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PRACTICE GUIDELINE

AASLD Guidelines for Treatment of Chronic Hepatitis B

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Objectives and Guiding Principles

Guiding Principles

This document presents official recommendations of the American Association for the Study of Liver Diseases (AASLD) on the treatment of chronic hepatitis B (CHB) virus (HBV) infection in adults and children. Unlike previous AASLD practice guidelines, this guideline was developed in compliance with the Institute of Medicine standards for trustworthy practice guidelines and uses the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach.[1] 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.

This guideline focuses on using antiviral therapy in chronic HBV infection and does not address other related and important issues, such as screening, prevention, and surveillance. For broader issues related to diagnosis, surveillance, and prevention as well as treatment in special populations (e.g., liver transplant recipients) that are not addressed by this guideline, the previous AASLD guideline[2] and recent World Health Organization (WHO) guideline[3] are excellent additional resources.

Objectives

Guideline developers from the AASLD formulated a list of discrete questions that physicians are faced with in daily practice. These questions were:

1. ***Should adults with immune active CHB be treated with antiviral therapy to decrease liver-related complications?***
2. ***Should adults with immune-tolerant infection be treated with antiviral therapy to decrease liver-related complications?***
3. ***Should antiviral therapy be discontinued in hepatitis B e antigen (HBeAg)-positive persons who have developed HBeAg seroconversion on therapy?***
4. ***Should antiviral therapy be discontinued in persons with HBeAg-negative infection with sustained HBV DNA suppression on therapy?***
5. ***In HBV-monoinfected persons, does entecavir therapy, when compared to tenofovir therapy, have a different impact on renal and bone health?***
6. ***Is there a benefit to adding a second antiviral agent in persons with persistent low levels of viremia while being treated with either tenofovir or entecavir?***
7. ***Should persons with compensated cirrhosis and low levels of viremia be treated with antiviral agents?***
8. ***Should pregnant women who are hepatitis B surface antigen (HBsAg) positive with high viral load receive antiviral treatment in the third trimester to prevent perinatal transmission of HBV?***
9. ***Should children with HBeAg-positive CHB be treated with antiviral therapy to decrease liver-related complications?***

Target Audience

This guideline is intended primarily for health care professionals caring for patients with CHB. Additionally, this guideline may assist policy makers in optimizing the care of individuals living with CHB.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; anti-HBe, antibody to HBeAg; anti-HBs, antibody to HBsAg; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; CI, confidence interval; GRADE, Grading of Recommendation Assessment, Development and Evaluation; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HDV, hepatitis delta virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; IFN, interferon; NA, nucleos(t)ide analog; Peg-IFN, pegylated interferon; RCT, randomized, controlled trial; RR, relative risk; ULNs, upper limits of normal; WHO, World Health Organization.

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Table 1. Phases of CHB Infection

	ALT	HBV DNA	HBeAg	Liver Histology
Immune-tolerant phase	Normal	Elevated, typically >1 million IU/mL	Positive	Minimal inflammation and fibrosis
HBeAg-positive immune-active phase	Elevated	Elevated ≥20,000 IU/mL	Positive	Moderate-to-severe inflammation or fibrosis
Inactive CHB phase	Normal	Low or undetectable <2,000 IU/mL	Negative	Minimal necroinflammation but variable fibrosis
HBeAg-negative immune reactivation phase	Elevated	Elevated ≥2,000 IU/mL	Negative	Moderate-to-severe inflammation or fibrosis

Background

Burden of Disease

Globally, an estimated 240 million persons have CHB with a varying prevalence geographically, highest in Africa and Asia.[4] In the United States, the National Health and Nutrition Examination Survey (1999 to 2008) identified approximately 704,000 adults with CHB,[5] but with adjustments for hepatitis B infection among foreign-born persons, the upper estimate of CHB in the United States may be as high as 2.2 million.[6] Globally, deaths from cirrhosis and hepatocellular carcinoma (HCC) were estimated at 310,000 and 340,000 per year, respectively.[7] To reduce the morbidity and mortality of CHB in the United States and worldwide, there is a need for continued efforts to identify infected individuals through targeted screening, prevent new infections through vaccination, and monitor and treat those at risk for complications of their CHB, including surveillance for HCC.[8,9]

Natural History in Adults and Children

CHB has been traditionally characterized into four phases (Table 1), reflecting the dynamic relationship between viral replication and evolution and the host immune response. These phases are of variable duration and not every person infected with CHB will evolve through all phases. Given the dynamic nature of CHB infection, serial monitoring of HBV DNA and alanine aminotransferase (ALT) levels is important to characterize the phase of infection. A single ALT and HBV DNA level are insufficient to assign phase of infection and/or need for treatment. Of note, some persons will be in the "gray zones," meaning that their HBV DNA and ALT levels do not fall into the same phase. Longitudinal follow-up of ALT and HBV DNA levels and/or assessment of liver histology can serve to clarify the phase of infection.

i. ***Immune-tolerant phase: In this highly replicative/low inflammatory phase, HBV DNA levels are elevated, ALT levels are normal (<19 U/L for females and <30 U/L for males), and biopsies are without signs of significant inflammation or fibrosis. The duration of this phase is highly variable, but longest in those who are infected perinatally. With increasing age, there is an increased likelihood of transitioning from immune-tolerant to the HBeAg-positive immune-active phase.***
ii. ***HBeAg-positive immune-active phase: Elevated ALT and HBV DNA levels in conjunction with liver injury characterize this phase. Median age of onset is 30 years among those infected at a young age. The hallmark of transition from the HBeAg-positive immune-active to -inactive phases is HBeAg seroconversion. The rate of spontaneous seroconversion from HBeAg to antibody to HBeAg (anti-HBe) is less than 2% per year in children younger than 3 years of age and increases during puberty and among adults to 8% and 12% per year, respectively.***
iii. ***Inactive CHB phase: In this phase, HBV DNA levels are low or undetectable, ALT levels are normal, and anti-HBe is present. Liver histology***

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Table 2. Host, Viral/Disease, and Environmental Factors Associated With Cirrhosis and HCC

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

shows minimal necroinflammation, but variable fibrosis reflecting previous liver injury during the HBeAg-positive immune-active phase. Among persons who undergo spontaneous HBeAg seroconversion, 67%-80% will continue to remain in the inactive CHB phase. Approximately 4%-20% of inactive carriers have one or more reversions back to HBeAg positive.

iv. HBeAg-negative immune reactivation phase: Among those who seroconvert from HBeAg to anti-HBe positive, 10%-30% continue to have elevated ALT and high HBV DNA levels, and roughly 10%-20% of inactive carriers may have reactivation of HBV replication and exacerbations of hepatitis after years of quiescence. Most of these persons harbor HBV variants in the precore or core promoter region, and liver histology shows necroinflammation and fibrosis. Persons with HBeAg-negative CHB tend to have lower serum HBV DNA levels than those with HBeAg-positive CHB and are more likely to experience a fluctuating course.

Resolved CHB infection is defined by clearance of HBsAg with acquisition of antibody to HBsAg. Approximately 0.5% of persons with inactive CHB will clear HBsAg yearly; most will develop antibody to HBsAg (anti-HBs). Low levels of HBV DNA are transiently detected in the serum in the minority of persons achieving seroclearance.[10,11] Clearance of HBsAg, whether spontaneous or after antiviral therapy, reduces risk of hepatic decompensation and improves survival.

Risk of liver-related complications is variable. Among untreated adults with CHB, cumulative 5-year incidence of cirrhosis is 8%-20%, and among those with cirrhosis, 5-year cumulative risk of hepatic decompensation is 20%, and risk of HCC is 2%-5%.[12-14] Viral, host, and environmental factors influence risks of cirrhosis and HCC[13] (Table 2). HBV DNA levels, ALT levels, and HBeAg status are among the most important determinants of risk of progression to cirrhosis,[15,16] whereas HBV DNA levels (>2,000 IU/mL), HBeAg status, and cirrhosis are key predictors of HCC risk.[15-18] A biological gradient of risk has been shown in adults with HBV DNA levels above 2,000 IU/mL; a higher HBV DNA level is associated with progressively higher rates of cirrhosis and HCC.[15]

Diagnosis, Staging and Monitoring of Persons With CHB

The initial evaluation of persons with CHB should include a thorough history and physical examination, with special emphasis on risk factors for coinfection, alcohol use, and family history of HBV infection and liver cancer. Laboratory tests should include assessment of liver disease activity and function, markers of HBV replication, and tests for coinfection with hepatitis C virus (HCV),

Table 3. Initial Evaluation of HBsAg-Positive Patient

	History/Physical Examination	Routine Laboratory Tests	Serology/Virology	Imaging/Staging Studies
All patients	Symptoms/signs of cirrhosis Alcohol and metabolic risk factors Family history of HCC Vaccination status	CBC including platelet count, AST, ALT, total bilirubin, alkaline phosphatase, albumin, INR	HBeAg/anti-HBe HBV DNA quantitation Anti-HAV to determine need for vaccination	Abdominal ultrasound Vibration-controlled transient elastography or serum fibrosis panel (APRI, FIB-4, or FIbroTest)
Select patients		Tests to rule out other causes of chronic liver diseases if elevated liver test(s) AFP, GGT	HBV genotype Anti-HDV Anti-HCV Anti-HIV in those who have not undergone one-time screening (ages 13-64)	Liver biopsy

Abbreviation:s INR, international normalized ratio; GGT, gamma-glutamyl transpeptidase.

hepatitis delta virus (HDV), or human immunodeficiency virus (HIV) in those at risk (Table 3). Owing to the fluctuating nature of CHB, the accuracy of one high HBV DNA level at a single time point in predicting prognosis is poor and regular monitoring of disease status is imperative to determine need for antiviral therapy. The upper limits of normal (ULNs) for ALT values based on healthy subjects are lower than laboratory values derived from all populations, including those with subclinical liver disease.[19]

Determination of the stage of liver disease is important in guiding antiviral therapy decisions and need for surveillance. Liver biopsy provides an assessment of the severity of necroinflammation and fibrosis, rules out other causes of liver disease, and may be especially useful for persons who lack clear-cut indications for treatment. Whereas liver biopsy is regarded as the best method to assess the severity of inflammatory activity and fibrosis, noninvasive methods to assess fibrosis severity are also useful. Acute-on-chronic exacerbations of hepatitis B may lead to overestimation of fibrosis stage by noninvasive tests, and different cutoffs for significant and advanced fibrosis depending on ALT levels have been

Table 4. Approved Antiviral Therapies in Adults and Children

Drug	Dose in Adults*	Use in Children*	Pregnancy Category	Potential Side Effects†	Monitoring on Treatment†
Peg-IFN-2a(adult) IFN-α-2b (children)	180 μg weekly	≥1 year Dose: 6 million IU/m^2 TIW‡	C	Flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders in adults Anorexia and weight loss in children	CBC (monthly to every 3 months) TSH (every 3 months) Clinical monitoring for autoimmune, ischemic, neuropsychiatric, and infectious complications
Lamivudine	100 mg daily	≥2 years Dose: 3 mg/kg daily to max 100 mg	C	Pancreatitis Lactic acidosis	Amylase if symptoms Lactic acid levels if clinical concern
Telbivudine	600 mg daily	–	B	Creatine kinase elevations and myopathy Peripheral neuropathy Lactic acidosis	Creatine kinase if symptoms Cinical evaluation if symptoms Lactic acid levels if clinical concern
Entecavir	0.5 or 1.0 mg daily§	≥2 years Dose: weight-based to 10-30 kg; above 30 kg 0.5 mg daily‖	C	Lactic acidosis	Lactic acid levels if clinical concern
Adefovir	10 mg daily	≥12 years 10 mg daily	C	Acute renal failure Fanconi syndrome Nephrogenic diabetes insipidus Lactic acidosis	Creatinine clearance at baseline If at risk for renal impairment, creatinine clearance, serum phosphate, 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	300 mg daily	≥12 years 300 mg daily	B	Nephropathy, Fanconi syndrome Osteomalacia Lactic acidosis	Creatinine clearance at baseline If at risk for renal impairment, creatinine clearance, serum phosphate, 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

*Doses need to be adjusted in persons with renal dysfunction.

