Chronic Hepatitis B Treatment Indications

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Disclosures

- None

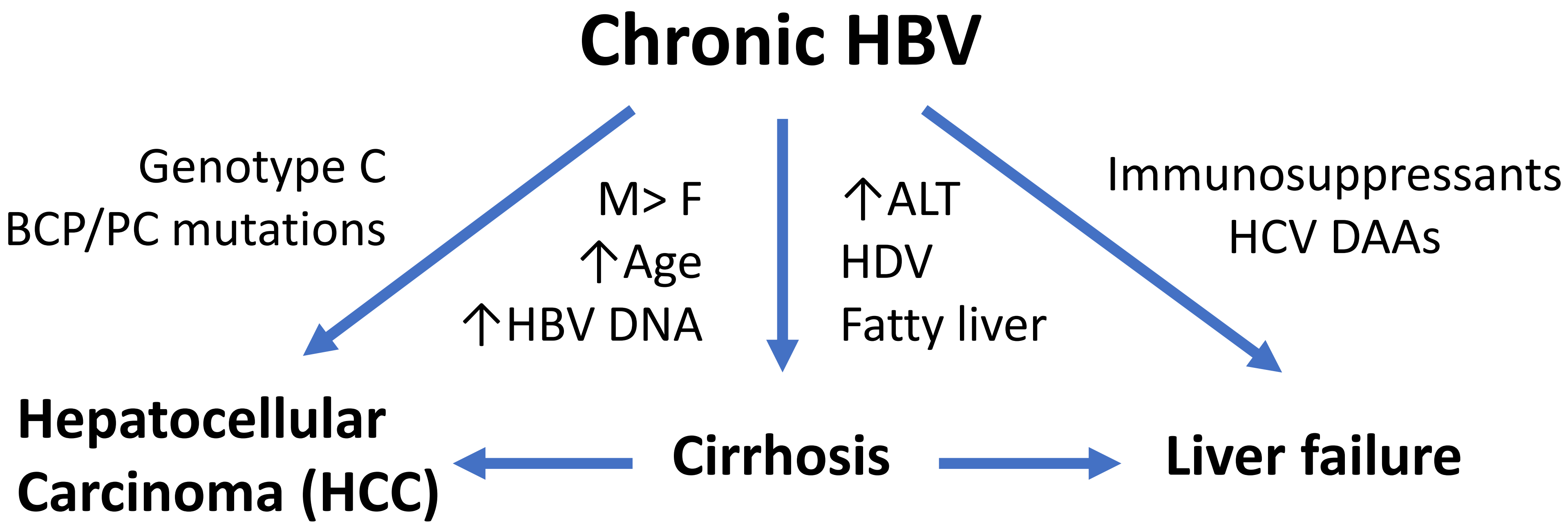
Objectives

- Review indications for treatment of chronic hepatitis B infection to prevent long-term liver complications
  - Summarize indications for treatment per American Association for the Study of Liver Diseases (AASLD) Guidelines
  - Summarize indications for treatment per HBV Primary Care Workgroup

HBV Natural History

1 in 4 of persons with chronic HBV will die prematurely from hepatocellular carcinoma, cirrhosis, or liver failure if unmonitored and untreated

How do we identify the 25% who are at risk for HBV complications?



Initial Evaluation of the HBsAg(+) Patient

History/Examination

- ☐ Symptoms/signs of cirrhosis
- ☐ Alcohol and metabolic risk factors
- ☐ Family history of hepatocellular carcinoma (HCC)
- ☐ Hepatitis A vaccination status

Routine Laboratory Tests

- ☐ CBC comprehensive
- ☐ Comprehensive metabolic panel including:
  - AST/ALT
  - Total bilirubin
  - Alkaline phosphatase
  - Albumin
  - Creatinine
- ☐ INR

Serology/Virology

- ☐ HBeAg/anti-HBe
- ☐ HBV DNA
- ☐ Anti-HAV (total or IgG) to determine need for vaccination if none documented
- ☐ Anti-HCV
- ☐ Anti-HDV
- ☐ Anti-HIV

Imaging/Staging Studies

- ☐ Abdominal ultrasound
- ☐ Elastography (e.g. FibroScan)
  or
  Serum fibrosis assessment[1] (e.g. APRI, FibroSure, FIB-4)

[1] APRI and FIB-4 scores can be calculated using platelet count and AST and ALT from routine labs. Calculators with score interpretation are available. See *Hepatitis B Online* APRI calculator and FIB-4 calculator. FibroSure and FibroTest are commercially available blood tests that can be ordered as well.

