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CLINICAL CARE OPTIONS®  
HEPATITIS

# Management of Patients With Chronic Hepatitis B

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# Faculty and Disclosures

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**Paul Y. Kwo, MD**, has disclosed that he has received consulting fees from AbbVie, Arrowhead, Bristol-Myers Squibb, Gilead Sciences, and Quest; has received funds for research support from Assembly, Bristol-Myers Squibb, and Gilead Sciences; and has served on a data and safety monitoring board for Johnson & Johnson.

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# AASLD US Recommendations for CHB



# 2018 AASLD Guidance: Whom to Treat

- AASLD recommendations for antiviral therapy
  - Adults with immune-active CHB (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications
    - Additional factors: age, family history of HCC or cirrhosis, previous treatment history, presence of extrahepatic manifestations, presence of cirrhosis
  - Select group of immune-tolerant adults older than 40 yrs of age with normal ALT and elevated HBV DNA (1,000,000 IU/mL) and liver biopsy specimen showing significant necroinflammation or fibrosis

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

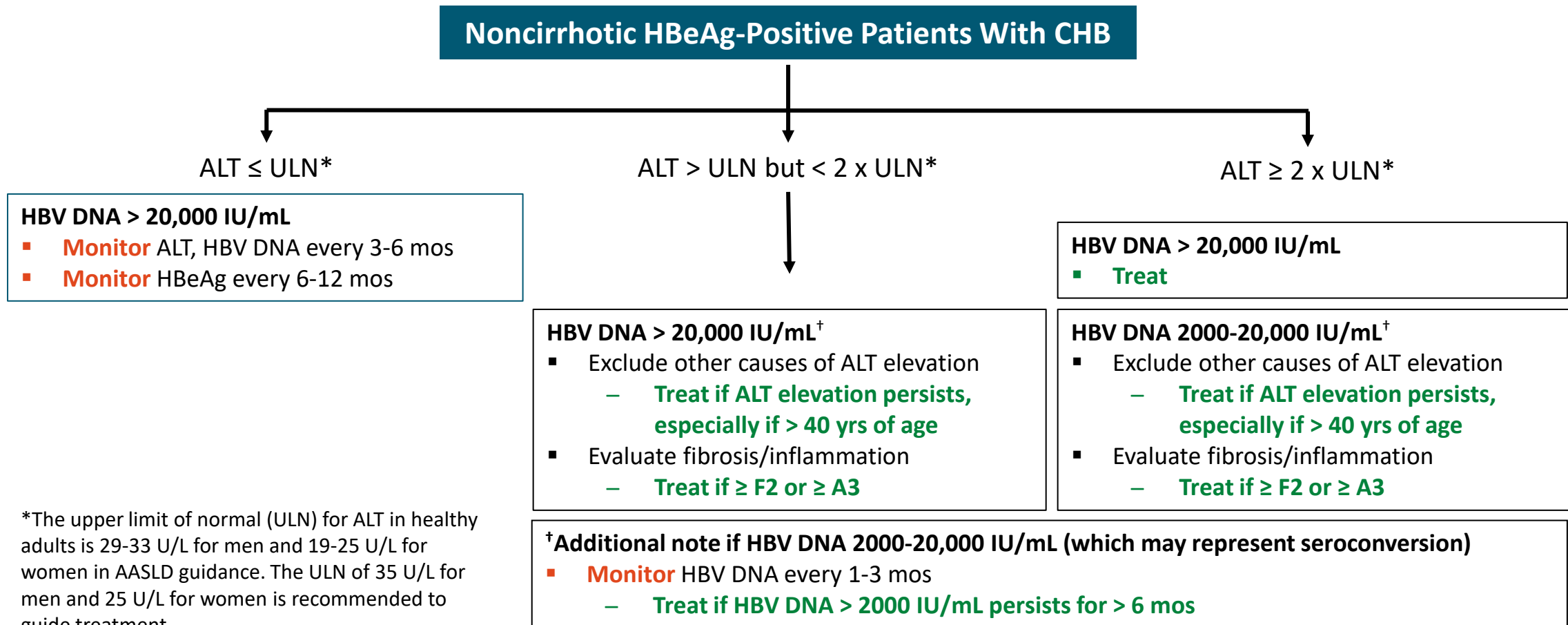
# 2018 AASLD Guidance: Defining Immune-Active vs Immune-Tolerant CHB

Phase	Diagnostic Criteria
Immune-active CHB	<ul style="list-style-type: none"><li>▪ HBsAg present for <math>\geq 6</math> mos</li><li>▪ Serum HBV DNA <math>&gt; 20,000</math> IU/mL in HBeAg+ CHB and <math>&gt; 2000</math> IU/mL in HBeAg- CHB</li><li>▪ Intermittently or persistently elevated ALT and/or AST levels</li><li>▪ Liver biopsy or noninvasive tests results show chronic hepatitis with moderate or severe necroinflammation <math>\pm</math> fibrosis</li></ul>
Immune-tolerant CHB	<ul style="list-style-type: none"><li>▪ HBsAg present for <math>\geq 6</math> mos</li><li>▪ HBeAg positive</li><li>▪ Very high HBV DNA levels (typically <math>&gt; 1</math> million IU/mL)</li><li>▪ Normal or minimally elevated ALT and/or AST</li><li>▪ Liver biopsy or noninvasive test results show no fibrosis and minimal inflammation</li></ul>

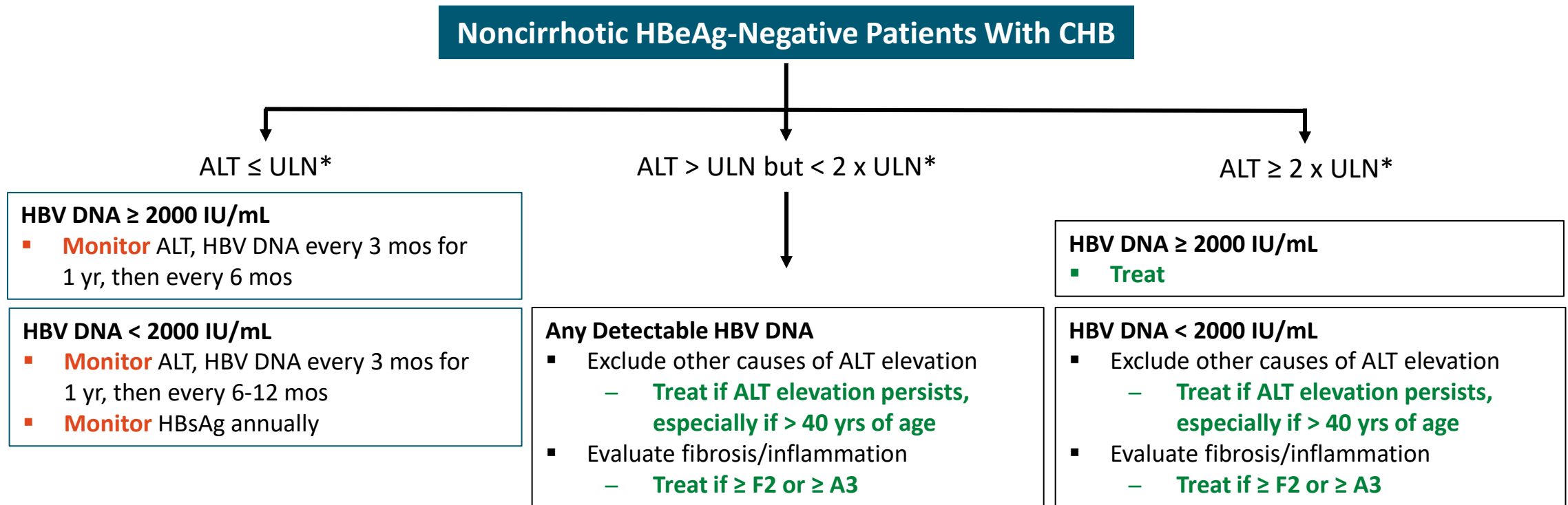
# 2018 AASLD Guidance: Assessment of HBV Disease

- Diagnostic tests used in management of CHB
  - ALT and/or AST
  - HBV DNA
  - Liver biopsy (if warranted) or noninvasive testing
  - Quantitative HBsAg
  - Viral resistance testing
  - HBV genotyping

# 2018 AASLD Guidance: Monitor vs Treat in HBeAg-Positive Patients



# 2018 AASLD Guidance: Monitor vs Treat in HBeAg-Negative Patients



\*The upper limit of normal (ULN) for ALT in healthy adults is 29-33 U/L for men and 19-25 U/L for women in AASLD guidance. The ULN of 35 U/L for men and 25 U/L for women is recommended to guide treatment.