†Per package insert.

‡Peg-IFN-α-2a is not approved for children with CHB, but is approved for treatment of chronic hepatitis C. Providers may consider using this drug for children with chronic HBV. The duration of treatment indicated in adults is 48 weeks.

§Entecavir dose in adults is 1 mg daily if lamivudine or telbivudine experienced or decompensated cirrhosis.

‖Entecavir doses in treatment-naïve children older than 2 and at least 10 kg are: 0.15 mg (10-11 kg), 0.2 mg (>11-14 kg), 0.25 mg (>14-17 kg), 0.3 mg (>17-20 kg), 0.35 mg (>20-23 kg), 0.4 mg (>23-26 kg), 0.45 mg (>26-30 kg), and 0.5 mg (>30 kg). For treatment-experienced children older than 2 and at least 10 kg, the entecavir doses are: 0.30 mg (10-11 kg), 0.4 mg (>11-14 kg), 0.5 mg (>14-17 kg), 0.6 mg (>17-20 kg), 0.7 mg (>20-23 kg), 0.8 mg (>23-26 kg), 0.9 mg (>26-30 kg), and 1.0 mg (>30 kg).

Abbreviations: CBC, complete blood counts; TSH, thyroid-stimulating hormone.

proposed.[20] Serum markers of fibrosis, such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4, FibroTest, and vibration-controlled transient elastography, have only moderate accuracy in identifying persons with significant fibrosis (fibrosis stage 2 or greater on the Metavir scale), but good diagnostic accuracy in excluding advanced fibrosis[21,22] and may be useful aids in decision making.

Antiviral Therapy

The goals of antiviral treatment are to decrease the morbidity and mortality related to CHB. The achievement of a sustained suppression of HBV replication has been associated with normalization of serum ALT, loss of HBeAg with or without detection of (anti-HBe), and improvement in liver histology. Historically, the term "cure" was avoided in treatment of CHB, given that persistence of covalently closed circular DNA (cccDNA), the transcriptional template of HBV,[23,24] in the nucleus of hepatocytes, even in persons with serological markers of resolved infection, poses a lifelong risk for reactivation of infection. However, an *immunological cure* may be defined by HBsAg loss and sustained HBV DNA suppression and a *virological cure* defined by eradication of virus, including the cccDNA form. The latter is not currently an attainable goal.

There are six therapeutic agents approved for the treatment of adults with CHB in the United States and five therapeutic agents approved for the treatment of children with CHB (Table 4). Side effects are more frequent with interferon (IFN) therapy than with nucleos(t)ide analogs (NAs) therapy. Overall, all NAs have an excellent safety profile across a wide spectrum of persons with CHB, including those with decompensated cirrhosis and transplant recipients.[25] The side effects listed in Table 4 for NAs are infrequent. For persons with HDV coinfection, the only effective treatment is pegylated interferon (Peg-IFN). For persons with HIV coinfection, treatment of HBV needs to be coordinated with HIV therapy given that several HBV drugs have anti-HIV activity (tenofovir, entecavir, lamivudine, and telbivudine).[26]

Biochemical, serological, virological, and histological endpoints are used to assess the success of therapy (Table 5). Assessments are performed on continuous therapy (NAs)[27-30] and after therapy discontinuation (Peg-IFN).[2,31,32] The best predictor of sustained remission off-treatment is HBsAg loss, but this is infrequently achieved with current therapies.

Methods of Guideline Development

The specific questions specified *a priori* for evaluation by the guidelines committee are shown in Table 6.

A methodologist moderated and facilitated the process of question development. A separate group of AASLD content experts collaborated with an independent research group with expertise in conducting systematic reviews to synthesize the available evidence informing these key questions. By multiple face-to-face meetings, phone conferences, and electronic communication, the systematic review group finalized evidence

Table 5. Efficacy of Approved Preferred Antiviral Therapies in Adults With Treatment-Naïve CHB and Immune Active Disease (Not Head-to-Head Comparisons)

	Peg-IFN* (%)	Entecavir† (%)	Tenofovir† (%)
HBeAg-Positive			
HBV DNA suppression‡	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)
HBeAg loss	32-36	22-25	–
HBeAg seroconversion	29-36	21-22	21
Normalization ALT‖	34-52	68-81	68
HBsAg loss	2-7 (6 mos post-treatment) 11 (at 3 yrs post-treatment)	2-3 (1 yr) 4-5 (2 yrs)	3 (1 yr) 8 (3 yrs)
(References)	31,33-35	36-38	30,39
HBeAg-Negative			
HBV DNA suppression§	43 (<4,000 IU/mL) 19 (<80 IU/mL)	90-91	93
Normalization ALT‖	59	78-88	76
HBsAg loss (%)	4 (6 mos post-treatment) 6 (at 3 yrs post-treatment)	0-1 (1 yr)	0 (1 yr)
(References)	40,41	42	39

*Assessed 6 months after completion of 12 months of therapy.
†Assessed after 2-3 years of continuous therapy.
‡HBV DNA <2,000-40,000 IU/mL for Peg-IFN; <60 IU/mL for entecavir and tenofovir.
§HBV DNA <20,000 IU/mL for Peg-IFN; <60 IU/mL for entecavir and tenofovir.
‖ALT normalization defined by laboratory normal.

Table 6. Clinical Questions Evaluated

Question	Population	Intervention	Comparison	Outcome(s)
1	Immune-active CHB	Antiviral therapy	No treatment	Cirrhosis, decompensation, HCC, death, loss of HBsAg
2	Immune-tolerant CHB, adults	Antiviral therapy	No treatment	Cirrhosis, decompensation, HCC, death, loss of HBsAg
3	HBeAg-positive immune-active chronic hepatitis, with HBeAg seroconversion on therapy	Continued antiviral therapy	Stopping antiviral therapy	Cirrhosis, HCC, reactivation, seroreversion, decompensation, loss of HBsAg
4	HBeAg-negative immune-active chronic hepatitis, with viral suppression on antiviral therapy	Continued antiviral therapy	Stopping antiviral therapy	Reactivation, decompensation, loss of HBsAg
5	CHB on treatment with oral therapy	Tenofovir	Entecavir	Renal function, hypophosphatemia, bone health
6	CHB on treatment with oral therapy with persistent viremia	Continue therapy	Change or switch therapy	HBV resistance, clinical flare, decompensation, loss of HBeAg
7	CHB with cirrhosis, with HBV DNA <2,000 IU/mL	Antiviral therapy	No treatment	Decompensation, HCC, death
8	Pregnant women with CHB	Antiviral therapy in third trimester	No treatment	CHB in the infant, maternal safety, fetal/infant safety
9	HBeAg-positive CHB, children/adolescents	Antiviral therapy	No treatment	Cirrhosis, decompensation, HCC, death, HBeAg seroconversion, loss of HBsAg

summaries following the GRADE approach (Table 7).[1] In this approach, the quality of evidence (i.e., certainty in evidence) is rated as high, moderate, low, or very low based on the domains of precision, directness, consistency, and risk of bias and publication bias. The guideline-writing group based its recommendations on the quality of evidence, balance of benefits and harms, patients' values and preferences, and clinical context. Recommendations are graded as strong (apply to most patients with minimal variation) or conditional (apply to the majority of patients whose values and preferences are consistent with the course of action). Technical remarks are added to recommendations to facilitate implementation. Evidence profiles corresponding to five of the key questions are presented as an appendix to this article. For the remaining questions with sparse and indirect evidence, relevant studies are summarized after each recommendation.

Treatment of Persons With Immune-Active CHB

Recommendations

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

Table 7. The GRADE Approach

1. Rating the Quality of Evidence

Study design	Initial rating of quality of evidence	Rate down when	Rate up when
RCT	High	Risk of bias	Large effect (e.g., RR: 0.5)
	Moderate	Inconsistency	Very large effect (e.g., RR: 0.2)
		Imprecision	Dose response gradient
Observational	Low	Indirectness	All plausible confounding would increase the association
	Very low	Publication bias	

2. Determinants of the Strength of a Recommendation

- Quality of evidence
- Balance of benefits and harms
- Patient values and preferences
- Resources and costs

3. Implications of the Strength of Recommendation

Strong	• Population: Most people in this situation would want the recommended course of action and only a small proportion would not. • Health care workers: Most people should receive the recommended course of action. • Policy makers: The recommendation can be adapted as a policy in most situations.
Conditional	• Population: The majority of people in this situation would want the recommended course of action, but many would not. • Health care workers: Be prepared to help patients make a decision that is consistent with their values using decision aids and shared decision making. • Policy makers: There is a need for substantial debate and involvement of stakeholders.

Quality/Certainty of Evidence: Moderate
Strength of Recommendation: Strong

1B. The AASLD recommends Peg-IFN, entecavir, or tenofovir as preferred initial therapy for adults with immune-active CHB.

Quality/Certainly of Evidence: Low
Strength of Recommendation: Strong

Technical Remarks

1. ***Immune-active CHB is defined by an elevation of ALT >2 ULN or evidence of significant histological disease* plus *elevated HBV DNA above 2,000 IU/mL (HBeAg negative) or above 20,000 IU/mL (HBeAg positive).***
2. ***The ULN for ALT in healthy adults is 30 U/L for males and 19 U/L for females.***
3. ***There is insufficient evidence for or against use of ALT criterion other than ALT ≥2 ULN. The decision to treat persons with ALT above the ULNs, but <2 ULN, requires consideration of severity of liver disease (defined by biopsy or noninvasive testing). Therapy is recommended for persons with immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level.***
4. ***Additional factors included in the decision to treat persons with immune-active CHB but ALT <2 ULN and HBV DNA below thresholds are:***
   - ***Age: Older age (>40 years) is associated with higher likelihood of significant histological disease.***
   - ***Family history of HCC***
   - ***Previous treatment history:***
   - ***Serological benefits of Peg-IFN (HBeAg and HBsAg loss) may occur months to years after treatment discontinuation (delayed).***
   - ***Previous NA exposure is a risk for drug resistance***
   - ***Presence of extrahepatic manifestations: Indication for treatment independent of liver disease severity***
5. ***Level of HBV DNA should be compatible with immune-active disease and the cutoffs recommended should be viewed as a sufficient, but not absolute, requirement for treatment.***
6. ***Head-to-head comparisons of antiviral therapies fail to show superiority of one therapy over another in achieving risk reduction in liver-related complications. However, in recommending Peg-IFN, tenofovir, and entecavir as preferred therapies, the most important factor considered was the lack of resistance with long-term use. Patient-specific factors that need to be considered in choosing between Peg-IFN, entecavir, and tenofovir include:***
   - ***Desire for finite therapy (see below)***
   - ***Anticipated tolerability of treatment side effects (Table 4).***
   - ***Comorbidities: Peg-IFN is contraindicated in persons with autoimmune disease, uncontrolled psychiatric disease, cytopenias, severe cardiac disease, uncontrolled seizures, and decompensated cirrhosis.***
   - ***Previous history of lamivudine resistance (entecavir is not preferred in this setting).***
   - ***Family planning: A finite therapy with Peg-IFN pre-pregnancy or use of oral antiviral that is safe in pregnancy is best (Table 4).***
   - ***HBV genotype: A and B genotypes are more likely to achieve HBeAg and HBsAg loss with Peg-IFN than non-A/B genotypes.***
   - ***Medication costs.***
7. ***Peg-IFN is preferred over nonpegylated forms for simplicity.***
8. ***For persons treated with Peg-IFN, 48 weeks duration is used in most studies and is preferred. This treatment duration yields HBeAg seroconversion rates of 20%-31%[31] and sustained off-treatment HBV DNA suppression <2,000 IU/mL in ~65% of persons who achieve HBeAg to anti-HBe seroconversion.[32] The combination of Peg-IFN and NAs has not yielded higher rates of off-treatment serological or virological responses and is not recommended.[43]***
9. ***Duration of therapy for NA-based therapy is variable and influenced by HBeAg status, duration of HBV DNA suppression, and presence of cirrhosis/decompensation. All NAs require dose adjustment in persons with creatinine clearance <50 mL/min.***
10. ***Evaluation for stage of disease using noninvasive methods or liver biopsy is useful in guiding treatment decisions including duration of therapy.***
11. ***Treatment with antivirals does not eliminate the risk of HCC, and surveillance for HCC should continue in persons who are at risk.***

Background

CHB is a dynamic disease characterized by variable periods of immune activity versus quiescence that culminates in the development of cirrhosis, liver cancer, and liver-related death in a proportion of persons. Elevated serum

ALT and HBV DNA levels are strongly predictive of risk of liver complications.[15,16] Other factors include older age, male sex, a family history of HCC, alcohol use, HIV infection, diabetes, HBV genotype C, and HBV precore and core promoter variants. The goal of HBV therapy is to prevent liver-related morbidity and mortality. Persons in the immune-active phases of infection (HBeAg positive and negative) display elevated ALT, histological evidence of liver injury (significant inflammation and/or fibrosis), and elevated HBV DNA levels with a greater risk of progressive liver disease and its associated complications.