Why don't we adopt a "treat-all" strategy, e.g. for HCV and HIV?

- HCV treatment is curative whereas current HBV treatment is not.
- HIV infection itself is believed to cause systemic inflammation, even in persons with low viral load
- Universal HIV treatment also aims to prevent transmission to others since there is no HIV vaccine
- HBV treatment guidelines have gradually lowered viral load treatment thresholds, e.g. from 20,000 to 2000 for HBeAg neg and from 1 million to 200,000 for HBV pregnant women
- An individual's own immune control (off antiviral) is believed to be protective against liver complications
- The majority (~75%) of persons with CHB will not develop significant liver complications

How do we risk-stratify patients for HBV complications?

Viral load (HBV DNA)

↓

HBeAg status (relative to age)

Basal core promotor/precore mutations

Liver inflammation (ALT)

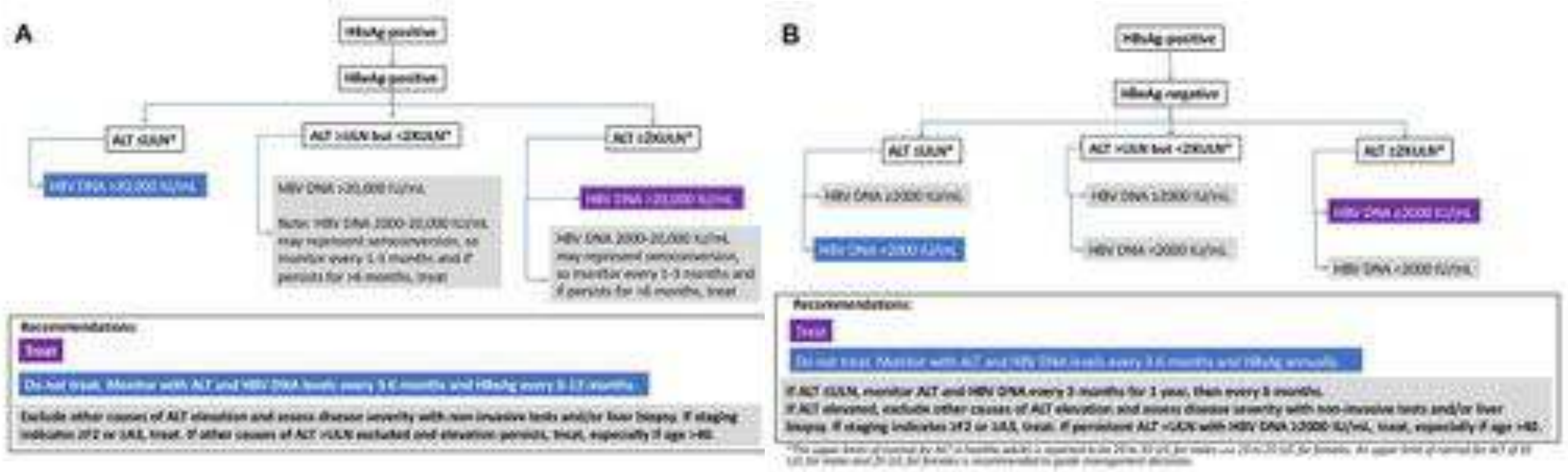
↓

Liver fibrosis (METAVIR score)

Goals of HBV Treatment

- Improve survival and quality of life by preventing disease progression and development of hepatocellular carcinoma
- Prevent mother to child transmission
- Prevent hepatitis B reactivation

AASLD 2018 Updated Treatment Guidelines



- Compensated cirrhosis and low level viremia < 2000 IU/mL. Treatment suggested regardless of ALT level
- Decompensated cirrhosis: treatment recommended regardless of HBV DNA or ALT level

