We Can Do Better



Primary care providers are equipped to **screen, vaccinate,** and **monitor** persons at increased risk for HBV

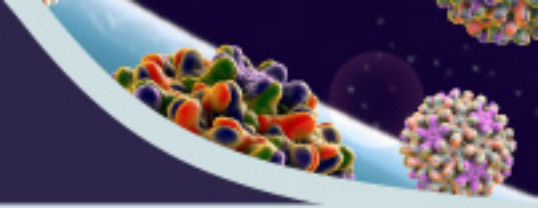
1. Screen and vaccinate as part of routine preventative care
2. Monitor liver enzymes and HBV DNA every 6 months for chronic HBV patients
3. Screen for liver cancer (HCC) with ultrasound

Patient Case: TR



- TR is a 45-year-old Mandarin-speaking man presents to your clinic for an initial visit.
- He immigrated from southern China 5 years ago.
- *You ask if he's ever been tested for hepatitis B and he reports an episode of acute hepatitis as a child but was told he is now just a "carrier"*

It's Game Time! Round 1

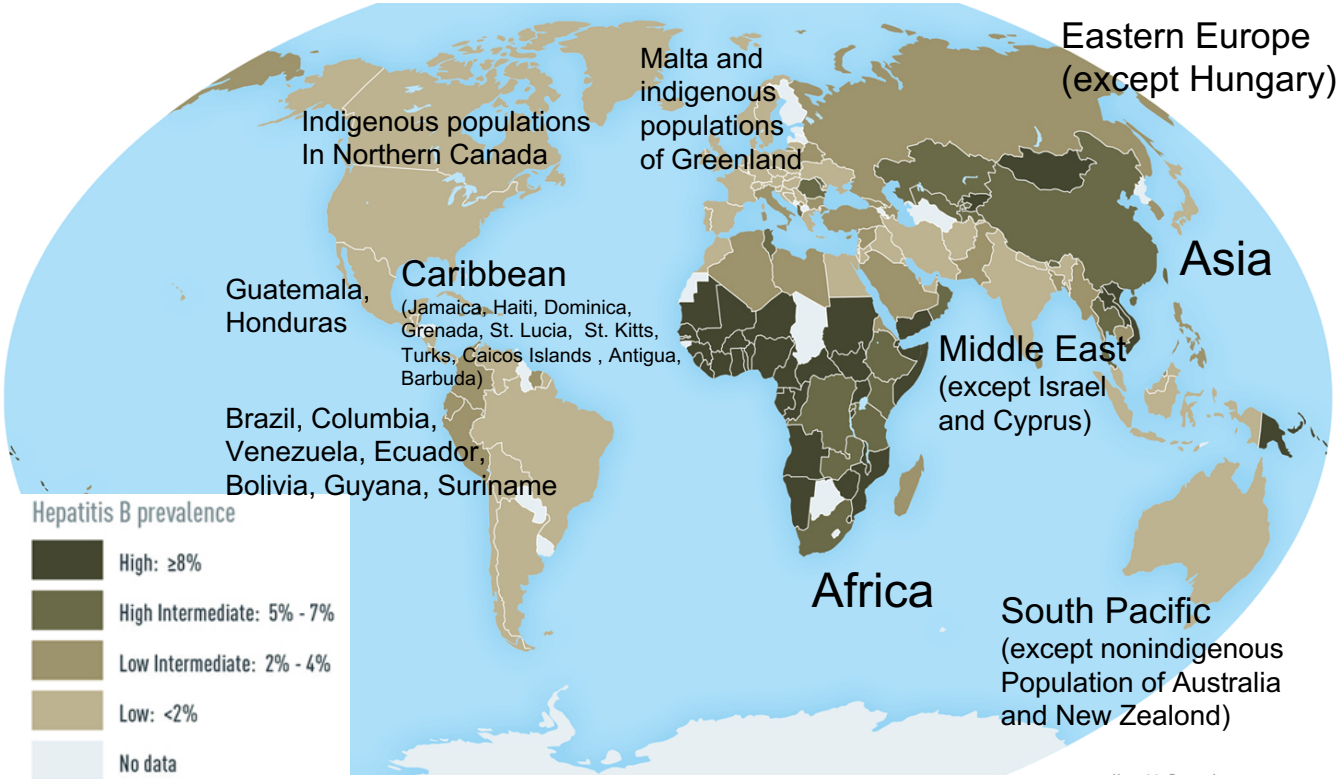


Based on TR's history and feedback you should:

A. Monitor him for symptoms for 6 months
B. Order HBsAg only
C. Order HBsAg and anti-HBs
D. Order HBsAg, anti-HBc and anti-HBs

Screen Persons Born in Countries with 2% or Higher HBV Prevalence

Approximately 70% of persons with chronic HBV in the US are foreign-born, and the prevalence among foreign-born persons is 3% to 5% compared to 0.3% in the general population



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

ACP-CDC Screening Recommendations by HBV Transmission Risk Factors

Vertical transmission • Persons born in countries with 2% or higher HBV prevalence • Pregnant women • Infants born to HBV-infected mothers	**Blood* transmission** • Persons who inject drugs • Incarcerated persons • Household contacts of HBV-infected persons • Persons with end-stage renal disease (including hemodialysis patients) • Blood and tissue donors
Sexual transmission • Men who have sex with men • Sexual contacts of HBV-infected persons	**HBV reactivation/liver complication** • Persons requiring immunosuppressive therapy • Persons infected with hepatitis C virus • HIV positive persons • Persons with elevated ALT levels

**HBV can survive outside the body at least 7 days and still be capable of causing infection*

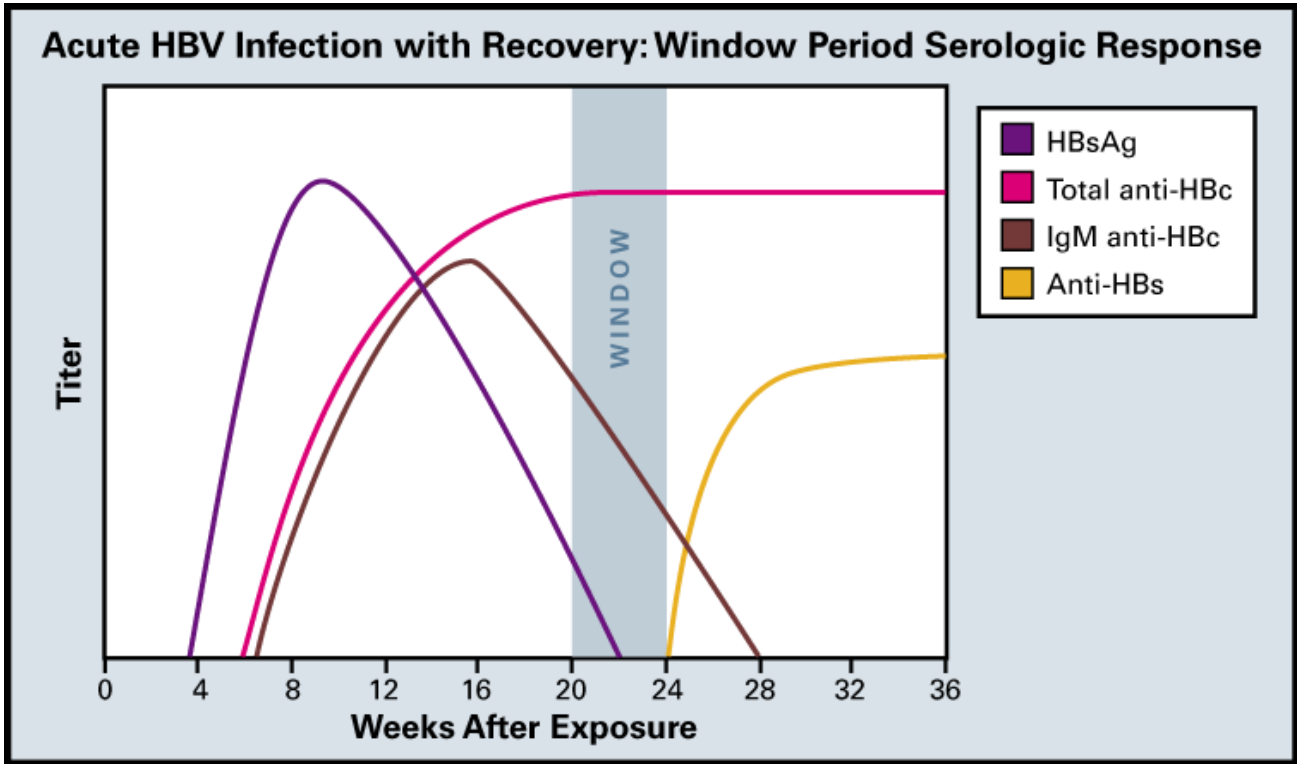
Abara WE, et al. *Ann Intern Med*. 2017;167(11):794-804.

How to Screen for HBV

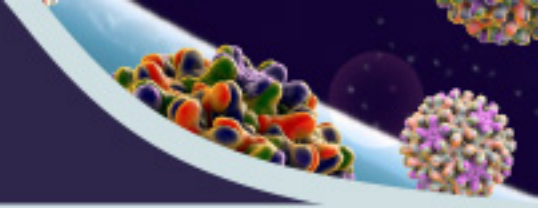
HBsAg = current infection

anti-HBs = immunity

total anti-HBc = ever infected



Test Your Knowledge: Round 2



You order HBV screening tests for TR and his lab results indicate

- hepatitis B surface antigen (HBsAg) positive
- hepatitis B surface antibody (anti-HBs) negative
- total hepatitis B core antibody (anti-HBc) positive

How do you interpret these results?

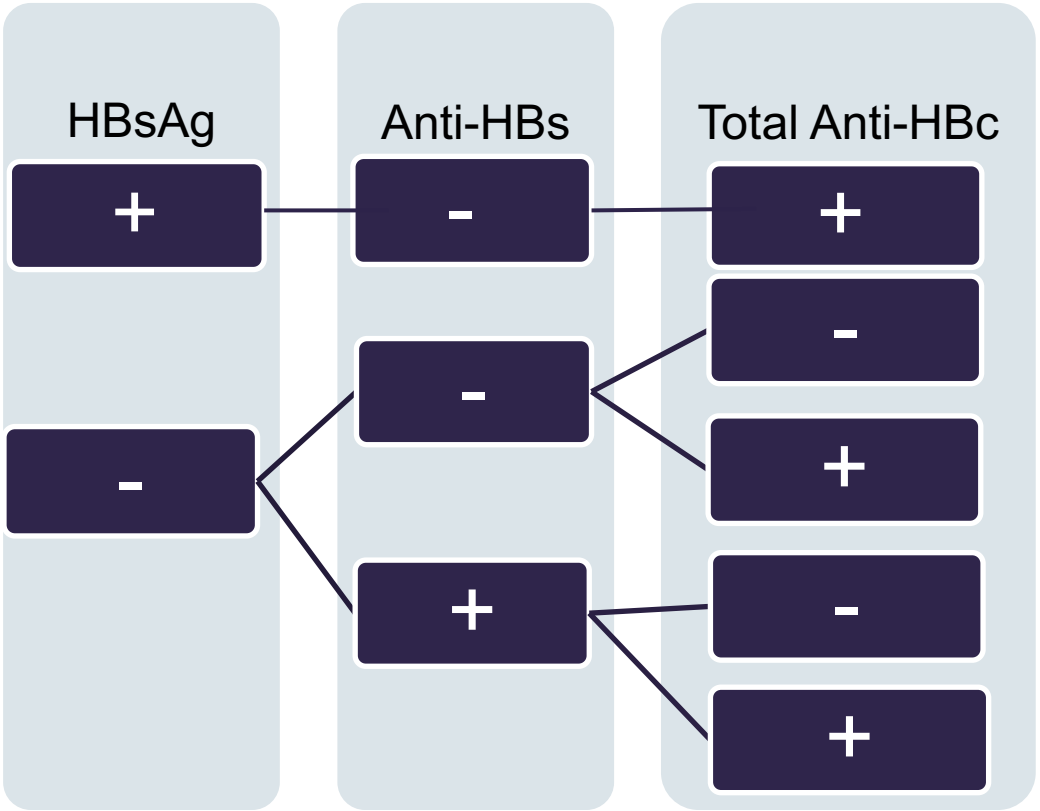
A. TR is immune and no further testing is needed

B. TR is uninfected, but not immune and should be vaccinated

C. TR has chronic hepatitis B and warrants additional testing and management

D. TR has a prior HBV infection and should be counseled on reactivation risk if on immunosuppression therapy

HBV Serology Interpretation



Current infection > can order IgM if concern for acute HBV

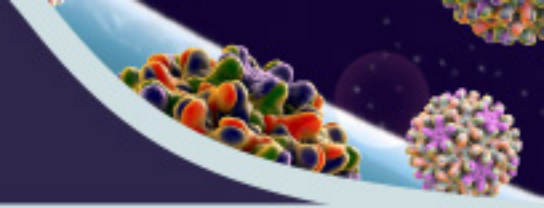
Susceptible > give complete HBV vaccine series unless nonresponse to 2 series

Isolated core > prior infection v. occult HBV v. false positive v. “window period” of acute infection

Immune from vaccination > reassurance

Prior infection > counsel on reactivation risk

Who Should be Vaccinated for HBV?



Vertical transmission
- Persons born in countries with 2% or higher HBV prevalence
- Pregnant women at risk for HBV infection during pregnancy
- Infants born to HBV-infected mothers

Blood transmission
- Persons who inject drugs
- Incarcerated persons
- Household contacts of HBV-infected persons
- Persons with end-stage renal disease (including hemodialysis patients)
- Blood and tissue donors
- Residents and staff of facilities for developmentally disabled persons
- Public safety workers at risk for exposure to blood or blood-contaminated body fluids
- *Adults with diabetes mellitus < 60 years*

Sexual transmission
- Men who have sex with men
- Sexual partners of HBV-infected persons
- Sexually active persons not in a mutually monogamous relationship
- Persons seeking evaluation or treatment for a sexually transmitted infection

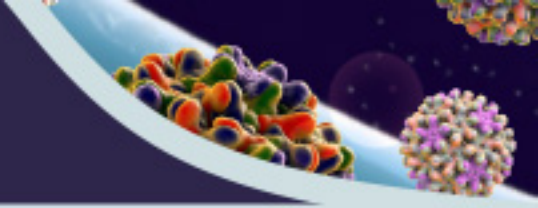
HBV reactivation/liver complication
- Persons requiring immunosuppressive therapy
- Persons infected with hepatitis C virus
- HIV positive persons
- Persons with elevated ALT levels
- Adults with chronic liver disease

International travelers to regions with high or intermediate levels of endemic HBV infection

Any adult seeking protection from HBV infection

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

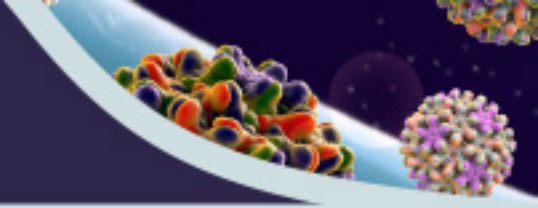
HBV Vaccination



- HBV vaccine was incorporated into the universal pediatric immunization schedule in the early 1990s, thus most US born adults > 30 yo have not been vaccinated and are still susceptible to HBV
- Standard HBV vaccine administered as a 3-dose series on 0-, 1-, 6-month schedule to achieve immunity, though higher dosages may be required for immunocompromised persons
- New FDA approved and ACIP recommended 2-dose HBV vaccine (hepatitis B vaccine [recombinant], adjuvanted) now available, administered 1 month apart to achieve immunity
- HBV immune globulin (HBIG) and HBV vaccine administered together are effective in preventing transmission after exposure to HBV

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

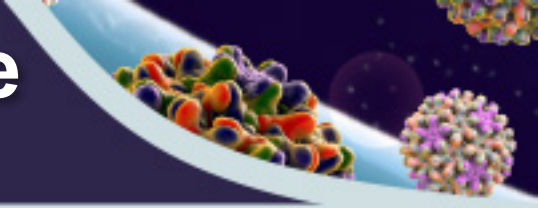
Test Your Knowledge: Round 3



Given TR's lab results of HBsAG positive, anti-HBs negative, and anti-HBc positive, how do you counsel him relative to next steps?