Evidence and Rationale

The evidence profile is summarized in Supporting Table 1.[44] A total of 42 studies were included comparing antivirals to no treatment and reporting outcomes of cirrhosis, HCC, decompensation, or death. Seven studies were randomized, controlled trials (RCTs) and 35 studies were observational; a total of 13 studies provided outcomes in persons with cirrhosis, and two studies provided outcomes in persons with decompensated cirrhosis. Regarding specific antiviral therapies, 16 studies compared IFN to no treatment and 27 studies compared NA therapy to no treatment. A network meta-analysis to compare antiviral therapies was not feasible owing to the small number of RCTs per analysis. The quality of evidence was generally higher for RCTs (range, very low to high; majority, low to moderate) versus observational studies (very low). Number of RCTs (range, 1-6 per outcome) was lower than observational studies (1-23 per outcome). For specific NAs, the number of studies was limited and quality highly variable. The magnitude of the treatment effect (40%-61% reduction in liver-related complications: cirrhosis, decompensation, HCC, and death) and consistency of risk reduction across studies and among subgroups contributed to strength of the recommendation despite lower quality of the studies.

Antiviral therapy (compared to no treatment) was associated with significant risk reductions in cirrhosis in observational studies (relative risk [RR] = 0.39; 95% confidence interval [CI]: 0.20-0.75) and RCTs (RR = 0.55; 95% CI: 0.38-0.78). Observational studies (n = 23) showed a risk reduction in HCC (RR = 0.49; 95% CI: 0.35-0.70) and death (RR = 0.6; 95% CI: 0.5-0.8) and RCTs showed a risk reduction in decompensation (RR = 0.44; 95% CI: 0.29-0.68). Among the subgroup of persons with cirrhosis, antiviral therapy (vs. no treatment) yielded risk reductions of HCC (RR = 0.54; 95% CI: 0.41-0.72) and decompensated liver disease (RR = 0.45; 95% CI: 0.22-0.89), but not in mortality (RR = 0.68; 95% CI: 0.40-1.18). In assessment by type of therapy, IFN and NAs achieved long-term benefits of preventing cirrhosis and HCC, but only NAs were associated with reduced rates of decompensation and death.

The primary indication for treatment initiation in a person with immune-active disease is the presence of significant liver injury or fibrosis, as reflected by elevated ALT levels or moderate-to-severe necroinflammatory activity on histology and/or fibrosis plus active HBV viremia. Clinical trials of treatment in adults used laboratory ULNs for ALT to define elevated ALT and typically required ALT elevation 1.3-2.0 times ULNs for inclusion. It is recognized that the normal ALT levels of healthy adults are $\leq$30 U/L for males and $\leq$19 U/L for females.[19] Thus, using these ALT cutoffs for normal, the recommendation to consider treatment of adults with ALT values of $\geq$2 times the ULN (>60 U/L for males and >38 U/L for females) is more inclusive than the ALT criteria used in the clinical trials. The HBV DNA levels used to define immune-active disease are based on historical cutoffs of clinical trials, with supportive evidence from natural history studies showing that the relative risk of liver-related complications increases with HBV DNA levels above 2,000 IU/mL.[15,16] In our systematic review, three studies comparing liver-related outcomes in persons receiving antiviral therapy versus control stratified by HBV DNA level (<2,000 vs. >2,000 IU/mL) and found no significant difference in outcomes.

Liver biopsies are not required to make treatment decisions. However, determination of the presence of advanced fibrosis previous to treatment is important in guiding treatment choices, duration of therapy, and therapeutic endpoints. Available evidence does not define the specific ALT and HBV DNA thresholds at which treatment should be initiated. A high baseline ALT, 2-5 times ULN (based on laboratory ULN), and moderate-to-high necroinflammatory activity on biopsy are associated with higher likelihood of achieving the intermediate outcomes with treatment (HBeAg seroconversion and HBV DNA <2000 IU/mL post-treatment). Noninvasive tests, such as elastography, may be useful in ruling out cirrhosis (i.e., have high negative predictive value), but are less accurate in predicting presence of significant fibrosis (F2 or higher). High necroinflammatory activity and high ALT levels are associated with increased stiffness and this needs to be taken into consideration in interpreting results.[45]

Future Research

Future studies are needed to better define risk benefit for treating persons with mild ALT elevation (e.g. 1-2 ×

ULN) and low-level HBV DNA (e.g., <20,000 IU/mL for HBeAg positive and <2,000 IU/mL for HBeAg negative) who are currently in the "gray zone" for ALT and HBV DNA criteria for treatment versus observation. Studies to define the use of noninvasive measures of disease severity in treatment algorithms are important. There is also a great need for newer treatment approaches that eliminate the HBV cccDNA to achieve virological cure.

Treatment of Adults With Immune-Tolerant CHB

Recommendations

2A. The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB.

Quality/Certainly of Evidence: Moderate
Strength of Recommendation: Strong

Technical Remark

1. Immune-tolerant status should be defined by ALT levels utilizing ≤30 U/L for men and ≤19 U/L for women as ULNs rather than local laboratory ULNs.

2B. The AASLD suggests that ALT levels be tested at least every 6 months for adults with immune-tolerant CHB to monitor for potential transition to immune-active or -inactive CHB.

Quality/Certainly of Evidence: Very low
Strength of Recommendation: Conditional

2C. The AASLD suggests antiviral therapy in the select group of adults >40 years of age with normal ALT and elevated HBV DNA (≥1,000,000 IU/mL) and liver biopsy showing significant necroinflammation or fibrosis.

Quality/Certainly of Evidence: Very low
Strength of Recommendation: Conditional

Technical Remark

1. Moderate-to-severe necroinflammation or fibrosis on liver biopsy is a reason to consider initiation of antiviral therapy, if other causes of liver disease are excluded.

Background

Natural history studies have found a strong association between serum HBV DNA levels and the development of HCC and cirrhosis, independent of serum ALT level, HBV genotype, and HBeAg status in adults.[15,16] This raises the issue of whether adults in the immune-tolerant phase of infection would benefit from antiviral therapy. Of note, these natural history studies used ALT<45 U/L as ULNs. In cross-sectional studies using more-stringent ALT criteria of ≤30 U/L for males and ≤19 U/L for females, significant histological disease (fibrosis ≥2/4 and necroinflammatory score ≥2/4) is found in the minority (~20%) of HBeAg-positive adults with high HBV DNA (>10^6 IU/mL).[46,47] In persons who acquired their infection at birth or in early childhood, the average age of transitioning from immune-tolerant to immune-clearance phases is 30 years.[47] Age over 40 years is associated with higher likelihood of significant histological disease in HBeAg-positive persons with normal ALT levels.[46,48]

Evidence and Rationale

The evidence profile is summarized in Supporting Table 2. Among 17 studies of interventions in immune-tolerant adults, only two examined adults with ALT less than ULNs, whereas most used ALT less than 2 times ULNs for inclusion. All were RCTs with treatment duration of 24-48 weeks for IFN or 48 weeks for NAs with 6-12 months of post-treatment follow-up. All studies used HBeAg loss and seroconversion as the primary endpoint, whereas only two studies evaluated HBsAg loss. Five studies comparing antiviral therapy to placebo/no treatment were the primary studies informing this recommendation. The remaining 12 studies were head-to-head comparisons of different antiviral therapies.

Compared to untreated/placebo controls, any antiviral therapy resulted in a significantly higher rate of HBeAg loss (RR, 2.69; 95% CI: 1.19-6.09) and seroconversion (RR, 2.22; 95% CI: 1.2-4.09). Stratification of results by treatment type (IFN and NAs, all lamivudine) yielded RR that included 1 (not significantly different from untreated controls). The RCT studies were low-to-moderate quality and the RCTs limited to persons with baseline ALT values less than ULNs were very low to low quality.

There are no studies demonstrating that antiviral therapy is beneficial in reducing rates of HCC, cirrhosis, and liver-related death in persons with immune-tolerant CHB. Finite treatment duration for 24-48 months yields higher rates of HBeAg seroconversion, but not HBsAg seroconversion, and only among studies including persons with ALT <2 ULN. The latter group likely included persons with HBeAg-positive immune active disease, a group recommended for antiviral therapy. Given the lack of evidence of benefit to those with ALT <ULN (indicative of immune-tolerant CHB), the potential harms of finite (or longer) antiviral therapy, including cost, antiviral drug side effects, and

development of resistance (with NAs), outweigh benefits. Additionally, there are no data to inform a recommendation for earlier treatment initiation of immune-tolerant persons with family history of HCC.

Whereas the minority of persons with persistently normal ALT levels and high HBV DNA levels have significant fibrosis and/or necroinflammation on liver biopsy, the likelihood of significant histological abnormalities increases with age.[46] Thus, for adults with an immune-tolerant profile but moderate-to-severe necroinflammation or fibrosis, antiviral therapy is suggested, but the strength of this recommendation is weak.

Future Research

Additional studies of longer-term therapy and follow-up are needed to better assess safety and benefits of antiviral therapy in adults in the immune-tolerant phase of CHB, particularly in persons with family history of HCC.

Treatment of HBeAg Positive Immune-Active Chronic Hepatitis Persons Who Seroconvert to Anti-HBe on NA Therapy

Recommendations

3A. The AASLD suggests that HBeAg-positive adults without cirrhosis with CHB who seroconvert to anti-HBe on therapy discontinue NAs after a period of treatment consolidation.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

Technical Remarks

1. ***The period of consolidation therapy generally involves treatment for at least 12 months of persistently normal ALT levels and undetectable serum HBV DNA levels.***
2. ***It is not currently known whether a longer duration of consolidation would further reduce rates of virological relapse. Thus, an alternative approach is to treat until HBsAg loss.***
3. ***Decisions regarding treatment duration and length of consolidation before treatment discontinuation require careful consideration of risks and benefits for health outcomes including: (i) risk for virological relapse, hepatic decompensation, liver cancer, and death; (ii) burden of continued antiviral therapy, financial concerns associated with medication costs and long-term monitoring, adherence, and potential for drug resistance with treatment interruptions; and (iii) patient and provider preferences. These considerations apply for both HBeAg-positive adults without and with cirrhosis who seroconvert to anti-HBe on therapy.***
4. ***Persons who stop antiviral therapy should be monitored every 3 months for at least 1 year for recurrent viremia, ALT flares, seroreversion, and clinical decompensation.***

3B. The AASLD suggests indefinite antiviral therapy for HBeAg-positive adults with cirrhosis with CHB who seroconvert to anti-HBe on NA therapy, based on concerns for potential clinical decompensation and death, unless there is a strong competing rationale for treatment discontinuation.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

Technical Remarks

1. ***Persons with cirrhosis who stop antiviral therapy should be monitored closely (e.g., monthly for first 6 months, then every 3 months) for recurrent viremia, ALT flares, seroreversion, and clinical decompensation.***
2. ***Treatment discontinuation may be considered in persons who have demonstrated loss of HBsAg. However, there is currently insufficient evidence to definitively guide treatment decisions for such persons.***

Background

HBeAg seroconversion, HBsAg loss, and sustained HBV DNA suppression are desirable goals of antiviral therapy in HBeAg-positive persons, especially those without evidence of cirrhosis. Whereas HBsAg loss or seroconversion is the best marker of immune control potentially allowing cessation of antiviral therapy, persons with HBeAg-positive immune active disease who are treated with antiviral therapy may be able to stop treatment after achievement of the intermediate endpoint of HBeAg seroconversion. Alternatively, treatment with antiviral therapy until HBsAg seroconversion is achieved may be an alternative strategy, but may not be feasible for all persons owing to costs of medication and need for long-term follow-up. It is unknown whether health outcomes, such as HCC, cirrhosis, or decompensation, are different in persons who stopped after HBeAg seroconversion compared to those who continued antiviral therapy until HBsAg seroconversion.

