Project ECHO®
Chronic Liver Disease Foundation
New Jersey

HBV Alliance:

Expert Recommendations on Managing Patients with Chronic Hepatitis B

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Current Management of Chronic Hepatitis B

AASLD 2018 Hepatitis B Guidance

- Previous CHB guidelines were published in 2009 and 2016
- AASLD guidelines published Feb. 2018, include updates on:
  - Treatment
  - Screening, counseling, and prevention
  - Specialized virological and serological tests
  - Monitoring untreated patients
  - Treatment in special populations
- Developed by consensus of expert panel based on analysis of published literature, WHO guidance and authors experience
- Lead author, Norah A Terrault, MD, UCSF Medical Center

AASLD 2018 Hepatitis B Guidance: General Considerations

- **Preferred Initial Treatment:**
  - Peg-IFN, entecavir, tenofovir (TDF) or tenofovir (TAF)
  - Consider TAF or entecavir in patients with or at risk for renal dysfunction or bone disease
- **Additional treatment considerations:**
  - Lack of resistance in long term use a primary consideration
  - TAF not recommended for CKD patients with creatinine clearance < 15mL/min unless on hemodialysis
  - Previous LAM resistance: entecavir not recommended
  - Family planning: TDF preferred during pregnancy
  - HBV genotype: A and B more likely to achieve eAg and sAg loss with peg-IFN x 48 weeks
  - Medication cost
  - Entecavir and TDF require dose adjustment in patients with cc < 50mL/min; TAF same untill Ccr < 15mL/min unless hemodialysis
  - Treatment with antivirals does not eliminate risk of HCC, surveillance must continue

Criteria Used for Treatment Candidacy in Treatment Guidelines

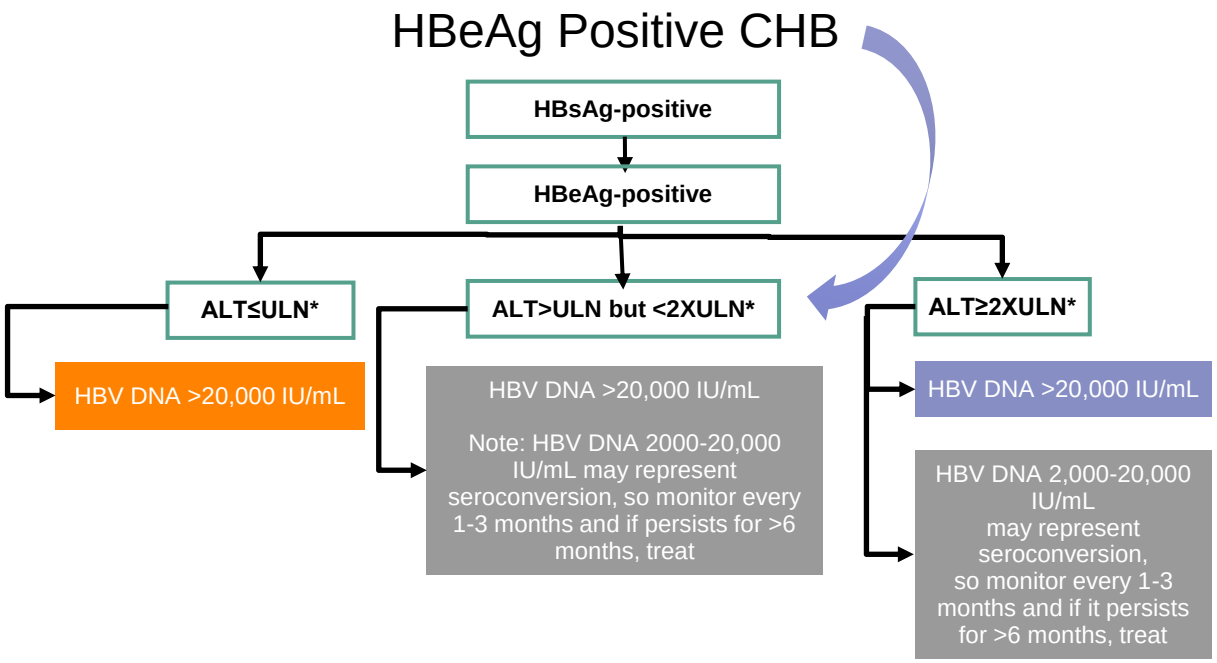
- Level of HBV DNA
- ALT levels
- HBeAg status (positive or negative)
- Liver histology
- *Age*
- *Ethnicity*
- *Family history of liver cancer*
- *Extrahepatic manifestations*