From Terrault et al. Hepatology 2018, Vol. 67, No. 4

<table>
<tr><th></th><th>ALT (ULN = 25 F; 35 M)</th><th>HBV DNA (IU/mL)</th><th>Interval management</th><th>Treatment (Tx)</th></tr>
<tr><td rowspan="3">HBeAg +
w/o cirrhosis[1]</td><td>< 1 x ULN
Immune-tolerant phase</td><td>>1,000,000</td><td>q6mo ALT and HBV DNA, q6-12mo HBeAg</td><td>Consider tx if F3+ AND age > 40yo</td></tr>
<tr><td>1-2 x ULN</td><td rowspan="2">>20,000</td><td>q3mo ALT and HBV DNA, q6-12mo HBeAg
Reassess fibrosis</td><td>Consider tx if F2+, age > 40yo, or FHx HCC</td></tr>
<tr><td>> 2 x ULN
Immune-active phase</td><td>q1-3mo ALT and HBV DNA, q6-12mo HBeAg
Rule out other causes of elevated ALT</td><td>Tx if persistent[3]</td></tr>
<tr><td rowspan="3">HBeAg -
w/o cirrhosis[1]</td><td>< 1 x ULN
Inactive phase</td><td>< 2000</td><td>q6-12mo ALT and HBV DNA
q1-2y HBsAg for clearance</td><td>None</td></tr>
<tr><td>1-2 x ULN</td><td rowspan="2">>2000</td><td>q3mo ALT and HBV DNA
Reassess fibrosis</td><td>Consider tx if F2+, age > 40yo, or FHx HCC</td></tr>
<tr><td>> 2 x ULN
Immune reactivation phase</td><td>HBV core promotor/precore mutation testing optional</td><td>Tx if persistent[4]</td></tr>
</table>

Antiviral Tx Monitoring

1. If evidence of cirrhosis, initiate antiviral tx indefinitely regardless of HBeAg status, HBV DNA level, or ALT level to decrease risk of worsening liver-related complications.
2. Once on tx, follow ALT and HBV DNA q3-6mo. If HBV DNA not undetectable or rising after 12mo tx initiation, eval for med inadherence.
3. HBeAg+ adults without cirrhosis who seroconvert to HBeAg- on tx may discontinue tx after a consolidation period of at least 12mo of persistently nL ALT and undetectable serum HBV DNA levels.
4. Indefinite antiviral therapy for adults with HBeAg- immune activation, unless HBsAg seroclearance or a competing rationale for tx discontinuation
5. If antiviral is discontinued, monitor hepatic enzymes (e.g. ALT, tbili) for post-treatment flare (e.g. at 1, 3, and 6mo).


Hepatitis B Online
Hepatitis B Management: Guidance for the Primary Care Provider
Hepatitis B Management
Guidance for the Primary Care Provider

Management of the HBsAg(+) Patient[1]

Cirrhosis	HBV DNA (IU/mL)	ALT (U/L)	Management
YES	Any	Any	> TREAT with antiviral medication (page 6) > Monitor HBV DNA and ALT every 6 months > Refer to specialist for screening endoscopy and, if needed, for other cirrhosis-related complications > HCC surveillance, including in persons who become HBsAg(-) (page 7) > All patients with decompensated cirrhosis[2] should be promptly referred to a hepatologist
NO	>2,000	Elevated[3]	> TREAT with antiviral medication (page 6) > Monitor HBV DNA and ALT every 6 months > Monitor HBeAg and anti-HBe every 6 months in patients who are HBeAg+ at time of treatment initiation to evaluate for seroconversion from HBeAg(+)/anti-HBe(-) to HBeAg(-)/anti-HBe(+) > Check HBsAg annually if/when HBeAg negative
		Normal	> Monitor HBV DNA and ALT every 6 months > Liver fibrosis assessment every 2 to 3 years
	≤2,000	Elevated[3]	> Evaluate other etiologies for elevated ALT > Monitor HBV DNA and ALT every 6 months
		Normal	> Monitor HBV DNA and ALT every 6 months and HBsAg every 1 year for seroclearance

Which patients with chronic HBV should receive treatment?