A. Inform him no further testing is needed for 1 year
B. Screen him for hepatocellular carcinoma (HCC)
C. Refer him to a hepatologist

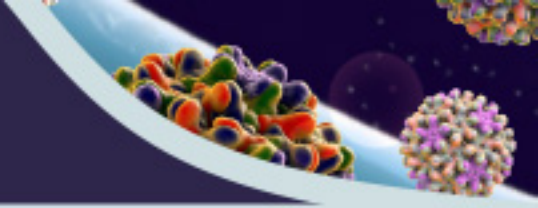
Counseling of Persons Who Are HBsAg Positive



- Screen sexual and household contacts
- Educate on HBV transmission to prevent spread and dispel myths
- Minimize or abstain from alcohol use
- Healthy exercise and diet to prevent concurrent metabolic syndrome and fatty liver disease
- Need for routine HBV monitoring, including during pregnancy
- Screen for liver cancer

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

History and Physical



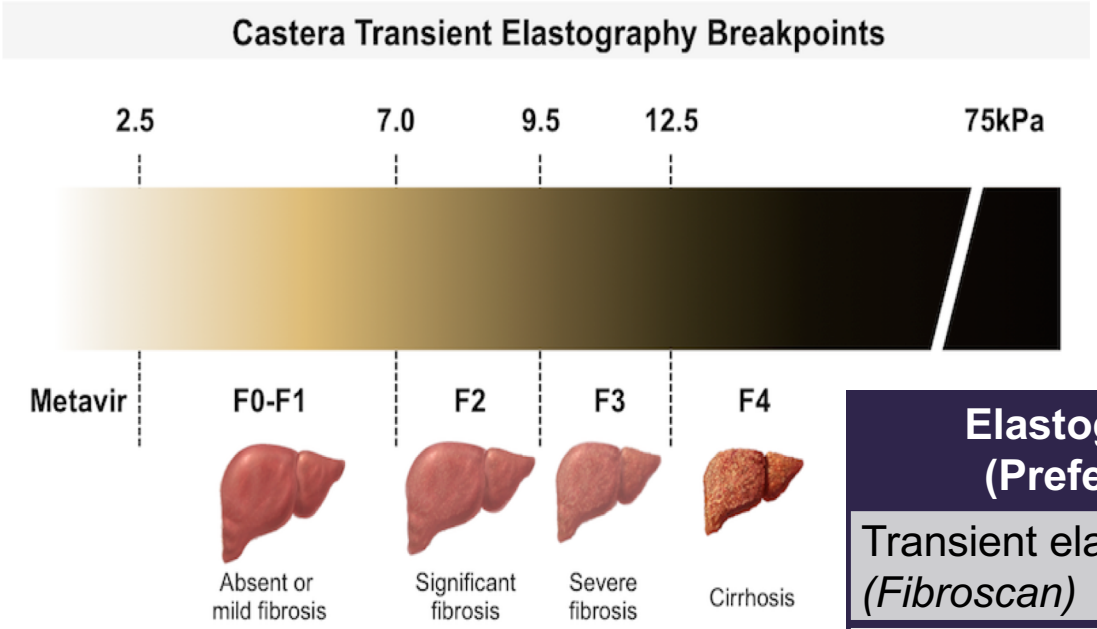
- HPI: Symptoms of cirrhosis
- PMH: Prior vaccination for hepatitis A
- Medications: herbals, hepatotoxic drugs, hormonal contraception
- Social history: alcohol and tobacco use
- Family history of HBV or liver cancer
- Vitals, BMI
- PEx: Signs of cirrhosis

Labs and Imaging

- Routine: CMP, CBC, PT/INR
- HBV activity: HBeAg/anti-HBe, HBV DNA
- Coinfections: Anti-HAV, Anti-HCV, Anti-HIV
- In select patients: anti-HDV, HBV genotype, AFP
- Baseline abdominal ultrasound

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

Non-Invasive Fibrosis Assessment



Elastography (Preferred)	Serum Fibrosis Markers
Transient elastography *(Fibroscan)*	FibroSure or FibroTest
Acoustic radiation force impulse (ARFI) elastography	AST to Platelet Ratio Index (APRI)
MR elastography	Fibrosis-4 (FIB-4)

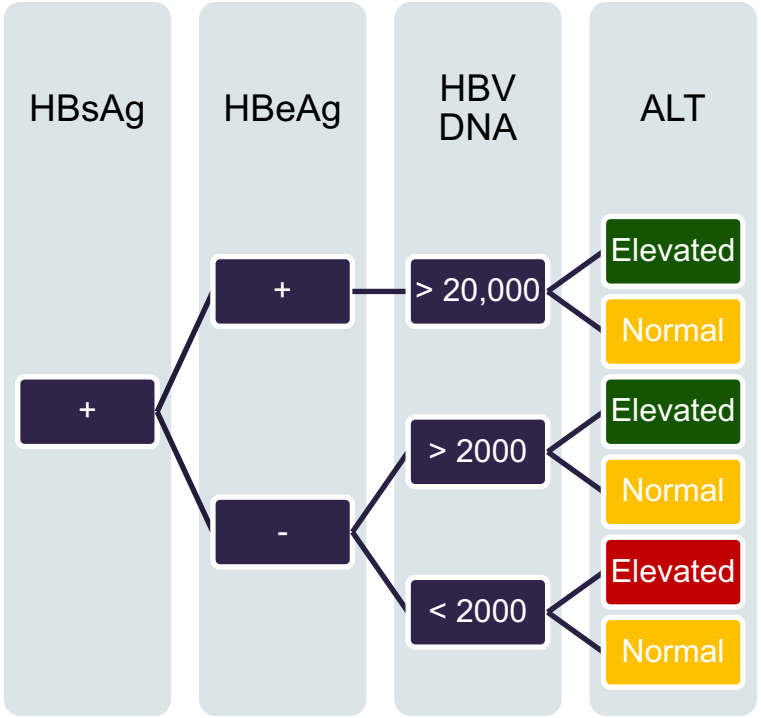
Parikh P, et al. *Ann Transl Med.* 2017;5(3):40.

Test Your Knowledge: Round 4

The AASLD 2018 Hepatitis B Guidance update indicates that for the purpose of guiding management of CHB, the upper limits of normal (ULN) for ALT for males and females is which of the following?

A. 19 U/L in females; 30 U/L in males
B. 20 U/L in females; 33 U/L in males
C. 23 U/L in females; 29 U/L in males
D. 25 U/L in females; 35 U/L in males

Chronic* HBV Monitoring



Minimum q6mo monitoring ALT and HBV DNA

*HBsAg persistent over 6mo
Or IgM neg, total anti-HBc pos
Or asymptomatic from endemic area

Immune active: Treat

Immune tolerant: Monitor ALT & HBeAg/eAb q6mo

Immune reactive: Treat

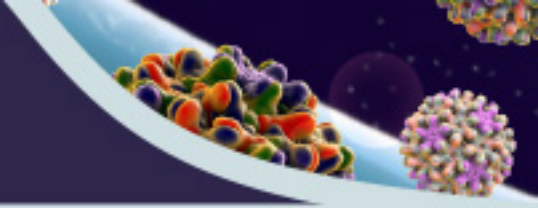
Consider treatment if FHx HCC, F2+

Evaluate other causes of ALT elevation

Inactive: Monitor ALT & HBV DNA q6mo
HBsAg q1y

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599; Terrault NA, et al. *Hepatology*. 2016;63:261-283.

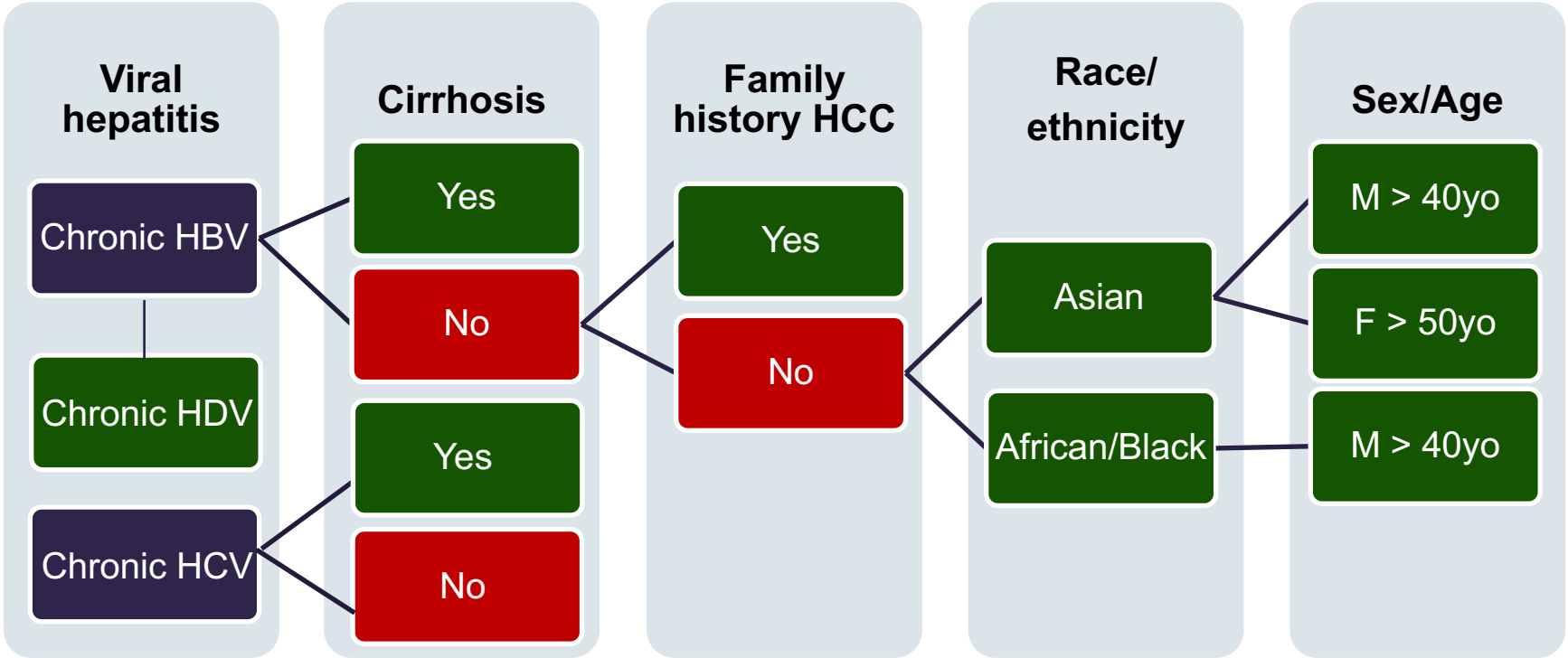
Hepatocellular Carcinoma (HCC) Epidemiology



- Unlike HCV, chronic HBV infection can cause liver cancer in patients without cirrhosis
- Chronic HBV increases odds of liver cancer 50 to 100 times, hepatitis C 15 to 20 times
- Viral hepatitis is driving the 38% increase in liver cancer in the US between 2003 and 2012

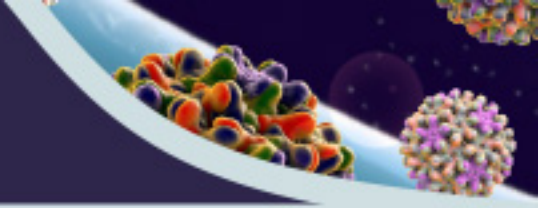
Briux J, et al. *Hepatology*. 2011 Mar; 53(3): 1020–1022. National Academies of Sciences, Engineering, and Medicine. Available at http://nationalacademies.org/hmd/Reports/2017/national-strategy-for-the-elimination-of-hepatitis-b-and-c.aspx.

AASLD Indications for Screening



Bruix J, et al. *Hepatology* 2011;53:1020-1022.

HCC Surveillance: Additional Risk Factors



- Basal core promoter (BCP) or precore mutations
- Genotype C
- Coinfection with HCV, HIV, HDV
- Persistently high HBV DNA
- Late HBeAg loss (40+ years)
- Persistent elevation of LFTs (>1.5 ULN*)
- Alcohol use, smoking
- Cirrhosis

*Abnormal ALT is: male ≥35 U/L or female ≥25 U/L

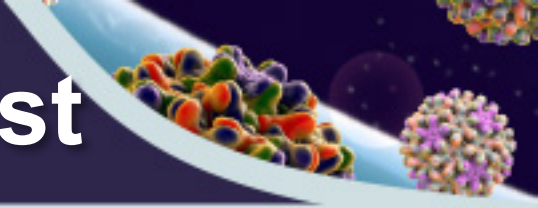
Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599; Bruix J, et al. *Hepatology*. 2005;42:1208-1236; Chan HL, et al. *Gut*. 2004;53(10):1494-1498.

HCC Surveillance Methods

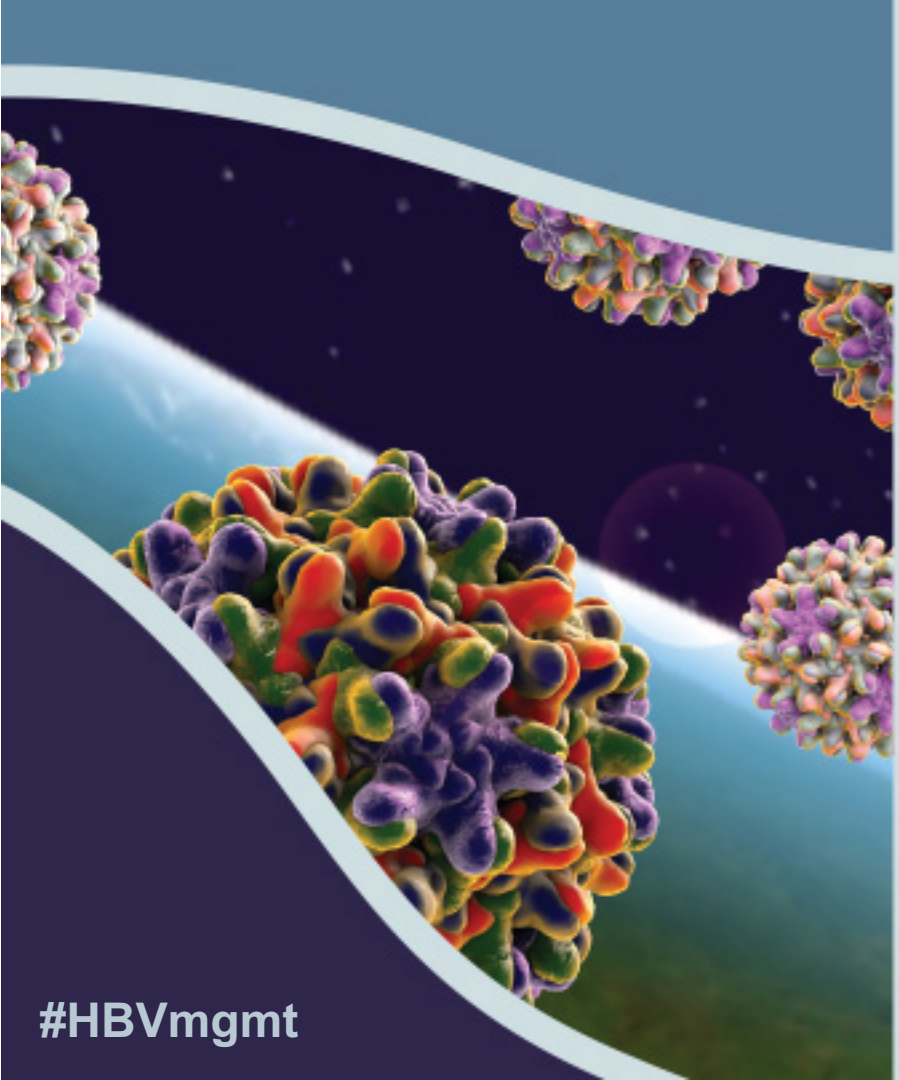
- Liver ultrasound every 6 months
- +/- serum alphafetoprotein (AFP)
- Follow-up MRI or CT abdomen with and without contrast may be indicated to evaluate suspicious lesions identified on ultrasound
- Hepatocellular carcinoma can be diagnosed by imaging alone

Heimbach JK, et al. *Hepatology*. 2018;67(1):358-380; Bruix J, et al. *Hepatology.* 2011;53:1020-1022.

