AASLD/IDSA Practice Guideline on Treatment of Chronic Hepatitis B

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Background and Aims: Accumulating data related to prevention, surveillance and treatment of chronic hepatitis B (CHB) provided the impetus for this updated guideline, using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach.

Methods: The guideline was developed in compliance with the National Academy of Medicine standards. The guideline panel developed structured questions following the Population, Intervention Comparison, Outcomes (PICO) framework. The panel addressed 6 PICO questions covering prevention (maternal to infant transmission and horizontal transmission), surveillance for liver cancer (among hepatitis B surface antigen positive (HBsAg) persons co-infected with hepatitis C virus, hepatitis D virus and/or human immunodeficiency viruses and after HBsAg loss) and treatment (HBsAg positive persons in immune-tolerant or indeterminate phases as well as withdrawal of antiviral therapy), providing evidence-based recommendations on these topics. Four systematic reviews of the literature were conducted, and two existing systematic reviews were utilized to support the recommendations in this practice guideline.

Conclusions: This evidence-based guideline provides updated recommendations to optimize the care of persons with CHB.

Core Concepts Regarding Chronic Hepatitis B (CHB):

- Chronic hepatitis B (CHB) is a dynamic disease that can be characterized into five phases (Table 1): **immune-tolerant** (hepatitis B e antigen [HBeAg]-positive, HBV DNA >10,000,000 IU/mL and normal alanine aminotransferase (ALT) defined as <35 U/L for males and <25 U/L for females); **HBeAg-positive immune active** (HBeAg-positive, ALT elevated 2x upper limit of normal (ULN) or greater and HBV DNA >20,000 IU/mL); **HBeAg-negative immune active** (HBeAg-negative, ALT elevated 2xULN or greater and HBV DNA >2000 IU/mL); **inactive** (HBeAg-negative, normal ALT and HBV DNA <2000 IU/mL); and hepatitis B surface antigen (HBsAg)-negative immune clearance (HBV DNA undetectable, ± antibody to HBsAg (anti-HBs)).(1) As persons transition across phases over the lifetime of their infection, regular monitoring is essential to identify when a change of management is indicated, including use of antiviral therapy.

- **Indeterminate phases** refer to persons who are HBsAg-positive, HBeAg-positive or negative and have ALT and HBV DNA levels that do not meet the thresholds for immune active phase and are outside the thresholds defining immune tolerant or inactive CHB (**Table 1**). Up to 40% of adults with CHB do not meet one or more criteria for a defined phase and are in indeterminate phases.(2, 3) Indeterminate phases are more common in persons who are HBeAg-negative than HBeAg-positive.(2-4) An alternative term used to refer to these phases is "grey zone".

- Determination of liver disease severity is integral to monitoring because of its importance to making treatment and surveillance decisions. Non-invasive tests of fibrosis, such as hepatic transient elastography or serum markers such as FIB-4 can be considered for fibrosis staging, with elastography generally showing better performance than FIB-4.(5, 6) Liver biopsy is infrequently used but is the most accurate means of defining severity of inflammation.(7)

- Two classes of drugs are approved for the treatment of CHB: peginterferon and nucleos(t)ide analogues (NAs). Peginterferon is rarely used, given its limitations of applicability, safety and tolerability, compared with NA therapy. There are three NAs that are preferred for treatment of CHB: entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). All 3 drugs provide high efficacy in achieving HBV DNA suppression, have low rates of antiviral resistance, and are well tolerated and broadly applicable (including for persons with decompensated cirrhosis and immunocompromised states). Selecting among these drugs is based upon availability/cost, age, presence of renal or bone disease (avoid TDF), pregnancy (avoid ETV), HIV coinfection (avoid ETV unless HIV RNA suppressed on antiretroviral regimen), and prior treatment history (avoid ETV if prior lamivudine exposure). All drugs require consideration of renal function and/or dialysis. TAF is not recommended if creatinine clearance is less than 15ml/min and not yet on dialysis. ETV and

TDF need dose adjustment if renal dysfunction or on dialysis, though a change in NA is preferred for those on TDF with declining renal function.

- The goals of antiviral treatment are prevention of progression to cirrhosis, development of HCC and liver-related death. These clinical endpoints typically take years or decades to develop. Therefore, surrogate virological (HBV DNA undetectable by a PCR-based assay, HBeAg loss and seroconversion, HBsAg loss and seroconversion), biochemical (serum ALT normal) and infrequently, histological (improvement in necroinflammation by ≥ 2 points with no worsening of fibrosis) endpoints are used as measures of treatment efficacy.

- Other goals of antiviral therapy include reduction in onward transmission (both vertical (mother-to-child) and horizontal (e.g., sexual, parenteral, nosocomial)), improvement in patient reported outcomes and quality of life as well as decreased stigma.

- Increasingly, there is emphasis on the achievement of HBsAg loss as the desired endpoint for treatment (functional cure), because of its association with reduction in clinical outcomes and long-term durability, though it is recognized that functional cure is infrequent with current approved therapies, albeit higher with peginterferon than for NAs.

- Shared decision making is a collaborative process where a healthcare provider and patient make informed healthcare decisions by considering clinical evidence, taking into account the individual's personal values, preferences, and circumstances, allowing the patient to actively participate in choosing the best treatment option for them.

Introduction/Background

CHB affects ~258 million individuals (2022) globally(8) and leads to an estimated 1.1 million deaths annually due to complications of cirrhosis and hepatocellular carcinoma (HCC). Data from the National Health and Nutrition Examination Survey (2017-2020) identified an estimated 660,000 (Confidence Interval (CI): 410,000–1,000,000) persons with HBV infection(9) but with adjustments for infections among foreign-born persons immigrating to the United States (U.S.), the estimated disease burden of HBV infection may be as high as 1.8 million (C.I: 1.3–2.6 million).(10) Importantly, half of those infected are unaware of their diagnosis.(9) To reduce the morbidity and mortality of CHB, there is a need for continued efforts to identify infected individuals, prevent new infections through vaccination, initiate timely treatment with antiviral therapy and monitor for complications including surveillance for HCC. Consequently, the Centers for Disease Control and Prevention recommends screening for hepatitis B in all adults aged ≥18 years at least once during a lifetime and all pregnant persons during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing using a triple panel (HBsAg, anti-HBs, and total anti-HBc). HBV vaccination is recommended for all infants, all children and adolescents younger than 19 who have not been vaccinated, all adults aged 19-59 years regardless of risk factors and adults aged 60 years and older with risk factors for HBV or without known risk factors but who desire protection.

Antiviral therapy has been traditionally prioritized for persons at greatest risk for disease progression or development of HCC. These include those with immune active disease, as indicated by elevated ALT and hepatitis B virus (HBV) DNA levels and/or presence of significant liver inflammation or fibrosis. Treatment of these individuals has been shown to reduce the incidence of progression to cirrhosis, development of HCC, need for liver transplantation and HBV-related liver mortality.(11-13) Given the safety and excellent tolerability of NA therapy and the current gaps in HBV care and treatment,(11, 12) the World Health Organization (WHO) has recommended a simplification and expansion of antiviral treatment criteria,(13) in part to address the high disease burden in low and middle-income countries.

This guideline focuses on six specific issues related to management of CHB. Other recommendations for management of CHB addressed in the 2018 guidelines will continue to be applicable and the reader is referred to this document.(1) As this guideline was focused primarily on treatment, topics related to the screening and diagnosis of CHB were not included. The key questions addressed in this guideline are those commonly faced by providers in daily practice:

1. What is the optimal antiviral strategy for HBsAg-positive pregnant individuals with HBV DNA >200,000 IU/ml to prevent mother-to-child transmission of HBV?

2. Should antiviral therapy be provided to persons who are HBsAg-positive with viremia that do not meet disease-specific treatment indications to reduce transmission in high-risk scenarios?

3. Should HBsAg-positive individuals in the immune-tolerant phase start antiviral therapy versus observation?

4. Should HBsAg-positive, HBeAg-negative individuals without cirrhosis and in the indeterminate phase start antiviral therapy versus observation?

5. Should HBsAg-positive individuals without cirrhosis who have been on nucleos(t)ide analogue therapy for at least 3 years and who are HBeAg-negative with undetectable HBV DNA remain on or discontinue therapy?

6. Should individuals with chronic HBV without cirrhosis who clear HBsAg and HBsAg-positive persons with HCV, HDV, and/or HIV co-infection receive surveillance for HCC?

This guideline is intended primarily for health care professionals caring for those with CHB. Additionally, this guideline may assist policy makers in optimizing the care of individuals living with CHB. As with any clinical practice guideline, it provides general guidance to optimize the care of most individuals with CHB, but this should not replace clinical judgement where clinical considerations may justify a course of action that differs from this guideline. A shared decision-making approach between patient and provider is strongly endorsed.

Methods

Overview

This guideline was developed in compliance with the National Academy of Medicine standards for trustworthy practice guidelines and uses the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Multiple systematic reviews of the literature were conducted to support the recommendations in this practice guideline. An enhanced understanding of this guideline will be obtained by reading the applicable portions of the systematic reviews.

Formulation of clinical questions and determining outcomes of interest

The methodology team from the Mayo Clinic Evidence-based Practice Center facilitated brainstorming sessions in which the panel developed structured questions following the Population, Intervention Comparison, Outcomes (PICO) framework. The panel prioritized 6 questions. The panel also ranked the outcomes of interest to prioritize patient-important outcomes.

Review of Evidence

Existing systematic reviews were identified to address 2 of the 6 PICO questions. *De novo* systematic reviews were conducted for 4 PICO questions. A comprehensive search of several databases was conducted from each database's inception to February 13, 2024, (questions 1-3) and December 5th, 2024 (question 4). Databases included MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the methodology team. Controlled vocabulary and keywords were used to describe search concepts. Details of the systematic reviews, inclusion and exclusion criteria, risk of bias assessment and synthesis methods are detailed in the accompanying technical review.