Evidence and Rationale

There is no high-quality evidence reporting the clinically important outcomes of HCC, cirrhosis, or decompensation among HBeAg-positive persons who stopped NA antiviral therapy compared to those who continued

antivirals after HBeAg seroconversion. Two small, retrospective cohort studies compared continued therapy to stopping after a finite period of consolidation and reported outcomes of ALT elevation, virological breakthrough, and HBeAg seroreversion. One study demonstrated that persons who stopped treatment had a 90% rate of viremia and 38% rate of ALT flares, whereas none of the persons who continued treatment had either outcome.[49] The second study reported a cumulative 5-year incidence of ALT flares of 44% in those who stopped versus 16% in those who continued antiviral therapy. The incidence of undetectable HBV DNA was 0% in persons who stopped antivirals versus 78% in those who continued, and that of HBeAg seroreversion was 9% versus 0%, respectively.[50] Median duration of consolidation therapy from HBeAg seroconversion to antiviral treatment discontinuation was reported to be 12 [49] and 25 months.[50] In other studies, off-treatment durability of HBeAg seroconversion for entecavir was 73% at week 96,[38] and for telbivudine was 86% at 52 weeks.[51]

The rationale for discontinuing antiviral therapy is based on the paucity of evidence about benefits of lifelong therapy in terms of clinical outcomes (HCC, cirrhosis, and decompensation) along with the potential side effects, burden, and costs associated with indefinite antiviral therapy. Conversely, cessation of antiviral therapy may cause reduced durability of response and increased risk of liver disease progression in association with virological relapse. Additionally, the risk of HCC is higher in persons who are HBsAg positive/HBeAg positive than those who were HBsAg positive/HBeAg negative,[15,52,53] and the risk of cirrhosis is higher in persons with persistent HBeAg positivity.[54,55] A consolidation period of $\geq$6-12 months has been shown to reduce the risk of relapse after HBeAg seroconversion.[56,57] However, the optimal duration of consolidation after HBeAg seroconversion is unknown.

Future Research

Randomized, clinical trials for HBeAg-positive persons who seroconverted to anti-HBe should focus on long-term health outcomes, such as HCC, cirrhosis, or decompensation, in order to determine the (1) optimal duration of consolidation before discontinuation of antiviral therapy in persons without cirrhosis and (2) impact of stopping antiviral therapy in persons with cirrhosis.

Duration of Treatment in Persons With HBeAg-Negative Immune-Active CHB

Recommendations

4. The AASLD suggests indefinite antiviral therapy for adults with HBeAg-negative immune-active CHB, unless there is a competing rationale for treatment discontinuation.

Quality/Certainly of Evidence: Low
Strength of Recommendation: Conditional

Technical Remarks

1. ***A decision to discontinue therapy for HBeAg-negative adults without cirrhosis requires careful consideration of risks and benefits for health outcomes including: (i) risk for virological relapse, hepatic decompensation, liver cancer, and death; (ii) burden of continued antiviral therapy, financial concerns associated with medication costs and long-term monitoring, adherence, and potential for drug resistance with treatment interruptions; and (iii) patient and provider preferences.***
2. ***Treatment discontinuation in persons with cirrhosis is not recommended owing to the potential for decompensation and death, although data are limited.***
3. ***Treatment discontinuation may be considered in persons who have demonstrated loss of HBsAg. However, there is currently insufficient evidence to definitively guide treatment decisions for such persons.***
4. ***Persons who stop antiviral therapy should be monitored every 3 months for at least 1 year for recurrent viremia, ALT flares, and clinical decompensation.***
5. ***Antiviral therapy is not recommended for persons without cirrhosis who are HBeAg negative with normal ALT activity and low-level viremia (<2,000 U/mL; "inactive chronic hepatitis B").***

Background

The available NAs are highly effective in suppressing HBV DNA replication. However, they do not eliminate cccDNA or viral DNA integrated into the host genome.[58] Importantly, HBV viremia typically recurs upon treatment cessation despite successful virus suppression during therapy, in some with hepatitis flares and/or decompensation.[59] In this context, long-term antiviral therapy is considered. A previous AASLD hepatitis B practice guideline (2009)[2] recommended antiviral therapy for HBeAg-negative persons until HBsAg clearance was achieved.

Evidence and Rationale

The evidence profile is summarized in Supporting Table 3. We found no high-quality evidence comparing clinically important long-term outcomes, such as HCC,

cirrhosis, decompensation, and death, among HBeAg-negative persons who stopped compared to those who continued antiviral therapy. There were also no data examining optimal duration of therapy before stopping antiviral therapy in HBeAg-negative adults. Although an RCT compared continuing versus stopping adefovir therapy,[60] treatment duration and follow-up were short (only 1 year) with recurrence of viremia in most persons upon treatment discontinuation. Similarly, viremia recurred in most persons with 1 year or less of lamivudine therapy.[61,62]

Subsequently, four cohort studies examined the effect of treatment discontinuation in HBeAg-negative persons with longer duration of NA therapy (median 2 or more years) including 27 Chinese Canadians,[63] 61 Chinese,[64] 33 Greek,[65] and 95 Taiwanese persons.[66] These studies showed recurrent viremia to level ≥2,000 IU/mL in almost half and ALT elevation in approximately one third to one half of the persons. HBsAg loss was observed in 8 of 61 (13%) persons who stopped therapy after at least 24 months (median, 27; range, 24-66 months) of lamivudine therapy in one study[64] and in 13 of 33 (39%) after 4-5 years of adefovir therapy in another study.[65] Although there was no significant difference in clinical decompensation between adults with and without cirrhosis, decompensation occurred in 1 of 39 (2.6%) with cirrhosis in one study.[66] In a separate study from Taiwan[67] of 263 persons with CHB (including 147 HBeAg negative) who discontinued lamivudine therapy after recovery from a hepatitis B flare with hepatic decompensation, the cumulative incidence of hepatic decompensation at 1, 2, and 5 years was 8.2%, 12.5%, and 19.8%, respectively. Though there was no difference in the incidence of hepatic decompensation between persons with and without cirrhosis, 3 persons with cirrhosis died of hepatic decompensation.

Collectively, these foregoing studies suggest that virus suppression (<2,000 IU/mL) and ALT normalization may be sustained in almost half of the HBeAg-negative persons with treatment duration longer than 2 or more years. However, the effect of treatment discontinuation on long-term morbidity and mortality remains unclear, with persistent concern for hepatic decompensation and death (particularly in persons with cirrhosis). Thus, consideration for treatment discontinuation requires careful weighing of potential for harm and benefit.

Future Research

Given the knowledge gap regarding long-term health outcomes with and without antiviral therapy, more RCTs with longer duration of follow-up are needed to determine whether antiviral therapy can safely be stopped in HBeAg-negative, HBV-infected persons with and without cirrhosis. Alternative treatment strategies for patients on long-term NA therapy, such as adding or switching to Peg-IFN therapy, warrant further study. Additional studies are needed to identify potential predictors for safe treatment discontinuation, including HBsAg levels (not available in the United States) and cccDNA.

Renal and Bone Disease in Persons on NA Therapy

Recommendation

5. The AASLD suggests no preference between entecavir and tenofovir regarding potential long-term risks of renal and bone complications.

Quality/Certainly of Evidence: Very Low (bone); Low (renal)

Strength of Recommendation: Conditional

Technical Remarks

1. ***The existing studies do not show significant differences in renal dysfunction, hypophosphatemia, or bone mineral density between HBV-infected persons treated with tenofovir or entecavir. However, renal events, such as acute renal failure or hypophosphatemia, have been reported in tenofovir-treated persons.***
2. ***In persons on tenofovir, renal safety measurements, including serum creatinine, phosphorus, urine glucose, and urine protein, should be assessed before treatment initiation and periodically (e.g., at least annually and more frequently if preexisting or high risk for renal dysfunction).***
3. ***In the absence of other risk factors for osteoporosis/osteomalacia, there is insufficient evidence for or against monitoring of bone mineral density in HBV-infected persons on tenofovir.***
4. ***In cases of suspected tenofovir-associated renal dysfunction and/or osteoporosis/osteomalacia, tenofovir should be discontinued and substituted with an alternate NA with consideration for previous drug resistance.***
5. ***Dosage of NAs should be adjusted based on renal function and creatinine clearance, as recommended by manufacturers.***

Background

Entecavir and tenofovir are both approved as first-line therapeutic options for CHB. However, tenofovir therapy has been associated with acute and chronic kidney disease involving proximal tubular dysfunction with Fanconi-like

syndrome (metabolic acidosis, hypophosphatemia, and glycosuria) and nephrogenic diabetes insipidus, based mostly on studies from HIV-infected persons.[25,68,69] Long-term tenofovir therapy in HIV-infected persons has been associated with reduced bone density and osteomalacia.[70] However, there was no increased risk for severe proteinuria, hypophosphatemia, or fractures associated with tenofovir therapy in HIV-infected persons in a systematic review and meta-analysis of 17 RCTs.[71]

Renal dysfunction, hypophosphatemia, and Fanconi-like syndrome have also been reported in HBV-infected persons on tenofovir. Though HBV infection and liver disease can also contribute to kidney disease, the initial registration trials of tenofovir showed a favorable side-effect profile compared to adefovir.[25] Hypophosphatemia is the proposed mechanism for osteomalacia/osteoporosis. The incidence of renal and bone events for up to 7 years of treatment was low in a recent study, with 1.7% showing elevated serum creatinine and no significant change in bone mineral density between years 4 and 7.[72] Another report from "real-life" cohorts identified a need for dose adjustment in 4% of persons for renal causes over an approximately 2-year period.[73]

All NAs carry a U.S. Food and Drug Administration black box warning for lactic acidosis. The only clinical report of lactic acidosis with currently approved HBV antivirals was in 5 of 16 persons with decompensated cirrhosis treated with entecavir, and risk of lactic acidosis was correlated with the individual components of Model for End-Stage Liver Disease, including serum creatinine.[74,75]

Evidence and Rationale

The evidence profile is summarized in Supporting Table 4. The use of tenofovir and entecavir was compared in 13 studies[76-87] with average sample sizes of 62 per treatment group (range, 22-148). The first RCT of HBV-infected adults with decompensated cirrhosis showed no significant difference in serum creatinine or creatinine clearance over 48 weeks of tenofovir (n = 45) or entecavir (n = 22).[76-87] The second RCT of 200 HBV-infected adults (100 on tenofovir, 100 on entecavir) showed no significant decline in renal function and no difference in adverse events.[88] However, treatment duration was relatively brief in both studies (~48 weeks). In the remaining 11 cohort studies, eight showed no difference in serum creatinine and/or creatinine clearance between the two treatment options.