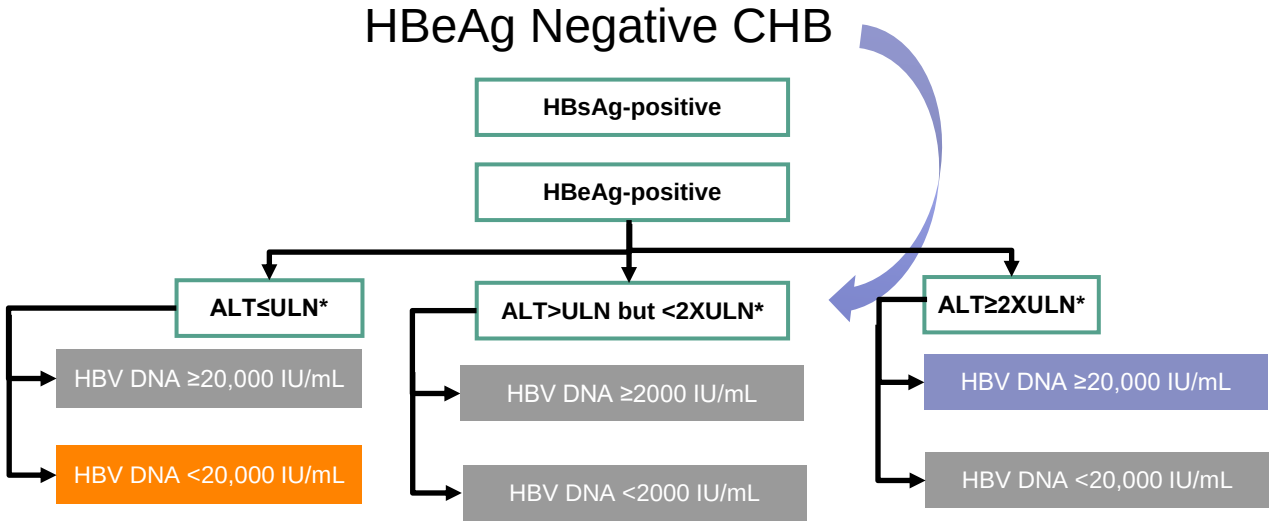
Management of CHB in Patients Without Cirrhosis: There are Differences Among the Guidelines

Threshold for Treatment	APASL[1] (2015)	EASL[2] (2017)	US Algorithm[3] (2018)	AASLD[4] (2018)
HBV DNA, IU/mL				
• HBeAg positive	> 20,000	> 2000	≥ 2000	> 20,000
• HBeAg negative	> 2000	> 2000	≥ 2000	≥ 2000
ALT	> 2 x ULN	> ULN	> ULN	≥ 2 x ULN
• ULN for males	40 IU/mL	40 IU/L	30 IU/L	35 U/L
• ULN for females	40 IU/mL	40 IU/L	19 IU/L	25 U/L

1. Sarin. *Hepatol Int*. 2016;10:1; 2. EASL. *J Hepatol*. 2017;67:370; 3. Martin. *Clin Gastroenterol Hepatol*. 2018;13:2071; 4. Terrault. *Hepatology*. 2018;67:1560.

AASLD Guidelines: A Detailed Look





Exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT >ULN excluded and elevation persists, treat, especially if age>40.

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg every 6-12 months.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months. If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT>ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

*The upper limit of normal for ALT in healthy adults is reported to be 29 to 33 U/L for males and 19 to 25 U/L for females. An upper limit of normal for ALT of 35 U/L for males and 25 U/L for females is recommended to guide management decisions.

Terrault NA, et al. *Hepatology*. [online ahead of print February 5, 2018]. doi: 10.1002/hep.29800.