Development of recommendations

This guideline follows the GRADE approach.(14) The approach starts with determining certainty in the evidence (i.e., how trustworthy are the estimates of effect). Certainty can be high, moderate, low or very low. Randomized trials start by warranting high certainty and nonrandomized studies low certainty. Certainty can then be rated down due to risk of bias, imprecision, inconsistency, indirectness or publication bias. Certainty can be rated up due to large effects, dose-response gradients and based on the direction of plausible confounding.(15) The second step of GRADE is to apply the evidence to decision (EtD) framework to balance the desirable and undesirable effects and consider contextual factors such as patient values, resource use, feasibility, acceptability and equity.(16) Recommendations can be strong or conditional based on the judgments of the EtD criteria. A majority vote by the panel determined the direction and strength of the recommendations.

Interpretation of strong and conditional recommendations

A strong recommendation is made when guideline developers believe that all or almost all informed people would make the recommended choice for or against an intervention. A conditional recommendation is made when guideline developers believe most informed people would choose the recommended course of action, but a substantial number would not. A strong recommendation implies uniformity and the need to facilitate implementation, whereas a conditional recommendation means that the focus of providers and patients should be on shared-decision-making and eliciting values and preferences. For policymakers, the implication of a strong recommendation is that the recommendation can be adopted as a policy in most situations because variability in clinical practice would likely be inappropriate. Conversely, a conditional recommendation implies that variability between individuals or regions may be appropriate.(17)

PICO Question 1: What is the optimal antiviral strategy for HBsAg-positive pregnant individuals with HBV DNA >200,000 IU/ml to prevent mother-to-child transmission of HBV?

Population: HBsAg-positive pregnant individuals with HBV DNA levels >200,000 IU/mL

Intervention: Maternal antiviral therapy with TDF or TAF

Comparator: TDF vs no antiviral intervention, or TDF vs TAF during pregnancy

Outcome: (a) Mother-to-child transmission if the infants receive standard immunoprophylaxis and (b) antiviral safety⌐SEP⌐

Recommendation:
1. For pregnant persons with HBV DNA levels greater than 200,000 IU/mL at any time point during pregnancy, regardless of HBeAg status, AASLD recommends initiating tenofovir disoproxil fumarate or tenofovir alafenamide at gestational week 28 to prevent mother-to-child transmission. Tenofovir disoproxil fumarate has a more extensive safety record in pregnancy than tenofovir alafenamide.
Strength of recommendation: Strong *Certainty of evidence: Moderate*

Implementation Considerations

- For pregnant persons who have been receiving HBV treatment with TDF or TAF, we suggest continuing therapy. For those receiving entecavir or other antivirals, we suggest switching to TDF or TAF, given their established efficacy and safety in pregnancy.

- Amniocentesis increases the risk of perinatal transmission in those with HBV DNA >2,000,000 IU/mL. Therefore, initiating TDF or TAF early in pregnancy to achieve viral suppression should be considered when invasive procedures are anticipated. Similarly, if the pregnant individual has a high risk for preterm labor, earlier TDF or TAF treatment should be considered.

- The optimal timing of initiation of TDF/TAF prophylaxis is at gestational week 28. For mothers with HBV DNA levels >200,000 IU/mL who seek perinatal care later than week 28, TDF or TAF prophylaxis should still be initiated immediately to reduce the risk of MTCT.

- For mothers with HBV DNA levels >200,000 IU/mL, TDF or TAF prophylaxis should be initiated at gestational week 16 in combination with subsequent infant vaccination, if hepatitis B immune globulin (HBIG) use in the infant is unavailable.

- For pregnant persons for whom the sole purpose of treatment is to prevent perinatal transmission, we suggest TDF or TAF can be discontinued at delivery.

- For pregnant persons in whom treatment is discontinued, AASLD suggests HBV DNA and ALT should be monitored for withdrawal flares at intervals of 1-3 months for a period of up to six months. Treatment should be reinitiated in the event of a significant withdrawal flare (ALT ≥5 x upper limit of normal).

- For breastfeeding persons who require or are on HBV treatment, AASLD suggests the use of TDF or TAF.

Background

Screening for HBV infection in all pregnant persons during their initial prenatal visit, for every pregnancy, using a triple panel (HBsAg, anti-HBs and total anti-HBc) is strongly recommended by the CDC and U.S. Preventive Services Task Force guidelines (USPSTF).[18, 19] A positive HBsAg result should be followed by quantitative HBV DNA, HBeAg, and ALT testing to determine the risk of perinatal transmission and to assess the severity of maternal liver disease.[20-22] Non-invasive tests for fibrosis may not be reliable during pregnancy;[5] however, assessment for cirrhosis using ultrasound and/or clinical evaluation is important, as it could alter management.

Despite the appropriate administration of HBIG and birth-dose vaccination within 24 hours of birth [22], perinatal transmission of HBV occurs in approximately 8–10% of infants born to HBsAg-positive pregnant persons with HBV DNA levels >200,000 IU/mL.[20, 22] The 2018 AASLD conditional recommendations for these individuals included initiating TDF therapy (preferred) at gestational weeks 28–32, continuing until delivery or up to three months postpartum.[1] Interim data from clinical trials have provided additional safety data on TAF as well as the timing of antiviral prophylaxis initiation and discontinuation for pregnant persons whose only indication for antiviral therapy is the prevention of MTCT.[23]

Evidence and Rationale

Prophylactic TDF therapy, initiated from the start of the third trimester (gestational week 28 onwards) until delivery, among pregnant persons with high viremia (≥200,000 IU/mL) effectively reduces maternal viremia and decreases the rate of MTCT.(20, 23-25) A systematic review evaluating the efficacy and safety of TDF versus TAF in preventing MTCT included 31 studies: 2,588 highly viremic pregnant individuals received TDF, 280 received TAF, and 1,600 received no treatment. Compared to no treatment, TDF and TAF were equally effective (risk ratio: 1.09, 95% CI 0.15–7.65) and safe (risk ratio 1.11 (95% CI 0.5–2.5 for TDF).(23) TDF or TAF are preferred over lamivudine or telbivudine due to their lower risk of antiviral resistance(20, 26) and established long-term safety data in infants of HBV-infected and/or HIV-infected pregnant persons(23, 24, 27). There are insufficient safety data to recommend ETV use during pregnancy.(20, 27)

In the absence of birth-dose HBIG, the rate of MTCT of HBV among untreated HBeAg-positive persons is 16-25%. A recent RCT found that starting TDF at gestational week 16 with infant's HBV vaccination was noninferior to starting TDF at week 28 with HBIG and vaccination in preventing transmission in pregnant individuals with HBV DNA >200,000 IU/mL (0.76% [1/131] vs. 0% [0/142]). Thus, TDF initiation at week 16 should be considered for viremia control with subsequent infant HBV vaccination if HBIG is not an option for the infant.(28) Amniocentesis increases the risk of perinatal transmission in those with HBV DNA >2,000,000 IU/mL.(29)

Post-delivery, the continuation of antiviral therapy should be guided by maternal CHB treatment needs through shared decision-making, considering clinical factors, maternal values and preferences, as well as future conception plans (**Figure 1**). Discontinuing TDF or TAF prophylaxis post-delivery is appropriate if continued antiviral treatment is not necessary. The risks of ALT flares are comparable regardless of TDF cessation at delivery versus at postpartum weeks 4–12.(23) Close monitoring with HBV DNA and ALT every 1–3 months for up to six months after discontinuation is suggested, with the potential reintroduction of antiviral therapy warranted for significant hepatitis flares (defined as ALT ≥5x ULN).(23, 25) Breastfeeding does not increase HBV transmission risk, and TDF or TAF use during lactation is safe for both the mother and the infant.(30-33)

PICO Question 2: Should antiviral therapy be provided to persons who are HBsAg-positive with viremia that do not meet disease-specific treatment indications to reduce transmission in high-risk scenarios?

Population: HBsAg-positive persons in high-risk settings to transmit to HBsAg-negative persons

Intervention: Use of antiviral therapy

Comparator: No use of antiviral therapy

Outcomes: (a) New HBV infection in exposed uninfected individual (HBsAg negative person tests HBsAg positive); (b) Safety of antivirals

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Recommendation 2:

For persons who are HBsAg-positive with viremia not meeting disease-specific treatment indications and who are in high-risk scenarios for transmission to others, AASLD suggests a shared decision-making approach regarding antiviral treatment.

Strength of recommendation: Conditional

Certainty of evidence: Very Low

Implementation Considerations

- Individuals who are viremic and in high-risk scenarios for transmission may be offered antiviral treatment to reduce risk of transmission, though there are limited data on this issue. Shared decision-making is critical to evaluate exposure and transmission risk and to consider the vaccine and immunity status of those who are potentially exposed, favoring antiviral treatment if they are unvaccinated, may have inadequate response to vaccine, have compromised immune systems, and/or have unknown vaccine status (**Table 2**). As risks may not always be disclosed, individuals requesting treatment for prevention of transmission can be prescribed antiviral medication.

- It is essential to avoid stigmatizing practices or messages in discussions regarding horizontal transmission. People with CHB should not be restricted in their daily activities, contact sports, school activities, professional training, and should not be required to take antivirals due to risk of transmission in those settings. Within households, worksites, and other settings, routine contact, sharing meals, and hugging are not considered routes of transmission, though sharing of personal hygiene items (e.g., toothbrush, razor) should be avoided.

- Most healthcare workers with CHB are not in high-risk scenarios to transmit HBV to their patients, but healthcare workers performing Society for Healthcare Epidemiology of America (SHEA) category III exposure-prone procedures are at higher risk for HBV transmission and should follow guidelines from SHEA and the Centers for Disease Control and Prevention (CDC) and may require antiviral treatment to reduce transmission risk.(34, 35) Both CDC and SHEA recommend against the need for healthcare worker disclosure to patients and staff. CHB is a protected condition by the American with Disabilities Act and people with CHB are protected from discrimination in employment, education and other areas, and all cases of discrimination should be reported to appropriate authorities.

- All persons considering or initiating antiviral therapy for prevention of HBV transmission should be counseled regarding the risks of treatment cessation. The decision to continue or stop antiviral therapy should be guided by shared decision-making. If the primary indication is the reduction of horizontal transmission risk, the continuation of antiviral therapy may be revisited when transmission risks are no longer high. Examples include healthcare workers no longer engaged in category III/exposure-prone procedures and those for whom the risk of transmission has decreased via harm reduction and/or immunization of susceptible persons. The decision to continue or stop antiviral therapy should be guided by shared decision-making, considering clinical factors, personal values and preferences, and potential risks of post-cessation ALT flare.