Only one study showed a difference in abnormal proximal tubular handling of phosphate for tenofovir versus entecavir (48.5% vs. 12.5%; $P = 0.005$) without a difference in bone mineral density in 42 tenofovir- and 44 entecavir-treated adults with an average treatment duration of 29 ± 19 months.[77] Two additional studies reported hypophosphatemia in 2 of 90 [86] and in 1 of 72 adults[82] treated with tenofovir, with an additional case of acute renal failure in one study.[86] A recent study of 53,500 chronically HBV-infected persons with median follow-up of 4.9 years showed generally low risk for renal and bone side effects (all below 2%). There was a slightly greater risk for persons on nucleotide than nucleoside therapy for hip fracture, although the overall risk was very low (0.21% vs. 0.18%; $P = 0.001$).[89]

The short duration of follow-up (<2 years in most of the available studies) with low- to very-low quality data showing little to no significant differential effect resulted in low to very low certainty of evidence in the recommendation for long-term therapy. Nonetheless, these reports of renal dysfunction in tenofovir-treated persons suggest that HBV-infected persons on tenofovir should have renal status monitored at least annually.

Future Research

Large, population-based studies with longer treatment duration comparing nucleoside and nucleotide analogs are needed to evaluate potential renal and bone effects associated with long-term therapy, in addition to studies examining early predictors and potential approaches to prevent renal- and bone-related complications.

Management of Persons With Persistent Low-Level Viremia on NA Therapy

Recommendations

6A. The AASLD suggests that persons with persistent low-level viremia (<2,000 IU/mL) on entecavir or tenofovir monotherapy continue monotherapy, regardless of ALT.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

6B. The AASLD suggests one of two strategies in persons with virological breakthrough on entecavir or tenofovir monotherapy: either switch to another antiviral monotherapy with high barrier to resistance or add a second antiviral drug that lacks cross-resistance.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

Technical Remarks

1. ***Counseling patients about medication adherence is important, especially in those with persistent viremia on antiviral therapy.***

Table 8. Antiviral Options for Management of Antiviral Resistance

Antiviral Resistance	Switch Strategy	Add Strategy: 2 Drugs Without Cross-Resistance	Ref(s)
Lamivudine-resistance	Tenofovir	Continue lamivudine; add tenofovir (or alternative emtricitabine-tenofovir)	90
Telbivudine-resistance	Tenofovir	Continue telbivudine; add tenofovir	—
Adefovir-resistance	Entecavir	Continue adefovir; add entecavir	91
Entecavir-resistance	Tenofovir	Continue entecavir; add tenofovir (or alternative emtricitabine-tenofovir)	92,93
Multi-drug resistance	Tenofovir	Combined tenofovir and entecavir	92,94

2. ***Persistent viremia has traditionally been defined as detectable HBV DNA after 48 weeks of treatment. This time point was defined by outcomes of virological response in clinical trials and reflects an era of antiviral therapy with drugs of lower antiviral potency and higher rates of resistance. With the current preferred therapies of entecavir and tenofovir, persistent viremia is defined as a plateau in the decline of HBV DNA and/or failure to achieve undetectable HBV DNA level after 96 weeks of therapy. There is insufficient comparative evidence to advocate for adding a second drug or switching to another drug in lieu of continuing monotherapy. Resistance testing in this setting may not be technically possible if viral levels are low. Medical providers should ensure patient adherence to therapy.***
3. ***Viral breakthrough is defined by an increase in HBV DNA by >1 log compared to nadir or HBV DNA ≥100 IU/mL in persons on NA therapy with previously undetectable levels (<10 IU/mL). Confirmatory testing should be obtained before making a therapy change. Resistance testing may assist with decisions regarding subsequent therapy. A confirmed virological breakthrough constitutes a rationale for switching to another antiviral monotherapy with high genetic barrier to resistance or adding a second antiviral with a complementary resistance profile (Table 8). There is insufficient long-term comparative evidence to advocate one approach over another. Based upon virological principles, the risk of viral resistance is predicted to be lower with combination antiviral therapy compared to monotherapy.***
4. ***Although the optimal frequency of HBV DNA monitoring has not been fully evaluated, monitoring of HBV DNA levels every 3 months until HBV DNA is undetectable and then every 3-6 months thereafter allows for detection of persistent viremia and virological breakthrough.***
5. ***For persons on treatment with NAs other than tenofovir or entecavir, viral breakthrough warrants a switch to another antiviral monotherapy with high genetic barrier to resistance or the addition of a second antiviral with a complementary resistance profile (Table 8).***

Background

Not all persons achieve viral suppression on entecavir or tenofovir therapy after 96 weeks of therapy. Among those treated with entecavir, 70%-83% of HBeAg-positive persons[37,95,96] and 91%-98% of HBeAg-negative persons[37,96] achieve viral suppression. For those treated with tenofovir, viral suppression rates were 76% for HBeAg-positive persons and 90% for HBeAg-negative persons.[97] For persons on therapy who fail to achieve an undetectable HBV DNA level after 96 weeks of therapy, but do not meet criteria for virological breakthrough, it is controversial as to whether a change of therapy is needed. The clinical efficacy of adding on an additional high-potency antiviral therapy to an existing monotherapy versus switching to another high-potency antiviral monotherapy versus continuing monotherapy has not been established. In contrast, virological breakthrough[98,99] on antiviral treatment is typically associated with viral resistance and warrants a change of therapy.[100]

Evidence and Rationale

There was no evidence of harm owing to continued monotherapy among persons with persistent low-level viremia, though the quality of evidence was low regarding the clinical outcomes of persons with persistent low-level viremia who continued entecavir or tenofovir monotherapy compared to persons who switched to another monotherapy with high genetic barrier to resistance or added a second antiviral with complementary resistance profile to achieve viral suppression.

Among limited studies of persons on NAs with persistent viremia plus viral resistance or virological breakthrough on monotherapy, there was support in favor of either switching to a potent monotherapy or adding a

second antiviral with a complementary resistance profile. In a randomized study of 90 persons with entecavir resistance treated with tenofovir alone or tenofovir and entecavir, the rate of viral suppression at week 48 was 71% and 73% ($P > 0.99$) in the two groups, respectively.[93] In another randomized study of 102 persons with adefovir resistance treated with tenofovir alone or tenofovir and entecavir for 48 weeks, there was no difference in the proportion of viral suppression between the two groups (62% vs. 64%; $P = 0.88$).[94] Studies are of insufficient duration to fully ascertain whether combination therapy offers benefits in terms of lower risk for resistance with longer-term treatment courses.

Future Research

RCTs are needed to determine optimal clinical care for persons with persistent viremia or virological breakthrough on antiviral monotherapy. Future research is needed to determine the long-term health outcomes of continuing, switching, and adding on potent antiviral therapy. We specifically need criteria that should trigger a change in antiviral therapy, and studies evaluating the cost-effectiveness of different strategies.

Management of Adults With Cirrhosis and Low-Level Viremia

Recommendations

7A. The AASLD suggests that adults with compensated cirrhosis and low levels of viremia (<2,000 IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level.

Quality/Certainly of Evidence: Very Low
Strength of Recommendation: Conditional

Technical Remarks

1. ***Tenofovir and entecavir are preferred because of their potency and minimal risk of resistance. Antivirals with a low genetic barrier to resistance should not be used because the emergence of resistance can lead to decompensation.***
2. ***Peg-IFN is not contraindicated in persons with compensated cirrhosis, but NAs are safer.***
3. ***If treatment is not offered to persons with compensated cirrhosis and low levels of viremia, they must be closely monitored (every 3-6 months) for a rise in HBV DNA and/or clinical decompensation. Treatment should be initiated if either occurs.***
4. ***The ALT level in these persons is typically normal or less than 2 times the ULN. Higher ALT levels (>2 times the ULN) warrant consideration of other causes for ALT elevation and, if none is found, is a stronger indication for antiviral therapy.***
5. ***Current evidence does not provide an optimal length of treatment. If therapy were discontinued, close monitoring (at least every 3 months for at least 1 year) would allow for early detection of viral rebound that could lead to decompensation.***
6. ***Persons with compensated cirrhosis and high HBV DNA levels (>2,000 U/mL) are treated per recommendations for HBeAg-positive and -negative immune-active CHB (Recommendation 1A/B).***
7. ***Treatment with antivirals does not eliminate the risk of HCC and surveillance for HCC should continue.***

7B. The AASLD recommends that HBsAg-positive adults with decompensated cirrhosis be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status, or ALT level to decrease risk of worsening liver-related complications.

Quality/Certainly of Evidence: Moderate
Strength of Recommendation: Strong

Technical Remarks

1. ***Entecavir and tenofovir are preferred drugs.***
2. ***Peg-IFN is contraindicated in persons with decompensated cirrhosis owing to safety concerns.***
3. ***Concurrent consideration for liver transplantation is indicated in eligible persons.***
4. ***Lactic acidosis has been reported with some NAs, and persons with advanced decompensated cirrhosis may be at higher risk. Close follow-up of laboratory and clinical status is necessary.***
5. ***Treatment with antivirals does not eliminate the risk of HCC and surveillance for HCC should continue.***

Background

The objective of HBV treatment is to prevent fibrosis progression and liver-related complications through achievement of sustained suppression of viremia.[2] In those with significant inflammation and/or fibrosis on histology and/or elevated ALT in association with elevated HBV DNA levels, the risk of liver-related complications is highest and the rationale for treatment can be made. Whether persons with cirrhosis (histologically severe disease), but normal ALT levels and low levels of viremia (<2,000 IU/mL), are at risk is less clear.

Evidence and Rationale

Studies have reported that reactivation of hepatitis B (rise in viral load to >2,000 IU/mL in conjunction with

an increase in ALT) occurs at a rate of 1%-2% per year in persons with inactive disease. Persons with a viral load between 1,000 and 2,000 IU/mL appear to be at the highest risk.[101-103] Although there is no high-quality evidence for using antiviral therapy in persons with cirrhosis and low levels of HBV viremia, studies provide indirect evidence that decompensation and liver-related death can occur if reactivation or a flare occurs. In one study of 55 persons with cirrhosis having HBV DNA <20,000 IU/mL and HBeAg negative at the onset, 4% developed decompensation over 5 years.[104] On the other hand, no difference in HCC risk was evident among low-viremia patients comparing those with HBV DNA <2,000 versus <200 IU/mL.[107] However, treatment with NAs is safe and has been associated with a decreased risk of disease progression in persons with cirrhosis, including decompensation, HCC, and liver-related death, and may lead to regression of fibrosis and reversal of cirrhosis over time.[108-110]

Outcomes in persons with decompensated cirrhosis were reported in five studies. A meta-analysis of 13 RCTs to compare the effects of entecavir and lamivudine for treatment of decompensated cirrhosis reported a similar reduction in mortality with both drugs (6.37% vs. 7.89%).[111] A retrospective-prospective cohort study of 253 persons with decompensated cirrhosis, including 102 untreated persons, reported that 5-year mortality was significantly lower in the treated group (22% vs. 14% in the treated group) regardless of HBeAg status. In another study of 707 persons on treatment with antiviral therapy after decompensation, 423 treated persons had significantly better 5-year transplant-free survival than untreated persons (59.7% vs. 46%).[112] In addition, 33.9% of treated persons were subsequently delisted. In a smaller study of 30 decompensated persons with cirrhosis treated with lamivudine and compared to untreated historical controls, a significant clinical improvement with a reduction in the Child-Pugh score and improved survival was observed in treated persons.[113] However, liver-related deaths occurred in 5 of 8 who developed virological breakthrough. In a study comparing compensated and decompensated persons with cirrhosis treated with entecavir, no virological response at 12 months on therapy was a risk factor for developing subsequent HCC.[114] Lactic acidosis has been reported with some NAs, and persons with advanced decompensated cirrhosis may be at higher risk.[74]

Future Research

Further studies examining treatment strategies in HBeAg-negative persons with compensated cirrhosis and low-level viremia are needed. Additional information on the long-term effects of antiviral therapy on reversal of cirrhosis is required before recommendations on frequency of monitoring and surveillance studies (for HCC and varices) can be changed.

Treatment of CHB in Pregnancy

Recommendations

8A. The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL.