# 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	<p><b>ALT: every 3-6 mos</b></p> <ul style="list-style-type: none"> <li>If ALT level rises to &gt; ULN, evaluate ALT and HBV DNA more frequently</li> </ul> <p><b>HBeAg status: every 6-12 mos</b></p> <ul style="list-style-type: none"> <li>Treat if HBeAg+ with HBV DNA &gt; 20,000 IU/mL for 3-6 mos and ALT &gt; 2 x ULN</li> </ul> <p><b>Liver biopsy or noninvasive assessment of fibrosis</b></p> <ul style="list-style-type: none"> <li>Consider with slight, persistent ALT elevation, particularly if &gt; 40 yrs of age and infected for long duration</li> </ul>	<p><b>ALT and HBV DNA: every 3 mos for first yr, then every 6-12 mos</b></p> <ul style="list-style-type: none"> <li>If ALT level rises to &gt; ULN, evaluate ALT and HBV DNA more frequently</li> </ul> <p><b>HBsAg: annually</b></p>	<p><b>ALT and HBV DNA monitoring no longer required</b></p> <p><b>HCC surveillance</b></p> <ul style="list-style-type: none"> <li>Continue if individual has cirrhosis, a first-degree family member with HCC, or a long duration of infection</li> </ul>

# Hep B Consult: Young Man With HBeAg-Positive CHB, Elevated HBV DNA, and Normal ALT

- Here, you see recommendations for a 27-yr-old man with HBeAg-positive CHB and the following characteristics:
  - ALT 1.2 x ULN
  - HBV DNA 1.5 million IU/mL
  - No liver necroinflammation or fibrosis
  - No other comorbidities

Enter your patient characteristics  
for instant guidance!  
[clinicaloptions.com/HepBConsult](https://clinicaloptions.com/HepBConsult)

## Your Patient Case

Do you want to see recommendations from the US, European, or Asian Pacific guidelines? US (AASLD)  
Before we begin, do any of the following special considerations apply? None apply  
HBeAg status and HBV DNA level? HBeAg positive, HBV DNA > 20,000 IU/mL  
ALT level? > ULN but < 2 x ULN  
Liver histology/fibrosis? Minimal inflammation or fibrosis  
Extrahepatic manifestations or family history of hepatocellular carcinoma (HCC) or cirrhosis? No  
With or at risk of renal dysfunction or bone disease? No  
Comorbid autoimmune disease, uncontrolled psychiatric disease or seizures, cytopenia, or severe cardiac disease? No  
What approach are you considering? Unsure  
Are you a healthcare practitioner? Yes

## Recommendations

**Start treatment after excluding other causes of elevated ALT.**

- Treat if ALT elevation persists after other possible causes have been excluded, especially if older than 40 years of age

For more information on this recommendation, see the module, [“Insights on the Management of Patients With Chronic Hepatitis B.”](#)



# AASLD: Selecting Initial Antiviral Therapy in CHB



# 2018 AASLD Guidance: What to Start as Initial HBV Therapy

Treatment	Preferred	Notes
Entecavir	Yes	High potency, high genetic barrier to resistance
TAF	Yes	High potency, high genetic barrier to resistance
TDF	Yes	High potency, high genetic barrier to resistance
PegIFN	Yes	Less safe in patients with cirrhosis, contraindicated in patients with decompensated cirrhosis
Adefovir	No	Low genetic barrier to resistance
Lamivudine	No	Low genetic barrier to resistance
Telbivudine	No	Low genetic barrier to resistance

# 2018 AASLD Guidance: Peginterferon

- **PegIFN alfa-2a 180 µg/wk by subcutaneous injection**
- Duration of therapy: 48 wks
  - Yields HBeAg seroconversion in 20% to 31% and sustained off-treatment HBV DNA suppression < 2000 IU/mL in 65% who achieve HBeAg to anti-HBe seroconversion
- Monitoring during treatment:
  - Complete blood count every 1-3 mos
  - TSH every 3 mos
  - Clinical monitoring for autoimmune, ischemic, neuropsychiatric, and infectious complications
- Potential AEs: influenzalike symptoms, fatigue, mood disturbances, cytopenia, and autoimmune disorders in adults

# 2018 AASLD Guidance: Nucleos(t)ide Analogues

- **ETV 0.5 mg/day, TAF 25 mg/day, or TDF 300 mg/day**
- Potent, high genetic barrier to resistance
- Drug-related monitoring
  - All: HIV at BL, lactic acid during therapy if clinical concern
  - TAF: serum creatinine and phosphorus; urine glucose and protein
  - TDF: BL CrCl, renal monitoring if renal risk, BL bone density

# 2018 AASLD Guidance: Therapy Duration on NAs

- **For most, NA treatment duration is indefinite**
  - HBeAg-positive adults without cirrhosis who seroconvert to anti-HBe on therapy: **discontinue therapy** after a period of treatment consolidation *if this endpoint is met*
  - HBeAg-positive adults with cirrhosis who seroconvert to anti-HBe on NA therapy: **indefinite therapy**, *unless there is a strong competing rationale for treatment discontinuation*
  - HBeAg-negative adults with immune-active CHB: **indefinite therapy**

# 2018 AASLD Guidance: Efficacy of First-line Antiviral Therapies in Treatment-Naive Adults With CHB

Outcomes From Separate Studies (Not Head to Head)	PegIFN*	ETV†	TAF‡	TDF†
<b>HBeAg positive</b>				
▪ HBV DNA suppression, <sup>§</sup> % (IU/mL)	30-42 (< 2000-40,000)	61 (< 50-60 IU/mL)	73 (< 29)	76 (< 60)
▪ HBeAg loss, %	32-36	22-25	22	--
▪ HBeAg seroconversion, %	29-36	21-22	18	21
▪ Normalization ALT, %	34-52	68-81	--	68
▪ HBsAg loss, %	2-7	4-5	1	8
<b>HBeAg negative</b>				
▪ HBV DNA suppression, <sup>¶</sup> % (IU/mL)	43 (< 4000)	90-91 (< 50-60)	90 (< 29)	93 (< 60)
▪ Normalization ALT, %	59	78-88	81	76
▪ HBsAg loss,%	4	0-1	< 1	0

\*Assessed 6 mos after completion of 12 mos of therapy. †Assessed after 3 yrs of continuous therapy. ‡Assessed after 2 yrs of continuous therapy.

<sup>§</sup>HBV DNA < 2000-40,000 IU/mL for pegIFN; < 60 IU/mL for ETV and TDF; < 29 IU/mL for TAF. <sup>¶</sup>HBV DNA < 20,000 IU/mL for pegIFN; < 60 IU/mL for ETV and TDF; < 29 IU/mL for TAF. <sup>||</sup>ALT normalization defined by laboratory normal rather than < 35 U/L for men and 25 U/L for women.



# 2018 AASLD Guidance:

## Criteria for Selecting ETV vs TAF vs TDF

Comparative Measure	ETV	TAF	TDF
Dose	0.5 mg/day	25 mg/day	300 mg/day
Presence of LAM resistance	Increase dose	Active	Active
Anticipated pregnancy	Pregnancy Category C	No human data in pregnancy	Pregnancy Category B
Renal disease	Decrease dose if CrCl < 50 mL/min	Do not use if CrCl < 15 mL/min or if on dialysis*	Decrease dose if CrCl < 50 mL/min
Bone disease	Recommended	Recommended	Recommended
HIV coinfection	Only recommended in addition to complete ART regimen	Coformulated ART regimen	Coformulated ART regimen
Cost considerations	Generic available	No generic	Generic available

\*By contrast, EASL guidelines recommend either ETV or TAF in patients receiving hemodialysis. Since February 2019, TAF prescribing information notes that no dose adjustment is necessary in individuals with CrCl > 15 mL/min or in individuals with CrCl < 15 mL/min who are receiving hemodialysis.



# Hep B Consult: Middle-Aged Woman With HBeAg-Negative CHB, Elevated HBV DNA and ALT

- Here, you see recommendations for a 45-yr-old woman with HBeAg-negative CHB and the following characteristics:
  - ALT 2.7 x ULN
  - HBV DNA 455,000 IU/mL
  - No liver necroinflammation or fibrosis
  - No other comorbidities

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## Your Patient Case

Do you want to see recommendations from the US, European, or Asian Pacific guidelines? US (AASLD)  
Before we begin, do any of the following special considerations apply? None apply  
HBeAg status and HBV DNA level? HBeAg negative, HBV DNA  $\geq 2000$  IU/mL  
ALT level?  $\geq 2 \times$  ULN  
Liver histology/fibrosis? Minimal inflammation or fibrosis  
Extrahepatic manifestations or family history of hepatocellular carcinoma (HCC) or cirrhosis? No  
With or at risk of renal dysfunction or bone disease? No  
Comorbid autoimmune disease, uncontrolled psychiatric disease or seizures, cytopenia, or severe cardiac disease? No  
What approach are you considering? Unsure  
Are you a healthcare practitioner? Yes

## Recommendations

**Start treatment with entecavir, tenofovir alafenamide, tenofovir DF, or peginterferon alfa.**

Choice of therapy may be informed by:

- Preference for finite therapy
  - 48 weeks is usual duration of peginterferon alfa; nucleos(t)ide therapy is usually indefinite
- HBV genotype
  - HBV genotypes A and B more responsive to peginterferon alfa than are other genotypes