AASLD 2018 Hepatitis B Guidance: A Synthesis

- **Treatment Recommendations of Patients with Chronic Hepatitis B**
  - Immune active CHB: elevated ALT 2x ULN males >35, females > 25
  - HBV DNA > 2,000 IU/mL, HBeAg negative
  - HBV DNA > 20,000 IU/mL, HBeAg positive
  - Or evidence of significant histologic disease
- **Factors for consideration to treat immune-active CHB when above criteria are not present**
  - Age > 40, associated with higher likelihood of histologic disease
  - Family Hx of cirrhosis or HCC
  - Previous treatment: prior NA exposure is a risk for drug resistance
  - Presence of extrahepatic manifestations, treatment indication **independent** of liver disease severity
  - Presence of cirrhosis

2017 EASL HBV Guideline Updates

Key Updates: Treatment Indications

Primarily based on HBV DNA, serum ALT and severity of liver disease

Recommended treatment indications:

Should be treated

- **Patients with HBeAg(+) or (-) CHB** (HBV DNA >2000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation/fibrosis)
- **Patients with cirrhosis**, any detectable HBV DNA, regardless of ALT level
- **Patients with HBV DNA >20,000 IU/mL and ALT>2x ULN**, regardless of severity of histological lesions

May be treated

- Patients with HBeAg(+) CHB infection (persistently normal ALT and high HBV DNA levels) **>30 years old,** regardless of severity of liver histological lesions

Can be treated

- Patients with HBeAg(+) or (-) CHB infection and **family history** of HCC or cirrhosis and extrahepatic manifestations, even if typical treatment indications are not fulfilled

EASL CPG HBV. *J Hepatol.* 2017;67:370–98.

Treatment of Compensated Cirrhosis

AASLD	EASL	APASL
Any level of viremia regardless of ALT	Any detectable HBV DNA level regardless of ALT	HBV DNA > 2000 IU/mL if normal ALT; HBV DNA detectable if elevated ALT

Terrault N et al. *AASLD Guidance*. 2018;67:1560-99; EASL. *J Hepatol.* 2017;67(2):370-398 2017 Aug;67(2):370-398;
Sarin SK et al. *Hepatol Int*. 2016;10:1–98.

Guidelines on Treatment of HBV With Decompensated Cirrhosis

AASLD	EASL	APASL
Treat all decompensated HBsAg+ adults with antiviral therapy indefinitely	Treat irrespective of the level of HBV replication, and assess for liver transplantation	Treat for any detectable level of HBV DNA

- Peg-IFN use is contraindicated with decompensation
- TAF has not been studied in decompensated cirrhotics, use entecavir or TAF
- Consider OLT referral, monitor for lactic acidosis

Terrault N et al. *AASLD Guidance*. 2018;67:1560-99; Sarin SK et al. *Hepatol Int*. 2016;10:1–98.

Monitoring Patients Treated With ETV, TDF or TAF

- Periodical monitoring and long-term surveillance is required in patients

Recommendations (monitoring)
ALT and serum HBV DNA* • All patients treated with NAs q3-4 months for first year then q6 months
Renal monitoring† • Patients at risk of renal disease treated with any NA • All patients treated with TDF, regardless of renal risk
Switch to ETV or TAF‡ • Should be considered in patients on TDF at risk of development of and/or with underlying renal or bone disease
Recommendations (long-term surveillance)
HCC surveillance recommended • All patients under effective long-term NA therapy
HCC surveillance mandatory • All patients with cirrhosis or with moderate or high HCC risk scores at the onset of NA therapy

l*Liver function tests should be performed every 3–4 months during the first year and every 6 months thereafter. Serum HBV DNA should be determined every 3–4 months during the first year and every 6–12 months thereafter; †Including at least eGFR and serum phosphate levels. Frequency of renal monitoring can be every 3 months during the first year and every 6 months thereafter, if no deterioration. Closer renal monitoring is required in patients who develop CrCl <60 ml/min or serum phosphate evels <2 mg/dl; ‡Depending on previous LAM exposure.

EASL CPG HBV. *J Hepatol.* 2017;67:370–98.

AASLD and EASL Guidelines on Stopping NA's

AASLD

- Indefinite therapy for **HBeAg-negative** patients unless there is a compelling rationale for stopping.
- In non-cirrhotic **HBeAg-positive patients** who achieve stable HBeAg seroconversion, undetectable HBV DNA, normal ALT for at least 12 months of consolidation therapy. "Not known if a longer duration of consolidation therapy would reduce rates of relapse." Alternative approach: treat until HBsAg loss.