Quality/Certainty of Evidence: Low
Strength of Recommendation: Conditional

Technical Remarks

1. ***The infants of all HBsAg-positive women should receive immunoprophylaxis (HBV vaccination ± hepatitis B immunoglobulin, per WHO/Centers for Disease Control and Prevention recommendations).***
2. ***The only antivirals studied in pregnant women are lamivudine, telbivudine, and tenofovir.***
3. ***Antiviral therapy was started at 28-32 weeks of gestation in most of the studies.***
4. ***Antiviral therapy was discontinued at birth to 3 months postpartum in most of the studies. With discontinuation of treatment, women should be monitored for ALT flares every 3 months for 6 months.***
5. ***There are limited data on level of HBV DNA for which antiviral therapy is routinely recommended. The level of >200,000 IU/mL (1 million copies/mL) is a conservative recommendation.***
6. ***For pregnant women with immune-active hepatitis B, treatment should be based on recommendations for nonpregnant women.***
7. ***Breastfeeding is not contraindicated. These antivirals are minimally excreted in breast milk and are unlikely to cause significant toxicity. The unknown risk of low-level exposure to the infant should be discussed with mothers.***
8. ***There are insufficient long-term safety data in infants born to mothers who took antiviral agents during pregnancy and while breastfeeding.***
9. ***C-section is not indicated owing to insufficient data to support benefit.***

8B. The AASLD recommends against the use of antiviral therapy to reduce the risk of perinatal

transmission of hepatitis B in the HBsAg-positive pregnant woman with an HBV DNA ≤200,000 IU/mL.

Quality/Certainty of Evidence: Low
Strength of Recommendation: Strong

Background

The majority of perinatal transmission is thought to occur at delivery, given that a combination of hepatitis B immunoglobulin and vaccination given within 12 hours of birth has reduced the rate of perinatal transmission from >90% to <10%.[1-4] Of the vaccine and hepatitis B immunoglobulin failures, almost all occur in HBeAg-positive women with very high viral loads, generally above 2×10^5-10^7 IU/mL.[115-118] The oral antiviral drugs are pregnancy class C except for telbivudine (class B) and tenofovir (class B).

Evidence and Rationale

The evidence profile is summarized in Supporting Table 5.[119] In 11 controlled studies (1,504 mother-infant pairs) examining the use of any antiviral therapy in the third trimester, a significant reduction in perinatal transmission was reported (RR, 0.32; 95% CI: 0.23-0.46).[5,12] Antivirals studied include lamivudine, telbivudine, and tenofovir. There is no high-quality evidence comparing these antiviral agents. However, tenofovir is considered a preferred choice, owing to its antiviral potency, the available safety data of use during pregnancy, and concerns for resistance with the other antiviral agents. A recent study reported that whole-body bone mineral content of tenofovir-exposed infants born to HIV-infected mothers was 12% lower than for unexposed infants.[120] The long-term clinical significance of these changes is unknown. In available studies, antiviral therapy was started between weeks 28 and 32 of pregnancy. No studies have addressed the duration of therapy (stopping at delivery vs. after delivery). Women need to be monitored for flares if antiviral therapy is discontinued during pregnancy or early after delivery.

A perinatal transmission rate as high as 9% in infants born to mothers whose viral loads were $>10^8$ copies/mL ($>2 \times 10^7$ IU/mL) has been reported.[115] In a study from China, the rate of immunoprophylaxis failure by predelivery HBV DNA level was 0% for levels $<10^6$ copies/mL (~200,000 IU/mL), 3.2% for levels of $10^{6\text{-}6.99}$ copies/mL (~2×10^5-10^6 IU/mL), 6.7% for levels between $10^{7\text{-}7.99}$ copies/mL (~2×10^6-10^7 IU/mL), and 7.6% for levels $>10^8$ copies/mL ($>2 \times 10^7$ IU/mL).[117] No perinatal transmission has also been reported in infants born to mothers with viral loads $<10^6$ copies/mL ($<2 \times 10^5$ IU/mL) in other studies.[115,121] Thus, the HBV DNA threshold to consider antiviral therapy to prevent perinatal transmission is $>2 \times 10^5$ IU/mL.[117]

The safety of lamivudine and tenofovir during breastfeeding has not been well studied in women infected with CHB. As a result, drug labels recommend avoidance of breastfeeding when on these drugs. However, data from the HIV literature support the safety of these drugs during breastfeeding. Several studies have investigated lamivudine levels in breastfed infants.[122-124] One study of 30 mother-infant pairs demonstrated that the lamivudine concentration in breastfed infants was only 3.7% of the mother's level.[122] In another study, it was calculated that the daily lamivudine dose to infants by breast milk was only 2% of the recommended dose for treatment of HIV in infants greater than 3 months of age.[123] Similar findings have been reported in studies looking at tenofovir and breastfeeding.[125,126] In a small study of 5 women, the median amount of tenofovir ingested from breast milk was only 0.03% of the recommended pediatric dose.[125]

Rates of C-section, postpartum hemorrhage or creatine kinase elevation were not increased with antiviral therapy.[127] From the Antiretroviral Pregnancy Registry, there is no evidence of adverse outcomes in infants born to mothers who have been treated with lamivudine, tenofovir, or telbivudine during pregnancy.[128] The safety of entecavir in pregnancy is not known and IFN therapy is contraindicated. The rationale for a strong recommendation against treatment in pregnant women at low risk of transmission is based on placing higher value on preventing unknown maternal and fetal side effects of treatment during pregnancy.

Future Research

Although data are converging on the appropriate HBV threshold and time at which to initiate antivirals to prevent perinatal transmission, the exact viral load threshold and the exact week within the third trimester at which to initiate therapy has not been fully established and requires further study. In addition, data on longitudinal follow-up of infants exposed to antivirals late in pregnancy and safety of breastfeeding while women are on antiviral therapy are needed.

Treatment of CHB in Children

Recommendations

9A. The AASLD suggests antiviral therapy in HBeAg-positive children (ages 2 to <18 years) with both elevated ALT and measurable HBV DNA levels, with the goal of achieving sustained HBeAg seroconversion.

Quality/Certainty of Evidence: Moderate
Strength of Recommendation: Conditional

Technical Remarks

1. ***Most studies required ALT elevation (>1.3 times ULN) for at least 6 months with HBV DNA elevations for inclusion. Given that HBV DNA levels are typically very high during childhood (>10^6 IU/mL), there is no basis for a recommendation for a lower-limit value with respect to treatment. However, if a level <10^4 IU/mL is observed, therapy might be deferred until other causes of liver disease and spontaneous HBeAg seroconversion are excluded.***
2. ***Interferon-α-2b is approved for children 1 year of age and older, whereas lamivudine and entecavir are approved for children 2 years of age and older. Peg-IFN-α-2a (180 μg/1.73 m^2 body-surface area to maximum 180 μg once-weekly) is not approved for children with CHB, but is approved for treatment of chronic hepatitis C for children 5 years of age or older. Providers may consider using this drug for children with chronic HBV.***
3. ***Treatment with entecavir is associated with a lower risk of viral resistance compared to lamivudine.***
4. ***Tenofovir is approved for children 12 years of age and older.***
5. ***Duration of treatment with interferon-α-2b is 24 weeks.***
6. ***Duration of treatment with oral antivirals that has been studied is 1-4 years. It may be prudent to use HBeAg seroconversion as a therapeutic endpoint when oral antivirals are used, continuing treatment for an additional 12 months of consolidation, as recommended in adults. It is currently unknown whether a longer duration of consolidation would reduce rates of virological relapse.***
7. ***Children who stop antiviral therapy should be monitored every 3 months for at least 1 year for recurrent viremia, ALT flares, and clinical decompensation.***

Background

Most children with CHB have persistently normal ALT values, with HBeAg and high levels of HBV DNA in serum, consistent with the immune-tolerant phase of infection. However, immune activation does occur in a minority of children, and these children may benefit from treatment in order to halt disease progression and mitigate the possibility of advanced liver disease and its complications either later in childhood or during young adulthood. Studies of therapy in children typically include only HBeAg-positive children, and most have required at least mildly elevated ALT values (>1.3 times the ULNs, with 30/U/L used as the ULN).[129] Surrogate endpoints have been used, because the hard endpoints of cirrhosis, HCC, and death are very rare within the several year follow-up incorporated into these clinical trials. These factors may somewhat limit generalizability and are the reason for the conditional strength of the recommendation.

Evidence and Rationale

The evidence profile is summarized in Supporting Table 6.[130] Additionally, in a recent multinational RCT in children ages 2-18, a significantly higher rate of HBeAg seroconversion plus HBV DNA <50 IU/mL was achieved with entecavir compared to placebo (24.4% vs. 2.4%; $P = 0.005$).[131] Not all of the reviewed studies had the same primary endpoints. Responses included ALT normalization, HBV DNA suppression or clearance, HBeAg loss and seroconversion, and combinations of these outcomes. Nevertheless, in children carefully selected to have persistently abnormal ALT values and evidence of active HBV replication, rates of response were higher in the groups treated with antivirals compared to those treated with placebo or untreated controls. Although these are surrogate outcomes for significant clinical events, such as cirrhosis and HCC, the therapeutic agents were shown to be safe and well tolerated in children and adolescents. Therefore, the risk-benefit ratio in this selected population of children favors therapy.

Pediatric studies of antiviral agents for CHB utilized various HBV DNA assays, but all required HBeAg positivity. Most children with CHB are HBeAg positive, and viremia levels are typically high. For these reasons, it is not possible to indicate an HBV DNA level that is an indication for treatment in children with persistently elevated ALT. There are no studies of therapy of HBeAg-negative CHB in children.

For children with persistently elevated ALT levels, other potential causes of liver disease need to be excluded. Often, this requires a liver biopsy. The optimal duration of oral antivirals in children is uncertain. However, data derived from adults treated with oral antivirals suggest that treatment should be continued for at least 1 year after HBeAg seroconversion. Although data are limited, there has been no observed benefit from combination therapy with an oral antiviral and IFN.

9B. The AASLD recommends against use of antiviral therapy in HBeAg-positive children (ages 2 to <18 years) with persistently normal ALT, regardless of HBV DNA level.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Strong

Technical Remarks

1. ***Normal ALT in children has not been clearly defined, but a conservative value based on***

clinical trial definitions and limited literature is 30 U/L.

2. ***Although some studies of IFN included children with normal ALT values, studies of oral antiviral agents did not include children with normal ALT values.***

Background

Immune-tolerant HBV-infected children have normal or minimally elevated ALT levels. Histological findings are minimal in these children, as in young adults.[47] ALT values are typically normal after spontaneous HBeAg seroconversion, defining the "inactive carrier" state, and in this phase of chronic infection, liver disease does not progress. There has been no clear evidence that treating immune-tolerant or -inactive carrier children changes the natural history or the frequency of important clinical outcomes. Immune-tolerant children typically have very high HBV DNA levels, often >8 $\log_{10}$ copies/mL ($\sim 2 \times 10^7$ IU/mL).

Evidence and Rationale

The evidence profile is summarized in Supporting Table 6. One study in healthy children of normal-weight indicated that the 95th percentile for ALT values was 25.8 U/L in boys and 22 U/L in girls.[132] Clinical trials of HBV antivirals have used ULN for ALT values ranging from 30 to 45 U/L. Although antiviral therapy decreases HBV DNA levels over time, the time to undetectable HBV DNA is longer in children with baseline high HBV DNA levels than that observed with lower baseline values, perhaps increasing the likelihood of emergence of drug-resistant viral variants. In addition, children with normal ALT values and high HBV DNA levels had the poorest response rates to IFN therapy. In pediatric trials of IFN, lamivudine, and adefovir, response rates improved as baseline ALT values increased. Thus far, there are no comparative studies indicating benefit of treatment of children with consistently normal ALT. Given the lack of evidence of benefit in immune-tolerant children, the potential harms, including growth effects from IFN and the risk for development of drug resistance to the oral antiviral agents, outweigh benefits.

Future Research

Comparative studies of entecavir, tenofovir, and peginterferon in children will assist in optimizing treatment algorithms. Well-conducted studies to assess benefit versus harm of treatment during the immune-tolerant phase are another priority. Long-term follow-up of treated children is needed to validate the use of intermediate biochemical and virological outcomes for clinically important outcomes.