When to Refer to a Specialist



- All primary care providers must screen and vaccinate individuals at increased risk for HBV
- Patients identified with chronic HBV infection must be counseled, monitored, and evaluated for treatment
  - Chronic HBV is a dynamic disease and requires lifelong monitoring by a primary care provider or a specialist
- All patients identified with HCC or cirrhosis should be referred to a specialist

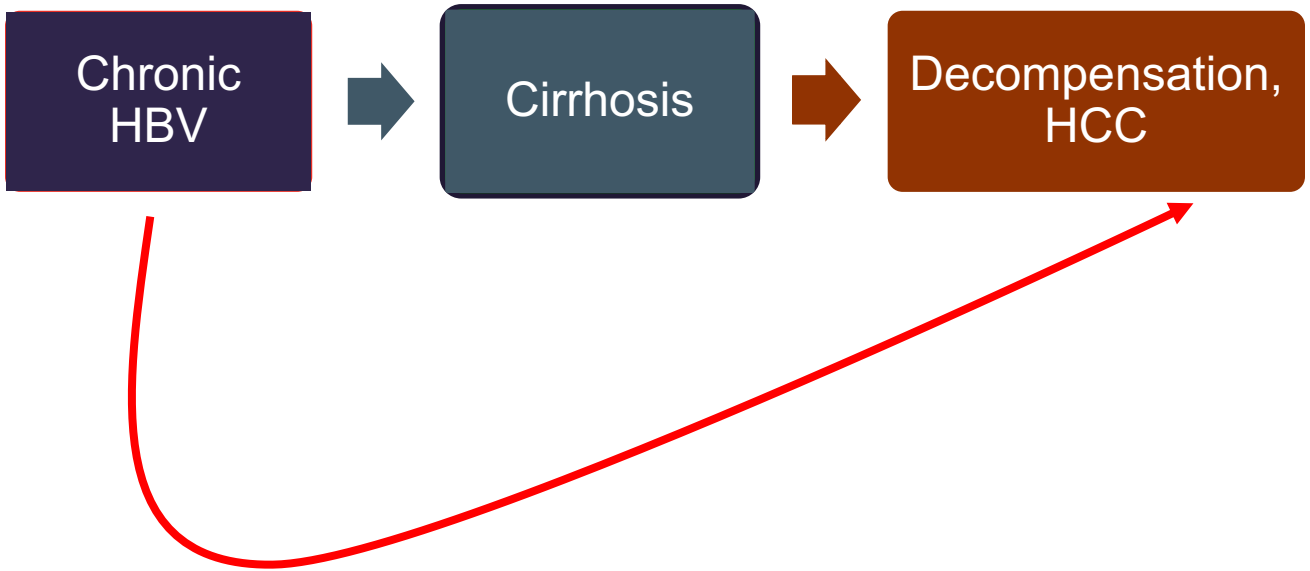


Guideline-Directed Treatment Choices in HBV

In Whom and When to Initiate HBV Treatment

#HBVmgmt

Natural History of HBV



Perz JF, et al. *J Hepatol*. 2006;45(4):529-538; Ocama P, et al. *Am J Med*. 2005; 118(12):1413; Weinbaum CM, et al. *MMWR Recomm Rep*. 2008;57(RR-8):1-20.

Phases of Chronic HBV

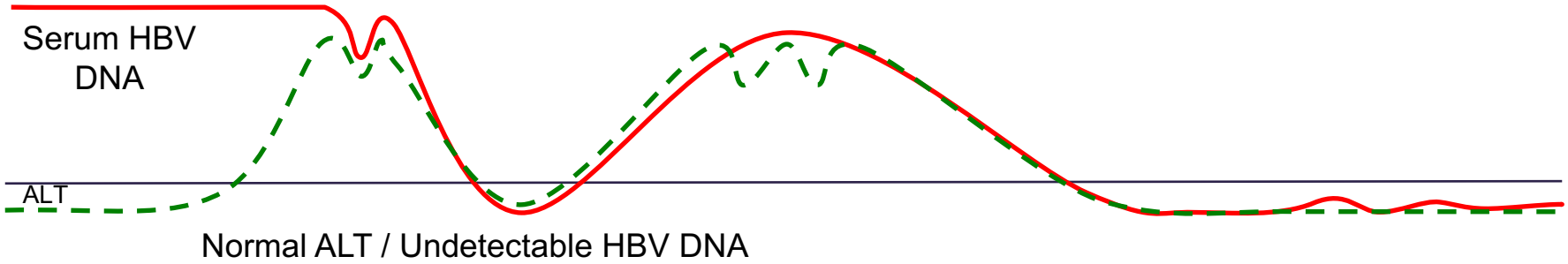
Immune Tolerant
- High HBV DNA
- Normal or low ALT
- HBeAg(+)
- High serum levels of HBeAg & HBsAg
- Mild or no necroinflammation
- No or slow fibrosis progression
- Decreased IL-10, IL-6, IL-8 & TNF-α
- No HBV DNA mutations

Immune Active~ HBeAg(+) Chronic hepatitis
- High HBV DNA, changing to low or undetectable
- High decreasing to normal ALT
- Acute or intermittent hepatitis
- Declining HBeAg & HBsAg
- Eventual loss of HBeAg
- High inflammation changing to minimal necroinflammation

Immune Reactive~ HBeAg(-) Chronic hepatitis
- Moderate to high HBV DNA
- High, fluctuating ALT
- Low HBsAg levels
- Persistent hepatitis
- Necroinflammation
- Progressive liver disease
- Immune clearance attempts ineffective
- May be preceded by inactive phase

Inactive
- Low or undetectable HBV DNA
- HBeAg(-)
- Very low HBsAg levels
- Normal ALT

HBsAg Loss/Occult Hepatitis B
- Serum HBV DNA phases, alternating undetectable and very low but detectable
- Detectable HBV DNA & ccc DNA in the liver
- Intrahepatic replication-competent HBV genomes such as HBV cccDNA
- Integrated HBV DNA
- Anti-HBc (+) only



Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6(12):1315-1341.

Goals of Care

- Impact the natural history of HBV
- Prevent cirrhosis, HCC, death

HBV DNA undetectable

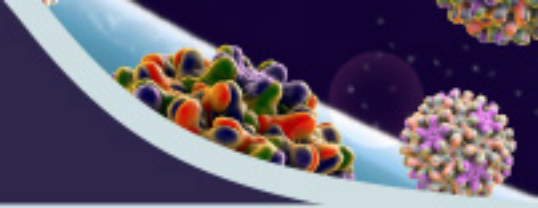
ALT "Normal"

HBeAg loss, Seroconversion

HBsAg loss, Seroconversion

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599; Terrault NA, et al., *Hepatology*. 2016;63(1):261-268.

Test Your Knowledge: Round 5



According to AASLD treatment algorithms, in which of the following is immediate treatment indicated?

A. HBeAg+, ALT ≤ ULN, and HBV DNA < 20,000IU/mL
B. HBeAg+, ALT ≥ 2x ULN, and HBV DNA < 20,000IU/mL
C. HBeAg-, ALT ≤ ULN, and HBV DNA < 2000 IU/mL
D. HBeAg-, ALT ≥ 2x ULN, and HBV DNA > 2000 IU/mL

AASLD, EASL Guidelines

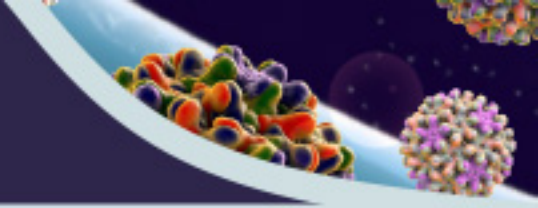
Guideline	HBeAg Positive			HBeAg Negative		
	HBV DNA, IU/mL	ALT	Liver Disease	HBV DNA, IU/mL	ALT	Liver Disease
AASLD[1,2]	> 20,000	≥ 2 x ULN	N/A	≥ 2000	≥ 2 x ULN	N/A
	N/A	N/A	Cirrhosis	N/A	N/A	Cirrhosis
EASL[3]	> 2000	> ULN*	Moderate inflammation or fibrosis*	> 2000	> ULN*	Moderate inflammation or fibrosis*
	> 20,000	> 2 x ULN	N/A	> 20,000	> 2 x ULN	N/A
	N/A	N/A	Cirrhosis	N/A	N/A	Cirrhosis

*In patients with HBV DNA > 2000 IU/mL, treatment indicated if ALT > ULN and/or at least moderate fibrosis.

Use liver biopsy or transient elastography to detect fibrosis, inflammation in unclear situations.

[1]Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599; [2]Terrault NA, et al. *Hepatology*. 2016;63:261-283; [3]EASL. *J Hepatol*. 2017;67:370-398.

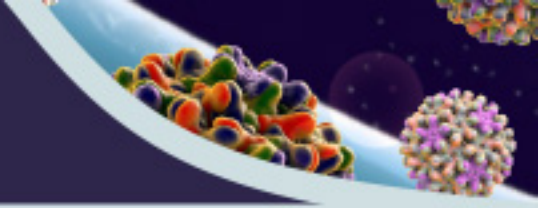
Test Your Knowledge: Round 6



Of the FDA-approved agents to treat HBV in patient TR, which of the following has the least favorable safety profile?

A. Entecavir
B. Peginterferon
C. Tenofovir alafenamide (TAF)
D. Tenofovir disoproxil fumarate (TDF)

AASLD Guidelines: Initial Treatment



Treatment	Preferred	Notes
Entecavir	Yes (unless previous history of lamivudine resistance)	High potency, high genetic barrier to resistance
Tenofovir	Yes	High potency, high genetic barrier to resistance
PegIFN	Yes	Less safe in pts with cirrhosis
Adefovir	No	Low genetic barrier to resistance
Lamivudine	No	Low genetic barrier to resistance
Telbivudine	No	Low genetic barrier to resistance

Treatment with antivirals does not eliminate the risk of HCC, and surveillance for HCC should continue in persons who are at risk

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

Efficacy of Approved First-Line Antiviral Therapies in HBeAg Positive Chronic HBV

HBeAg Positive	Peg-IFN	Entecavir	Tenofovir Disoproxil Fumerate	Tenofovir Alafenamide
% HBV-DNA suppression (cut-off to define HBV-DNA suppression	30-42 (< 2,000-40,000 IU/ml) 8-14 (< 80 IU/ml)	61 (< 50-60 IU/ml)	76 (< 60 IU/ml)	73 (< 29 IU/ml)
% HBeAg loss	32%-36%	22%-25%	-	22%
% HBeAg seroconversion	29%-36%	21%-22%	21%	18%
% Normalization of ALT	34%-52%	68%-81%	68%	-
% HBsAg loss	2%-7% 11% (at 3 years post-treatment)	4%-5%	8%	1%

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

Efficacy of Approved First-Line Antiviral Therapies in HBeAg Negative Chronic HBV

HBeAg Negative	Peg-IFN	Entecavir	Tenofovir Disoproxil Fumerate	Tenofovir Alafenamide
% HBV-DNA suppression (cut-off to define HBV-DNA suppression	43 (< 4,000 IU/ml) 19 (< 80 IU/ml)	90-91 (< 50-60 IU/ml)	93 (< 60 IU/ml)	90 (< 29 IU/ml)
% Normalization of ALT	59%	78%-88%	76%	81%
% HBsAg loss	4% 6% (at 3 years post-treatment)	0%-1%	0%	< 1%

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

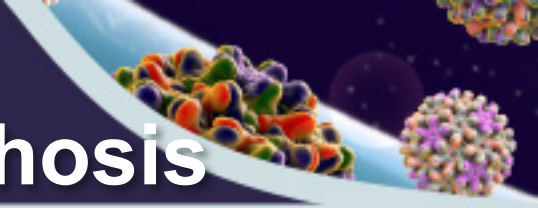
Treatment Recommendations: First-Line Therapy in Patients Without Cirrhosis

Preferred	Not Preferred
Tenofovir DF	Adefovir
Tenofovir AF	Lamivudine
Entecavir	Telbivudine
Peg-IFN alfa-2a	

Tenofovir DF, tenofovir AF, entecavir, and pegIFN alfa-2a are preferred primarily because of lack of resistance with long-term use. Before initiating treatment, all patients should have a baseline assessment of liver fibrosis for evaluating histologic response to therapy.

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599; Terrault NA, et al. *Hepatology*. 2016;63:261-283; Martin P, et al. *Clin Gastroenterol Hepatol.* 2015;13:2071-2087.