Background

Vaccination of susceptible persons, universal precautions, harm reduction strategies to reduce transmission by injection drug use (e.g., needle exchange programs), and barrier methods during sex are mainstays of preventing horizontal transmission of HBV. Despite recommendations for HBV vaccination in the U.S., including more recently universal vaccination of all persons 59 years of age or younger,(36) many individuals are susceptible to acquiring HBV infection (anti-HBc and anti-HBs negative) due to missed HBV vaccination opportunity or insufficient response.(37) In the U.S., the number of people with acute HBV infection remains high, with an estimated 13,000 or more cases per year in 2022.(34)

People who are HBsAg positive but do not meet disease-specific treatment indications may be in high-risk settings where horizontal transmission of HBV may occur (**Table 2).** Possible high-risk scenarios for horizontal transmission of HBV include persons who are engaging in unprotected sex or with multiple partners, persons who are injecting drugs with inconsistent harm reduction practices, persons living with susceptible household members and healthcare workers performing level III exposure-prone procedures.(38) Extrapolating from more robust data regarding the prevention of vertical transmission from mother to child,(20) a systematic review was conducted to investigate if antiviral treatment may prevent horizontal transmission.(39) SHEA and other committees worldwide have established guidance for managing healthcare workers engaged in category III/exposure-prone procedures with variable HBV DNA thresholds allowed.(38, 40) Antiviral therapy is recommended in these scenarios to suppress HBV DNA below these thresholds despite a paucity of data indicating such strategies' effectiveness.

Evidence and Rationale

Indirect evidence from a few nonrandomized studies suggests that use of antiretroviral regimens with activity against HBV may prevent de-novo HBV infection among unvaccinated HIV positive individuals engaged in high-risk behavior.(41-44) Additionally, there are no reported transmissions in the literature from healthcare workers with low or undetectable HBV DNA

while on therapy to their patients.(34,35) While the absence of reports does not completely exclude the possibility of transmission from people with suppressed HBV DNA, there is biological plausibility that lowering HBV DNA with antiviral therapy reduces the risk of horizontal transmission**.** There is high acceptability, especially for those concerned about transmission including healthcare workers, due to ethical responsibilities to avoid harm to others. Due to biological plausibility, high acceptability, and lack of significant harm, for people who are HBsAg positive with viremia but do not meet disease-specific treatment indications and are in high-risk scenarios for transmission to others, AASLD suggests a shared decision-making approach with the individual regarding use of antiviral treatment to reduce transmission to others.

PICO Question 3: Should individuals in the immune-tolerant phase start antiviral therapy versus observation?

Population: Persons who are HBsAg-positive, HBeAg-positive without cirrhosis with HBV DNA>10^7 IU/mL with normal ALT

Intervention: Antiviral therapy

Comparator: Monitoring or no therapy

Outcome: Hepatocellular carcinoma

Recommendation 3:

For persons in the immune-tolerant phase (defined as HBeAg-positive, HBV DNA >10^7 IU/mL, and normal ALT levels), the AASLD suggests antiviral therapy for those over age 40 years or with significant liver inflammation (grade 2 or higher) or fibrosis (F2 or greater) on liver biopsy or noninvasive tests. For persons under age 40 years who are interested in starting treatment earlier, the AASLD suggests shared decision-making with consideration of risk factors as well as the benefits and risks of treatment.

Strength of Recommendation: Conditional

Quality and Certainty of Evidence: Very low

Implementation Considerations

- Accurate identification of immune-tolerant phase requires persistently normal ALT levels with HBV DNA >10^7 IU/mL in HBeAg-positive persons. Upper limits of normal ALT levels are 35 U/L for males and 25 U/L for females based on ≥2 measurements ≥6 months apart. HBeAg-positive individuals with ALT above ULN or with HBV DNA levels <10^7 IU/mL may be transitioning to immune active CHB and are not the focus of this recommendation.

- Non-invasive tests of fibrosis, such as hepatic transient elastography or serum markers such as FIB-4 can be considered for fibrosis assessment, with elastography showing better performance than FIB-4. A vibration-controlled transient elastography cutoff value of 7 kPa yielded a sensitivity of 69% and a specificity of 83% for identifying F2 or higher fibrosis.(45)
- For persons younger than 40 years or without significant inflammation or fibrosis, factors to guide decision making should include age (child/adolescent versus adult), family history of HCC, and likelihood of adherence to treatment and monitoring, and prevention of transmission to others. As the duration of therapy is anticipated to be many years, addressing the need for long-term adherence and monitoring is important and particularly relevant for children and adolescents being considered for antiviral therapy.
- Close monitoring is recommended if antiviral treatment is not initiated. HBV DNA and ALT levels should be tested at least every 6 months for adolescents and adults with immune-tolerant CHB to monitor for transition to immune-active CHB. A similar monitoring schedule is suggested for children, though the optimal interval has not been determined.

Background

In persons who acquire HBV infection at birth or in infancy, most begin life in the immune-tolerant phase of CHB **(Table 1),**(46) characterized by HBeAg-positivity and very high HBV DNA levels $>10^7$ IU/mL, but persistently normal ALT levels and minimal or no hepatic inflammation or fibrosis on liver biopsy.(1) Although some have questioned whether the immune system is truly tolerant to HBV, the name reflects that despite persistently high levels of replication for years, overt inflammation and fibrosis do not occur in most individuals. However, the strong association between HBV DNA level and HCC risk has raised the question of whether treatment should be considered during the immune-tolerant phase.(47-50)

Transition from the immune-tolerant to immune active phase of CHB may occur in childhood, adolescence, or adulthood, with the average age of transition around 30 years.(51, 52) Age over 40 years is associated with higher likelihood of significant histological disease in HBeAg-positive persons with normal ALT and late HBeAg seroconversion (beyond age 40) has been associated with an increased risk of HCC.(50, 51, 53) Young individuals who remain consistently in the immune-tolerant phase have a low risk of disease progression or HCC but those with falling HBV DNA levels and rising ALT are likely transitioning from the immune-tolerant to the immune active phase.(54, 55) The natural history and impact of therapy in those who fall between the definitions of immune-tolerant and immune active (HBV DNA $<10^7$ IU/mL and/or ALT 1-2x ULN) phases, the HBeAg-positive indeterminate phase **(Figure 2)**, are less well defined.(1)

Evidence and Rationale

Antiviral therapy with NA suppresses HBV DNA replication, although due to very high levels of replication seen during the immune-tolerant phase, HBV DNA levels may not be suppressed to undetectable levels, even with long-term therapy. Studies have largely compared different antiviral strategies rather than treatment versus no treatment (or placebo), with a focus on virological rather than clinical outcomes. Consequently, the impact of treatment during the immune-tolerant phase on cirrhosis and HCC risk is unknown.

The systematic review of studies evaluating treatment in the immune-tolerant phase included 16 studies,(52, 56-68) of which 9 were comparative (including 4 RCTs) and 4 were in children. The comparative studies evaluated NA vs interferon, NA vs NA combination or NA + interferon vs no treatment. The other 7 studies (3 pediatric) were single-arm observational studies of NA +/- interferon. Based on the systematic review, treatment with NA with peginterferon for 1-1.5 years was associated with a significant decrease in HBV DNA but had limited effect on HBeAg and HBsAg loss/seroconversion. In an adult study of 4 years of TDF alone vs. TDF plus emtricitabine, combination therapy increased suppression of HBV DNA to <69 IU/mL (OR 2.60 95% CI 1.21, 5.56) but did not improve HBeAg or HBsAg loss.(67) Notably, by 4 years of treatment, only 55% in the TDF alone arm achieved HBV DNA <69 IU/mL compared to 76% in the TDF plus emtricitabine arm.

Only one retrospective study of NA therapy for up to 80 months that used propensity score matching reported on HCC incidence or mortality with a HR for HCC of 0.23 (95% CI 0.05, 1.104) and HR for mortality of 0.24 (95% CI 0.066, 0.83).(69) Indirect evidence that may support treatment of older persons in the immune-tolerant phase comes from a Korean study showing that treated individuals in the immune active phase of CHB had lower rates of HCC than those untreated in the immune-tolerant phase, though 26% of those in the immune-tolerant group had HBV DNA levels $<10^7$ IU/mL.(54) Individuals who continued to meet all criteria for immune-tolerant disease (HBeAg-positive, ALT<ULN and HBV DNA $>10^7$ IU/mL) had a very low risk of HCC.(55, 70, 71) Persons who are older, male, with lower HBV DNA levels, higher ALT, and lower platelet count had been reported to have a higher risk of HCC but they may be more likely to be transitioning out of the immune-tolerant phase. These data reinforce that serial follow-up is essential to identify transition out of the immune-tolerant phase.

Antiviral therapy may decrease HCC risk by suppressing viral replication, thereby decreasing clonal expansion and integration of HBV DNA into the host genome.(72, 73) No direct evidence has shown a lower risk of HCC or mortality in persons in the immune-tolerant phase with HBV DNA levels $>10^7$ IU/mL treated with antiviral therapy. Because subclinical liver injury is associated with an increased HCC risk and is more commonly reported in persons above age 40 in the immune-tolerant phase, the benefit of treatment in older individuals and those with significant fibrosis (F2 or greater) likely outweighs the risks.

Although the potential benefits of treatment in the immune-tolerant phase are uncertain, if treatment reduces the incidence of HCC, the benefits may be substantial. Other considerations may include treatment duration (long-term treatment likely required with non-negligible cost and

monitoring burden), adverse events (overall low), risk of resistance mutations (low with ETV and TDF/TAF but may be increased due to very high replication levels in immune-tolerant phase), need for monitoring if treatment is not initiated and transmission risk to personal contacts (limited data). Transition from the immune-tolerant to immune active phase of CHB is usually asymptomatic. Therefore, individuals in the immune-tolerant phase not on antiviral therapy require regular laboratory testing to assess transition to the immune active phase of CHB.

PICO Question 4: Should HBsAg-positive, HBeAg-negative individuals without cirrhosis and in the indeterminate phase start antiviral therapy versus observation?