For more information on this recommendation, see the module, [“Insights on the Management of Patients With Chronic Hepatitis B.”](#)



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# Hep B Consult: Case Revisited

- What if she were older or had risk of renal or bone disease?
- In this case, the guidelines recommend treatment with ETV or TAF, as TDF is associated with decreases in bone density and renal function

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## Your Patient Case

Do you want to see recommendations from the US, European, or Asian Pacific guidelines? US (AASLD)  
Before we begin, do any of the following special considerations apply? None apply  
HBeAg status and HBV DNA level? HBeAg negative, HBV DNA  $\geq$  2000 IU/mL  
ALT level?  $\geq$  2 x ULN  
Liver histology/fibrosis? Minimal inflammation or fibrosis  
Extrahepatic manifestations or family history of hepatocellular carcinoma (HCC) or cirrhosis? No  
With or at risk of renal dysfunction or bone disease? Yes  
Comorbid autoimmune disease, uncontrolled psychiatric disease or seizures, cytopenia, or severe cardiac disease? No  
What approach are you considering? Unsure  
Are you a healthcare practitioner? Yes

## Recommendations

**This person meets indications for treatment.**

- Consider **entecavir** or **tenofovir alafenamide**
- Avoid tenofovir alafenamide in patients on dialysis or with creatinine clearance < 15 mL/min

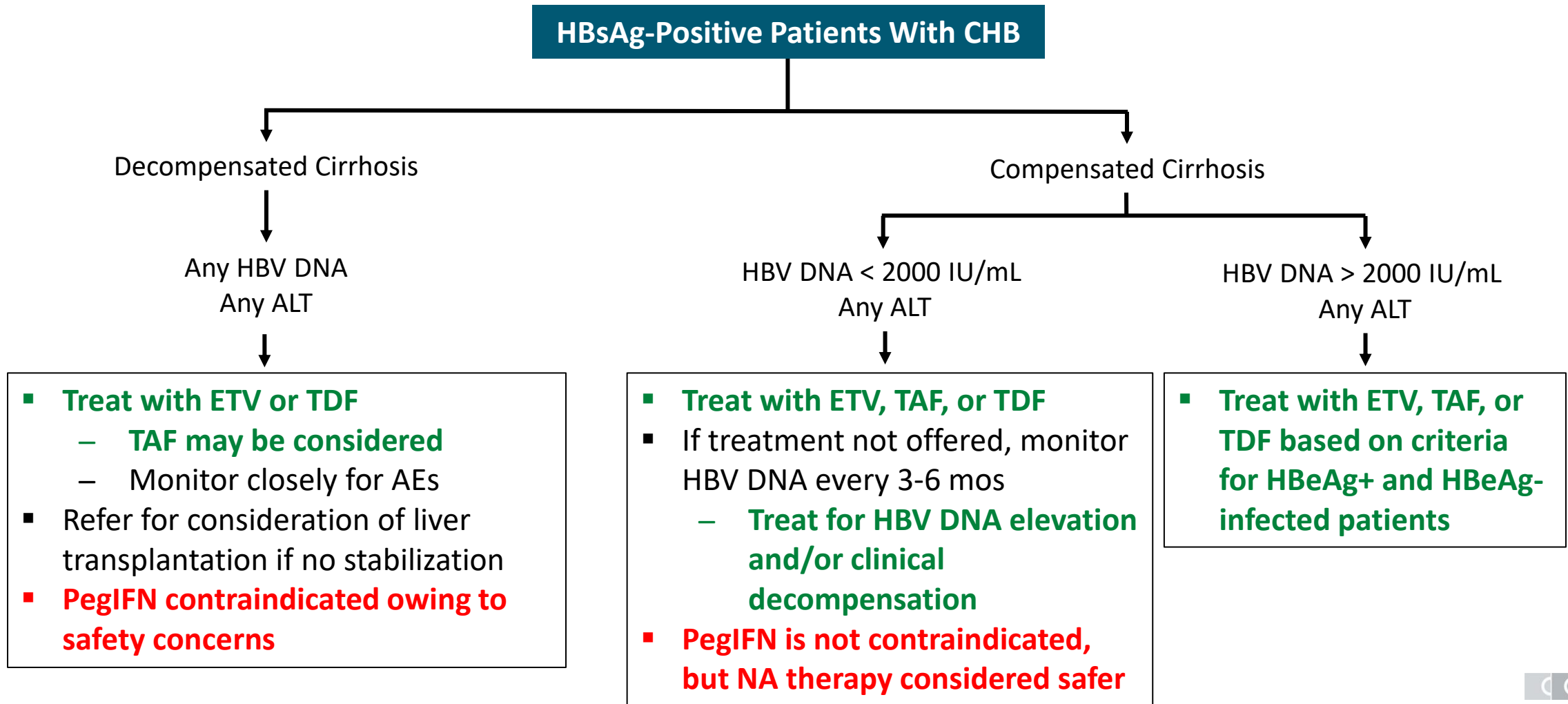
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# AASLD: Managing CHB in Special Populations

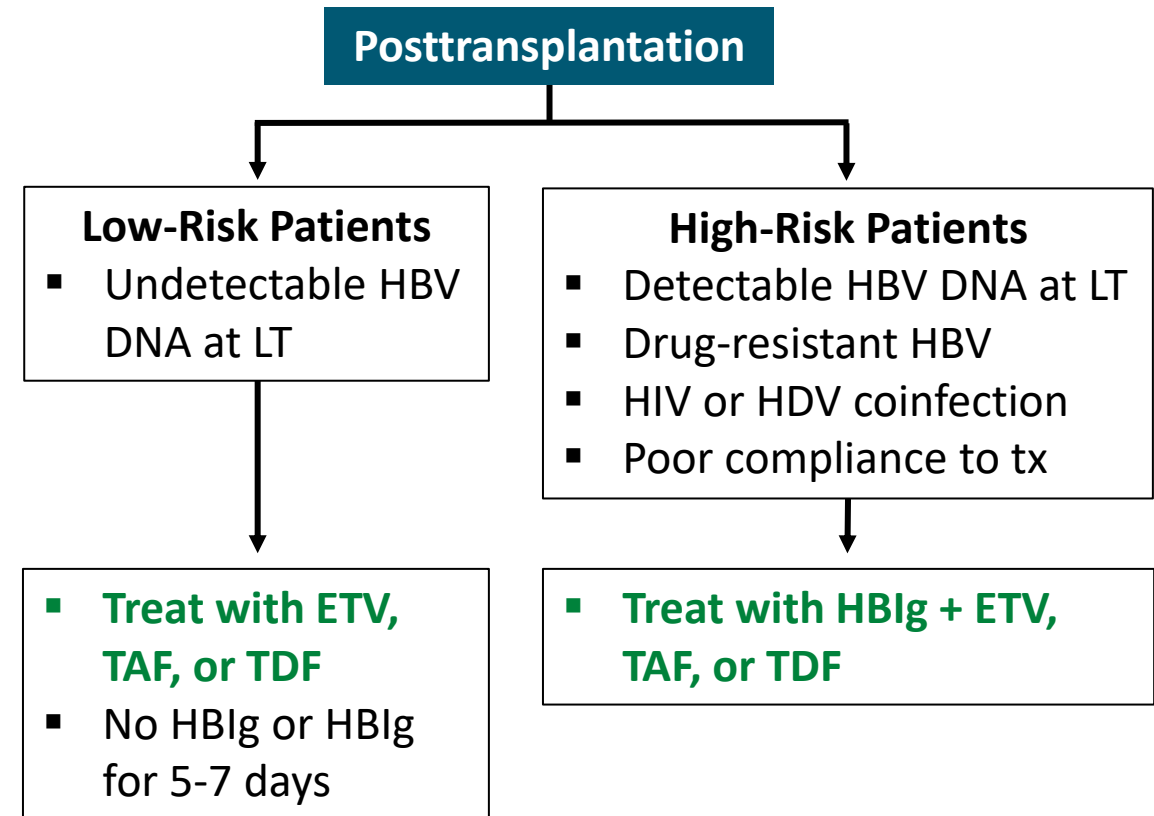


# 2018 AASLD Guidance: Cirrhosis



# 2018 AASLD Guidance: Liver Transplantation

- Pretransplantation
  - Administer ETV, TAF, or TDF to reduce HBV DNA level and risk of HBV reinfection
- Posttransplantation
  - Lifelong prophylactic therapy with NAs recommended
  - HBsAg- patients receiving HBsAg-/anti-HBc+ grafts should be managed with lifelong NA therapy without HBIg