Treatment Recommendations: Chronic HBV Patients With Cirrhosis



Compensated Cirrhosis

Preferred	Alternative	Not Preferred
Tenofovir DF	PegIFN alfa-2a†	Lamivudine
Entecavir		Telbivudine
Tenofovir AF		

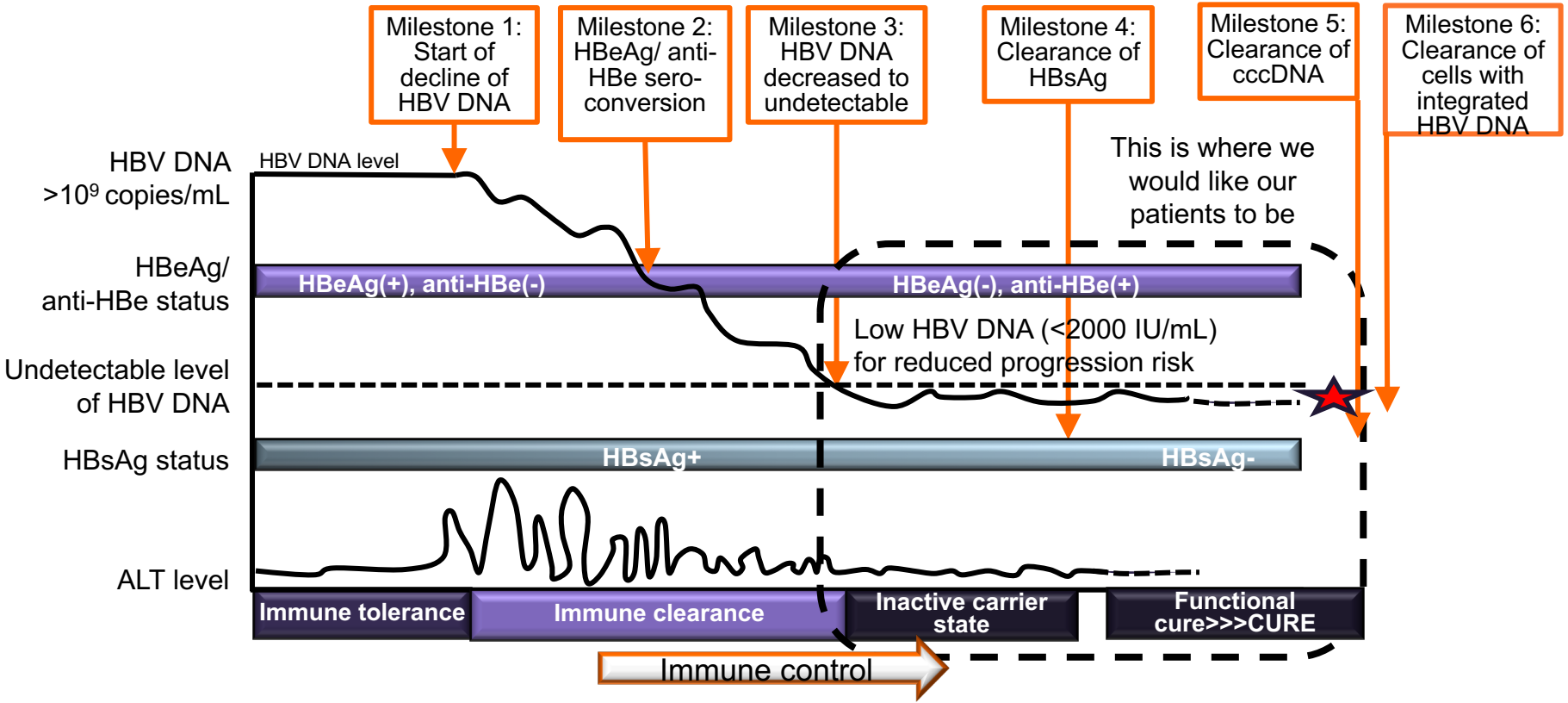
Decompensated Cirrhosis

Preferred	Not Preferred
Tenofovir DF	PegIFN alfa-2a and alfa-2b‡
Entecavir	

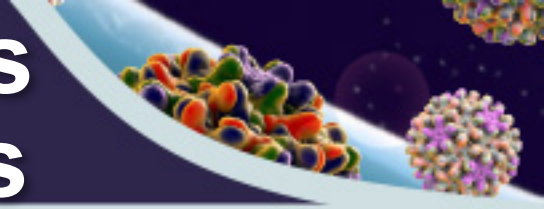
All HBeAg-positive or HBeAg-negative patients with cirrhosis (compensated or decompensated) and any level of detectable HBV DNA should receive treatment for chronic HBV.

†Well-compensated cirrhosis only.
‡Contraindicated due to safety concerns.
Terrault NA, et al. *Hepatology*. 2016;63:261-283.; Martin P, et al. *Clin Gastroenterol Hepatol*. 2015;13:2071-2087.

Milestones in HBV Treatment



Limitations/Considerations of Current HBV Treatments



No immunological effect
- Rare HBsAb seroconversion
- HBeAg seroconversion sustainability
- No cure = Suppressive therapy life-long for HBeAg- patients

Long-term compliance
- Asymptomatic
- Resistance development

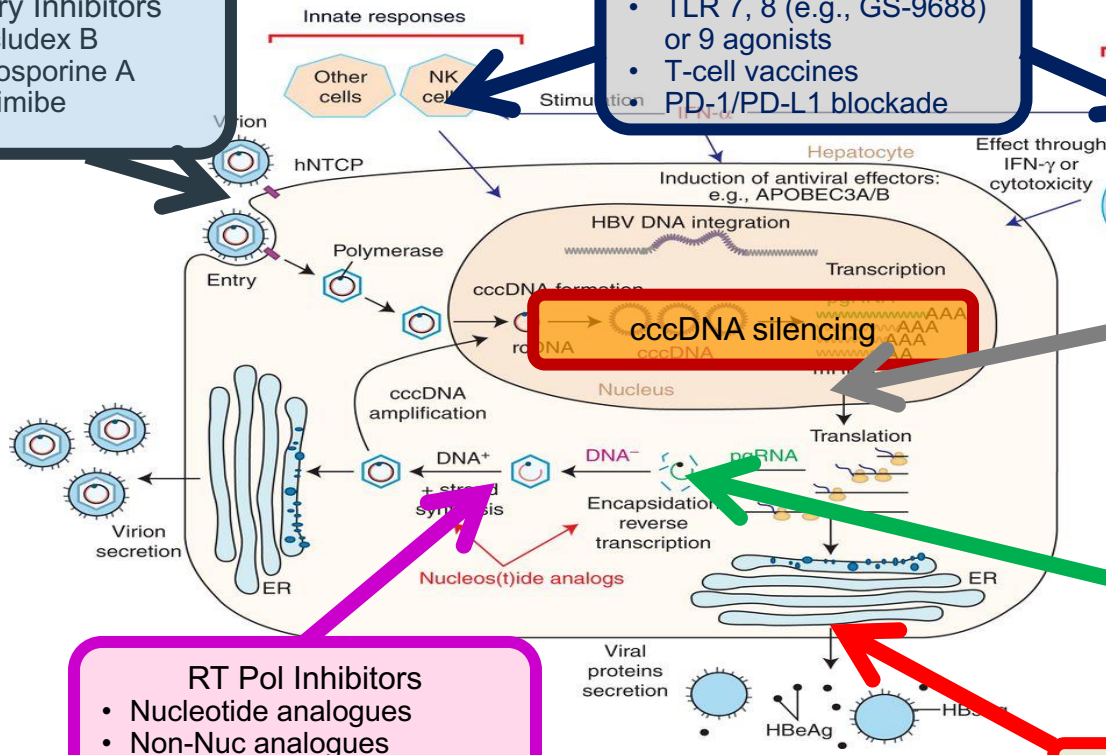
High costs

Long-term safety
Nephrotoxicity
Bone disease
Lactic acidosis

Emerging Treatments for HBV Cure

Entry Inhibitors
- Myrcludex B
- Cyclosporine A
- Ezetimibe

Immunodulators
- TLR 7, 8 (e.g., GS-9688) or 9 agonists
- T-cell vaccines
- PD-1/PD-L1 blockade



cccDNA silencing

Inhibit protein translation by siRNA
- ARO-HBV
- AB-452
- ALN-HBV
- GSK3228836

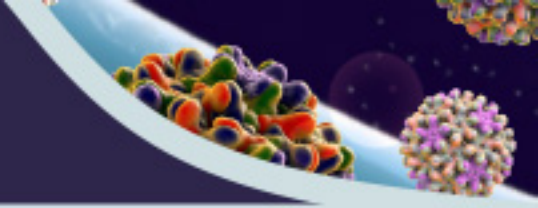
Core inhibitors
- AL-3778
- AIC649
- ABI-H0731
- RG7909

RT Pol Inhibitors
- Nucleotide analogues
- Non-Nuc analogues
- RNAseH inhibitors

HBsAg release Inhibitor
- NAP

Adapted from Zoulim F, et al. *Cold Spring Harb Perspect Med*. 2015;5(4):pii:a021501.

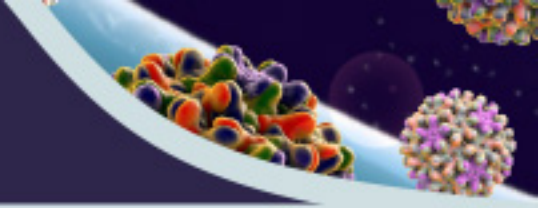
HBV in Pregnancy



- Normal changes in liver tests in pregnancy
  - Elevated Alk phos
  - ALT lower in 2nd and 3rd trimesters
- HBV flares are uncommon in pregnancy ~ 6%
- Primary concern is with flares in women already on antiviral therapy who discontinue treatment once pregnancy is diagnosed
  - 67%
- Drug safety of HBV treatment in pregnancy
  - Tenofovir dipovoxil fumarate (Class B)
  - Tenofovir alafenamide (insufficient evidence to inform drug-associated risk)
  - Telbivudine (Class B)
  - Lamivudine (Class C)

Brown RS, et al. *Hepatology*. 2016;63:319-333.; Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

HBV Reactivation



Well-Characterized Syndrome

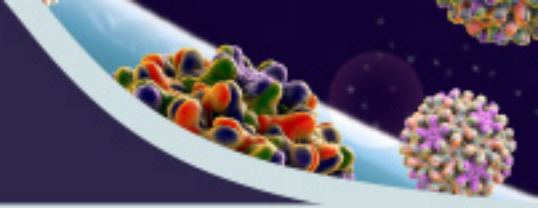
- Abrupt reappearance or rise of HBV DNA in previously inactive or resolved HBV infection
- Often, but not always, accompanied by reappearance of disease activity
- May occur spontaneously or as a result of immunosuppression

Potential Consequences

- May lead to clinically apparent acute hepatitis
  - Can be severe
  - Can result in acute liver failure and death
- Many cases are subclinical and resolve spontaneously, or result in persistent infection
- May go undetected until
  - Advanced liver disease is present
  - Disease has been transmitted to sexual or family contacts

Bessone F, et al. *World J Hepatol*. 2016;8:385-394.

Importance of the Primary Care Physician

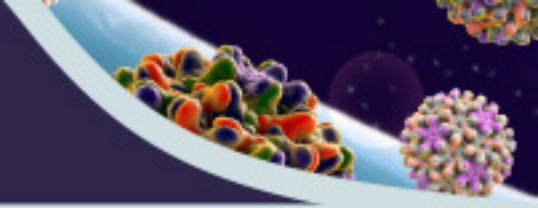


Often has the **first opportunity** to **make the diagnosis**

Can make a **timely referral** for treatment

Can provide long-term, **continuity of care**: counseling, complications monitoring

Test Your Knowledge: Round 7

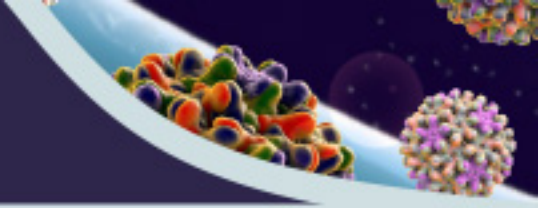


What was the most important takeaway that will impact your patient care?

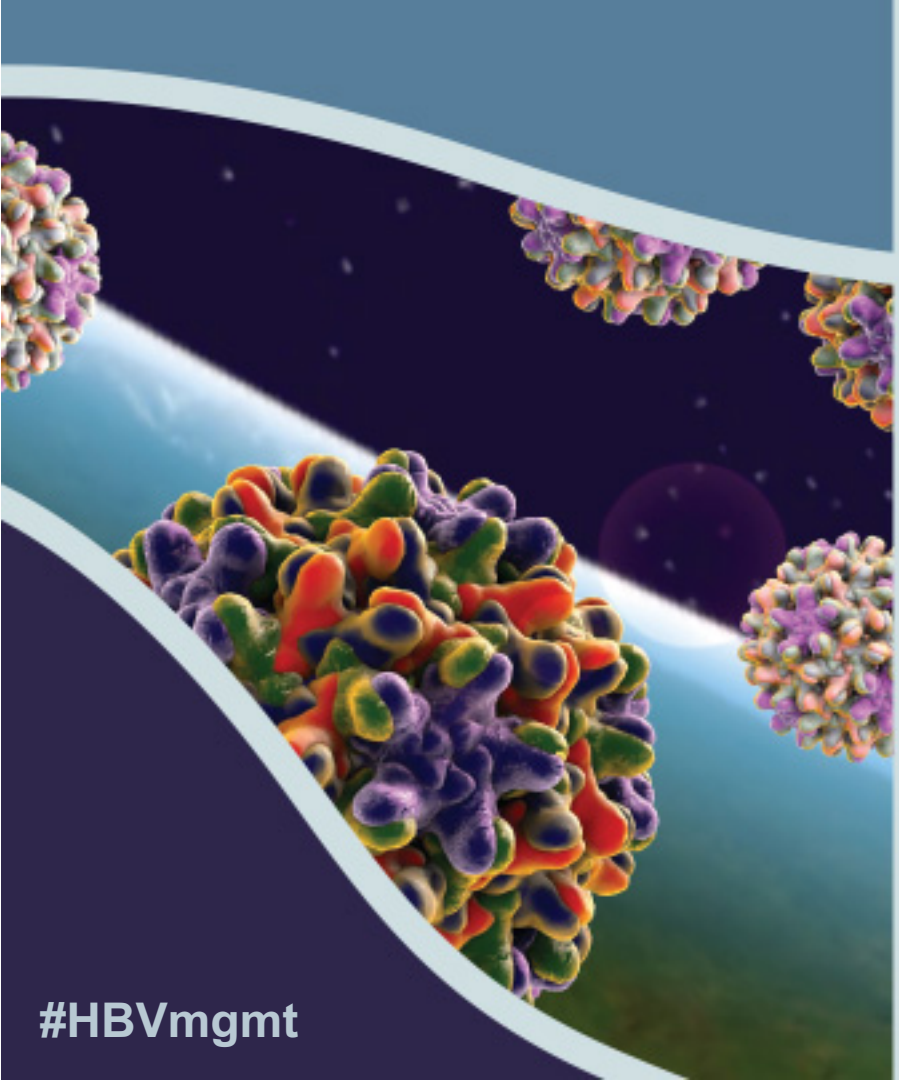
1. I will increase my screening of at-risk populations
2. Chronic HBV patient under my care should be monitored at least every 6 month with HBV viral load and ALT
3. Liver cancer can develop in the absence of cirrhosis and should be surveilled every 6 month
4. I will follow AASLD HBV treatment guidelines