Cirrhosis?

NO* → **HBV DNA > 2000?**

YES → **TREAT**

HBV DNA > 2000?

NO → **DO NOT TREAT**
Continue to monitor

YES → **Elevated ALT?**

Elevated ALT?

NO → **Monitor closely, consider treatment if > F2 fibrosis or FHx HCC**

YES → **Monitor closely, TREAT if persistent (e.g. > 3-6mo) elevation**

*<u>Need to actively rule out cirrhosis in all patients</u> with a baseline fibrosis assessment, e.g. *Fibroscan, FibroSure*

Assessing Treatment Response and Endpoints for Antiviral Discontinuation

After initiation of HBV antiviral, recheck HBV DNA every 3 months until undetectable, then every 6 months once undetectable. If the patient does not achieve undetectable HBV DNA after 1 year of antiviral therapy and the HBV DNA levels are not downtrending, obtain expert consultation or refer to a specialist.

- Persons with cirrhosis: Do not stop antiviral treatment, unless guided by expert consultation.
- Persons without cirrhosis and HBeAg(+) at baseline: Patients with persistent undetectable HBV DNA, normal ALT, and persistent HBeAg(-) and anti-HBe(+) 1 year after HBeAg seroconversion [from HBeAg(+)/anti-HBe(-) to HBeAg(-)/anti-HBe(+)] may trial off antiviral treatment.
- Persons without cirrhosis and HBeAg(-) at baseline: Continue antiviral treatment until HBsAg clearance.

Preferred Antiviral Treatment of the HBsAg(+) Patient

Drug	Adult dose	Pregnancy category[1]	Side effects	Monitoring on treatment
Entecavir *Baraclude*	Standard: 0.5 mg by mouth daily Decompensated liver disease: 1 mg by mouth daily Take 2 hours before or after food	Formerly FDA category C Limited pregnancy exposure, pregnancy exposure registry available Insufficient human data to assess risk of major birth defects No adverse effects observed in animal studies	Headache, fatigue, dizziness, nausea reported in □3% Post-marketing surveillance include infrequent reports of: > lactic acidosis > severe hepatomegaly	Adjust dose with CrCl <50 mL/min Avoid in pregnant patients Avoid in patients with prior exposure to lamivudine or known lamivudine resistance Lactic acid levels if clinical concern
Tenofovir disoproxil fumarate (TDF) *Viread*	300 mg by mouth daily Take without regard to food	Formerly FDA category B Pregnancy exposure registry available Extensive data from pregnant women with HIV or HBV infections indicate no increase in pregnancy complications or major birth defects	Nausea (9%) Post-marketing surveillance include infrequent reports of: > nephropathy > Fanconi syndrome > osteomalacia > lactic acidosis	Adjust dose with CrCl <50 mL/min Serum creatinine at baseline; if at risk for renal impairment, serum creatinine and phosphorus, and urine glucose and protein at least annually Consider bone density study at baseline and during treatment in persons with history of fracture or risks for osteopenia Lactic acid levels if clinical concern
Tenofovir alafenamide (TAF) *Vemlidy*	25 mg by mouth daily Take with food	No human data in pregnancy No adverse effects observed in animal studies	Headache (12%) Lactic acidosis/ severe hepatomegaly with steatosis is a warning for tenofovir AF due to rare reports with use of tenofovir DF	Avoid with CrCl <15 mL/min if not receiving hemodialysis Dose after HD in those on HD If at risk for renal impairment, serum creatinine and phosphorus, and urine glucose and protein as clinically indicated. Lactic acid levels if clinical concern

The worst adverse side effect of HBV antiviral is post-treatment flare from premature discontinuation of antiviral!

Ensure the patient understands the importance of long-term medication adherence before initiation antiviral

[1] In 2015, the US FDA replaced the pregnancy risk designation by letters A, B, C, D, and X with more specific language on pregnancy and lactation. This new labeling is being phased in gradually and, to date, only tenofovir alafenamide includes these additional data.

[2] Decompensated liver disease defined as Child-Turcotte-[illegible](see *Hepatitis B Online* CTP calculator).