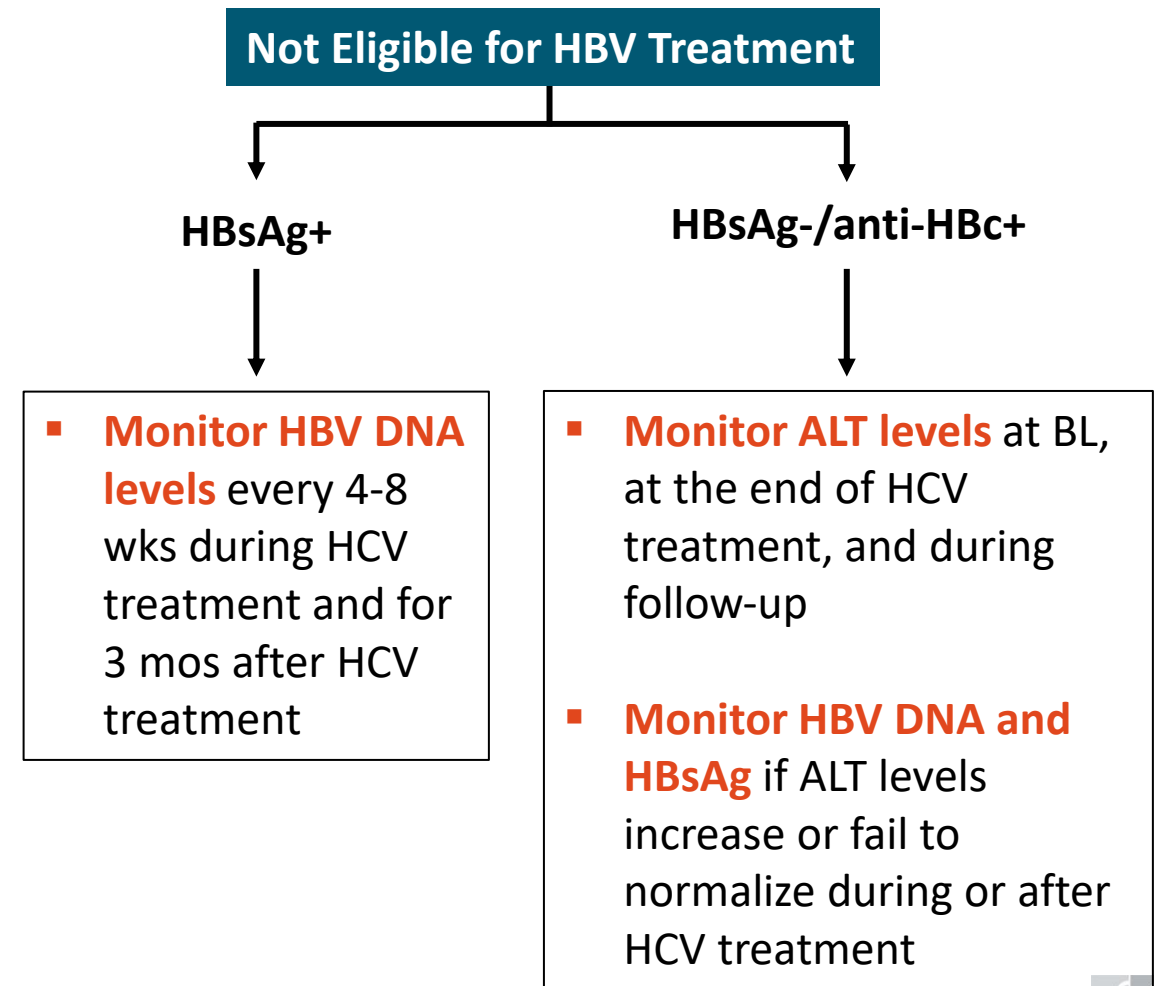


# 2018 AASLD Guidance: HIV Coinfection

- All patients with HBV and HIV coinfection should receive HIV antiretroviral therapy that includes 2 drugs with activity against HBV
- (TAF or TDF) + (FTC or 3TC) + third agent active against HIV recommended
  - Do not use TDF, 3TC, or ETV as single agents
    - ETV should only be used in combination with a fully suppressive HIV regimen
  - Do not use adefovir or telbivudine
- If HIV therapy is altered, drugs effective against HBV should not be stopped to avoid hepatitis flares

# 2018 AASLD Guidance: HCV Coinfection

- Measure HCV RNA, HBV DNA before selecting a therapeutic strategy
  - HCV treatment with DAAs is indicated for patients with HCV viremia
  - HBV treatment is determined by HBV DNA and ALT levels by same criteria used in monoinfected patients
- Monitor those not eligible for HBV treatment during and after HCV treatment based on HBsAg status



# 2018 AASLD Guidance: HDV Coinfection

- Treat with pegIFN-alfa for 12 mos
  - Treatment success defined as undetectable HDV RNA 24 wks after completing treatment
  - Assessment of HDV RNA warranted if ALT elevation occurs following treatment because of the high rates of relapse
  - Given the limited efficacy of current therapies, may refer patients to specialized centers that offer access to experimental therapies for HDV
- In patients with elevated HBV DNA, concurrent treatment with ETV, TAF, or TDF recommended

# 2018 AASLD Guidance: Pregnancy and Breastfeeding

- Pregnant women with immune-active hepatitis should be treated per recommendations for nonpregnant women
- In HBsAg+ pregnant women with HBV DNA > 200,000 IU/mL, antiviral therapy recommended to prevent perinatal transmission
  - TDF preferred due to its potency and high barrier to resistance
- Infants born to HBsAg+ women should receive immunoprophylaxis (ie, HBV vaccination ± HBIG per WHO and CDC recommendations)
- Breastfeeding is not contraindicated in women receiving NA therapy

# 2018 AASLD Guidance: Immunosuppressive Therapy or Chemotherapy

- Screen for HBsAg and anti-HBc before initiation of immunosuppressive or cytotoxic therapy
  - If HBsAg+ and anti-HBc+, give prophylactic NA therapy
  - If HBsAg- and anti-HBc+, either give prophylactic NA therapy or monitor ALT, HBV DNA, and HBsAg
    - If monitoring chosen, measure HBV DNA every 1-3 mos; treat with an NA upon first sign of reactivation (ie, HBV DNA elevation, HBsAg seroreversion)
  - All patients receiving anti-CD20 therapy (eg, rituximab) or undergoing stem cell transplantation should receive anti-HBV prophylaxis, regardless of HBsAg status
- Preferred prophylaxis: ETV, TAF, or TDF during and for 6-12 mos after immunosuppressive therapy

# EASL European Recommendations for CHB



# 2017 EASL Guidelines: Criteria for Treatment of CHB

Standard Indications				
HBV DNA, IU/mL		ALT		Liver Disease
> 2000	+	> ULN*	+	Moderate necroinflammation or fibrosis
Any	+	Any	+	Cirrhosis
> 20,000	+	> 2 x ULN*	+	Any

\*ULN ~40 IU/L.

## Other Indications, Even if Standard Indications Are Not Met

CHB and family history of HCC or cirrhosis with extrahepatic manifestations

HBeAg positive, high HBV DNA, persistently normal ALT, and aged > 30 yrs

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

# 2017 EASL Guidelines: Monitoring Frequency in CHB Patients Not Eligible for Antiviral Therapy

Monitoring Frequency	HBeAg Positive	HBeAg Negative	
		HBV DNA < 2000 IU/mL	HBV DNA ≥ 2000 IU/mL
ALT	At least every 3 mos	Every 6-12 mos	Every 3 mos for first yr, then every 6 mos
HBV DNA	Every 6-12 mos	Periodically (every-3 yrs is suggested)	Annually
Noninvasive markers of liver fibrosis	Every 12 mos	Periodically (every 2-3 yrs is suggested)	Annually
Additional recommendations		<ul style="list-style-type: none"> <li>Quantitative assessment of HBsAg helpful for determining frequency of follow-up                             <ul style="list-style-type: none"> <li><i>If HBsAg &lt; 1000 IU/mL:</i> ALT every 12 mos, HBV DNA and liver fibrosis every 3 yrs</li> <li><i>If HBsAg ≥ 1000 IU/mL:</i> ALT every 6 mos, HBV DNA and liver fibrosis every 2 yrs</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Follow for life if patient meets no treatment indication within first 3 yrs of follow-up</li> </ul>

# Hep B Consult: Young Man With HBeAg-Positive CHB, Elevated HBV DNA, and Normal ALT

- Here, you see recommendations for a 27-yr-old man with HBeAg-positive CHB and the following characteristics:
  - ALT 1.2 x ULN
  - HBV DNA 1.5 million IU/mL
  - No liver necroinflammation or fibrosis
  - No other comorbidities

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## Your Patient Case

Do you want to see recommendations from the US, European, or Asian Pacific guidelines? European (EASL)  
Before we begin, do any of the following special considerations apply? None apply  
HBeAg status and HBV DNA level? HBeAg positive, HBV DNA > 20,000 IU/mL  
ALT level? > Upper limit of normal (ULN) but < 2 x ULN  
Liver histology/fibrosis? Minimal liver necroinflammation or fibrosis  
Age? < 30 years  
Preexisting or risk of bone or renal disease? No  
What approach are you considering? Unsure  
Are you a healthcare practitioner? Yes

## Recommendations

**Monitor every 3-6 months without treatment.**

*Evidence grade II-2, recommendation grade 1*

- **ALT determination:** Every 3 months
- **HBV DNA determination:** Every 6-12 months
- **Noninvasive assessment of liver fibrosis:** Every 12 months

Re-evaluate for treatment candidacy at each assessment.