Population: Persons who are HBsAg-positive, HBeAg-negative without cirrhosis in indeterminate phase

Intervention: Antiviral therapy

Alternative: Monitoring without therapy

Outcome: Hepatocellular carcinoma or cirrhosis

Recommendation 4:

In adults with HBsAg-positive, HBeAg-negative chronic HBV infection without cirrhosis and in the indeterminate phase, AASLD suggests antiviral therapy using a shared decision-making approach by assessing risks and benefits and to reevaluate that decision at each follow-up visit if treatment has not been initiated.

Strength of recommendation: Conditional

Certainty of evidence: Very low

Implementation Considerations (**Figure 3**)

- Factors relevant to decision-making are stage of fibrosis, age, and sex. For example, those who are older (>40 years), male, and with low normal platelet counts (<180 k/mm^3) may be more likely to benefit from treatment. Persons with advanced fibrosis (F3/F4) are recommended for treatment. The non-invasive tests thresholds with high sensitivity for advanced fibrosis are FIB-4 of >1.45 and vibration-controlled elastography of ≥8 kPa. Other factors to consider in shared decision making include pill burden, cost of therapy (although entecavir and tenofovir disoproxil fumarate are generic) and the requirement for regular monitoring.

- If treatment is not initiated, individuals should be monitored with ALT and HBV DNA testing every 3-6 months for the first year and every 6 months thereafter.
- The decision regarding initiation of treatment should be re-assessed at each follow-up visit as preferences and values may change over time. Progression to advanced fibrosis/cirrhosis, or transition to the HBeAg-negative immune active phase should prompt initiation of treatment.
- Individuals with persistently elevated ALT but HBV DNA <2000 IU/mL should be evaluated for other etiologies of liver injury and managed for those etiologies if found.

Background

Previous guidance did not recommend treatment of those in the HBeAg-negative indeterminate phase **(Table 1)**.(1) Instead, it recommended that such individuals be monitored and have treatment initiated if they transitioned to an immune active phase. In addition, prior guidance suggested that treatment should be initiated if there is evidence of significant fibrosis (≥F2) or moderate inflammation (≥A3) or persistently elevated ALT (>ULN) with HBV DNA ≥2000 IU/mL, especially if over the age of 40 years.(1)

Individuals who are HBeAg-negative and in the indeterminate phase are predominantly comprised of two subgroups: (I) those with normal (<ULN) or mildly elevated (<2XULN) ALT but HBV DNA ≥2000 IU/mL, and (II) those with elevated ALT (>ULN) but HBV DNA <2000 IU/mL. Since fluctuations in ALT and HBV DNA levels may occur during the course of CHB, phase determination should be based on results of ALT and HBV DNA tests on ≥2 occasions over a 6-to-12-month period. While some individuals in the indeterminate phase may transition to an immune active or an inactive phase, many remain in the indeterminate phase for years. Several cohort studies suggest that individuals who remain in the indeterminate phase are at risk of HCC.(3, 74)

Evidence and Rationale

HBsAg-positive, HBeAg-negative adults without evidence of cirrhosis in the indeterminate phase are at risk of hepatitis flares, cirrhosis, hepatic decompensation, and HCC though the range in risk is wide.(75) Studies show that antiviral treatment can decrease these risks in those persons who meet current indications for treatment,(76, 77) although the impact on HCC development is small compared to other outcomes such as hepatic decompensation and liver-related mortality.(78) Thus, the potential benefit of antiviral therapy in persons who are HBsAg-positive, HBeAg-negative without evidence of cirrhosis and are in the indeterminate phase, in reducing the risk of adverse clinical outcomes, particularly HCC, are expected to be smaller and must be balanced against the need for long-term and often lifelong treatment. Data from a recently published systematic review and meta-analysis(75) were leveraged to address the benefits versus harms of initiating antiviral therapy compared to monitoring among HBeAg-negative adults without cirrhosis in the indeterminate phase.

The systematic review for the incidence of HCC in persons in the indeterminate phase included 37 cohorts (9 with and 28 without antiviral therapy) from 32 studies (1 RCT and 31 observational – 6 prospective, 1 retrospective/prospective and 24 retrospective) involving 14,691 individuals.(75) The analysis included 4 studies of HBsAg-positive adults who were exclusively HBeAg-positive, 14 with exclusively HBeAg-negative, and 14 with a mix of HBeAg-positive and HBeAg-negative. The pooled annual incidence rate of HCC was 0.32% (95%CI 0.21%-0.48%) overall, 0.24% (95%CI 0.08-0.70%) in those treated and 0.34% (95%CI 0.22-0.53%) in those untreated. On multivariate models adjusted for age, sex, and HBeAg status, age, percentage male, positive HBeAg status, and retrospective study design were associated with a higher incidence of HCC, while use of antiviral treatment, higher platelet count, and better study quality were associated with a lower incidence of HCC. The significant association between use of antiviral treatment and lower incidence of HCC (aIRR 0.36, 95%CI 0.16-0.81) persisted after adjusting for age, sex, HBeAg status, and platelet count. There were fewer studies on incident cirrhosis (13 cohorts) and hepatic decompensation (10 cohorts) precluding assessment of the impact of antiviral therapy on these outcomes.

Of the 14 cohorts (2 treated and 12 untreated) that included only adults who were HBeAg-negative, the annual incidence rate of HCC was 0.13% (95%CI 0.01-0.34) overall, 0% in treated and 0.17% (95%CI 0.01-0.43%) in untreated persons.(79) There were too few events for meaningful comparisons between those treated vs. untreated.

These data suggest that antiviral treatment may decrease the risk of HCC among adults with CHB who are HBeAg-negative without cirrhosis and in the indeterminate phase; however, the strength of the evidence is low because of cross-comparisons across observational studies, a wide range in risk of HCC overall, and a wide range in benefit. Thus, AASLD suggests that the decision to start antiviral treatment should be individualized with each person discussing the risks and benefits with their provider.

While NA treatment is safe and available as generics in most countries, the need for long-term and in many cases, lifelong treatment can be a burden to individuals and a financial burden to healthcare systems given that those in the HBeAg-negative indeterminate phase comprises up to 40% of persons with CHB.(2, 3) The alternative strategy of close monitoring and initiation of antiviral therapy once the individual has transitioned to immune active CHB has been shown to be associated with very low risk of HCC in a large prospective North American study.(80) This strategy requires adherence to monitoring but starting treatment in the indeterminate phase also requires adherence to monitoring on treatment.

PICO Question 5: Should HBsAg-positive individuals without cirrhosis who have been on nucleos(t)ide analogue therapy for at least 3 years and who are HBeAg-negative with undetectable HBV DNA remain on or discontinue therapy?

Population: HBsAg-positive, HBeAg-negative, HBV DNA undetectable for at least 2 years, after at least 3 years of NA therapy, and no cirrhosis

Intervention: Stop NA therapy

Comparator: Continue NA therapy

Outcomes: (a) HBsAg loss; (b) Clinical relapse defined as HBV DNA >2000 and ALT >2x
ULN; (c) Resumption of antiviral treatment

Recommendation 5:

In adults with chronic hepatitis B, who are HBeAg-negative without cirrhosis, with sustained
undetectable HBV DNA on nucleos(t)ide analogue therapy, AASLD suggests not withdrawing
nucleos(t)ide analogue therapy until HBsAg loss.

Strength of recommendation: Conditional

Certainty of evidence: Very Low

Implementation Considerations (**Table 3**)

- Persons who have a desire to discontinue therapy should engage in a shared decision-making
  process with their providers considering the benefits (HBsAg loss) and risks (hepatitis flare,
  liver decompensation and need for re-treatment) and need for frequent monitoring.

- Those who may consider stopping treatment should meet all the following criteria:

  o no history of advanced fibrosis/cirrhosis, hepatic decompensation (variceal bleed,
    ascites, hepatic encephalopathy, hepatorenal syndrome), HCC or extrahepatic
    complications of HBV.

  o if HBeAg-positive at start of antiviral therapy, have seroconverted to HBeAg-
    negative and anti-HBe-positive for ≥1 year and have undetectable HBV DNA
    maintained for at least 2 years.

  o If HBeAg-negative at start of antiviral therapy, the duration of undetectable HBV
    DNA should be at least 2 years.

  o have no co-infection with human immunodeficiency virus (HIV) or hepatitis D virus
    (HDV).

  o have a quantitative HBsAg level <100 IU/mL.

  o be willing to adhere to frequent monitoring after stopping treatment.

- Following withdrawal of treatment, serum ALT and HBV DNA should be monitored every
  1-3 months for the initial 6 months, then every 3 months for the next 6 to 12 months.
  Thereafter, monitor at 3 to 6 month intervals depending on the ALT and HBV DNA values.

- Treatment should be re-started immediately if any of the following criteria are met:

- o an HBV DNA level ≥10,000 IU/mL (4 log IU/mL) regardless of ALT level, or

- o ALT ≥5 x ULN regardless of HBV DNA or

- o total bilirubin >2.5 mg/dL, or

- o any symptoms of hepatic decompensation.

- Treatment may also be re-started anytime for any of the following reasons: personal wish to re-start, extrahepatic complications of HBV, or if treatment initiation criteria are met (HBV DNA >2000 IU/mL and ALT >2x ULN).

Background

Annual rates of spontaneous and on-treatment NA-related HBsAg loss remain very low (~0.5-1%).(21, 81) A small uncontrolled cohort study reported a remarkably high rate of HBsAg loss of 39% at four years, following withdrawal of NA (adefovir) therapy.(82) Subsequently, several prospective randomized and retrospective cohort studies have reported variable rates of HBsAg loss ranging from 2-20% over follow-up of up to three years after NA discontinuation.(83-87) These findings led the Asian Pacific Association for the Study of Liver and European Association for the Study of the Liver to recommend consideration of withdrawal of NA therapy as a strategy to enhance HBsAg loss in adults with HBeAg-negative CHB who have achieved sustained HBV DNA suppression for at least 2-4 years,(88, 89) while WHO recommends discontinuation in exceptional circumstances.(13) The primary risks related to NA withdrawal are ALT flares and worsening of liver disease, including decompensation. A systematic review was conducted to address the benefits and downsides of stopping versus continuing NA therapy among persons who are HBeAg-negative, who do not have cirrhosis and have been on NA therapy for at least three years with undetectable HBV DNA for at least two years. The analysis also included those who were HBeAg-positive at treatment initiation, who experienced HBeAg seroconversion and completed at least one year of consolidation therapy.