EASL

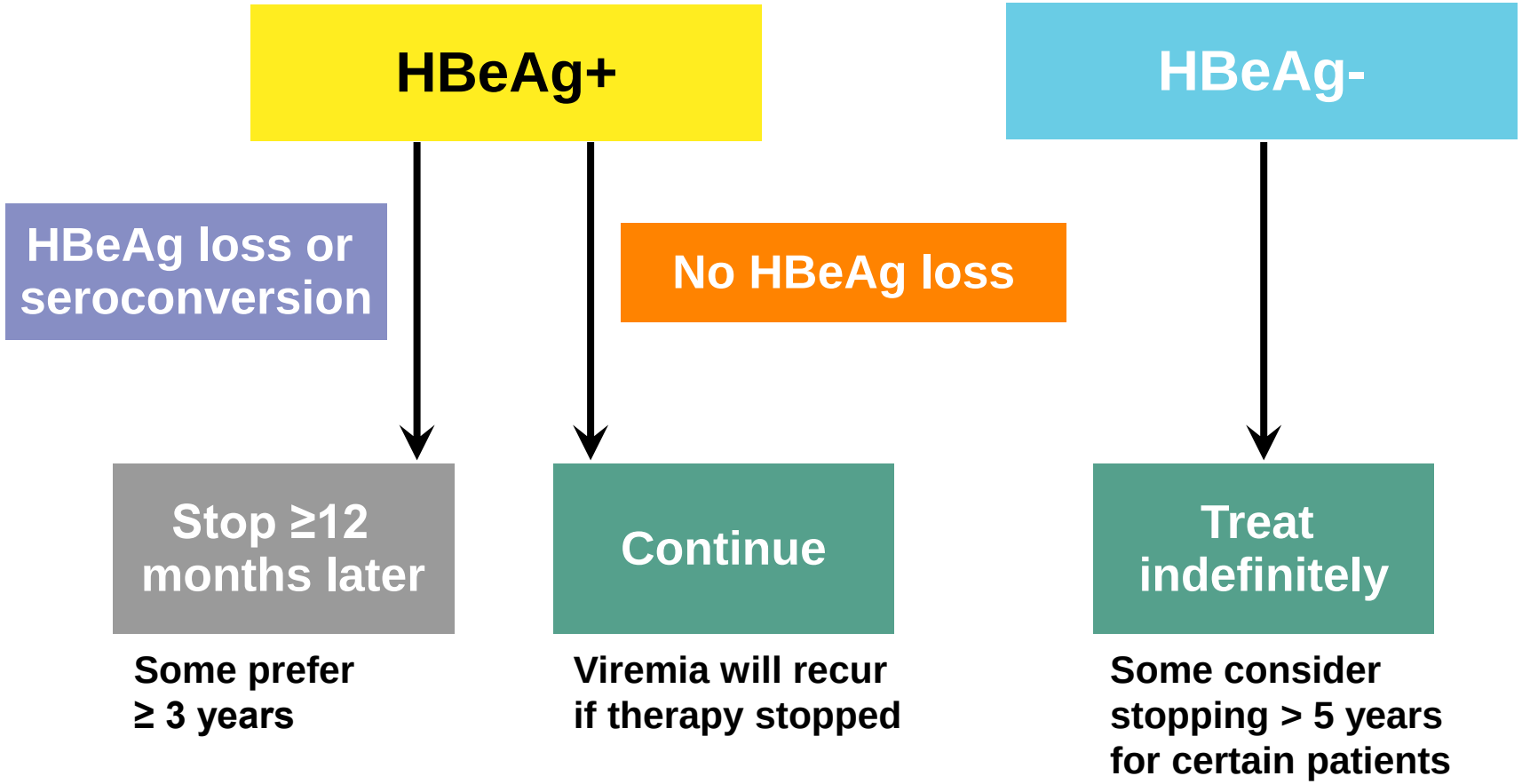
- In non-cirrhotic **HBeAg-negative** patients who have achieved long-term (≥3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed.
- In non-cirrhotic **HBeAg-positive patients** who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy.