For more information on this recommendation, see the module, "[Insights on the Management of Patients With Chronic Hepatitis B.](#)"



# EASL: Selecting Initial Antiviral Therapy in CHB



# 2017 EASL Guidelines:

## What to Start as Initial HBV Therapy

Treatment	Preferred	Notes
Entecavir	Yes	High potency, high genetic barrier to resistance
TAF	Yes	High potency, high genetic barrier to resistance
TDF	Yes	High potency, high genetic barrier to resistance
PegIFN	Should only be considered as initial therapy for patients with mild/moderate CHB or selected patients with compensated cirrhosis (no portal hypertension)	Less safe in patients with cirrhosis, contraindicated in patients with decompensated cirrhosis
Adefovir	No	Low genetic barrier to resistance
Lamivudine	No	Low genetic barrier to resistance
Telbivudine	No	Low genetic barrier to resistance

# 2017 EASL Guidelines:

## Indications for Choosing ETV, TAF vs TDF

### Indications for using ETV or TAF over TDF:

- Aged > 60 yrs
- Bone disease
  - Chronic steroids or other meds that affect bone
  - History of fragility fracture
  - Osteoporosis
- Renal abnormalities
  - eGFR < 60 mL/min/1.73 m<sup>2</sup>
  - Albuminuria > 30 mg or moderate proteinuria
  - Low phosphate (< 2.5 mg/dL)
  - Hemodialysis

### When to prioritise TAF over ETV:

- Previous nucleoside exposure
  - Lamivudine with or without adefovir resistance
- HIV/HBV coinfection
- No dose adjustment for CrCl ≥ 15 mL/min

### When to prioritise ETV over TAF:

- If less expensive (generic available)
- Dosing guidelines for CrCl < 15 mL/min

# Hep B Consult: Middle-Aged Woman With HBeAg-Negative CHB, Elevated HBV DNA and ALT

- Here, you see recommendations for a 45-yr-old woman with HBeAg-negative CHB and the following characteristics:
  - ALT 2.7 x ULN
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## Your Patient Case

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Before we begin, do any of the following special considerations apply? None apply  
HBeAg status and HBV DNA level? HBeAg negative, HBV DNA > 20,000 IU/mL  
ALT level? > 2 x ULN  
Liver histology/fibrosis? Minimal liver necroinflammation or fibrosis  
Age? 30-60 years  
Preexisting or risk of bone or renal disease? No  
What approach are you considering? Unsure  
Are you a healthcare practitioner? Yes

## Recommendations

**This person meets indications for treatment.**

Use **entecavir**, **tenofovir alafenamide**, or **tenofovir DF**.  
*Evidence grade I, recommendation grade 1*

A finite course of **peginterferon alfa** can be considered for individuals with mild to moderate CHB.  
*Evidence grade I, recommendation grade 2*

**Extending peginterferon alfa** treatment beyond 48 weeks may benefit some individuals.  
*Evidence grade II-1, recommendation grade 2*

For more information on this recommendation, see the module, "[Insights on the Management of Patients With Chronic Hepatitis B](#)."



# Hep B Consult: Case Revisited

- What if she were older or had risk of renal or bone disease?
- In this case, the guidelines recommend treatment with ETV or TAF, as TDF is associated with decreases in bone density and renal function

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## Your Patient Case

Do you want to see recommendations from the US, European, or Asian Pacific guidelines? European (EASL)

Before we begin, do any of the following special considerations apply? None apply

HBeAg status and HBV DNA level? HBeAg negative, HBV DNA > 20,000 IU/mL

ALT level? > 2 x ULN

Liver histology/fibrosis? Minimal liver necroinflammation or fibrosis

Age? 30-60 years

Preexisting or risk of bone or renal disease? Yes

What approach are you considering? Unsure

Are you a healthcare practitioner? Yes

## Recommendations

**This person meets indications for treatment.**

Use a **potent nucleos(t)ide analogue with a high resistance barrier.**

*Evidence grade I, recommendation grade 1*

**Entecavir or tenofovir alafenamide** is preferred over tenofovir DF.

*Ungraded*

For more information on this recommendation, see the module, [“Insights on the Management of Patients With Chronic Hepatitis B.”](#)



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# EASL: Managing CHB in Special Populations



# 2017 EASL Guidelines: Decompensated Cirrhosis

- Patient should be referred to specialist and treated immediately using NA with high resistance barrier, **regardless of HBV DNA levels**
  - Preferred: ETV or TDF (TAF may be an option, but studies lacking)
    - With ETV, increase dose to 1 mg QD
- Monitor closely for drug tolerability, rare AEs (eg, lactic acidosis, kidney dysfunction)
  - Close monitoring strongly recommended in those with MELD score > 22 and impaired renal function
- Assess for liver transplantation
- **PegIFN is contraindicated in the setting of decompensated cirrhosis**

# 2017 EASL Guidelines: Liver Transplantation

- All individuals with HBV-related liver disease on a transplant waiting list should be referred to a specialist and should receive treatment with NA
- After liver transplantation, patients should receive combination of potent NA plus HBIg to prevent HBV recurrence
  - Those at low risk for recurrence (eg, negative for HBV DNA at time of transplant) can discontinue HBIg but must continue prophylaxis with potent NA
- HBsAg-negative patients receiving livers from anti-HBc–positive donors should receive prophylaxis with NA
  - Typically lifelong prophylaxis with lamivudine

# 2017 EASL Guidelines: Viral Coinfection

Viral Coinfection	Recommendations
HIV	<ul style="list-style-type: none"><li>▪ All patients should initiate ART, regardless of CD4+ cell count</li><li>▪ All patients should receive a fully suppressive TDF- or TAF-based ART regimen</li></ul>
HDV	<ul style="list-style-type: none"><li>▪ <i>Recommended in those with compensated liver disease:</i> pegIFN for at least 48 wks, regardless of on-treatment response, if well tolerated</li><li>▪ <i>In those with ongoing HBV DNA replication (persistently &gt; 2000 IU/mL):</i> consider NA therapy<ul style="list-style-type: none"><li>— May also consider NA therapy to prevent residual HBV replication in those with advanced liver disease</li></ul></li></ul>
HCV	<ul style="list-style-type: none"><li>▪ <b>HCV treatment with DAAs may cause HBV reactivation</b></li><li>▪ Patients meeting standard criteria for HBV treatment should undergo NA therapy</li><li>▪ <i>In HBsAg-positive patients receiving DAAs:</i> consider concomitant NA prophylaxis until Wk 12 post-DAA, monitor closely</li><li>▪ <i>In HBsAg-negative, anti-HBc-positive patients receiving DAAs:</i> monitor and test for HBV reactivation in cases of ALT elevation</li></ul>

# 2017 EASL Guidelines: Healthcare Workers

- Among healthcare workers with serum HBV DNA > 200 IU/mL who are conducting exposure-prone procedures, consider NA therapy to reduce transmission risk
  - HBsAg-positive healthcare workers with HBV DNA > 200 IU/mL may receive potent NA (ie, ETV, TDF, TAF) to decrease HBV DNA levels until undetectable or at least < 200 IU/mL prior to resuming exposure-prone procedures
  - In practicing surgeons, monitoring for compliance and efficacy is required
  - Antiviral therapy may be required even if healthcare worker does not meet standard indications for treatment
- HBV infection alone does not disqualify healthcare workers from surgery, dentistry, medicine, or allied health fields

# 2017 EASL Guidelines: Pregnancy

Pregnancy Scenario	Recommendations
Woman of childbearing age, planning pregnancy in near future	<ul style="list-style-type: none"><li>Without advanced fibrosis: consider delaying antiviral therapy until after birth</li><li>With advanced fibrosis: consider pegIFN</li></ul>
First trimester	<ul style="list-style-type: none"><li>Screen for HBsAg</li></ul>
Pregnant woman with CHB, advanced fibrosis/cirrhosis	<ul style="list-style-type: none"><li>Treat with TDF</li></ul>
Pregnant woman on NA therapy	<ul style="list-style-type: none"><li><i>Receiving TDF</i>: continue TDF</li><li><i>Receiving ETV or other NA</i>: switch to TDF</li></ul>
Pregnant woman with HBV DNA > 200,000 IU/mL or HBsAg levels > 4 log <sub>10</sub> IU/mL	<ul style="list-style-type: none"><li>Initiate prophylaxis with TDF at gestation Wk 24-28 and continue for up to 12 wks post delivery</li></ul>
Breastfeeding	<ul style="list-style-type: none"><li>Breastfeeding is <b>not</b> contraindicated in untreated, HBsAg-positive women or those receiving TDF-based therapy or prophylaxis</li></ul>