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

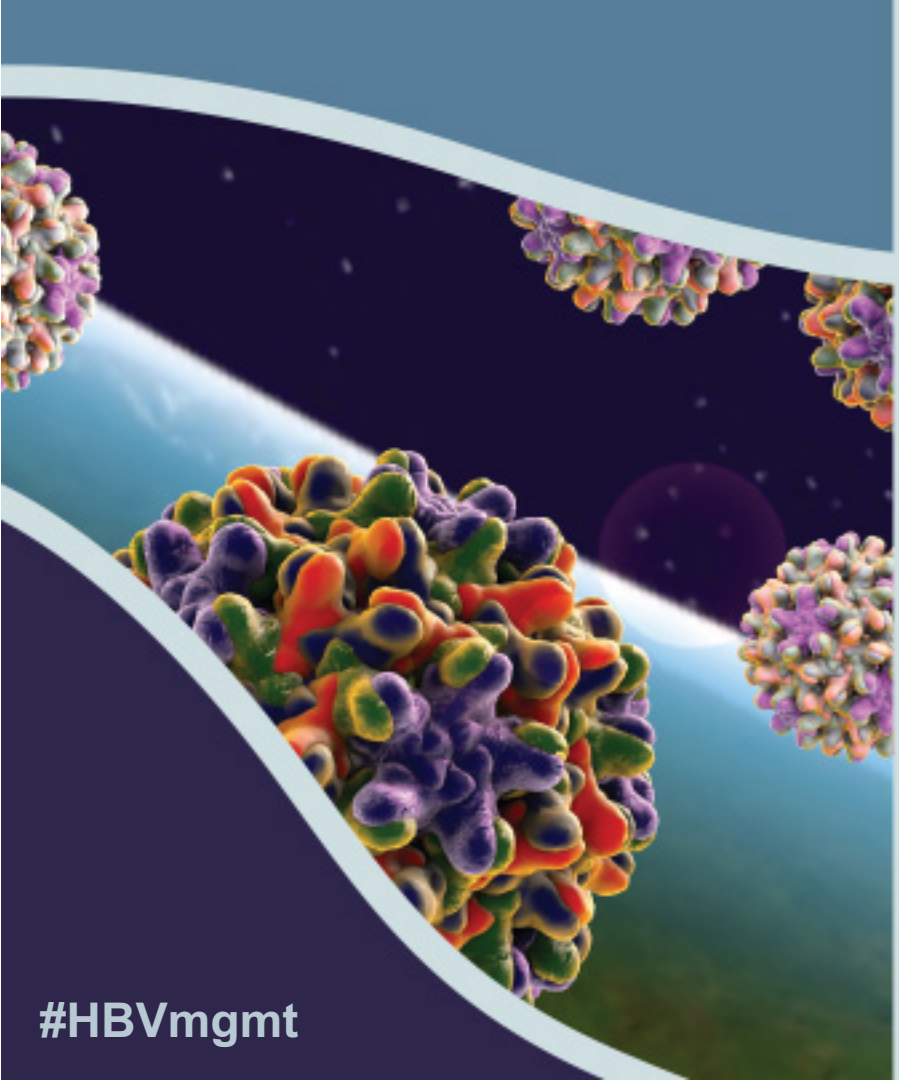


- Utilize serologic markers such as HBsAg, anti-HBs, and anti-HBc to screen for HBV
- Utilize AASLD 2018 Guidance Hepatitis B updates to effectively treat and monitor hepatitis B
- Per AASLD guidance, incorporate the use of tenofovir AF as a first-line HBV therapy in addition to entecavir, tenofovir DF, and peginterferon



Questions & Answers

#HBVmgmt



Thank You!

#HBVmgmt

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3. Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so we can submit your credit to ABIM.

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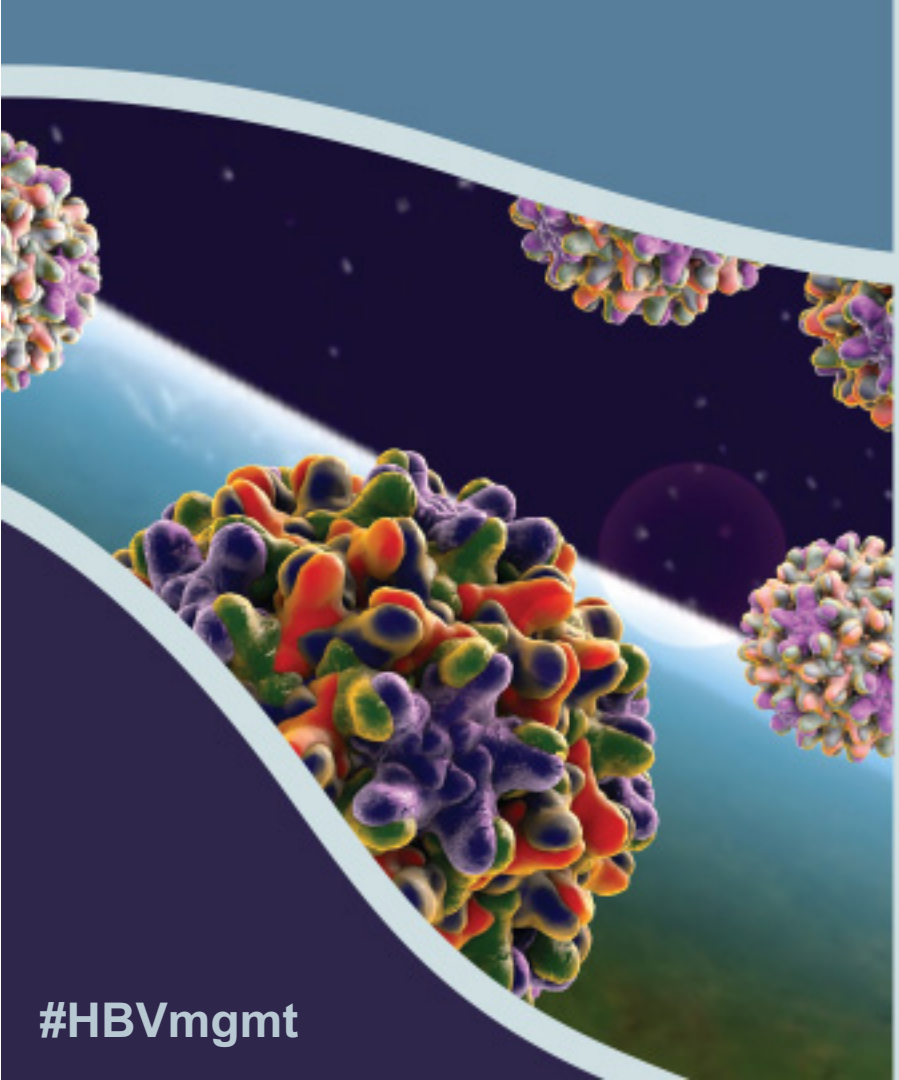
Thank you!



Resource slides

#HBVmgmt

Risk Factors, Prevalence, and Testing for Chronic HBV Infection

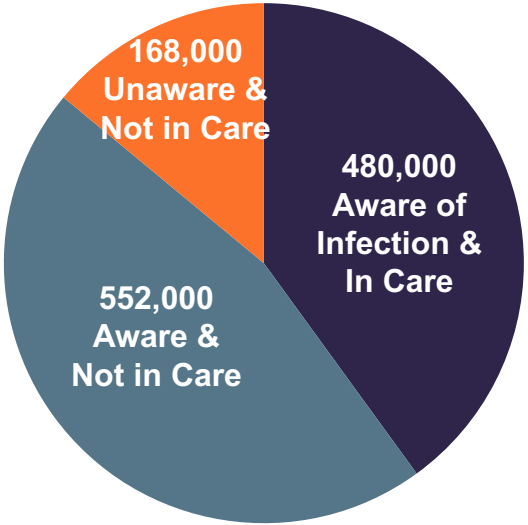
Risk Factor	Prevalence of HBsAg (95% CI), %*	Organizations Recommending Screening		
		USPSTF, 2014	CDC, 2008	AASLD, 2009
Born in region with intermediate-to-high prevalence (≥2%)	4.5–10.3 (2.5–12.9)	✓	✓	✓
Men who have sex with men		✓	✓	✓
Aged <30 y	1.1–2.3 (0–3.0)			
Co-infected with HIV	7 (5–10)			
U.S.-born persons not vaccinated as infants whose parents were born in regions with high prevalence (≥8%)	–	✓	✓	✓
Injection drug users	11.8 (3.5–20)	✓	✓	✓
Co-infected with HIV	7 (6–8)			
HIV-positive persons	4–17 (–)	✓	✓	✓
Household contacts or sexual partners of persons with known HBV infection	3–20 (–)	✓	✓	✓
Pregnant women†	0.38 (–)	✓	✓	✓
Persons requiring immunosuppressive therapy	–		✓	✓
Persons with end-stage renal disease, including those receiving hemodialysis	2.8 (2.3–3.3)		✓	✓
Elevated alanine aminotransferase or aspartate aminotransferase levels	–		✓	✓
Infants born to HBsAg-positive mothers†	1.1 (–)		✓	
Donors of blood, plasma, organs, tissue, or semen	–		✓	
Persons who are sources of blood or body fluids for exposures that might require postexposure prophylaxis‡	–		✓	
Inmates of correctional facilities	1.0–3.7			✓
Persons with HCV infection	1.4 (1.3–1.5)			✓
Persons with multiple sexual partners or a history of sexually transmitted infections	–			✓

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

Impact of National Screening Strategies HIV vs. HBV Care Cascade

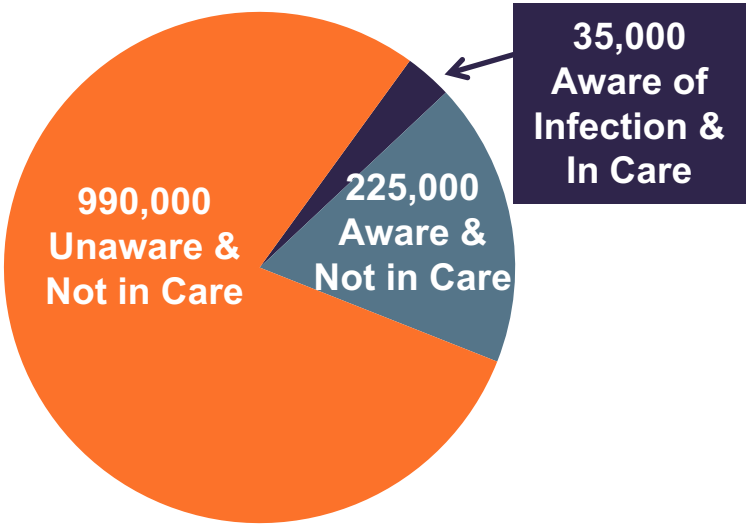
1,200,000 in US with **HIV**[1]

Routine Screening
One time for all adults, as of 2006



1,250,000 in US with Chronic **HBV**[2]

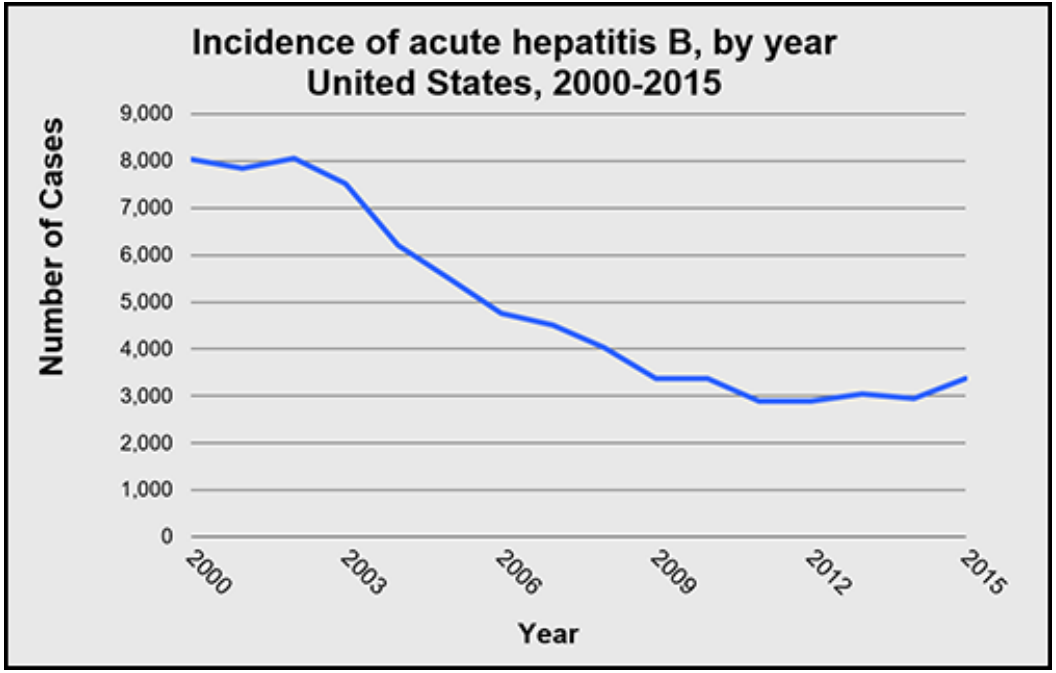
Risk-Based Screening



[1]Cohen C. *J Vir Hepat*. 2011;18:377–383.; [2]CDC. Available at https://www.cdc.gov/vitalsigns/hiv-aids-medical-care/

HBV Incidence

- Since 2014, there has been an increase in the rate of new HBV infections, which is likely due to increasing injection drug use



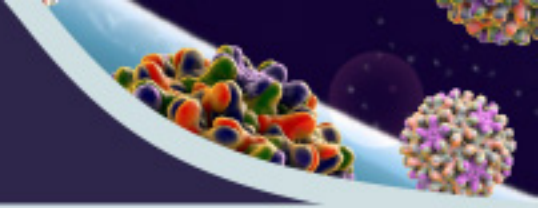
Harris AM, et al. *MMWR Morb Mortal Wkly Rep*. 2016;65(3):47-50.

Use of Hepatitis B Vaccination for Adults with Diabetes Mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

- Hepatitis B vaccination should be administered to unvaccinated adults with diabetes mellitus who are aged 19 through 59 years (recommendation category A; evidence type 2).
- Hepatitis B vaccination may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes mellitus who are aged ≥60 years (recommendation category B; evidence type 2).
- Risk for HBV Infection
  - Continuing outbreaks of acute HBV in long term care facilities
  - Percutaneous exposure to HBV occur as a result of assisted monitoring of blood glucose shared between persons
  - Higher fatality rate among acute HBV-infected persons with diabetes compared to those without diabetes

CDC. *MMWR Morb Mortal Wkly Rep*. 2011 Dec 23;60(50):1709-1711.

Hepatocellular Carcinoma Surveillance



Groups for whom HCC surveillance in recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated

Surveillance recommended		
Population group	**Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)**	**Incidence of HCC**
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemachromatosis and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

HCC surveillance is considered cost-effective if the annual risk of HCC is > = .2% per year.

Bruix J, et al. *Hepatology.* 2011;53(3):1020-1022; Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

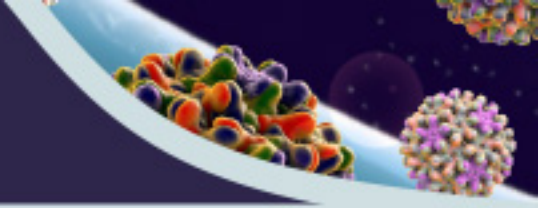
Factors Associated with Cirrhosis and HCC

Host, Viral/Disease, and Environmental Factors Associated With Cirrhosis and HCC

	Cirrhosis	HCC
Host	>40 years of age Male sex Immune compromised	>40 years of age Male sex Immune compromised Positive family history Born in Sub-Saharan Africa
Viral/ disease	High serum HBV DNA (>2,000 IU/mL) Elevated ALT levels Prolonged time to HBeAg seroconversion Development of HBeAg-negative CHB Genotype C	Presence of cirrhosis High serum HBV DNA (>2,000 IU/mL) Elevated ALT Prolonged time to HBeAg seroconversion Development of HBeAg-negative CHB Genotype C
Environmental	Concurrent viral infections (HCV, HIV, and HDV) Heavy alcohol use Metabolic syndrome (obesity, diabetes)	Concurrent viral infections (HCV, HIV, and HDV) Heavy alcohol use Metabolic syndrome (obesity, diabetes) Aflatoxin Smoking

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

Limitations of AFP Alone



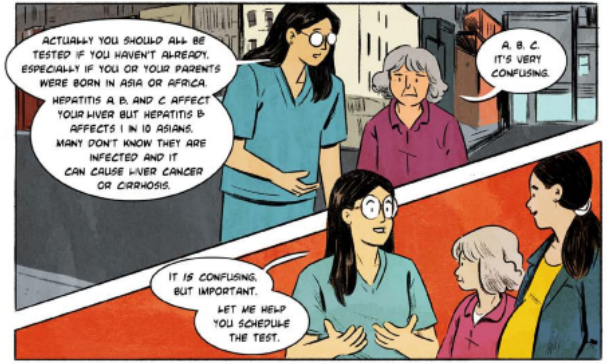
- HCC can produce AFP values ranging from normal to >100,000 ng/mL[1]
  - No correlation with stage or size of tumor
- Limitations of AFP alone:[2]
  - Often increased in patients with chronic liver disease in the absence of cancer
  - May be elevated in patients with HCC, embryonic carcinomas, gastric cancer, and lung cancer
- AFP alone is not recommended except in those circumstances where US is unavailable or cost is an issue.[3]

[1]Koteish A, et al. *J Vasc Interv Radiol.* 2002;13(9 Pt 2):S185-190; [2]Gomaa AI, et al. *World J Gastroenterol.* 2009;15(11):1301-1314; [3] Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.