Evidence and Rationale

There is consensus that persons with a history of or current evidence of cirrhosis (clinical or histological), history of decompensation or HCC should not stop therapy, due to an increased risk for hepatitis flare and hepatic decompensation following virological relapse; thus, these persons were excluded from this systematic review.(90) The decision to stop antiviral therapy among persons who are HBeAg-negative without cirrhosis with the intended goals of enhancing the rate of HBsAg loss, maintaining off-treatment suppression of HBV DNA (partial cure), and removing the burden of chronic therapy is complex. These potential benefits must be weighed carefully against the risk for virological relapse, which may lead to ALT flares, hepatic decompensation, liver transplantation, death, and need for re-treatment. The systematic review included 11 studies (4 RCTs and 7 observational studies) involving 1,957 individuals (948 in the discontinuation group and 1,009 in the continuation group).(91) The studies spanned multiple

geographical regions, including China, Taiwan, Germany, Belgium, Canada, and the USA. All studies predominantly enrolled adults, with ages ranging from 30 to 57 years with the proportion of female participants varying from 14.3% to 42%. In the decision-making process, the committee considered that the majority of the evidence supporting the benefit of stopping therapy was derived from four small prospective RCTs in which the rates of HBsAg loss were modest, 10.6% over two years (versus 0% in those who remained on therapy, RR 12.65 (1.58 to 101.51) while the downsides, i.e. ALT flares 26.9% (RR 11.63 [0.15 to 891.61]) at two years and retreatment 23% (RR 0.24 [0.07-0.4]) at 1.5 years were substantial.(83, 84, 86, 87) Seven uncontrolled retrospective cohort studies from routine practice settings reported even higher rates of adverse complications including decompensation and death.(92-98) Collectively, the analyzed studies revealed considerable variability in outcomes leading to a very low certainty of evidence. The evidence from RCTs suggested the rate of HBsAg loss was small (11% at 2 years) but the risks of stopping therapy (ALT flares, 27% at two years, decompensation 0% at 1.5 years and need for re-treatment 42% at 5 years) were moderate. Given the long-term safety of NA treatment and availability of low cost-generics and reportedly higher rates of adverse complications including decompensation and death after NA discontinuation, from large cohort studies, the committee recommended against withdrawal of therapy until functional cure was achieved.

Of the biomarkers currently available to predict outcomes in NA withdrawal, quantitative HBsAg at the end of treatment is the best. Lower levels of quantitative HBsAg are associated with higher likelihood of HBsAg loss and lower likelihood of re-treatment.(99-103) While there is some heterogeneity in the literature regarding the optimal cut-off to guide the decision to stop NAs, a level of quantitative HBsAg <100 IU/mL is regarded as a conversative value that maximizes likelihood of HBsAg loss and minimizes risk of clinical relapse and need for re-treatment. However, achievement of quantitative HBsAg level <100 IU/ml does not guarantee absence of risk and close monitoring after NA withdrawal is still required.

PICO Question 6: Should individuals with chronic HBV without cirrhosis who cleared HBsAg and HBsAg-positive persons with HCV, HDV, and/or HIV co-infection receive surveillance for HCC?

Population: Persons with HBV infection who either achieved HBsAg loss or have hepatitis C virus (HCV), hepatitis D virus (HDV), and/or human immunodeficiency virus (HIV) co-infection

Intervention: Hepatocellular carcinoma (HCC) surveillance

Comparator: No HCC surveillance

Outcome: Early HCC diagnosis

Recommendations:

6. In persons who achieved HBsAg loss, AASLD suggests continued HCC surveillance for those with cirrhosis, with family history of HCC, men who experienced HBsAg loss after age 40, and women who experienced HBsAg loss after age 50.

Strength of recommendation: Conditional

Certainty of evidence: Very Low

7. In persons with HBV-HDV co-infection, AASLD suggests HCC surveillance of adults independent of cirrhosis status. The decision to undertake surveillance in children should be individualized due to the risk of HCC being unknown in this population.

Strength of recommendation: Conditional

Certainty of evidence: Very Low

8. In persons with HBV-HIV co-infection, AASLD suggests HCC surveillance for men ≥18 years of age and women ≥ 40 years of age.

Strength of recommendation: Conditional

Certainty of evidence: Very Low

9. In persons with HBV-HCV co-infection, AASLD recommends treatment for HCV and suggests HCC surveillance as per criteria for HBV mono-infection.

Strength of recommendation: Conditional

Certainty of evidence: Very Low

Implementation Considerations

- Determination of HCC risk after HBsAg clearance using specific prediction models may be used to aid in decision making for surveillance of intermediate-to-high risk persons but these models require further validation. For those persons for whom the timing of HBsAg loss is unknown, the decision to undertake surveillance should be individualized, with consideration of cirrhosis and family history of HCC.

- Direct acting antiviral (DAA) therapy is recommended for all persons with chronic HCV infection. For those with prior HCV infection (anti-HCV positive, HCV RNA negative), surveillance for HCC is the same as those with HBV alone.

- As the risk of HCC among children and adolescents with HDV coinfection is largely unknown, the decision to undertake surveillance should be individualized, with consideration of age, family history and stage of fibrosis.

- For those with prior HDV infection (anti-HDV positive, HDV RNA negative), surveillance for HCC is the same as those with HBV alone.

- For persons with triple or quadruple viral infections (HBV plus HIV, HDV and/or HCV), the surveillance recommendation should be that of the coinfection with the highest associated risk. For example, if HBV-HDV-HCV, the surveillance would follow that for HBV-HDV.

- HCC surveillance with ultrasound and serum AFP performed at semiannual (approximately every 6 months) intervals is recommended as the most cost-effective approach per the 2023 AASLD HCC guideline.(104)

Background

CHB infection is the most common cause of HCC worldwide.(105) HCC can occur in persons with CHB without cirrhosis and in persons who have cleared HBsAg. Prior studies of persons with CHB (106) with or without cirrhosis (107) have shown that regular HCC surveillance can increase survival. The 2023 AASLD HCC guideline (104) recommends HCC surveillance **(Table 4)** for persons with cirrhosis and those with a higher risk (annual HCC incidence about ≥ 0.2%).

As HCC risk may differ in those who have achieved HBsAg loss (108, 109) and those with other viral co-infection,(110, 111) systematic reviews were performed to obtain HCC risk information for these populations to inform the current guideline.

Evidence and Rationale

For individuals who have cleared HBsAg, one study reported an annual HCC incidence of 0.86% overall, 2.42% in those with cirrhosis, 0.43% in those without cirrhosis, 1.07% for males, 0.57% for females, 1.21% if ≥ 50 years, and 0.33% if <50 years,(112) while another reported a rate of 0.4% for male and 0% for female without cirrhosis.(113) In a meta-analysis of 24 studies of 33,838 persons who cleared HBsAg, the pooled proportions of HCC occurrence ranged from 0.35% to 0.78% following treatment-induced or spontaneous HBsAg loss, respectively.(109) Another meta-analysis reported higher HCC risk if persons were older (45-50 years) at the time of HBsAg loss.(108) Both meta-analyses showed a strong association between male sex and family history of HCC with risk of HCC after HBsAg loss. Taken together, following HBsAg loss whether spontaneous or with antiviral therapy, significant HCC risk remains for those with established cirrhosis and for those without cirrhosis who were 45-50 years or older at the time of HBsAg loss. A recently proposed risk score after HBsAg clearance based on age, presence of cirrhosis, family history of HCC, and moderate alcohol consumption can also be used to consider HCC surveillance for intermediate-to-high risk persons.(112)

There are no FDA-approved therapies for HDV and persons with HDV coinfection are at higher risk for progressive liver disease in the absence of effective therapies. For persons with HDV co-

infection, a U.S. study of 4817 persons with HBV including 158 with HDV found an HCC incidence per 1,000 person-years of 18.65 in HBV/HDV versus 4.84 in HBV mono-infected individuals.(114) The large majority of both mono-infected (92.3%) and co-infected (87.3%) participants in this study did not have cirrhosis. These data suggest that the annual HCC risk for those with HBV/HDV coinfection is above the cost-effective HCC surveillance threshold (i.e. >0.2%) even for persons without cirrhosis.(104) Natural history data on children and adolescents are sparse(115) but HCC has been reported in this age group, leading to the recommendation to individualize the decision to undertake surveillance with consideration of age (e.g. older adolescents), stage of fibrosis (if F2 or higher) or family history of cirrhosis or HCC.

For persons with HBV and HIV co-infection, a U.S. study reported an HCC incidence rate of 2.09 (1.60-2.73) per 1000 person-years in the modern combination antiretroviral therapy era (2006-2015).(116) In another analysis inclusive of HBV/HIV individuals from 1995-2016, the incidence rate of HCC per 1000 person-years was 1.8 overall, 1.0 if < 40 years of age, 2.1 if 40-49 years, 2.6 if ≥ 50 years, 0.7 for females, 1.8 for males, 3.3 if HBV DNA is detectable and 1.9 if not, suggesting that male sex and age ≥ 40 represent higher risk groups who may benefit from HCC surveillance.(117)

For persons with HBV and HCV co-infection, the systematic review identified 4 studies that provide HCC incidence, all in the pre-DAA era.(39, 116, 118-120) A large study from Australia including 2604 HBV/HCV co-infected persons with a median age of 35 years reported low HCC incidence per 10,000 person-years of 5.9 overall, 6.52 for males and 3.86 for females.(118) The other two studies included few participants (<140) and the fourth study was a systematic review, which reported substantially lower HCC risk with HCV cure among HBV/HCV. DAA therapy is recommended for all persons with chronic HCV infection.(121) Those with HBV/HCV co-infection are expected to have similar HCC risk after HCV cure to that of HBV mono-infected persons, highlighting the importance of achieving HCV cure as an important means of reducing HCC risk.

Limitations of this Guideline and Research Gaps

1. Most of the guideline recommendations have low or very low certainty of evidence, highlighting the need for higher quality data to aid in refining future recommendations.