- **PegIFN is contraindicated in pregnancy**

# 2017 EASL Guidelines: Immunosuppressive Therapy or Chemotherapy

Population	Recommendations
<b>All candidates for immunosuppressive therapy and chemotherapy</b>	<ul style="list-style-type: none"><li>▪ Test for HBV markers prior to immunosuppression</li></ul>
<b>HBsAg-positive CHB patients</b>	<ul style="list-style-type: none"><li>▪ Treat with ETV, TAF, or TDF</li></ul>
<b>HBsAg-negative, anti-HBc-positive patients</b>	<ul style="list-style-type: none"><li>▪ Antiviral prophylaxis</li></ul>
<ul style="list-style-type: none"><li>▪ If at high risk for HBV reactivation, (including those undergoing stem cell transplantation or rituximab treatment in onco-hematological setting)</li><li>▪ If at moderate or low risk of HBV reactivation</li></ul>	<ul style="list-style-type: none"><li>▪ Preemptive therapy (but not prophylaxis):<ul style="list-style-type: none"><li>– HBsAg and/or HBV DNA monitored every 1-3 mos during and following immunosuppression</li><li>– ETV, TDF, or TAF therapy initiated in event of HBsAg seroreversion or detectable HBV DNA</li></ul></li></ul>

# 2017 EASL Guidelines:

## Dialysis and Renal Transplantation

- All candidates for dialysis and renal transplantation should be tested for HBsAg, anti-HBs and anti-HBc before starting therapy
  - If HBV seronegative, vaccination is recommended

Patient Groups	Action	Special Notes
HBsAg-positive dialysis patients	If initiating treatment, use ETV or TAF	May need to adjust dose of NA based on renal function
HBsAg-positive renal transplant recipients	Initiate prophylaxis or treatment with ETV or TAF	Monitor renal function carefully
HBsAg-negative, anti-HBc–positive dialysis patients or renal transplant recipients	No prophylaxis or treatment	Monitor HBsAg

# 2017 EASL Guidelines: Extrahepatic Manifestations

## Example Extrahepatic Manifestations

Vasculitis

Purpura

Polyarteritis nodosa

Arthralgias

Peripheral neuropathy

Glomerulonephritis

## Recommendations

- May respond to antiviral therapy with NAs
- Avoid pegIFN
  - May worsen some immune-mediated extrahepatic manifestations

# APASL Asia-Pacific Recommendations for CHB



# 2015 APASL Guidelines: Criteria for Treatment of CHB

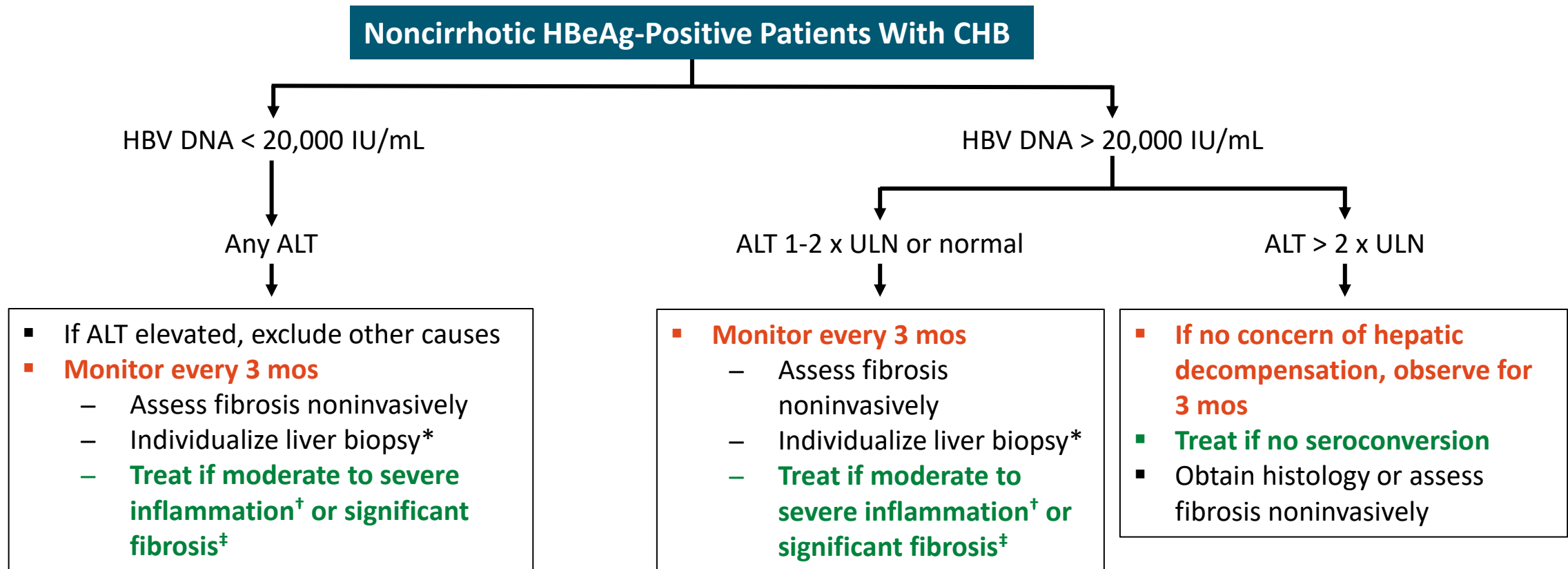
- Indication for treatment of CHB primarily based on:
  - Serum HBV DNA level
  - Serum ALT level
  - Severity of liver disease
    - Assessed via clinical evaluation, biopsy, or noninvasive methodology
- Additional considerations: HBeAg status, age, family history of HCC or cirrhosis, extrahepatic manifestations

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

# 2015 APASL Guidelines: Extrahepatic Manifestations

- Extrahepatic manifestations associated with CHB
  - Glomerulonephritis
  - Polyarteritis nodosa
  - Mixed cryoglobulinemia
  - Dermatological manifestations
- If HBsAg+ with active HBV replication, extrahepatic manifestations may respond to antiviral therapy
- Immune-mediated hepatic manifestations may be worsened by pegIFN
  - Plasmapheresis, corticosteroids, or IVIG useful with NA therapy in severe cases

# 2015 APASL Guidelines: Monitor vs Treat in HBeAg-Positive Patients



\*Biopsy if noninvasive tests suggest significant fibrosis, ALT persistently elevated, aged > 35 yrs, or family history of HCC or cirrhosis.

<sup>†</sup>METAVIR activity score A2/3 or Ishak activity score > 3/18 by biopsy.

<sup>‡</sup>METAVIR fibrosis score F ≥ 2 or Ishak fibrosis stage ≥ 3 by liver biopsy, liver stiffness ≥ 8 kPa by *FibroScan*, or APRI ≥ 1.5.

# Hep B Consult: Young Man With HBeAg-Positive CHB, Elevated HBV DNA, and Normal ALT

- Here, you see recommendations for a 27-yr-old man with HBeAg-positive CHB and the following characteristics:
  - ALT 1.2 x ULN
  - HBV DNA 1.5 million IU/mL
  - No liver necroinflammation or fibrosis
  - No other comorbidities

Enter your patient characteristics  
for instant guidance!  
[clinicaloptions.com/HepBConsult](https://clinicaloptions.com/HepBConsult)

## Your Patient Case

Do you want to see recommendations from the US, European, or Asian Pacific guidelines? Asian Pacific (APASL)

Before we begin, do any of the following special considerations apply? None apply

HBeAg status and HBV DNA level? HBeAg positive, HBV DNA > 20,000 IU/mL

ALT level? 1-2 x upper limit of normal (ULN)

Liver histology/fibrosis? Minimal or no inflammation or fibrosis

Renal dysfunction or renal replacement therapy? No

What approach are you considering? Unsure

Are you a healthcare practitioner? Yes

## Recommendations

**Monitor every 3 months without treatment.**

*Evidence grade B, recommendation grade 1*

- Assess fibrosis noninvasively
- Biopsy if noninvasive tests suggest significant fibrosis, ALT persistently elevated, aged older than 35 years, or family history of HCC or cirrhosis