THE TEST
WRITTEN BY AMY CHU ART BY LOUIE CHIN
WA! WHERE ARE YOU GOING SO FAST? SLOW DOWN!
SORRY, AUNTIE FONG!
©7/2017


MY FIRST DAY WORKING AT THE HEALTH CLINIC AND I'M ALREADY LATE.
SEE, ANDREW? SHE'S A DOCTOR.
NURSE PRACTITIONER, AUNTIE.
SO? I BET SHE CAN'T MAKE BUBBLE TEA LIKE I CAN.


WA, YOU'RE WORKING AT THE HEALTH CLINIC. CAN I ASK YOU A QUESTION?
SURE.
HEPATITIS B. SOMEONE SAID I NEED TO GET TESTED.


ACTUALLY YOU SHOULD ALL BE TESTED IF YOU HAVEN'T ALREADY, ESPECIALLY IF YOU OR YOUR PARENTS WERE BORN IN ASIA OR AFRICA.
HEPATITIS A, B, AND C AFFECT YOUR LIVER BUT HEPATITIS B AFFECTS 1 IN 10 ASIANS. MANY DON'T KNOW THEY ARE INFECTED AND IT CAN CAUSE LIVER CANCER OR CIRRHOSIS.
A, B, C. IT'S VERY CONFUSING.
IT IS CONFUSING, BUT IMPORTANT.
LET ME HELP YOU SCHEDULE THE TEST.

「乙型肝炎 — 事實」

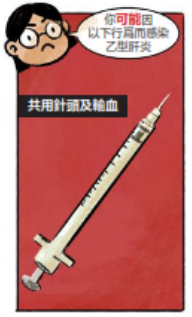

你不會因爲以下行爲而感染乙型肝炎
打噴嚏


分享食物及飲品


咳嗽


接吻

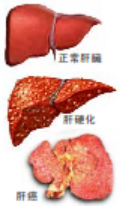

擁抱


你可能因以下行爲而感染乙型肝炎
共用針頭及輸血


分娩時


共用牙刷或剃鬚刀


進行沒有保護措施的性行爲



乙型肝炎

乙型肝炎是由乙型肝炎病毒所引起的嚴重肝臟感染。如沒有接受治療與護理，時間一長，乙型肝炎可能導致肝硬化、肝臟受損甚至肝癌。

即使你沒有感到不適，你仍然應該定期看醫生，瞭解病毒有否損壞你的肝臟。學習如何護肝，保持肝臟健康。

乙型肝炎在亞裔家庭中十分普遍。你的家族病史有助醫生為你選擇最佳的治療方法。如果你的家族成員曾經有以下的病況，請在方格內打勾:

- ☐ 乙型肝炎病毒
- ☐ 乙型肝炎病毒，並正在或曾經使用藥物
- ☐ 肝癌
- ☐ 肝硬化

把你的肝臟受到感染這個事實坦誠地告知家人和你關心的人，並鼓勵他們接受測試及注射疫苗。乙型肝炎是可以預防和治療的。

乙型肝炎的護理：

- 遵循預約去看醫生。
- 按照醫生的指示做化驗檢查。
- 善用這張卡，記錄你的健康情況。
- 按照醫生的處方服藥。
- 如果你打算或正在服食中草藥和其他藥物，請告訴你的醫生。因為它們可能對肝臟有害。
- 切勿飲酒，酒能傷肝。

保護你心愛的人：

乙型肝炎是透過血液與體液傳播的。

- 在進行性行為時，請使用安全套。
- 請勿與任何人共用牙刷或剃刀。

如你有任何疑問，請向醫生查詢。

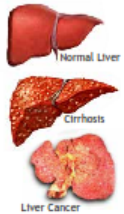
姓名：
Name: _____

診症號碼：
PID: _____

定期去看醫生是很重要的。謹請按照預約時間做乙型肝炎復診，並帶上這張卡。醫生會把你的測試結果記錄在卡上，讓你可以監察肝臟的健康狀況。

Seeing your doctor regularly is important. Remember to come to your scheduled hepatitis B follow up visits. Bring this card with you. Your doctor will record your lab results on the card. This will help monitor the health of your liver.

Charles B. Wang Community Health Center
王 far 康 社 區 醫 療 中 心



Hepatitis B

Hepatitis B is a serious liver infection caused by the hepatitis B virus. If not cared for or treated, over time hepatitis B can lead to cirrhosis (liver scarring), liver damage and liver cancer.

Even if you don't feel sick, you should still see your doctor regularly. You need to find out if the virus is damaging your liver. Learn how to care for your liver, and keep it healthy.

Hepatitis B is very common in Asian families. Your family history is helpful to your doctor to decide treatment for you. Check all the conditions that anyone in your family has had:

- ☐ Hepatitis B virus
- ☐ Hepatitis B virus and is/was on medication
- ☐ Liver cancer
- ☐ Cirrhosis

Be open and tell your family and loved ones about your liver infection. Encourage them to get tested and vaccinated too. Hepatitis B can be prevented and treated.

Tips on how to care for yourself:

- Come to your scheduled appointments.
- Get the lab tests your doctor orders.
- Use this card to keep track of your health condition.
- Take medication as prescribed by your doctor.
- Do not take any herbal products or medicine without telling your doctor. They may damage your liver.
- Do not drink alcohol. It can damage your liver.

Protect your loved ones.

Hepatitis B can spread through blood and body fluids.

- Use condoms when you have sex.
- Do not share your toothbrush or razor with anyone.

Talk to your doctor about any concerns.

心肝寶貝
悉心保養肝臟
你的個人紀錄

B Healthy

Keeping your liver healthy

Your personal record

乙型肝炎病毒(HBV)血液測試結果
YOUR HEPATITIS B VIRUS (HBV) BLOOD TEST

日期 Date	乙肝表面抗原 HBsAg Hepatitis B Surface Antigen	如果這項測試結果呈陽性(+)，表明你已經感染了乙肝病毒。 If this test result is positive (+), it means that you are infected with the hepatitis B virus.
日期 Date	乙肝表面抗體 HBsAb Hepatitis B Surface Antibody	如果這項測試結果呈陽性(+)，表明你對乙肝病毒產生免疫力。 If this test result is positive (+), it means that you are immune to the hepatitis B virus.
日期 Date	乙肝 "e" 抗原 HBeAg Hepatitis B "e" Antigen	如果這項測試結果呈陽性(+)，通常表明你血液內的病毒數量較高，你肥病毒傳染他人的機會較高。當"e"抗原呈陽性，通常稱為「大三陽」。 If this test is positive (+), it often means the amount of virus in your blood is higher. You may be more likely to spread the virus to others. When "e" antigen is +, it is often described as "big three positive."
日期 Date	乙肝 "e" 抗體 HBeAb Hepatitis B "e" Antibody	如果這項測試結果呈陽性(+)，表明你的血液內病毒數量較低。當"e"抗體呈陽性（而"e"抗原呈陰性），通常稱為「小三陽」。 If this test is positive (+), it can mean that the amount of virus in your blood is lower. When "e" antibody is + ("e" antigen is -), it is often described as "small three positive."

接受檢查，瞭解肝臟狀況
TESTS TO CHECK THE HEALTH OF YOUR LIVER

日期 Date	轉氨酶水平 ALT (U/L)	肝功能測試能夠衡量你的肝臟發炎的程度。假如結果呈上升，就表明你的肝臟已經受到影響。 Liver function tests measure inflammation in your liver. If the result is elevated, it means your liver is affected.
日期 Date	乙肝病毒含量 HBV Viral Load (IU/mL)	這項測試能夠顯示你血液內乙型肝炎的病毒含量。如果病毒含量開始上升，醫生會進一步監察你的健康狀況。 This test shows how much hepatitis B virus you have in your blood. If your viral load starts to increase, your doctor will need to monitor you carefully.
日期 Date	纖維化評分 Fibrosis Score	它估計肝臟中的瘢痕形成量，數值範圍由F0（正常）到 F4（肝硬化）。 It estimates the amount of scarring in the liver from a scale of F0 (normal)- F4 (cirrhosis).
日期 Date	超聲波 Ultrasound	這能夠幫助檢測肝硬化或肝癌。 It can help detect cirrhosis or cancer in the liver.
日期 Date	甲胎蛋白 AFP (ng/mL)	這項測試能夠幫助檢測肝癌。 This test can help detect liver cancer.
日期 Date	甲型肝炎抗體 Hepatitis A Ab (Hepatitis A Antibody)	如果這項測試結果呈陽性(+)，表明你對甲肝病毒產生免疫力。 If this test result is positive (+), it means that you are immune to the hepatitis A virus.
日期 Date	丙型肝炎 Hepatitis C	如果這項測試結果呈陽性，表明你感染了丙型肝炎病毒。 If this test is positive, it means that you are infected with the hepatitis C virus.

治療記錄

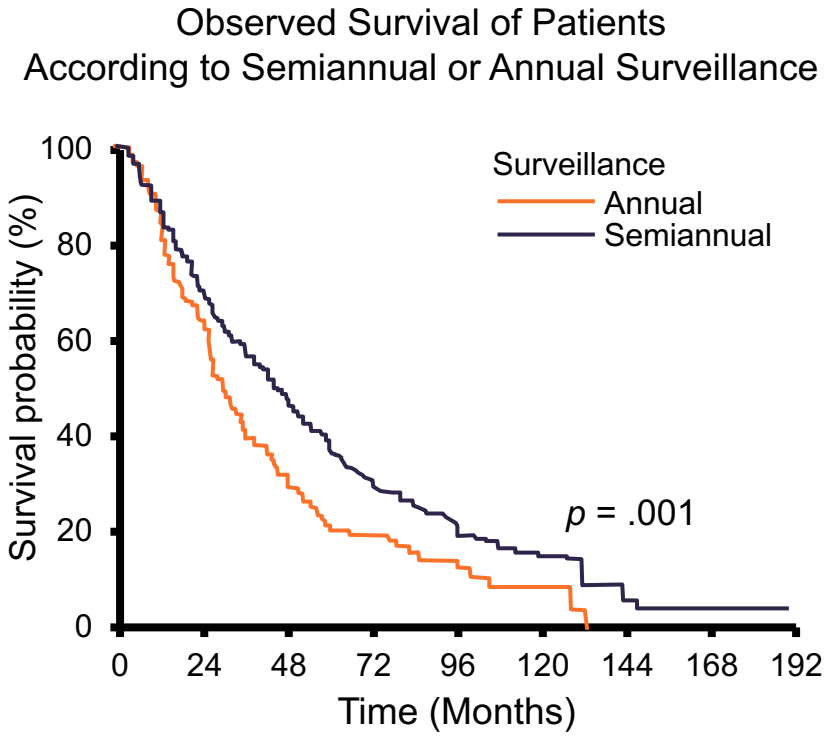
醫生將根據你的檢查報告、健康情況與家族史來決定你是否需要治療。

TRACK YOUR TREATMENT

Your doctor will decide if treatment is needed based on your test results, health condition and family history.

藥物名稱 Medication Name	劑量 Dosage	開始日期 Start Date	結束日期 End Date

How Often Should Patients Undergo Surveillance?



Santi V, et al. *J Hepatol*. 2010;53(2):291-297.

- Observed survival:
  - 45 months with semiannual surveillance
  - 30 months with annual surveillance
- Single small (≤2 cm) tumors were 5-fold more frequent in semiannual surveillance group

Goals of HBV Treatment

- Impact the natural history of HBV
- Prevent cirrhosis, HCC, death

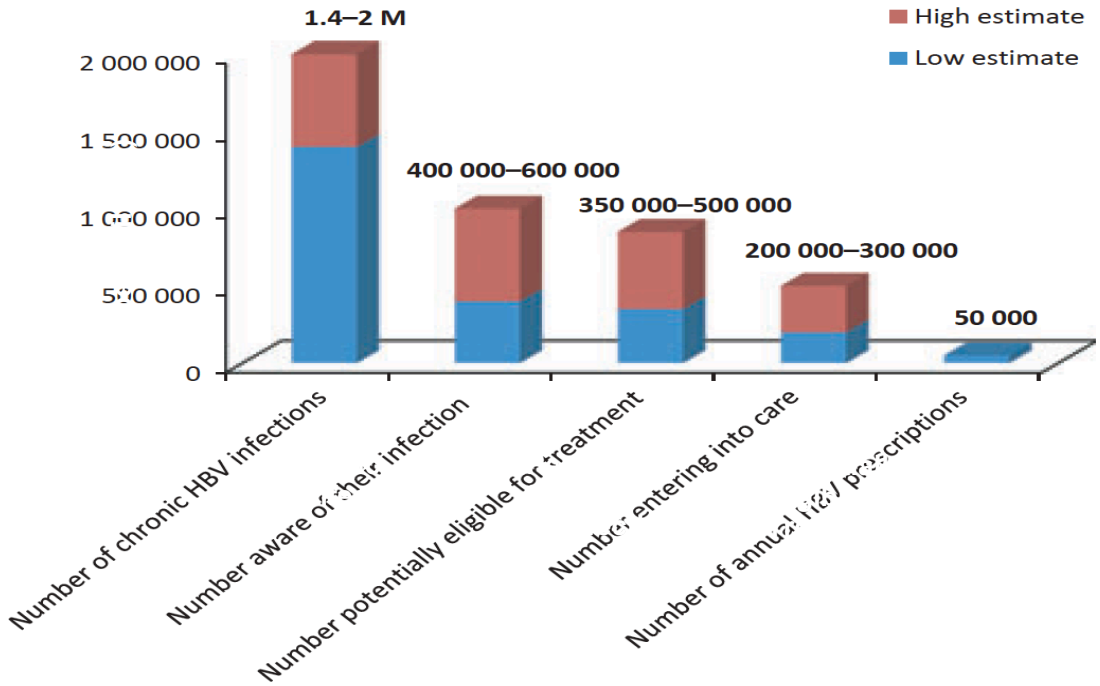
Treatment of Persons With Immune-Active CHB

Recommendations

1A. The AASLD recommends antiviral therapy for adults with immune-active CHB (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications.

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599; Terrault NA, et al., *Hepatology*. 2016;63(1):261-268; Lok ASF, et al. *Hepatology*. 2004;39:857-861; Keeffe EB, et al. *Clin Gastroentrol Hepatol*. 2006;4:936-962.