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References

1. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
2. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. HEPATOLOGY 2009;50:661-662.
3. WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva Switzerland: World Health Organization; May 12, 2015.
4. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012;30:2212-2219.
5. Ioannou GN. Hepatitis B virus in the United States: infection, exposure, and immunity rates in a nationally representative survey. Ann Intern Med 2011;154:319-28.
6. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. HEPATOLOGY 2012;56:422-433.
7. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-2128.
8. Weinbaum C, Williams I, Mast E, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008;57:1-20.
9. Chou R, Dana T, Bougatsos C, Blazina I, Khangura J, Zakher B. Screening for hepatitis B virus infection in adolescents and adults: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med 2014;161:31-45.
10. Seto WK, Wong DK, Fung J, Huang FY, Liu KS, Lai CL, et al. Linearized hepatitis B surface antigen and hepatitis B core-related antigen in the natural history of chronic hepatitis B. Clin Microbiol Infect 2014;20:1173-1180.

11. Kim GA, Lee HC, Kim MJ, Ha Y, Park EJ, An J, et al. Incidence of hepatocellular carcinoma after HBsAg seroclearance in chronic hepatitis B patients: a need for surveillance. J Hepatol 2015;62:1092-1099.
12. Fattovich G. Natural history and prognosis of hepatitis B. Sem Liver Dis 2003;23:47-58.
13. Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 2006;43(2 Suppl 1):S173-S181.
14. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009;49(5 Suppl):S45-S55.
15. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
16. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678-686.
17. Yang H, Lu S, Liaw Y, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168-174.
18. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004; 127(5 Suppl 1):S35-S50.
19. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137:1-10.
20. Vigano M, Paggi S, Lampertico P, Fraquelli M, Massironi S, Ronchi G, et al. Dual cut-off transient elastography to assess liver fibrosis in chronic hepatitis B: a cohort study with internal validation. Aliment Pharmacol Ther 2011;34:353-362.
21. WHO. Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. Geneva Switzerland: World Health Organization; 2015.
22. Chon YE, Choi EH, Song KJ, Park JY, Kim do Y, Han KH, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. PLoS One 2012; 7:e44930.
23. Moraleda G, Saputelli J, Aldrich CE, Averett D, Condreay L, Mason WS. Lack of effect of antiviral therapy in nondividing hepatocyte cultures on the closed circular DNA of woodchuck hepatitis virus. J Virol 1997;71:9392-9399.
24. Wong DK, Seto WK, Fung J, Ip P, Huang FY, Lai CL, et al. Reduction of hepatitis B surface antigen and covalently closed circular DNA by nucleos(t)ide analogues of different potency. Clin Gastroenterol Hepatol 2013;11:1004-1010.e1.
25. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009;49(5 Suppl):S185-S195.
26. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Accessed April 30, 2015.
27. Yao GB, Ren H, Xu DZ, Zhou XQ, Jia JD, Wang YM, et al. Virological, serological and biochemical outcomes through 3 years of entecavir treatment in nucleoside-naive Chinese chronic hepatitis B patients. J Viral Hepat 2010;17(Suppl 1):51-58.
28. Liu A, Ha NB, Lin B, Yip B, Trinh HN, Nguyen HA, et al. Low hepatitis B envelope antigen seroconversion rate in chronic hepatitis B patients on long-term entecavir 0.5 mg daily in routine clinical practice. Eur J Gastroenterol Hepatol 2013;25:338-343.
29. Zoutendijk R, Reijnders JG, Brown A, Zoulim F, Mutimer D, Deterding K, et al. Entecavir treatment for chronic hepatitis B: adaptation is not needed for the majority of naive patients with a partial virological response. Hepatology 2011;54:443-451.
30. Heathcote EJ, Marcellin P, Buti M, Gane E, De Man RA, Krastev Z, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology 2011;140:132-143.
31. Liaw YF, Jia JD, Chan HL, Han KH, Tanwandee T, Chuang WL, et al. Shorter durations and lower doses of peginterferon alfa-2a are associated with inferior hepatitis B e antigen seroconversion rates in hepatitis B virus genotypes B or C. Hepatology 2011;54:1591-1599.
32. Buster EH, Hansen BE, Lau GK, Piratvisuth T, Zeuzem S, Steyerberg EW, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. Gastroenterology 2009;137:2002-2009.
33. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352:2682-2695.
34. Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet 2005;365:123-129.
35. Buster EH, Flink HJ, Cakaloglu Y, Simon K, Trojan J, Tabak F, et al. Sustained HBeAg and HBsAg loss after long-term follow-up of HBeAg-positive patients treated with peginterferon alpha-2b. Gastroenterology 2008;135:459-467.
36. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001-1010.
37. Lok AS, Trinh H, Carosi G, Akarca US, Gadano A, Habersetzer F, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naive patients with chronic hepatitis B. Gastroenterology 2012;143:619-628.e1.
38. Gish RG, Lok AS, Chang TT, de Man RA, Gadano A, Sollano J, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterology 2007;133:1437-1444.
39. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442-2455.
40. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351:1206-17.
41. Marcellin P, Bonino F, Lau GK, Farci P, Yurdaydin C, Piratvisuth T, et al. Sustained response of hepatitis B e antigen-negative patients 3 years after treatment with peginterferon alpha-2a. Gastroenterology 2009;136:2169-2179.e1-4.
42. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011-1020.
43. Wong GL, Wong VW, Chan HL. Combination therapy of interferon and nucleotide/nucleoside analogues for chronic hepatitis B. J Viral Hepat 2014;21:825-834.
44. Lok A, McMahon B, Brown R, Wong JB, Ahmed HT, Wigdan F, et al. Antiviral therapy for chronic hepatitis B virus infection in adults: a systematic review and meta-analysis. Hepatology 2015; doi: 10.1002/hep.28280. http://onlinelibrary.wiley.com/doi/10.1002/hep.28280/full.
45. Kemp W, Levy M, Weltman M, Lubel J, Australian Liver A. Australian Liver Association (ALA) expert consensus recommendations for the use of transient elastography in chronic viral hepatitis. J Gastroenterol Hepatol 2015;30:453-462.
46. Lai M, Hyatt BJ, Nasser I, Curry M, Afdhal NH. The clinical significance of persistently normal ALT in chronic hepatitis B infection. J Hepatol 2007;47:760-767.
47. Andreani T, Serfaty L, Mohand D, Dernaika S, Wendum D, Chazouillères O, et al. Chronic hepatitis B virus carriers in the immunotolerant phase of infection: histologic findings and outcome. Clin Gastroenterol Hepatol 2007;5:636-641.
48. Hui CK, Leung N, Yuen ST, Zhang HY, Leung KW, Lu L, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. Hepatology 2007;46:395-401.
49. Chaung KT, Ha NB, Trinh HN, Garcia RT, Nguyen HA, Nguyen KK, et al. High frequency of recurrent viremia after hepatitis B e antigen seroconversion and consolidation therapy. J Clin Gastroenterol 2012;46:865-870.

50. Fung J, Lai CL, Tanaka Y, Mizokami M, Yuen J, Wong DK, et al. The duration of lamivudine therapy for chronic hepatitis B: cessation vs. continuation of treatment after HBeAg seroconversion. Am J Gastroenterol 2009;104:1940-1946.
51. Liaw YF. HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. Hepatol Int 2009;3:425-433.
52. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168-174.
53. You SL, Yang HI, Chen CJ. Seropositivity of hepatitis B e antigen and hepatocellular carcinoma. Ann Med 2004;36:215-224.
54. Chu CM, Hung SJ, Lin J, Tai DI, Liaw YF. Natural history of hepatitis B e antigen to antibody seroconversion in patients with normal serum aminotransferase levels. Am J Med 2004;116:829-834.
55. Lin SM, Yu ML, Lee CM, Chien RN, Sheen IS, Chu CM, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol 2007;46: 45-52.
56. Chien RN, Yeh CT, Tsai SL, Chu CM, Liaw YF. Determinants for sustained HBeAg response to lamivudine therapy. Hepatology 2003; 38:1267-1273.
57. Yoon SK, Jang JW, Kim CW, Bae SH, Choi JY, Choi SW, et al. Long-term results of lamivudine monotherapy in Korean patients with HBeAg-positive chronic hepatitis B: response and relapse rates, and factors related to durability of HBeAg seroconversion. Intervirology 2005;48:341-349.
58. Summers J, Mason WS. Residual integrated viral DNA after hepadnavirus clearance by nucleoside analog therapy. Proc Natl Acad Sci U S A 2004;101:638-640.
59. Vigano M, Mangia G, Lampertico P. HBeAg-negative chronic hepatitis B: why do I treat my patients with nucleos(t)ide analogues? Liver Int 2014;349Suppl 1):120-126.
60. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. N Engl J Med 2005;352:2673-2681.
61. Huang YH, Wu JC, Chang TT, Sheen IJ, Lee PC, Huo TI, et al. Analysis of clinical, biochemical and viral factors associated with early relapse after lamivudine treatment for hepatitis B e antigen-negative chronic hepatitis B patients in Taiwan. J Viral Hepat 2003;10:277-284.
62. Santantonio T, Mazzola M, Iacovazzi T, Miglietta A, Guastadisegni A, Pastore G. Long-term follow-up of patients with anti-HBe/HBV DNA-positive chronic hepatitis B treated for 12 months with lamivudine. J Hepatol 2000;32:300-306.
63. Fung SK, Wong F, Hussain M, Lok AS. Sustained response after a 2-year course of lamivudine treatment of hepatitis B e antigen-negative chronic hepatitis B. J Viral Hepat 2004;11:432-438.
64. Liu F, Wang L, Li XY, Wang JB, Zhang ZH, Wang YZ. Poor durability of lamivudine effectiveness despite stringent cessation criteria: a prospective clinical study in hepatitis B e antigen-negative chronic hepatitis B patients. J Gastroenterol Hepatol 2011;26:456-460.
65. Hadziyannis SJ, Sevastianos V, Rapti I, Vassilopoulos D, Hadziyannis E. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. Gastroenterology 2012;143:629-636.e1.
66. Jeng WJ, Sheen IS, Chen YC, Hsu CW, Chien RN, Chu CM, et al. Off-therapy durability of response to entecavir therapy in hepatitis B e antigen-negative chronic hepatitis B patients. Hepatology 2013;58: 1888-1896.
67. Chang ML, Jeng WJ, Liaw YF. Clinical events after cessation of lamivudine therapy in patients recovered from hepatitis B flare with hepatic decompensation. Clin Gastroenterol Hepatol 2015;13:979-986.
68. Laprise C, Baril JG, Dufresne S, Trottier H. Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: results from 10 years of follow-up. Clin Infect Dis 2013;56:567-575.
69. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. Am J Kidney Dis 2011;57:773-780.
70. Parsonage MJ, Wilkins EG, Snowden N, Issa BG, Savage MW. The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. HIV Med 2005;6:341-346.
71. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis 2010;51:496-505.
72. Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci 2015;60: 1457-1464.
73. Lampertico P, Soffredini R, Yurdaydin C, Idilman R, Papatheodoridis GV, Margariti A, et al. Four years of tenofovir monotherapy for NUC naïve field practice European patients suppresses HBV replication in most patients with a favorable renal safety profile but does not prevent HCC in patients with or without cirrhosis. Digestive and Liver Disease, Vol. 46, e14.
74. Liaw YF, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized open-label study. Hepatology 2011;54:91-100.
75. Lange CM, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology 2009;50:2001-2006.
76. Mauss S, Berger F, Filmann N, Hueppe D, Henke J, Hegener P, et al. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. J Hepatol 2011;55:1235-1240.
77. Tien C, Xu JJ, Chan LS, Chang M, Lim C, Lee S, et al. Long-term treatment with tenofovir in Asian-American chronic hepatitis B patients is associated with abnormal renal phosphate handling. Dig Dis Sci 2015;60:566-572.
78. Cholongitas E, Papatheodoridis GV, Goulis J, Vlachogiannakos J, Karatapanis S, Ketikoglou J, et al. The impact of newer nucleos(t)ide analogues on patients with hepatitis B decompensated cirrhosis. Ann Gastroenterol 2015;28:109-117.
79. Mallet V, Schwarzinger M, Vallet-Pichard A, Fontaine H, Corouge M, Sogni P, et al. Effect of nucleoside and nucleotide analogues on renal function in patients with chronic hepatitis B virus monoinfection. Clin Gastroenterol Hepatol 2015;13:1181-1188.e1.
80. Hung CH, Hu TH, Lu SN, Lee CM, Chen CH, Kee KM, et al. Tenofovir versus entecavir in the treatment of chronic hepatitis B with severe acute exacerbation. Antimicrob Agents Chemother 2015;59: 3168-3173.
81. Huang X, Xu Y, Yang Q, Chen J, Zhang T, Li Z, et al. Efficacy and biological safety of lopinavir/ritonavir based anti-retroviral therapy in HIV-1-infected patients: a meta-analysis of randomized controlled trials. Sci Rep 2015;5:8528.
82. Batirel A, Guclu E, Arslan F, Kocak F, Karabay O, Ozer S, et al. Comparable efficacy of tenofovir versus entecavir and predictors of response in treatment-naive patients with chronic hepatitis B: a multicenter real-life study. Int J Infect Dis 2014;28:153-159.
83. Ceylan B, Yardimci C, Fincanci M, Eren G, Tozalgan U, Muderrisoglu C, et al. Comparison of tenofovir and entecavir in patients with chronic HBV infection. Eur Rev Med Pharmacol Sci 2013;17:2467-2473.
84. Doğan ÜB, Kara B, Gümürdülü Y, Soylu A, Akin MS. Comparison of the efficacy of tenofovir and entecavir for the treatment of nucleos(t)ide-naive patients with chronic hepatitis B. Turk J Gastroenterol 2012;23:247-252.
85. Gish RG, Clark MD, Kane SD, Shaw RE, Mangahas MF, Baqai S. Similar risk of renal events among patients treated with tenofovir or entecavir for chronic hepatitis B. Clin Gastroenterol Hepatol 2012; 10:941-946; quiz, e68.