Alternative opinion:

- No rush to stop in HBeAg+ patients: wait 3 years to stop
- In general, best to continue long term in HBeAg- patients for now

Terrault N et al. *AASLD Guidance*. 2018;67:1560-99; EASL. *J Hepatol*. 2017;67(2):370-398.

Treatment Endpoints



Can stop therapy for HBsAg clearance documented for ≥ 6 months

2018 AASLD Guidance: Monitoring of CHB Patients Not on Antiviral Therapy

	Immune-Tolerant CHB	Inactive CHB	Resolved CHB
Definition of Population	HBeAg positive, high HBV DNA	HBeAg negative, normal ALT, low HBV DNA	HBsAg loss
Recommended Monitoring for Population	ALT: every 3-6 mos • If ALT level rises to > ULN, evaluate ALT and HBV DNA more frequently HBeAg status: every 6-12 mos • Treat if HBeAg+ with HBV DNA > 20,000 IU/mL for 3-6 mos and ALT > 2 x ULN Liver biopsy or noninvasive assessment of fibrosis • Consider with slight, persistent ALT elevation, particularly if > 40 yrs of age and infected for long duration	ALT and HBV DNA: every 3 mos for first yr, then every 6-12 mos • If ALT level rises to > ULN, evaluate ALT and HBV DNA more frequently HBsAg: annually	ALT and HBV DNA monitoring no longer required HCC surveillance • Continue if individual has cirrhosis, a first-degree family member with HCC, or a long duration of infection

If treatment is not indicated, actively monitor as candidacy may change with disease

1. Terrault. *Hepatology*. 2018;67:1560. www.aasld.org..

Special Patient Populations

AASLD 2018 Hepatitis B Guidance: Immune Tolerant Patients

- **Immune Tolerant CHB**
  - Defined by ALT levels, 35 ULN for men, 25 ULN for women rather than local lab ULN
  - Refers to HBeAg+ patients, high viral levels (HBV DNA>>6 logs), usually applies to younger age groups (<30-40 years old)
  - Liver histology without active inflammation, fibrosis
  - Antiviral treatment is not recommended
- **Additional Considerations**
  - Test ALT levels every 6 months
  - Monitor for potential transition to immune-active CHB
  - Special populations adults > 40 years with normal ALT and HBV DNA > 1,000,000 IU/mL ***or*** liver biopsy with moderate-severe fibrosis or necroinflammation, consider treatment

Terrault N et al. *Hepatology.* AASLD HBV Guidance. 2018.

Immune Tolerant HBV Infection: An Alternative View Not Reflected in any Guidelines at This Time

- Recent studies indicate that immune tolerant patients have:
  - Ongoing integration of HBV DNA into host genomes (oncogenic potential?)
  - Clonal hepatocyte expansion
  - Evidence of immunologic activity despite designation as “immune tolerant”
- Contrary opinion: “Withholding of antiviral therapy in IT patients requires reconsideration”.[2]
- Speaker’s opinion: It is appropriate to discuss the option of treatment with immune tolerant patients.

. Mason WS et al. *Gastroenterology*. 2016;151:986-98.

AASLD Guidance for Patients With CHB Undergoing Immunosuppressive or Cytotoxic Therapy

- HBsAg+ patients should initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic therapy
- In general, HBsAg-, anti-HBc+ patients should be carefully monitored with ALT, HBV DNA, and HBsAg with intent for on-demand therapy
- EXCEPTION: For HBsAg-, anti-HBc+ patients receiving anti-CD20 antibody therapy (e.g. rituximab) or undergoing stem cell transplantation, anti-HBV prophylaxis is recommended
- Entecavir, Tenofovir (either as TDF or TAF) preferred
- Antiviral therapy should be continued for at least 6 months after completion of immunosuppressive therapy or for at least 12 months for patients receiving anti-CD20 therapies (note: EASL guidelines recommend 18 months for anti-CD20 therapies)
- And, don't forget: HBsAg+ patients receiving DAA therapy for HCV should be given HBV antiviral before HCV treatment through 12 weeks post-completion

Terrault N et al. *AASLD Guidance*. 2018;67:1560-99; EASL Hepatitis Guidelines. *J Hepatol*. 2017.

