Evidence Synthesis

Number 194

Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: A Systematic Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
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Rockville, MD 20857
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Contract No. HHSA-290-2015-00009-I, Task Order No. 14

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AHRQ Publication No. 20-05262-EF-1
December 2020

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors thank AHRQ Medical Officers Kathleen Irwin, MD, MPH, Tracy Wolff, MD, MPH, and Iris Mabry-Hernandez, MD, MPH; as well as the U.S. Preventive Services Task Force.

Suggested Citation

Chou R, Blazina I, Bougatsos C, Holmes R, Selph S, Grusing S, Jou J. Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: A Systematic Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 194. AHRQ Publication No. 20-05262-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2020.

Structured Abstract

Background: A 2014 review for the US Preventive Services Task Force (USPSTF) found antiviral therapy for hepatitis B virus (HBV) infection associated with improved intermediate outcomes, although evidence on clinical outcomes was limited.

Purpose: To update the 2014 HBV screening review in nonpregnant adolescents and adults to inform the USPSTF.

Data Sources: We utilized the 2014 review, searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE (2014 to August 2019); with surveillance through July 24, 2020.

Study Selection: Eligible studies included randomized controlled trials **(**RCTs) and cohort studies on the benefits and harms of screening versus no screening, and the yield of alternative screening strategies; RCTs on the effects of antiviral therapy versus placebo or no therapy and preferred versus nonpreferred therapies on intermediate outcomes, clinical outcomes, and harms; and cohort studies on clinical outcomes and on the association between intermediate outcomes following antiviral therapy and clinical outcomes.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): Fifty total studies (30 trials and 20 cohort studies) with a total of 94,168 participants were included; of these, 22 were added for this update. No study directly evaluated the effects of screening for HBV infection versus no screening on clinical outcomes, such as mortality, hepatocellular carcinoma, or cirrhosis. Screening strategies that focused on risk factors such as ever having immigrated from high prevalence countries plus demographic and behavioral risk factors would identify nearly all HBV infection cases. In one study (N=21,008), only screening immigrants from high HBV prevalence countries would miss approximately two-thirds of infected persons. Based on 18 trials (N=2,972), antiviral therapy was associated with greater likelihood than placebo or no treatment for achieving intermediate outcomes, such as virologic suppression and hepatitis B e antigen or hepatitis B surface antigen loss or seroconversion; the numbers needed to treat ranged from 2.6 for virological suppression to 17 for hepatitis B e antigen seroconversion. Based on 12 trials (N=4,127), preferred (first-line) antiviral therapies were at least as likely as nonpreferred therapies to achieve intermediate outcomes. Based on 16 trials (N=4,809), antiviral therapy might be associated with improved clinical outcomes, but data were sparse and imprecise. Nine cohort studies (N=3,893) indicated an association between achieving an intermediate outcome following antiviral therapy and improved clinical outcomes, but were heterogeneous (hazards ratios ranged from 0.07 to 0.87). Antiviral therapy was associated with higher risk of withdrawal due to adverse events versus placebo or no antiviral therapy.

Limitations: Only English-language articles were included, clinical outcome data for antiviral therapies were limited, observational studies were included on effects of antiviral therapy on

long-term clinical outcomes and the association between intermediate and clinical outcomes, and some studies were conducted in countries where the prevalence and natural history of HBV infection are different from the United States.

Conclusions: There was no direct evidence for the clinical benefits and harms of HBV screening versus no screening. Antiviral therapy for HBV infection was associated with improved intermediate outcomes and may improve clinical outcomes. Research is needed to clarify effects of screening and subsequent interventions on clinical outcomes and to identify optimal screening strategies.

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Chapter 1. Introduction and Background

Purpose

This systematic review update will be used by the United States Preventive Services Task Force (USPSTF) to update its recommendation from 2014[1,2] on screening for hepatitis B virus (HBV) infection in nonpregnant adolescents and adults.[3,4] In 2014, the USPSTF recommended screening for HBV infection in persons at high risk for infection (***B recommendation***). The USPSTF recommendation noted an HBV prevalence of two percent or greater as a reasonable threshold for deciding to screen; this includes persons born in countries and regions with a prevalence of HBV infection of two percent or greater, U.S.-born persons not vaccinated as infants whose parents were born in regions with a HBV prevalence of eight percent or greater, HIV-positive persons, persons who inject drugs, men who have sex with men, and household contacts or sexual partners of persons with HBV infection.