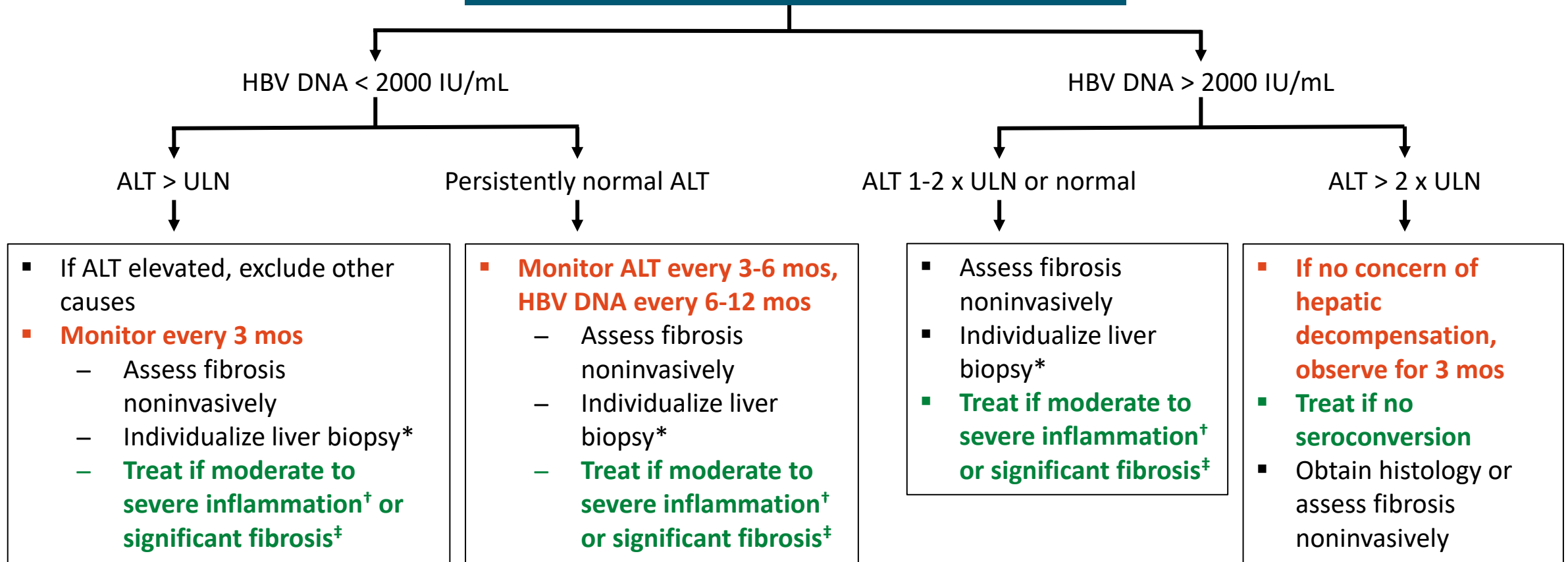
For more information on this recommendation, see the module, ["Insights on the Management of Patients With Chronic Hepatitis B."](#)



Slide credit: [clinicaloptions.com](https://clinicaloptions.com)

# 2015 APASL Guidelines: Monitor vs Treat in HBeAg-Negative Patients

## Noncirrhotic HBeAg-Negative Patients With CHB



\*Biopsy if noninvasive tests suggest significant fibrosis, ALT persistently elevated, aged > 35 yrs, or family history of HCC or cirrhosis.

<sup>†</sup>METAVIR activity score A2/3 or Ishak activity score > 3/18 by biopsy.

<sup>‡</sup>METAVIR fibrosis score F ≥ 2 or Ishak fibrosis stage ≥ 3 by liver biopsy, liver stiffness ≥ 8 kPa by *FibroScan*, or APRI ≥ 1.5.

# 2015 APASL Guidelines: Monitoring

- Follow patients not considered for treatment regularly
  - ALT level
  - HBV DNA
  - AFP
  - Ultrasonography
  - Fibrosis assessment

# APASL: Selecting Initial Antiviral Therapy in CHB



# 2015 APASL Guidelines:

## Criteria for Selecting PegIFN vs NAs

Comparative Measure	Peginterferon	Nucleos(t)ide Analogues
Strategy	Sustained off-therapy response (ie, immune control)	Maintained on-treatment response (ie, viral control)
Goal	HBV DNA < 2000 IU/mL, normal ALT	Undetectable HBV DNA, normal ALT
Duration	Finite	Prolonged or indefinite
Administration	Subcutaneous injection QW	Oral QD
Contraindications	Hepatic decompensation, pregnancy, immunosuppression, uncontrolled severe depression or psychosis	None
Key considerations	<ul style="list-style-type: none"> <li>▪ Frequent AEs (eg, influenzalike symptoms, headache, fatigue, myalgia, alopecia, ISRs)</li> <li>▪ More appropriate for young patients, those who are HBeAg+ with best change of seroconversion</li> </ul>	<ul style="list-style-type: none"> <li>▪ High rate of viral relapse upon therapeutic cessation</li> </ul>

# 2015 APASL Guidelines: Peginterferon

- **PegIFN alfa-2a or pegIFN alfa-2b**
- On-therapy monitoring
  - Full blood counts, serum ALT every mo
  - TSH, HBsAg every 3 mos
  - Safety through 12 mos of treatment
  - HBeAg and anti-HBe (if HBeAg+) and HBV DNA every 6 mos

# 2015 APASL Guidelines: Nucleos(t)ide Analogues

- NAs recommended for treatment-naïve patients include 3TC, adefovir, entecavir, telbivudine, and TDF
- **Preferred first-line options: TDF or entecavir**
  - Potent, high genetic barrier to resistance
- On-therapy monitoring
  - HBeAg, anti-HBe (if HBeAg+), and ALT every 3 mos
  - HBV DNA at Mo 3 and 6 of treatment, then every 3-6 mos
  - Renal function, bone profile every 3 mos in adefovir and TDF recipients

} **TAF not yet available when guidelines were published**

# Hep B Consult: Middle-Aged Woman With HBeAg-Negative CHB, Elevated HBV DNA and ALT

- Here, you see recommendations for a 45-yr-old woman with HBeAg-negative CHB and the following characteristics:
  - ALT 2.7 x ULN
  - HBV DNA 455,000 IU/mL
  - No liver necroinflammation or fibrosis
  - No other comorbidities

Enter your patient characteristics  
for instant guidance!  
[clinicaloptions.com/HepBConsult](https://clinicaloptions.com/HepBConsult)

## Your Patient Case

Do you want to see recommendations from the US, European, or Asian Pacific guidelines? Asian Pacific (APASL)

Before we begin, do any of the following special considerations apply? None apply

HBeAg status and HBV DNA level? HBeAg negative, HBV DNA > 2000 IU/mL

ALT level? > 2 x ULN

Liver histology/fibrosis? Minimal or no inflammation or fibrosis

Renal dysfunction or renal replacement therapy? No

What approach are you considering? Unsure

Are you a healthcare practitioner? Yes

## Recommendations

**Start treatment with entecavir, tenofovir DF, or peginterferon alfa.**

*Evidence grade A, recommendation grade 1*

*Note the APASL guidelines were released before the approval of tenofovir alafenamide.*

For more information on this recommendation, see the module, "[Insights on the Management of Patients With Chronic Hepatitis B.](#)"

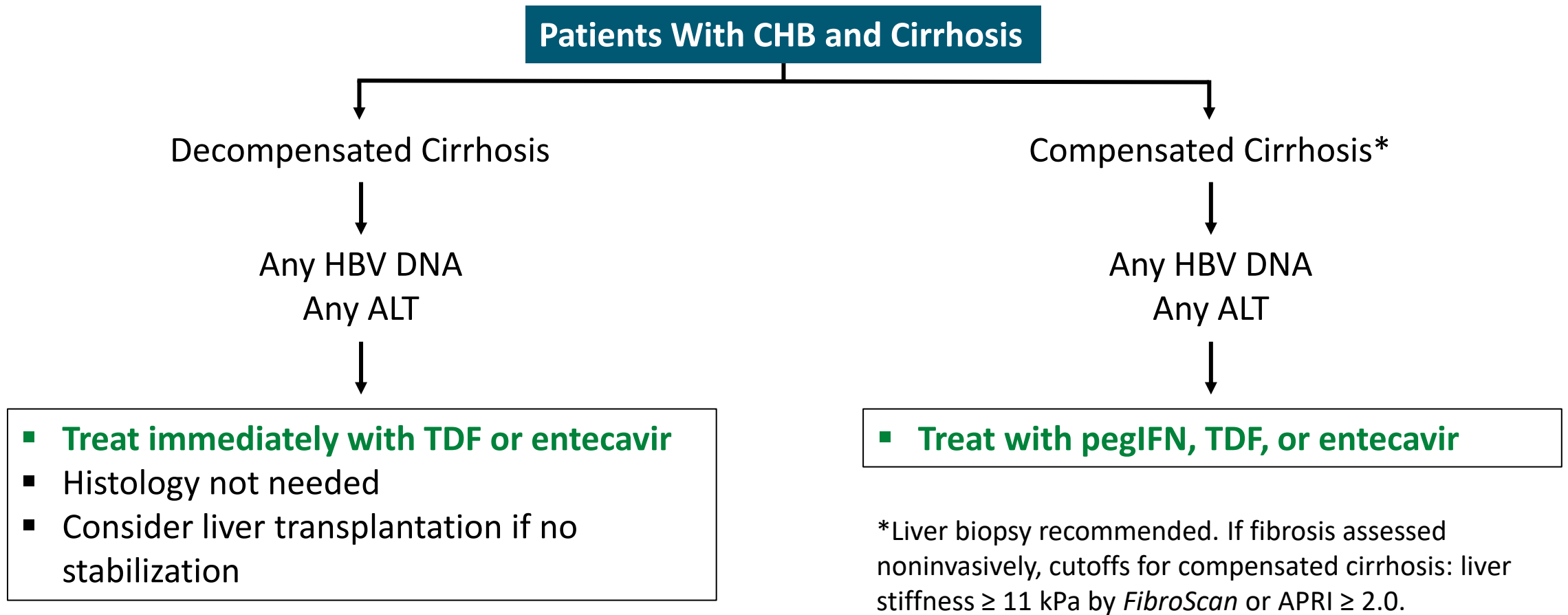


Slide credit: [clinicaloptions.com](https://clinicaloptions.com)