AASLD 2018 Hepatitis B Guidance

- **Management of CHB in Pregnancy**
  - HBsAg positive women with DNA > 200,000 IU/mL treat to reduce perinatal transmission
  - Infants receive HBV vaccine with HBIG
  - TDF is preferred agent
  - Treatment initiated at weeks 28-32 gestation in clinical trials, discontinued 3 months PP
  - Monitor for ALT flares 6 months
  - Breastfeeding is not contraindicated
  - C-section not indicated routinely

Recommendations From Association Guidelines for Preventing HBV MTCT

EASL	2017	TDF LAM, LdT	Second trimester of pregnancy	HBV DNA >2x10^5 IU/mL, HBsAg levels > 4 logs IU/mL
AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES	2018	TDF LAM, LdT	28-32 weeks of gestation	HBV DNA >2×10^5 IU/mL.
APASL	2015	TDF, LdT	28-32 weeks of gestation	HBV DNA >$10^{6–7}$ IU/mL

Screening Guidelines

AASLD 2018 Hepatitis B Guidance: Screening Guidelines

- **Screening Guidelines**
- U.S.-born persons not vaccinated as an infant whose parents were born in regions with high HBV endemicity (≥8%)
- Persons who have ever injected drugs
- Men who have sex with men
- Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatological or gastroenterologic disorders
- Individuals with other chronic liver disease
- Donors of blood, plasma, organs, tissues, or semen
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
- All pregnant women

AASLD 2018 Hepatitis B Guidance: Screening Guidelines

- **Screening Guidelines**
- Infants born to HBsAg-positive mothers
- Persons with HIV and/or HCV
- Household, needle-sharing, and sexual contacts of HBsAg-positive persons
- Persons who are not in a long-term, mutually monogamous relationship (e.g., >1 sex partner during the previous 6 months)
- Persons seeking evaluation or treatment for a sexually transmitted disease
- Health care and public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids
- Residents and staff of facilities for developmentally disabled persons
- Travelers to countries with intermediate or high prevalence of HBV infection
- Persons who are the source of blood or body fluid exposures that might require post exposure prophylaxis
- Inmates of correctional facilities
- Unvaccinated persons with diabetes who are aged 19 through 59 years (discretion of clinician for unvaccinated adults with diabetes who are aged ≥60 years)

Immunization

AASLD 2018 Hepatitis B Guidance

- **Counseling Guidelines**
- For HIV/immunocompromised patients, cirrhotics and patients on HD, double dose of HBV vaccine has shown to increase the percent of patients who achieve protective HBsAb titers.
- If HBsAb titer <10 mIU/ml. provide booster HBV vaccine to infants, HCW, immumocompromised and HD persons.
- Immunoprophylaxis: provide HBV +/- HHBI within 24 hours of percutaneous, mucosal and sexual exposure.
- Test HBsAb titers in children of HBsAg positive mothers between 9-15 months of age.

HCC Surveillance

AASLD Guidelines: Recommendations for HCC Surveillance

- Hepatitis B carriers at high risk[1]
  - All patients with cirrhosis
  - Patients with first-degree family member with history of HCC
  - Asian or black men older than 40 yrs of age
  - Asian women older than 50 yrs of age
  - Coinfected with HDV
- Liver ultrasound with or without AFP in high risk patients every 6 mos
  - Note: There is a role for MRI or CT in some situations

1. Terrault. *Hepatology*. 2018;67:1560; 2. Heimbach. *Hepatology*. 2018;67:358.

HCC Screening in HBsAg-Positive Persons

AASLD Guidance

- All patients with cirrhosis should be screened with ultrasound ± AFP every 6 months
- High risk patients without cirrhosis should have ultrasound ± AFP every 6 months
  - Asian or black men >40 yrs
  - Asian women >50 yrs
  - First-degree relative with hx HCC
  - Patients with HDV

?

Alternative View (Some Clinicians)

- Screen all HBsAg+ adults every 6 months
- When appropriate, use CT or MRI instead of alternating with ultrasound (MRI may be preferred to avoid repeated radiation exposures)
  - Obesity, cirrhosis or other factors preclude adequate visualization of liver on ultrasound
  - Follow-up of “indeterminate” lesions
  - Elevated AFP and negative ultrasound

Terrault NA et al. *Hepatology*. 2018;57:1560-99.

Thank You!