Considerations when selecting HBV antiviral treatment

Pregnant or woman of childbearing age?

- YES → **TDF**
- NO → **CKD/ESRD or osteopenia/osteoporosis?**
  - YES → **Entecavir or TAF**
  - NO → **Prior HBV tx with lamivudine?**
    - YES → **TAF or TDF**
    - NO → **Entecavir, TAF or TDF** (may choose based on insurance formularies, cost, affordability)

Prescribing affordable HBV antiviral treatment

- Gilead and Bristol-Myers Squibb Patient Assistance Program (PAP)
- 340B Program
- GoodRx.com

Hepatitis B Online (www.hepatitisb.uw.edu)

- A CDC-funded viral hepatitis training resource
- Free, up-to-date educational website for diagnosing, monitoring, managing, and preventing hepatitis B virus (HBV) infection
- Free CME credits and CNE contact hours
- Sections on HBV medications and vaccinations, nine clinical calculators
- Simplified clinical guidance for primary care providers developed in collaboration with the multi-disciplinary HBV Primary Care Workgroup

Hepatitis B Online is funded through CDC Cooperative Agreement PS16-1608 and developed by the University of Washington (UW) National Hepatitis Training Center.

Perinatal HBV Management

Screen for HBV during each pregnancy[1]

HBsAg(+)[2]

Screen all household and sexual contacts for HBV

See *Initial Evaluation, Counseling, Management, and Treatment of the HBsAg(+) Patient* (pages 4 5 6)

If treatment indicated for active HBV, start TDF and continue until stopping criteria met[4]

If not on HBV treatment, recheck HBV DNA at 26 to 28 weeks gestation age to determine MTCT risk

- HBV DNA ≤200,000 IU/mL → Low risk for MTCT, no HBV antiviral indicated
- HBV DNA >200,000 IU/mL → High risk for MTCT, start TDF between 28 to 32 weeks → Stop TDF at time of birth and monitor for ALT flares at least every 3 months for 6 months

HBsAg(–)

See *HBV Serology Interpretation and Management* (page 3)

If HBV susceptible and at high risk for HBV infection, vaccinate during pregnancy[3]

ALL infants of HBsAg(-) women should:

- Receive birth dose HBV vaccine within 24 hours of birth

ALL infants of HBsAg(+) women should:

- Receive birth dose HBV vaccine and HBIG within 12 hours of birth
- Complete HBV vaccine series on schedule[5]
- Receive a post-vaccination serology test at 9 to 12 months of age with HBsAg and anti-HBs to assess for mother-to-child transmission and confirm immunity

HBV and Breastfeeding

All HBsAg(+) mothers, including those on TDF, should be educated on the value and safety of breastfeeding and that HBV is not transmitted through breastmilk.

Breastfeeding mothers with cracked nipples should practice proper nipple care and be informed that HBV vaccination and HBIG will protect against transmission from such blood exposures.

Abbreviations

MTCT – mother-to-child transmission
TDF – tenofovir disoproxil fumarate
HBIG – hepatitis B immune globuline

REACH-B HCC risk estimator

The development cohort consisted of 3584 patients without cirrhosis from the community-based Taiwanese REVEAL-HBV study (of whom 131 developed HCC during follow-up), and a validation cohort of 1505 patients from three hospitals in Hong Kong and South Korea (of whom 111 developed HCC during follow-up). We used Cox multivariate proportional hazards model to predict risk of HCC at 3, 5, and 10 years. Variables included in the risk score were sex, age, serum alanine aminotransferase concentration, HBeAg status, and serum HBV DNA level. We calculated the area under receiver operating curve (AUROC) and calibration of predicted and observed HCC risk.

https://www.mdcalc.com/reach-b-score-hepatocellular-carcinoma-hcc

Chronic Hepatitis B Treatment Decision Tool For Adults by Stanford Asian Liver Center (Mobile App/Desktop)

https://med.stanford.edu/liver/resources/online-treatment-tool.html

Hep B Consult App

Other HBV Resources

Core IM Podcasts on HBV

https://www.clinicalcorrelations.org/?s=hepatitis+b