2. Nomenclature harmonization was not addressed in this guideline. These include:

- Terminology of the phases of infection/disease in CHB
- Determination of upper limits of normal for ALT for male and female adults and children
- Consensus on terminology of indeterminate versus grey zone to describe the groups with ALT and/or HBV DNA levels outside the phase of immune active and inactive CHB

These research gaps would be best addressed through a multi-society consensus process.

Topics well covered in previous AASLD 2018 Guidance and for which recommendations have not changed.

- Treatment of children
- Treatment of HBeAg positive and negative immune active CHB with ALT >2x ULN
- Strategies to enhance adherence with long-term therapy
- Persons with CHB on NA therapy with intermittent or persistent low-level viremia (Figure 4)
- Persons with evidence of virologic breakthrough (**Figure 4**)
- Treatment of persons with cirrhosis (**Figure 5**)
- Management of CHB in special populations such as those who are transplant recipients (liver and non-liver), those with acute HBV, and those with coinfections (HCV, HDV and HIV).

Controversial sections and additional topics that are not addressed in the current guideline.

Additional areas in the realm of CHB treatment not addressed were:

- Role of HBsAg quantitation, HBV RNA and hepatitis B core-related antigen (HBcrAg) in management of CHB
- Benefit of treatment to prevent HCC among inactive carriers with high HBsAg levels (>1000 IU/mL)
- Role of peginterferon add-on or switch therapy to NA as strategy to achieve functional cure
- Diagnostic and prognostic performance of NITs as a guide to antiviral treatment initiation
- While the WHO guideline excluded consideration of HBeAg status and used a single threshold (>2000 IU/ml) for HBV DNA to determine treatment eligibility, the AASLD guideline continues to endorse use of HBeAg and uses additional thresholds for HBV DNA to guide decision-making. This use reflects the ease of access to laboratory testing in the U.S. versus low and middle-income countries and the differences in level or viremia and responses to treatment in persons who are HBeAg-positive versus those who are HBeAg-negative.

Plans for updating

The topics listed above that were not covered in this guideline will be addressed in future guideline documents and expert practice opinion papers. As the field of HBV therapeutics is

robust and new drug therapies focused on functional cure are anticipated, updated guidelines can be anticipated as new therapies are FDA-approved.

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Figure 1: *Management algorithm for pregnant persons with chronic hepatitis B infection.* For persons who are found to be HBsAg-positive and not on antiviral therapy, HBV DNA should be assessed. Those with HBV DNA levels >200,000 IU/mL should initiate antiviral therapy with TDF (preferred) or TAF, preferably at gestational week 28 or any time prior to delivery. Antiviral therapy can be discontinued at delivery if there is no ongoing indication for treatment other than preventing perinatal transmission. If treatment is discontinued, HBV DNA and ALT should be monitored at intervals of 1-3 months for a period of up to six months for withdrawal flares. Treatment should be reinitiated in the event of a significant withdrawal flare (ALT ≥5 x upper limit of normal). Persons who are known to be HBsAg-positive and receiving antiviral therapy should continue antiviral therapy throughout pregnancy and after delivery. Persons receiving ETV should switch to TDF or TAF during pregnancy and breastfeeding. Breastfeeding is safe while taking TDF or TAF.

Infants born to HBsAg-positive women should receive hepatitis B immune globulin and first dose of HBV vaccine within 12 hours of birth. They should complete the HBV vaccine schedule based on birth weight. Testing for HBsAg and anti-HBs should occur at 9-12 months of age.

CHB: chronic hepatitis B; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide ETV Entecavir, ULN Upper limit of normal; hepatitis B surface antigen (HBsAg)
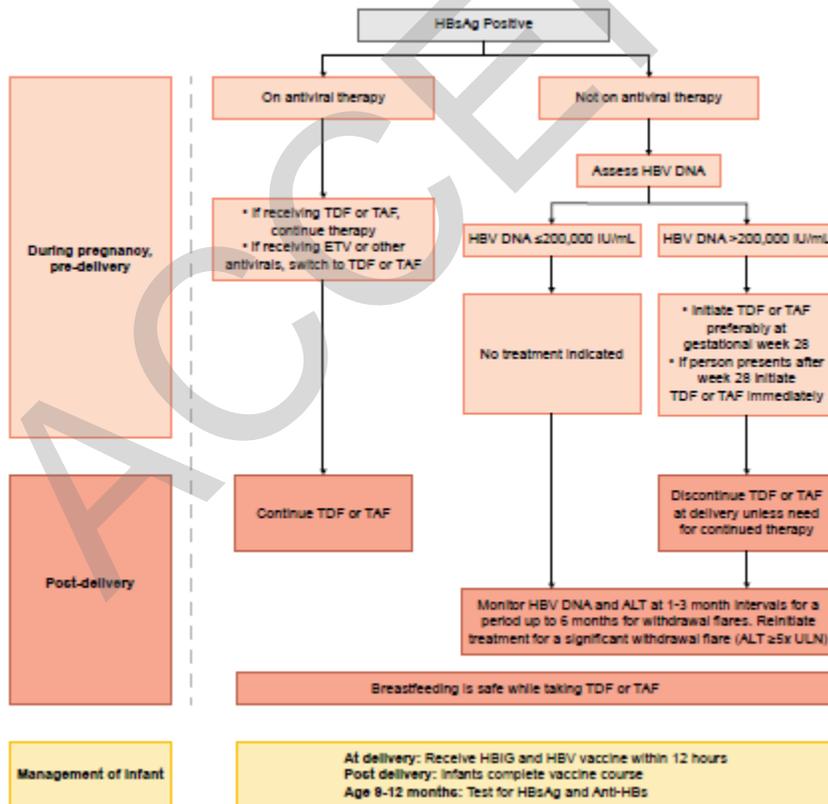
Figure 2: Management Algorithm for Persons without Cirrhosis who are HBsAg-positive and HBeAg-positive

For persons without cirrhosis who are HBeAg-positive, the decision to initiate antiviral therapy depends on HBV DNA and ALT levels. 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. Those who meet criteria for immune active CHB are recommended for treatment. Those meeting the strict definition of immune-tolerant are generally not recommended for treatment unless older (≥40 years), have significant fibrosis (≥F2) or have another reason for treatment (e.g., prevention of transmission), and those in the indeterminate phase warrant a shared-decision making approach with consideration of potential risks and benefits. Individuals who are HBeAg-positive with HBV DNA levels <20,000 IU/mL are extremely rare, but the treatment approach would be the same as those with HBV DNA ≥20,000 IU/mL.

ALT alanine aminotransferase; ULN Upper limit of normal; NIT non-invasive testing

HBsAg+ without Cirrhosis

HBeAg-positive

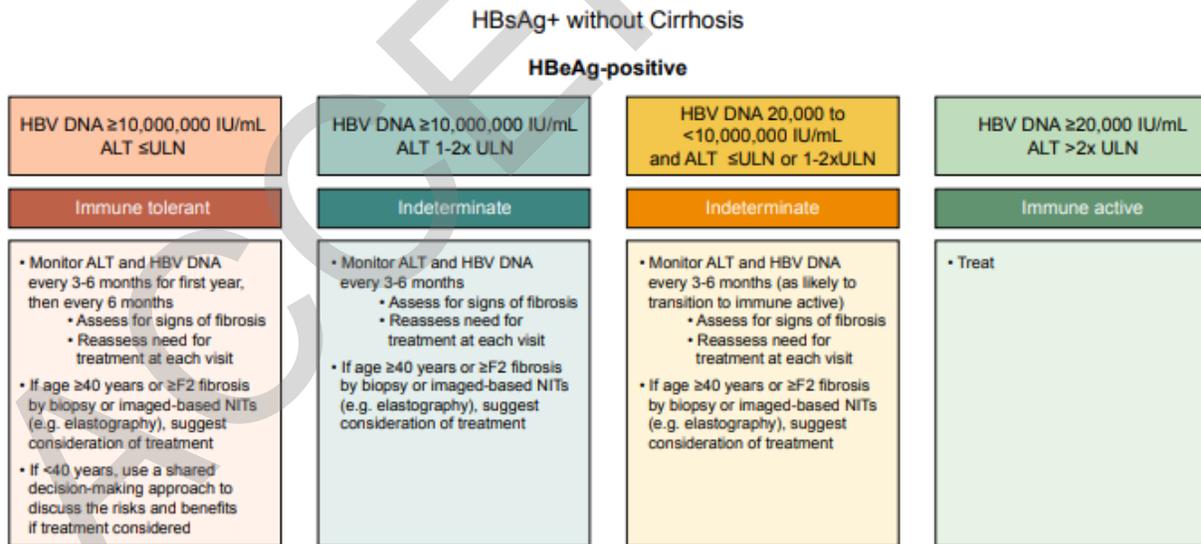| HBV DNA ≥10,000,000 IU/mL ALT ≤ULN	HBV DNA ≥10,000,000 IU/mL ALT 1-2x ULN	HBV DNA 20,000 to <10,000,000 IU/mL and ALT ≤ULN or 1-2xULN	HBV DNA ≥20,000 IU/mL ALT >2x ULN
Immune tolerant	Indeterminate	Indeterminate	Immune active
• Monitor ALT and HBV DNA every 3-6 months for first year, then every 6 months • Assess for signs of fibrosis • Reassess need for treatment at each visit • If age ≥40 years or ≥F2 fibrosis by biopsy or imaged-based NITs (e.g. elastography), suggest consideration of treatment • If <40 years, use a shared decision-making approach to discuss the risks and benefits if treatment considered	• Monitor ALT and HBV DNA every 3-6 months • Assess for signs of fibrosis • Reassess need for treatment at each visit • If age ≥40 years or ≥F2 fibrosis by biopsy or imaged-based NITs (e.g. elastography), suggest consideration of treatment	• Monitor ALT and HBV DNA every 3-6 months (as likely to transition to immune active) • Assess for signs of fibrosis • Reassess need for treatment at each visit • If age ≥40 years or ≥F2 fibrosis by biopsy or imaged-based NITs (e.g. elastography), suggest consideration of treatment	• Treat

Figure 3: Algorithm for Persons without Cirrhosis who are HBsAg-positive and HBeAg-negative

For persons without cirrhosis who are HBeAg-negative, the decision to initiate antiviral therapy depends on HBV DNA and ALT levels. 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. Those who meet criteria for immune active CHB are recommended for treatment. Those meeting the strict definition of inactive are not recommended for treatment and those in the indeterminate phases warrant further evaluation for other causes of liver enzyme elevation (if ALT>ULN and HBV DNA<2000 IU/mL) or consideration of risks for HCC (if ALT <2xULN and HBV DNA >2000 IU/mL). For those in the indeterminant phase, antiviral therapy is suggested using a shared decision-making approach by assessing risks and benefits with regular monitoring recommended for those who are not on antiviral therapy and reevaluation of the decision at each follow-up visit if treatment has not been initiated.