Undertreatment of HBV



< 5% of HBV patients are on Rx

Cohen C, et al. *J Viral Hepat*. 2011;18(6):377-383.

FDA-Approved Treatments for HBV

Nucleosides/Nucleotides		
Tenofovir Alafenamide (TAF)	2016	Preferred
Tenofovir Disoproxil Fumarate (TDF)	2008	Preferred
Telbivudine	2006	Nonpreferred
Entecavir	2005	Preferred (unless previous history of lamivude resistance)
Adefovir dipivoxil	2002	Nonpreferred
Lamivudine	1998	Nonpreferred
Interferons		
Peginterferon alfa-2a	2005	Preferred
Interferon alfa-2b, recombinant	1992	Preferred

Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599.

Tenofovir Disoproxil Fumarate (TDF)

Advantages

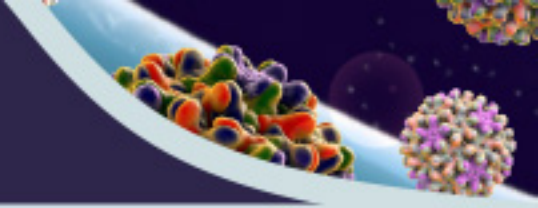
- Potent
- Effective in suppressing HBV in wild type and patients with lamivudine, telbivudine and entecavir resistance
- Pregnancy category B
- Antiviral activity against both HBV and HIV

Disadvantages

- Nephrotoxicity
- Bone loss

Martin P, et al. *Clin Gastroenterol Hepatol.* 2015;13:2071-2087; Buti M, et al. *Lancet Gastroenterol Hepatol.* 2016;1:196-206; Chan HL, et al. *Lancet Gastroenterol Hepatol.* 2016;1:185-195.

Entecavir (ETV)



Advantages:

- Potent
- Effective against wild type and adefovir-resistant
- Low rate of drug resistance
- Less nephrotoxic than adefovir, tenofovir

Disadvantages:

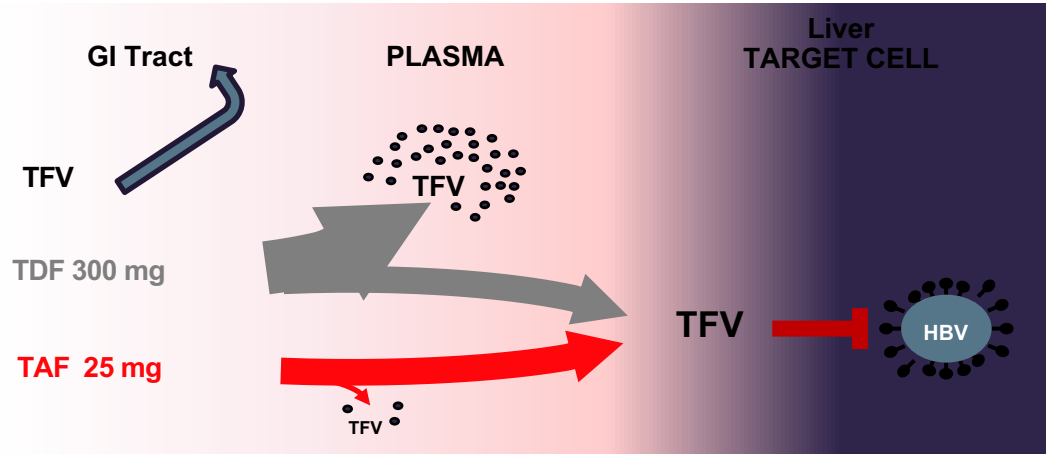
- Can lead to HIV resistance
- Increased risk of resistance in those with lamivudine-resistance

Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2008;6(12):1315-1341.

Tenofovir Alafenamide (TAF)

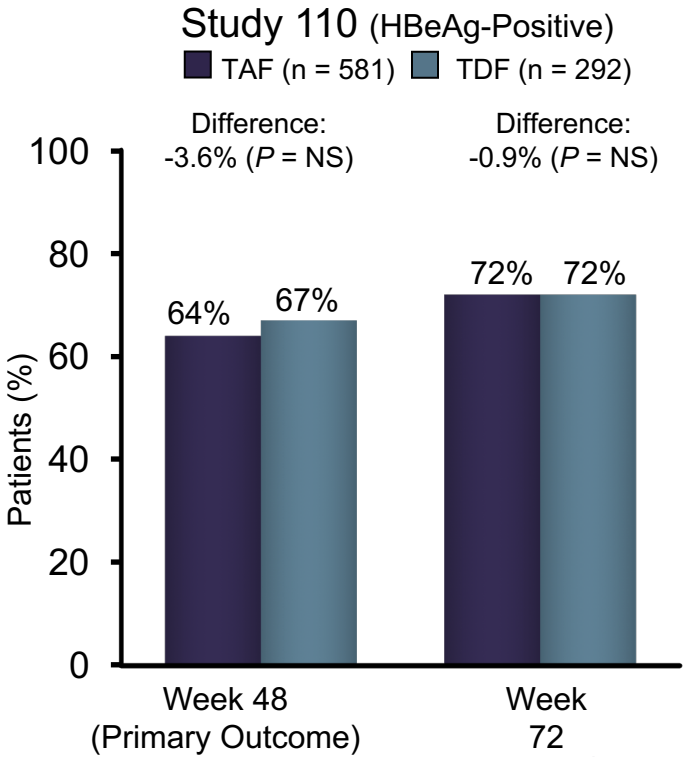
- Prodrug of tenofovir DF which is metabolized to active drug TFV
- TAF is more stable in plasma/tissues
- TDF but not TAF actively enters renal tubular cells via organic anion transporters
- TAF has a lesser effect on the proximal renal tubule

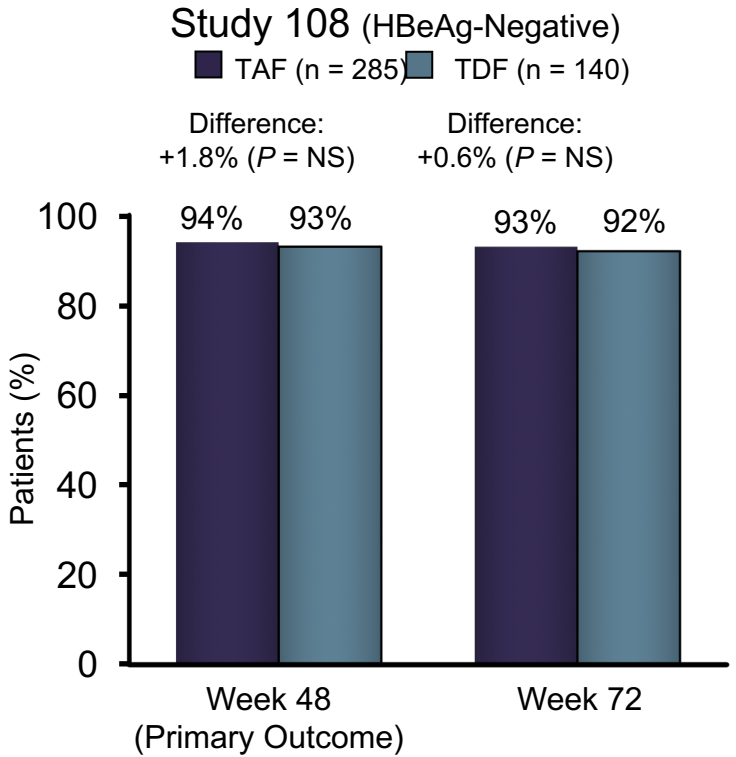
90% Lower TFV Levels in Plasma Minimizes Renal and Bone Effects While Maintaining High Potency for Suppressing HIV



Buti M, et al. *J Infect Dis*. 2017;216(Suippl 8):S792-S796.

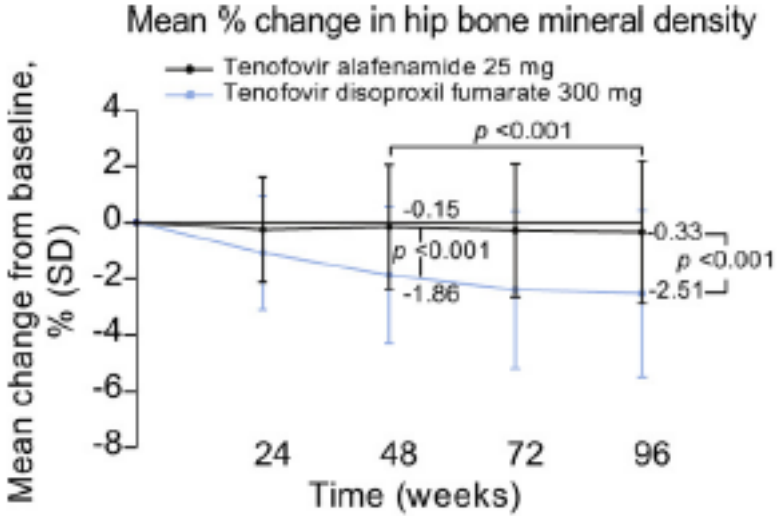
Studies 110 and 108: HBV DNA <29 IU/mL With Tenofovir AF vs. DF

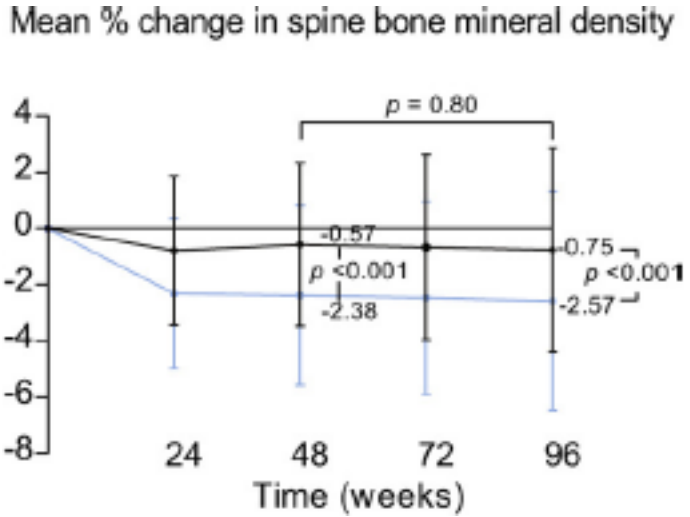




Seto W-K, et al. *Hepatology*. 2016;64(suppl S1):35A. Abstract 67. Buti M, et al. *Lancet Gastroenterol Hepatol*. 2016;1:196-206; Chan HL, et al. *Lancet Gastroenterol Hepatol*. 2016;1:185-195.

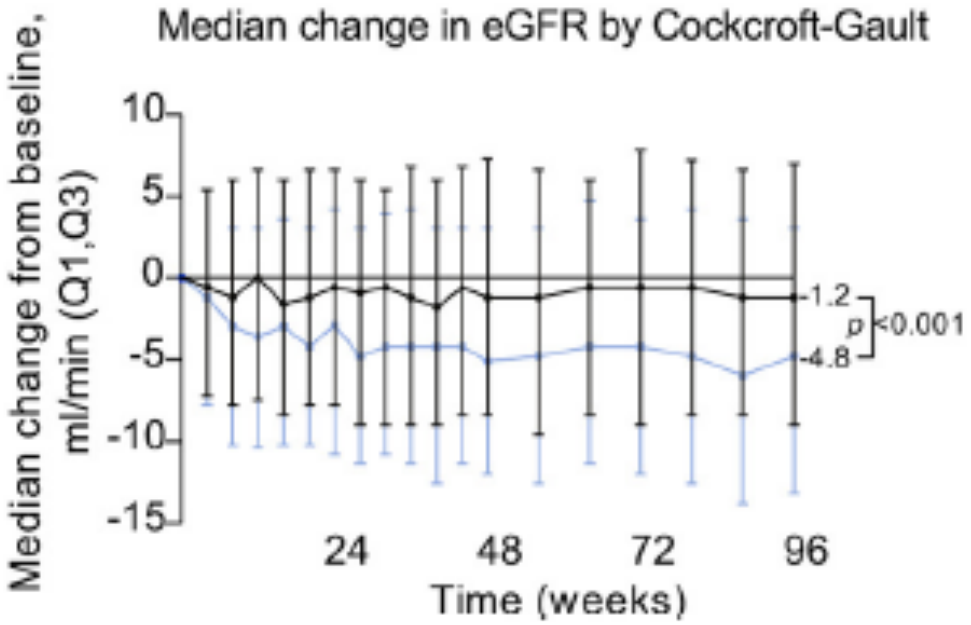
TAF vs. TDF on Hip and Spine Bone Mineral Density





Argawal K, et al. *J Hepatol*. 2018;68(4):672-681.

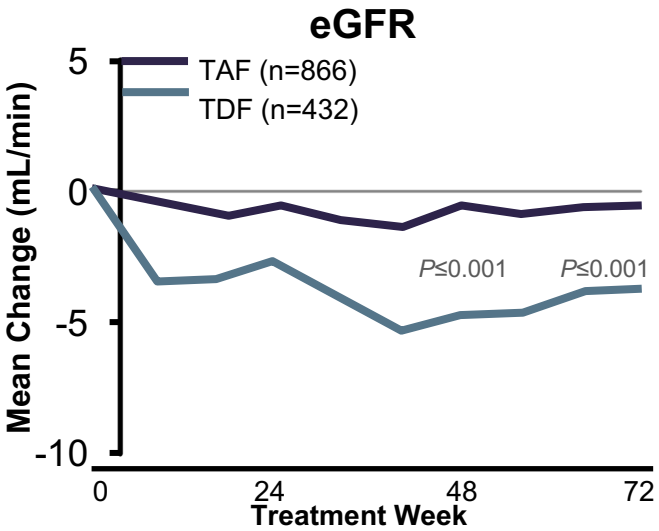
Smaller Median Decreases with TAF vs. TDF eGFR

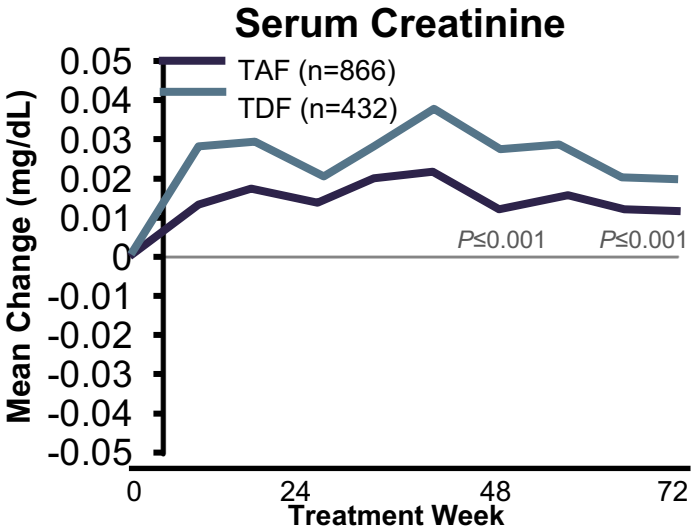


eGFR, estimated glomerular filtration rate

Argawal K, et al. *J Hepatol*. 2018;68(4):672-681.