86. Koklu S, Tuna Y, Gulsen MT, Demir M, Köksal AŞ, Koçkar MC, et al. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol 2013;11:88-94.
87. Liaw YF, Sheen IS, Lee CM, Akarca US, Papatheodoridis GV, Suet-Hing Wong F, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology 2011;53:62-72.
88. Sriprayoon T, Lueangarun S, Suwanwela C, Pattaranutaporn P, Tanwandee T. Efficacy and safety of entecavir versus tenofovir treatment in chronic hepatitis B patients: a randomized controlled trial. Gastroenterology 2012;142(Suppl 1):S695.
89. Wong GL, Tse YK, Wong VW, Fung TY, Choi KK, Chan HL. Long-term safety of oral nucleos(t)ide analogues for patients with chronic hepatitis B—a cohort study of 53,500 subjects. Hepatology 2015;62:684-693.
90. Fung S, Kwan P, Fabri M, Horban A, Pelemis M, Hann HW, et al. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2014;146:980-988.
91. Berg T, Zoulim F, Moeller B, Trinh H, Marcellin P, Chan S, et al. Long-term efficacy and safety of emtricitabine plus tenofovir DF vs. tenofovir DF monotherapy in adefovir-experienced chronic hepatitis B patients. J Hepatol 2014;60:715-722.
92. Lee YB, Lee JH, Lee DH, Cho H, Ahn H, Choi WM, et al. Efficacy of entecavir-tenofovir combination therapy for chronic hepatitis B patients with multidrug-resistant strains. Antimicrob Agents Chemother 2014;58:6710-6716.
93. Lim YS, Byun KS, Yoo BC, Kwon SY, Kim YJ, An J, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in patients with entecavir-resistant chronic hepatitis B with multiple drug failure: results of a randomised trial. Gut 2015 Jan 16. pii: gutjnl-2014-308353. doi: 10.1136/gutjnl-2014-308353. [Epub ahead of print]
94. Lim YS, Yoo BC, Byun KS, Kwon SY, Kim YJ, An J, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in adefovir-resistant chronic hepatitis B patients with multiple drug failure: results of a randomised trial. Gut 2015 Mar 23. pii: gutjnl-2014-308435. doi: 10.1136/gutjnl-2014-308435. [Epub ahead of print]
95. Chang TT, Lai CL, Kew Yoon S, Lee SS, Coelho HS, Carrilho FJ, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. Hepatology 2010;51:422-430.
96. Zoutendijk R, Reijnders JG, Brown A, Zoulim F, Mutimer D, Deterding K, et al. Entecavir treatment for chronic hepatitis B: adaptation is not needed for the majority of naive patients with a partial virological response. Hepatology 2011;54:443-451.
97. Perry CM, Simpson D. Tenofovir disoproxil fumarate: in chronic hepatitis B. Drugs 2009;69:2245-2256.
98. Thabut D, Thibault V, Bernard-Chabert B, Mouquet C, Di Martino V, Le Calvez S, et al. Long-term therapy with lamivudine in renal transplant recipients with chronic hepatitis B. Eur J Gastroenterol Hepatol 2004;16:1367-1373.
99. Papatheodoridis GV, Dimou E, Laras A, Papadimitropoulos V, Hadziyannis SJ. Course of virologic breakthroughs under long-term lamivudine in HBeAg-negative precore mutant HBV liver disease. Hepatology 2002;36:219-226.
100. Salpini R, Alteri C, Cento V, Pollicita M, Micheli V, Gubertini G, et al. Snapshot on drug-resistance rate and profiles in patients with chronic hepatitis B receiving nucleos(t)ide analogues in clinical practice. J Med Virol 2013;85:996-1004.
101. Tohme RA, Bulkow L, Homan CE, Negus S, McMahon BJ. Rates and risk factors for hepatitis B reactivation in a cohort of persons in the inactive phase of chronic hepatitis B-Alaska, 2001-2010. J Clin Virol 2013;58:396-400.
102. Chu CM, Liaw YF. Incidence and risk factors of progression to cirrhosis in inactive carriers of hepatitis B virus. Am J Gastroenterol 2009;104:1693-1699.
103. Zacharakis GH, Koskinas J, Kotsiou S, Papoutselis M, Tzara F, Vafeiadis N, et al. Natural history of chronic HBV infection: a cohort study with up to 12 years follow-up in North Greece (part of the Interreg I-II/EC-project). J Med Virol 2005;77:173-179.
104. Fattovich G, Pantalena M, Zagni I, Realdi G, Schalm SW, Christensen E. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. Am J Gastroenterol 2002;97:2886-2895.
105. Chang ML, Jeng WJ, Liaw YF. Clinical events after cessation of lamivudine therapy in patients recovered from hepatitis B flare with hepatic decompensation. Clin Gastroenterol Hepatol 2015;13:979-986.
106. Manolakopoulos S, Karatapanis S, Elefsiniotis J, Mathou N, Vlachogiannakos J, Iliadou E, et al. Clinical course of lamivudine monotherapy in patients with decompensated cirrhosis due to HBeAg negative chronic HBV infection. Am J Gastroenterol 2004;99:57-63.
107. Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. Gastroenterology 2012;142:1140-1149.
108. Schiff ER, Lee SS, Chao YC, Kew Yoon S, Bessone F, Wu SS, et al. Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. Clin Gastroenterol Hepatol 2011;9:274-276.
109. Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52:886-893.
110. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468-475.
111. Ye XG, Su QM. Effects of entecavir and lamivudine for hepatitis B decompensated cirrhosis: meta-analysis. World J Gastroenterol 2013;19:6665-6678.
112. Jang JW, Choi JY, Kim YS, Woo HY, Choi SK, Lee CH, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. Hepatology 2015;61:1809-1820.
113. Manolakopoulos S, Karatapanis S, Elefsiniotis J, Mathou N, Vlachogiannakos J, Iliadou E, et al. Clinical course of lamivudine monotherapy in patients with decompensated cirrhosis due to HBeAg negative chronic HBV infection. Am J Gastroenterol 2004;99:57-63.
114. Kim SS, Hwang JC, Lim SG, Ahn SJ, Cheong JY, Cho SW. Effect of virological response to entecavir on the development of hepatocellular carcinoma in hepatitis B viral cirrhotic patients: comparison between compensated and decompensated cirrhosis. Am J Gastroenterol 2014;109:1223-1233.
115. Wiseman E, Fraser M, Holden S, Glass A, Kidson BL, Heron LG, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust 2009;190:489-492.
116. Sun KX, Li J, Zhu FC, Liu JX, Li RC, Zhai XJ, et al. A predictive value of quantitative HBsAg for serum HBV DNA level among HBeAg-positive pregnant women. Vaccine 2012;30:5335-40.
117. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat 2012;19:e18-25.
118. Kubo A, Shlager L, Marks AR, Lakritz D, Beaumont C, Gabellini K, et al. Prevention of vertical transmission of hepatitis B: an observational study. Ann Intern Med 2014;160:828-835.
119. Brown RS, McMahon BJ, Lok A, Wong JB, Ahmed AT, Mouchli MA, et al. Antiviral therapy in chronic hepatitis B virus infection during pregnancy: a systematic review and meta-analysis. Hepatology 2015; doi: 10.1002/hep.28302. http://onlinelibrary.wiley.com/doi/10.1002/hep.28302/full.
120. Siberry GK, Jacobson DL, Kalkwarf HJ, Wu JW, DiMeglio LA, Yogev R, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. Clin Infect Dis 2015;61:996-1003.

121. Han L, Zhang HW, Xie JX, Zhang Q, Wang HY, Cao GW. A meta-analysis of lamivudine for interruption of mother-to-child transmission of hepatitis B virus. World J Gastroenterol 2011;17:4321-4333.
122. Shapiro RL, Holland DT, Capparelli E, Lockman S, Thior I, Wester C, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. J Infect Dis 2005;192:720-727.
123. Corbett AH, Kayira D, White NR, Davis NL, Kourtis AP, Chasela C, et al. Antiretroviral pharmacokinetics in mothers and breastfeeding infants from 6 to 24 weeks post-partum: results of the BAN Study. Antivir Ther 2014;19:587-595.
124. Mirochnick M, Thomas T, Capparelli E, Zeh C, Holland D, Masaba R, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. Antimicrob Agents Chemother 2009;53:1170-1176.
125. Benaboud S, Pruvost A, Coffie PA, Ekouévi DK, Urien S, Arrivé E, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. Antimicrob Agents Chemother 2011;55:1315-1317.
126. Mirochnick M, Taha T, Kreitchmann R, Nielsen-Saines K, Kumwenda N, Joao E, et al. Pharmacokinetics and safety of tenofovir in HIV-infected women during labor and their infants during the first week of life. J Acquir Immune Defic Syndr 2014;65:33-41.
127. Hu Y, Chen J, Wen J, Xu C, Zhang S, Xu B, et al. Effect of elective cesarean section on the risk of mother-to-child transmission of hepatitis B virus. BMC Pregnancy Childbirth 2013;13:119.
128. The Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 January 2015. http://apregistry.com/forms/exec-summary.pdf. Accessed August 1, 2015.
129. Jonas MM, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, et al. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. Hepatology 2010;52:2192-2205.
130. Jonas M, Lok A, McMahon BJ, Brown RS, Wong JB, Ahmed AT, et al. Antiviral therapy in management of chronic hepatitis B virus infection in children: a systematic review and meta-analysis. Hepatology 2015; doi: 10.1002/hep.28278. http://onlinelibrary.wiley.com/doi/10.1002/hep.28278/full
131. Jonas M, Chang MH, Sokal E, Schwarz KB, Kelly D, Kim KM, et al. Randomized controlled trial of entecavir versus placebo in children with HBeAg-positive chronic hepatitis B. Hepatology 2015 Jul 29. doi: 10.1002/hep.28015. [Epub ahead of print]
132. Schwimmer JB, Dunn W, Norman GJ, Pardee PE, Middleton MS, Kerkar N, et al. SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. Gastroenterology 2010;138:1357-1364.e2.

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