ALT alanine aminotransferase; ULN Upper limit of normal.

HBsAg+ without Cirrhosis

HBeAg-negative

HBV DNA <2,000 IU/mL ALT ≤ULN	HBV DNA <2,000 IU/mL ALT >ULN	HBV DNA >2,000 IU/mL ALT <2x ULN	HBV DNA >2,000 IU/mL ALT >2x ULN
Inactive	**Indeterminate**	**Indeterminate**	**Immune active**

• Monitor HBV DNA and ALT q 3-6 months for first year then q 6-12 months
• Assess for signs of cirrhosis
• Reassess need for HBV treatment at each visit
	• Evaluate for other etiologies of liver disease and treat accordingly
	• Monitor HBV DNA and ALT q 3-6 months for first year then q 6 months
	• Assess for signs of cirrhosis
	• Reassess need for HBV treatment at each visit
		• Consider treatment based on shared decision-making after discussion of risks and benefits, and factors associated with increased risk for HCC including male sex, age >40, platelet count <180k
		• If treatment is not initiated:
		  • Monitor ALT and HBV DNA q 3 months for first year then q 6 months
		  • Assess for signs of cirrhosis
		  • Reassess need for HBV treatment at each visit
			• Treat

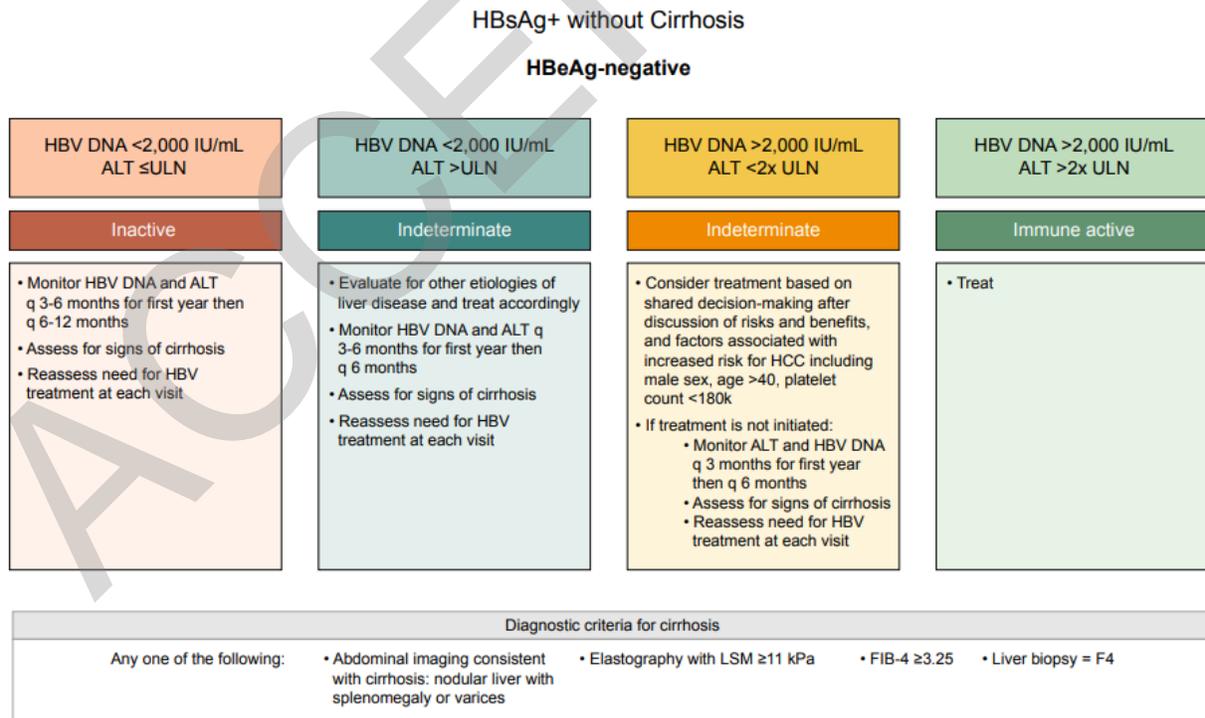| Diagnostic criteria for cirrhosis			
Any one of the following:	• Abdominal imaging consistent with cirrhosis: nodular liver with splenomegaly or varices	• Elastography with LSM ≥11 kPa	• FIB-4 ≥3.25 • Liver biopsy = F4

Figure 4: Management of Suboptimal Response to Antiviral Therapy(1)

There are different forms of suboptimal virologic response to NA therapy – slow decline, plateau, and breakthrough. In all cases of suboptimal response, the initial steps include evaluation and reinforcement of adherence, more frequent follow-up of HBV DNA levels to establish pattern and consideration of resistance testing (particularly if the individual meets criteria for virologic breakthrough). Once adherence confirmed, if a plateau or virological breakthrough is determined, consideration of an antiviral change should be considered. In most cases, a switch of antiviral is preferred (lower pill burden) but add-on therapy can also be considered. For those with slow decline, continued monitoring for decline without change of therapy is recommended.

Diagnostic criteria for cirrhosis
Any one of:
- Abdominal imaging consistent with cirrhosis: nodular liver with splenomegaly or varices
- Elastography with LSM ≥11 kPa
- FIB-4 ≥3.25
- Liver biopsy = F4

Advanced Chronic Liver Disease/Cirrhosis*

HBsAg+
Any level of HBV DNA

Compensated

Decompensated
(Variceal hemorrhage, ascites, hepatic encephalopathy, hepato-renal syndrome)

Antiviral Recommendations

Compensated:
- Treat with ETV, TDF, TAF until HBsAg loss

Decompensated:
- Treat with ETV, TDF, or TAF indefinitely
- Monitor for lactic acidosis [rare but likely more common adverse effect of NA therapy if decompensation]

Other Measures

Compensated:
- Assess for evidence of clinically significant portal hypertension
- HCC surveillance every 6 months

Decompensated:
- Refer for consideration of liver transplantation
- HCC surveillance every 6 months

*Includes persons diagnosed with liver cancer regardless of stage of disease
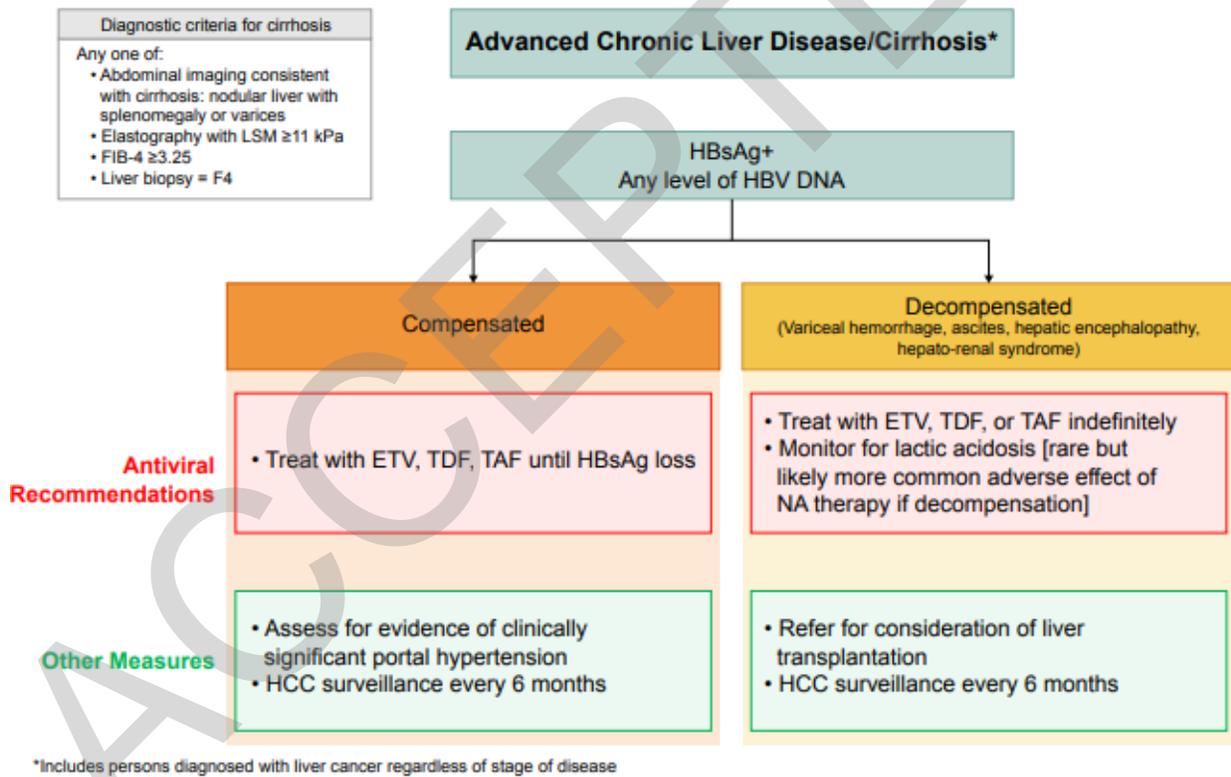
Figure 5: Management of HBsAg-positive Persons with Cirrhosis and HCC(1)