# APASL: Managing CHB in Special Populations

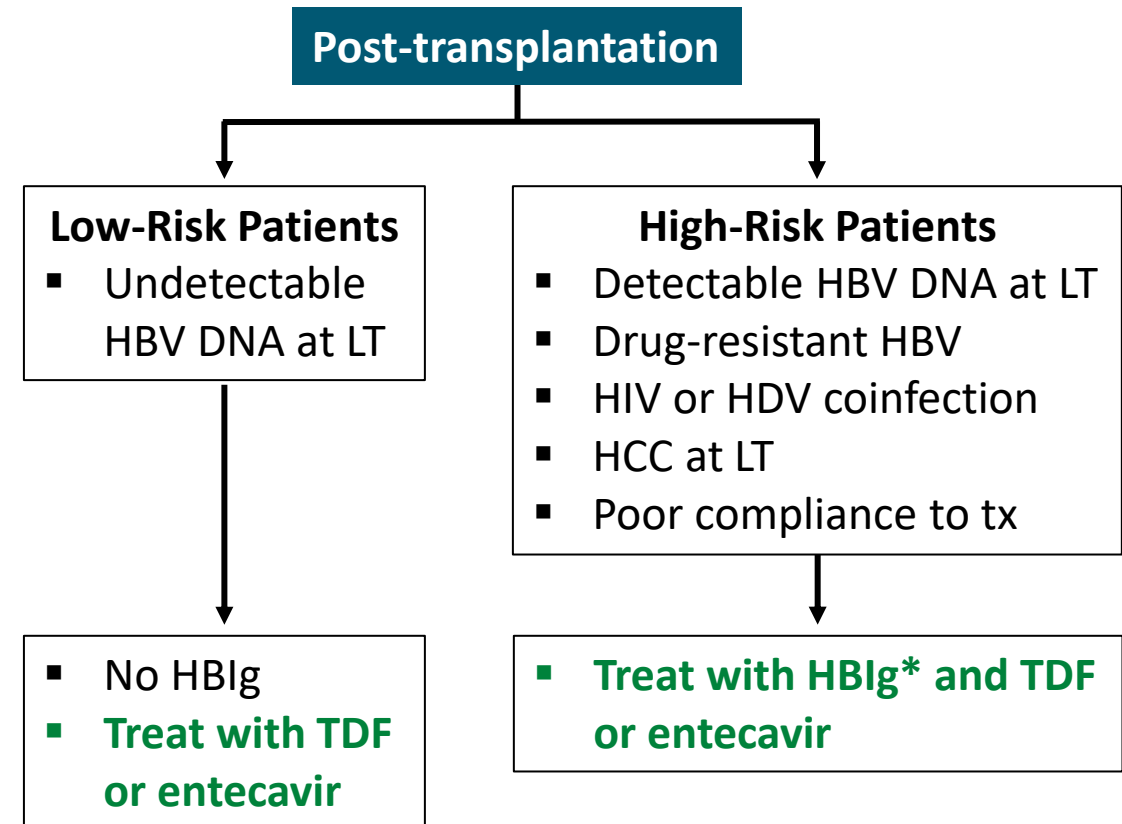


# 2015 APASL Guidelines: Cirrhosis



# 2015 APASL Guidelines: Liver Transplantation

- Pretransplantation
  - Administer TDF or entecavir to achieve undetectable HBV DNA, reduce risk of HBV recurrence
- Posttransplantation
  - Lifelong prophylactic therapy recommended



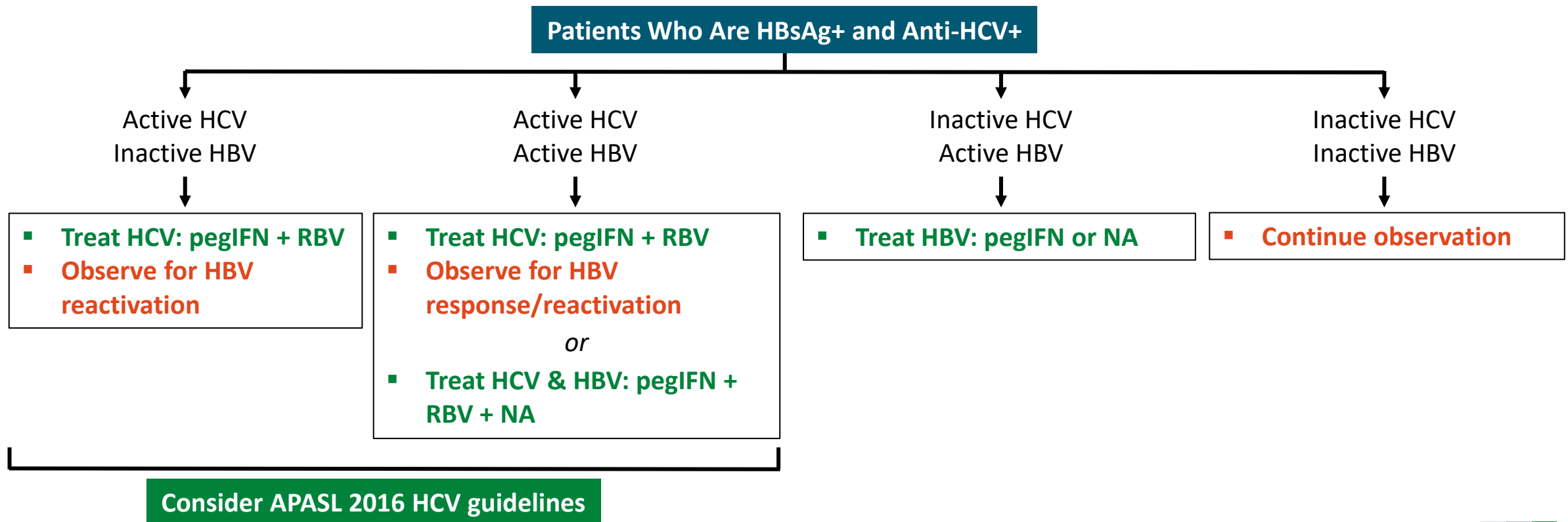
\*10,000 IU in anhepatic phase, then 600-1000 IU QD x 7 days, QW x 3 wks, monthly to keep anti-HBs > 100 mIU/mL for 1 yr.

# 2015 APASL Guidelines: HIV Coinfection

- Consider early dual HIV/HBV therapy, irrespective of immunologic, virologic, or histologic parameters
- TDF + (FTC or 3TC) + third agent active against HIV recommended
  - Do not use TDF, 3TC, or entecavir as single agents
  - Do not use adefovir or telbivudine

# 2015 APASL Guidelines: HCV Coinfection

- Identify dominant virus before selecting a therapeutic strategy
  - Measure HCV RNA, HBV DNA



# 2015 APASL Guidelines: HDV Coinfection

- In patients where HDV infection dominates, treat with pegIFN for 12-18 mos, then monitor for at least 6 mos
- In patients with persistent or fluctuating serum HBV DNA > 2000 IU/mL, consider treatment with NAs

# 2015 APASL Guidelines: Pregnancy and Breastfeeding

- If planning pregnancy soon
  - PegIFN-based therapy preferred for finite duration
  - Should be advised not to become pregnant on pegIFN therapy
- If pregnant
  - Monitor maternal HBeAg, HBV DNA status, and ALT level
  - TDF preferred during first to third trimesters in pregnant females with CHB requiring anti-HBV therapy; telbivudine may be considered
  - Short-term NAs beginning at 28-32 wks of gestation recommended for mothers with stable liver disease if HBV DNA > 6-7 log<sub>10</sub> IU/mL
- If breastfeeding
  - Discouraged during NA treatment

# 2015 APASL Guidelines: CKD, Dialysis, Renal Transplantation

- Monitor renal patients for anti-HBV treatment efficacy, stage of liver disease, and renal disease status
- PegIFN or NAs may be used in patients with CHB and renal dysfunction
  - Restrict to NAs in those receiving renal replacement therapy, adjust ETV or TDF dose if CrCl < 50 mL/min
  - Preferred first-line options: entecavir, telbivudine
- Administer prophylactic NAs in HBsAg+ patients undergoing renal transplantation
  - Avoid pegIFN for associated risk of rejection

# 2015 APASL Guidelines: Immunosuppressive Therapy or Chemotherapy

- Screen for HBsAg and anti-HBc prior to initiation of immunosuppressive or cytotoxic therapy
  - If HBsAg+ (any HBV DNA level), give prophylactic antivirals during and for 12 mos after therapy
  - If HBsAg- and anti-HBc+, test for HBV DNA
    - If HBV DNA detectable: treat similarly to HBsAg+ patients
    - If HBV DNA undetectable: monitor HBV DNA and ALT; treat with NAs upon reactivation before ALT elevation

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[Online module](#) with further insights on managing CHB



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