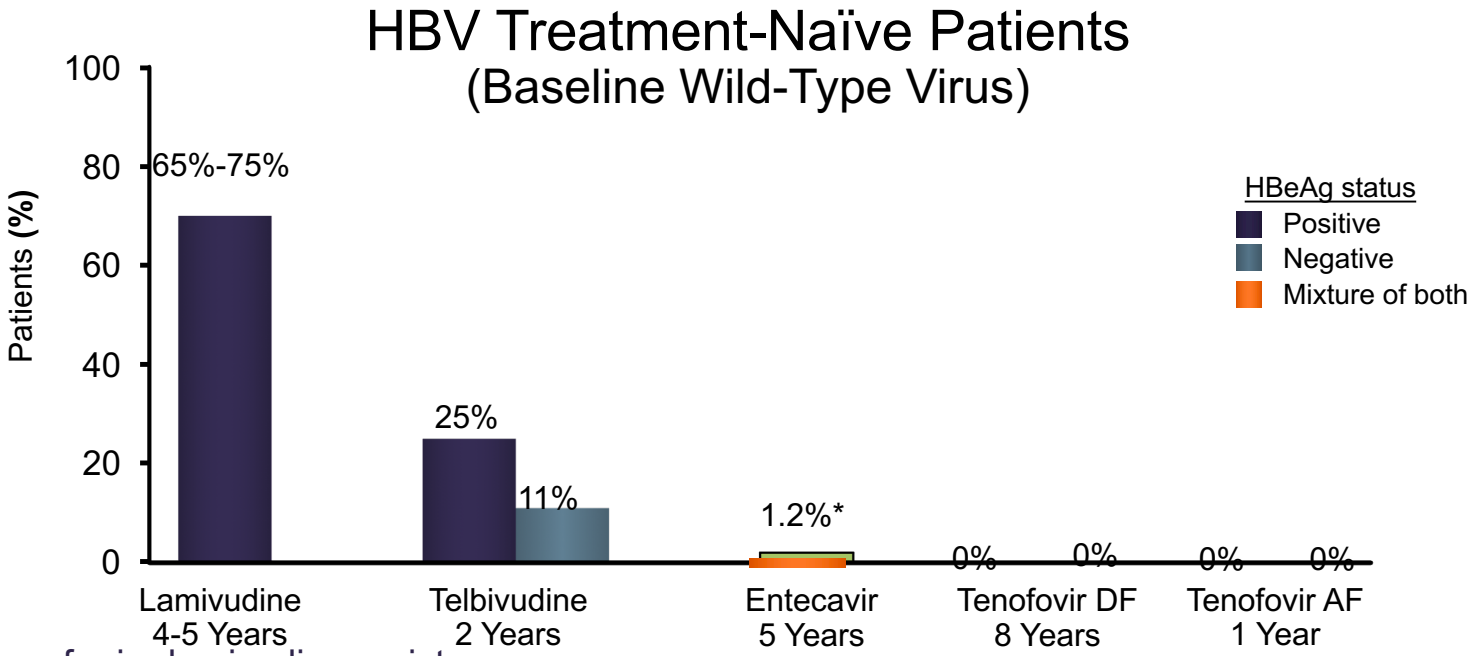
TAF vs. TDF on Renal Safety





Agarwal K, et al. *Hepatology.* 2016;64(suppl S1):910A. Abstract 1844.

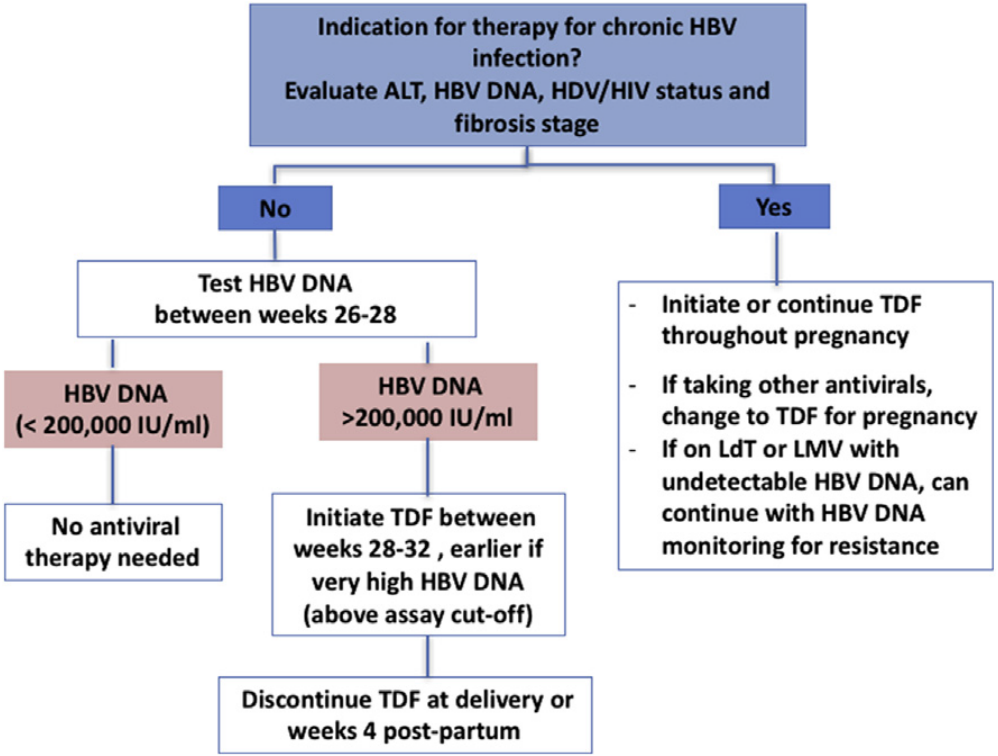
Cumulative Incidence of Drug Resistance During HBV Therapy



*Absence of prior lamivudine resistance.

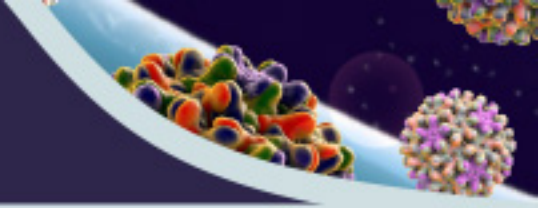
Martin P, et al. *Clin Gastroenterol Hepatol*. 2015;13:2071-2087.; Buti M, et al. *Lancet Gastroenterol Hepatol*. 2016;1:196-206.; Chan HL, et al. *Lancet Gastroenterol Hepatol*. 2016;1:185-195.

Management Algorithm of Chronic HBV Infection During Pregnancy



Zhou K, et al. *Best Prac & Res Clin Gastroenterol* 2017;31:311-320.

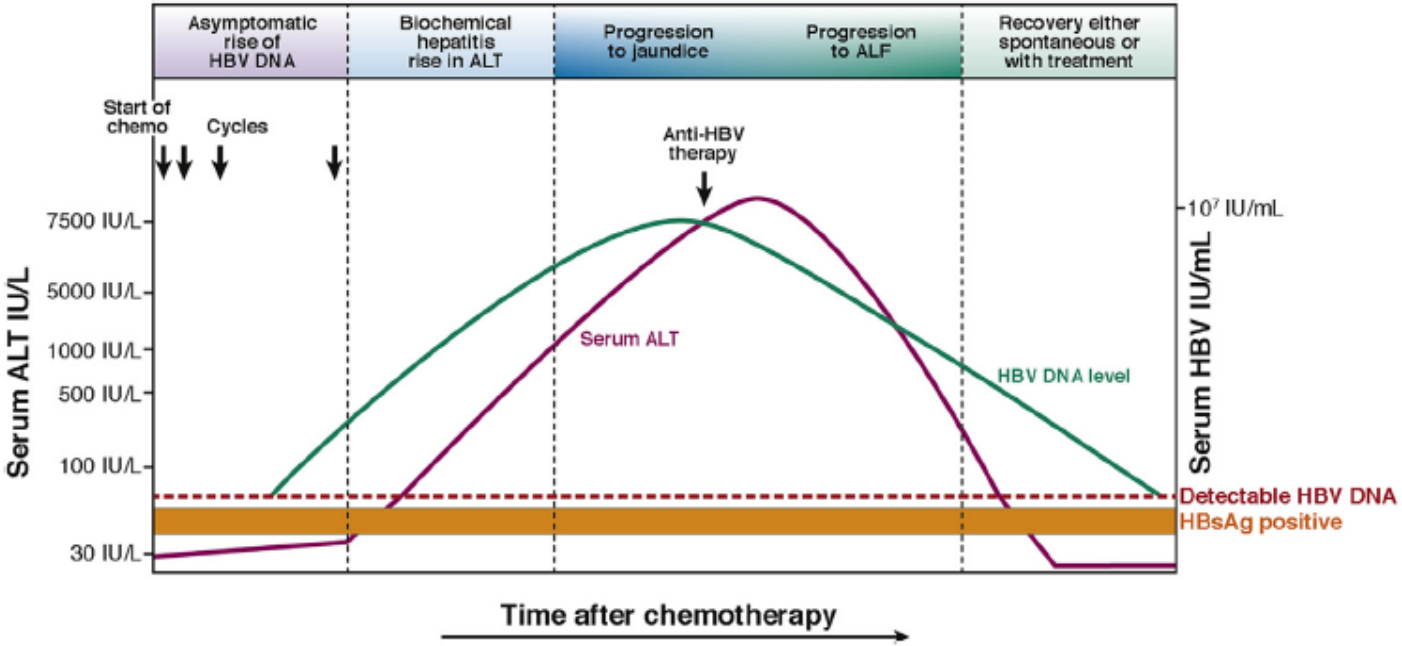
Long-Term Follow-Up and Management



- Multidisciplinary approaches for monitoring adherence
- Periodic Surveillance for Hepatocellular Carcinoma: AASLD Guidelines
  - Hepatitis B carriers at high risk
    - All cirrhotic hepatitis B carriers
    - Family history of hepatocellular carcinoma
    - Asian males ≥40 years of age
    - Asian females ≥50 years of age
    - Africans ≥20 years of age
    - High HBV DNA levels and ongoing hepatic inflammatory activity
    - Platelet count <170,000/μL
  - Liver ultrasound surveillance
    - HBV guidelines: every 6 to 12 months

Bruix J, et al. *Hepatology.* 2011;53:1020-1022.

Example Course of HBV Reactivation



Loomba R, et al. *Gastroenterology.* 2017;152:1297-1309.

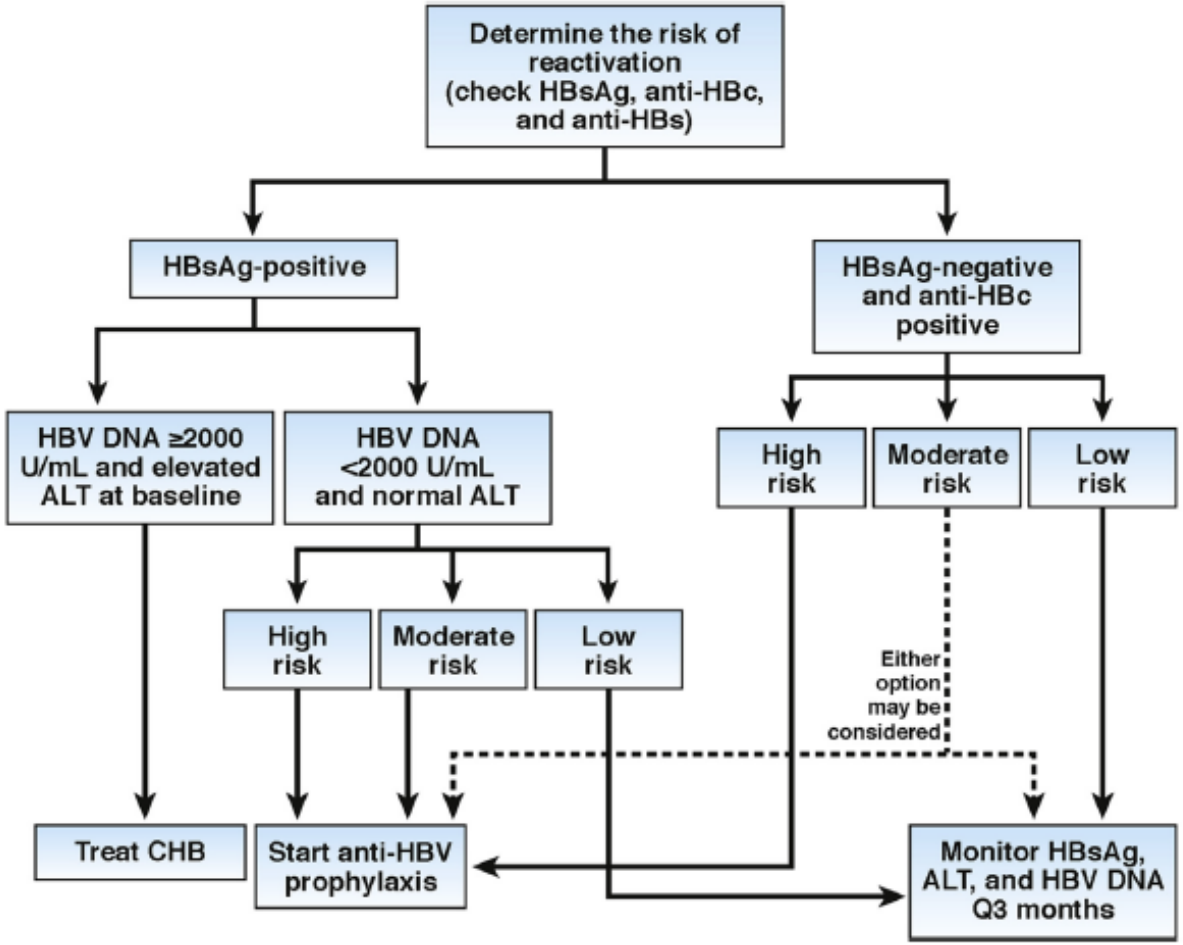
Reactivation Risk

HBsAg Pos	Drug
HIGH RISK	B-cell depleting agents: rituximab… High Dose Corticosteroids (>20mg x 4weeks) Anthracyclines:doxorubicin and epirubicin Potent TNF inhibitors: infliximab,adalimumab, certolizumab, golimumab Local therapy for HCC including TACE
MODERATE RISK	Less potent TNF inhibitors: etanercept Moderate Dose Corticosteroids Systemic chemotherapy Cytokine-based therapies: abatacept, ustekinumab, mogomulizumab, natalizumab, vedolizumab Immuophilin inh: cyclosporine Tyrosine-kinase inhibiors: imatinib, nilotinib Proteasome inhibitors such as bortezomib
LOW RISK	Antimetabolites: AZA, 6-MP, methotrexate Short term low dose steroids Intra-articular steroid injections

HBsAg NEG, Anti-HBc POS	Drug
HIGH RISK	B-cell depleting agents: rituximab…
MODERATE RISK	High Dose Corticosteroids (>20mg x 4 wks) Anthracyclines:doxorubicin and epirubicin Potent TNF inhibitors: infliximab, adalimumab, certolizuman, golimumab Local therapy for HCC including TACE Systemic chemotherapy Less potent TNF inhibitors: etanercept Cytokine-based therapies: abatacept, ustekinumab, mogomulizumab, natalizumab, vedolizumab Immuophilin inh: cyclosporine Tyrosine-kinase inhibiors including imatinib and nilotinib Proteasome inhibitors such as bortezomib Histone Deacetylase Inhibitors
LOW RISK	Moderate/Low Dose Corticosteroids Antimetabolites: AZA, 6-MP, methotrexate

Loomba R, et al. *Gastroenterology.* 2017;152:1297-1309.

Who Is At Risk for Reactivation?



Loomba R, et al. *Gastroenterology.* 2017;152:1297-1309.