All HBsAg-positive persons should undergo staging tests to determine if cirrhosis is present. Those with cirrhosis (compensated or decompensated) are recommended for antiviral treatment regardless of the level of HBV DNA or ALT. All require surveillance of HCC and those with decompensated cirrhosis should be referred for consideration of liver transplantation.
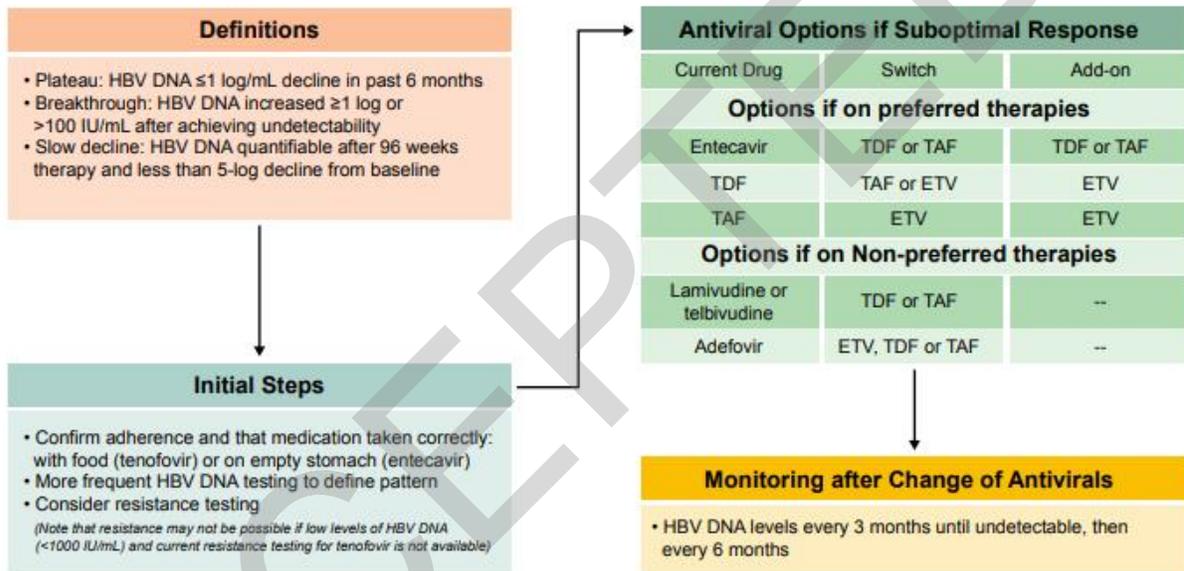
Suboptimal Responses to Antivirals

Definitions

- Plateau: HBV DNA ≤1 log/mL decline in past 6 months
- Breakthrough: HBV DNA increased ≥1 log or >100 IU/mL after achieving undetectability
- Slow decline: HBV DNA quantifiable after 96 weeks therapy and less than 5-log decline from baseline

Initial Steps

- Confirm adherence and that medication taken correctly: with food (tenofovir) or on empty stomach (entecavir)
- More frequent HBV DNA testing to define pattern
- Consider resistance testing

(Note that resistance may not be possible if low levels of HBV DNA (<1000 IU/mL) and current resistance testing for tenofovir is not available)

Antiviral Options if Suboptimal Response

Current Drug	Switch	Add-on
Options if on preferred therapies		
Entecavir	TDF or TAF	TDF or TAF
TDF	TAF or ETV	ETV
TAF	ETV	ETV
Options if on Non-preferred therapies		
Lamivudine or telbivudine	TDF or TAF	--
Adefovir	ETV, TDF or TAF	--

Monitoring after Change of Antivirals

- HBV DNA levels every 3 months until undetectable, then every 6 months

Table 1: Definitions and Terms

Phases of CHB	
Immune-tolerant CHB	HBeAg-positive, HBV DNA >10,000,000 IU/mL and normal ALT (<25 IU/mL in women, <35 IU/mL in men)
Immune active CHB	HBeAg-positive and ALT >2xULN and HBV DNA >20,000 IU/mL HBeAg-negative and ALT >2xULN and HBV DNA >2000 IU/mL
Inactive CHB	HBeAg-negative, HBV DNA <2000 IU/mL and normal ALT
Indeterminate CHB	HBeAg-positive or negative with HBV DNA level and/or ALT level outside those with immune-tolerant, immune active or inactive CHB (Figures 1 and 2). An alternative term used to refer to this group is "grey zone".
HBsAg loss	Loss of HBsAg on antiviral therapy or spontaneously in person who was previously HBsAg-positive
Key Terms	
Functional cure	HBsAg-negative and HBV DNA undetectable off treatment for at least 6 months (± anti-HBs)
Partial cure	HBsAg<100 IU/mL with HBV DNA undetectable off treatment for at least 6 months

Table 2: Implementation considerations for persons who are HBsAg positive and viremic, do not meet disease-specific treatment indications and are in high-risk scenarios for transmission

Non-pharmacologic measures are the mainstay of HBV prevention
• HBV vaccination is the primary intervention to prevent HBV transmission to susceptible individuals in all settings, including those with a known higher risk of exposure. • Screening for HBV infection in all people, including those potentially exposed to an individual who is HBsAg positive with viremia, household contacts and sex partners, is strongly recommended by the CDC and U.S. Preventive Services Task Force guidelines.(18, 19) • Other important risk mitigators include universal precautions in healthcare and first aid settings, harm reduction, and barrier methods during sex.
Considerations for antiviral treatment for the main purpose to prevent onward transmission
• HBV treatment to prevent onward transmission is not necessary for average risk scenarios for transmission* • Possible high -risk scenarios for horizontal transmission of HBV include persons who are engaging in unprotected sex or with multiple partners, persons who are injecting drugs with inconsistent harm reduction practices, persons living with susceptible household members and healthcare workers performing Society for Healthcare Epidemiology of America (SHEA) level III exposure-prone procedures • Utilize a shared decision-making approach to assess overall horizontal transmission risk and the individual's values and preferences regarding this risk and that of taking antivirals with the primary goal of preventing transmission to others • Decisions are influenced by the individual's hepatitis B viremia, the exposure scenario and the vaccine and immunity status of those who are potentially exposed. Situations favoring antiviral treatment of the viremic person include those where the person at risk for acquiring HBV is unvaccinated, has inadequate response to vaccine and/or has compromised immune systems,** or has unknown vaccine status. • Providers should avoid stigmatizing practices and messages • Once initiated for the prevention of HBV transmission, antiviral therapy should be continued until the high risk of transmission is no longer present • People starting antiviral therapy should be counseled regarding the risks of treatment cessation, which may include severe liver flares (see sections on MTCT and Nucleos(t)ide analog withdrawal) • Though there are not definitive studies on the lowest level of viral load transmissibility,*** the goal of HBV treatment is HBV DNA suppression to less than the lower limit of quantification
HBV is not transmitted from casual contact, and people with hepatitis B should not be restricted in their daily activities, contact sports, school activities or professional training, and

should not be required to be treated in those settings. Within households, worksites, and other settings, it is important to emphasize that routine contact, sharing meals, hugging are not considered routes of transmission, though sharing of personal hygiene items (e.g. toothbrush, razors) should be avoided.(13)

*** *Groups known to have inadequate response to vaccine include persons with immunocompromising conditions, persons with diabetes, persons with advanced liver disease, persons with advanced kidney disease, persons who smoke and obese individuals.(122)*

**** *For health care providers performing Category III procedures, the Society for Healthcare Epidemiology of America (SHEA) guidelines suggest maintaining HBV DNA <1000 IU/mL(35) (see reference for SHEA Category III procedures and recommendations).*

See Appendix

HBV hepatitis B virus; CDC Centers for Disease Control and Prevention; U.S. United States; SHEA Society for Healthcare Epidemiology of America

Table 3: Approach to Individual with Strong Desire to Discontinue Nuncleos(t)ide Analogue Therapy

Persons who have a strong desire to discontinue therapy should engage in a shared decision-making process with their providers	
Persons who consider stopping treatment must meet ALL the following criteria	No *history* of cirrhosis, any hepatic decompensation (variceal bleed, ascites, hepatic encephalopathy, hepatorenal syndrome), HCC or extrahepatic complications of HBV

HBeAg-negative/anti-HBe positive for a minimum of one year (if HBeAg-positive at start of treatment)

HBV DNA undetectable for a minimum of 2 years

HBsAg level <100 IU/mL

No co-infection with HIV or HDV

Agree to frequent monitoring |
| **Recommended monitoring schedule after stopping treatment** | Monitor HBV DNA and ALT levels every 1-3 months for the first 6 months, then every 3 months for the next 6-12 months and then every 3-6 months thereafter. |
| **Criteria for IMMEDIATE re-starting of antiviral therapy -- only need to meet ONE criterion** | HBV DNA level ≥10,000 IU/mL (4 log IU/mL) at any time (independent of ALT)

ALT increase >5xULN (independent of HBV DNA)

Total bilirubin >2.5 mg/dL

Hepatic decompensation |
| **Other criteria for re-starting treatment** | Personal desire to re-start

Extrahepatic complications of HBV

Meets treatment initiation criteria (HBV DNA >2000 IU/mL and ALT >2xULN) |

Table 4: Target Groups for Hepatocellular Carcinoma Surveillance

Chronic HBV infection with cirrhosis*	Child-Pugh A-B, and transplant-eligible Child-Pugh C
Chronic HBV infection without cirrhosis with increased HCC risk*	Man from endemic country[a] age > 40 y
	Woman from endemic country[a] age > 50 y
	Person from Africa at earlier age[b]
	Family history of HCC
	PAGE-B score ≥ 10[c]
Co-infection without cirrhosis	HBV/HDV coinfection: all persons
	HBV/HIV coinfection: men $\geq$18 years and women $\geq$ 40 years of age
HBsAg loss with increased risk	All persons with cirrhosis
	Man > 40 y at time of HBsAg loss
	Woman > 50 y at time of HBsAg loss
	Family history of HCC

Abbreviation: HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus

*Recommendations as per the 2023 AASLD HCC Practice Guidance

[a]Endemic country as defined as having $\geq$ 2% prevalence chronic HBV infection (most of Africa, Asia, the Middle East, and Eastern Europe; see Polaris Global Distribution maps for most up to date HBsAg prevalence: https://cdafound.org/polaris/global-distribution)

[b]Surveillance can be initiated as early as third decade of life given median age 46 years at HCC diagnosis

[c]Other risk calculators (e.g., REACH-B, REAL-B) can be considered. PAGE-B was specifically validated for those who have been on antiviral treatment; REACH-B was validated in untreated individuals.