Condition Background

Condition Definition

HBV is a double-stranded deoxyribonucleic acid (DNA) virus enclosed in a nucleocapsid protein (hepatitis B core antigen [HBcAg]) surrounded by an envelope protein (hepatitis B surface antigen [HBsAg]).[5] Serologic markers are usually the initial tests used to determine HBV infection status (**Table 1**); subsequent tests in persons with markers indicating active infection are performed to determine the presence and level of circulating HBV DNA (viral load). Acute HBV infection (within 6 months after infection) is typically characterized by the initial appearance of HBsAg with HBV e antigen (HBeAg) and HBV DNA; immunoglobulin M (IgM) antibody to the HBV core antigen (anti-HBc) appears soon after infection, evolving to anti-HBc immunoglobulin G (IgG).[6,7] Chronic infection is characterized by the persistent presence of HBsAg for longer than 6 months.[6-8] The presence of HBeAg is usually associated with high levels of HBV DNA in serum and high infectivity.[9,10] Resolution of HBV infection and disease inactivity are typically characterized by the disappearance of HBsAg and appearance of antibody to HBV surface antigen (anti-HBs). Inactive chronic HBV infection, characterized by the disappearance of HBeAg and appearance of antibody to HBeAg (anti-HBe), eventually occurs in most patients with chronic HBV infection, usually correlating with low levels of HBV DNA in serum and remission of liver inflammatory activity. Reactivation of HBV, or a flare in HBV activity in persons, can occur in persons with serological evidence of inactive or resolved (positive for anti-HBc, but negative for HBsAg) HBV infection.[11]

Prevalence and Burden of Disease/Illness

The incidence of acute symptomatic HBV infections in the United States reported to the Centers for Disease Control and Prevention (CDC)[12] fell from over 20,000 cases annually in the mid-1980s to 2,791 cases in 2014, with an increase to 3,409 in 2017.[12] Due to underreporting, the

actual number of cases is estimated to be 6.5 times higher than the number of reported cases.[12] From 2001 to 2010, the incidence of acute HBV infection declined among all age groups.[12] The highest incidence of acute HBV infections is among persons 40 to 49 years of age (2.5 cases/100,000 population in 2017), followed by persons 30 to 39 years of age; the rate of acute HBV infection is higher in men than women.[12] Since 2010, a rise in acute and chronic HBV infection related to drug use has been reported in several states.[13-15]

As of 2012, the overall prevalence of chronic HBV infection in the United States is about 0.3 percent.[16] In 2011 and 2012, an estimated 847,000 people in the United States were chronically infected with HBV.[12,16] Universal infant vaccination, instituted in 1991, has reduced the incidence and prevalence of chronic HBV infection. The number of persons with serological evidence of vaccine protection from HBV rose from 57.8 million in 1999 to 68.5 million in 2011 to 2012.[16] The prevalence of HBV infection in persons 6 to 19 years of age was 0.03 percent, compared with 0.4 percent among persons 20 to 49 years of age and 0.3 percent among persons ≥50 years of age. Effects of vaccination on the overall prevalence of chronic HBV infection have been offset by immigration from places where chronic HBV is endemic, such as Asia and Africa.[16] Foreign-born persons are estimated to account for approximately 95 percent of newly reported chronic HBV infections in the United States and have an estimated HBV prevalence of approximately 3.5 percent.[17,18] About half of prevalent U.S. cases of chronic infection are in non-Hispanic persons of Asian descent, a group representing 5 to 6 percent of the U.S. population.[19] In the National Health and Nutrition Examination Survey, the prevalence of chronic HBV infection in non-Hispanic persons of Asian descent was 3.1 percent in 2011 to 2012, or 10 times higher than in the general population.[16] The prevalence was 0.1 percent in non-Hispanic white persons, 0.6 percent in non-Hispanic black persons, and 0.06 percent in Mexican American persons. In 2017, there were an estimated 1,727 deaths associated with HBV infection (0.46 per 100,000 persons); death rates were higher in persons age 75 years and older compared to other age groups, persons of Asian/Pacific Islander race compared to other races/ethnicities, and males compared to females.[12]

Etiology and Natural History

HBV is spread through percutaneous or mucous membrane exposure to blood or blood-containing body fluids (serum, semen, or saliva), including sexual contact and injection drug use; horizontal transmission of HBV also occurs among close household contacts.[6,10,20] HBV infection can be transmitted from mother to infant during birth (perinatal transmission); the USPSTF addresses perinatal HBV screening in a separate review.[21] The liver is the primary site of HBV replication. Acutely infected individuals may be asymptomatic or present with symptoms of acute infection, such as nausea, anorexia, fatigue, low-grade fever, and abdominal pain.[5] Jaundice may also be present, and elevated liver enzymes (e.g., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) can be seen on standard assays.

If symptoms of acute disease occur, they can take from 6 weeks to 6 months to appear.[22] Acute infection generally self-resolves in 2 to 4 months, although mortality in this phase is about 1 percent. The risk of progression from acute to chronic infection varies according to age at the time of exposure. Risk of chronic infection is more than 90 percent in infants, 30 percent in children age 1 to 5 years, and less than 5 percent in those older than age 5 years.[10,22] Chronic

infection spontaneously resolves in 1 percent of individuals annually.[8] Some chronically infected individuals are asymptomatic, although others experience a range of symptoms, including nonspecific symptoms of fatigue or other symptoms related to hepatitis, cirrhosis, or hepatocellular carcinoma.[22] Extrahepatic manifestations of HBV infection include polyarteritis nodosa, membranous nephropathy, and membranoproliferative glomerulonephritis. Chronic HBV infection is characterized by several phases: 1) *immune tolerant*, characterized by the presence of HBeAg and very high levels of HBV DNA but normal ALT and minimal hepatic inflammation and fibrosis; 2) *immune active*, characterized by high levels of HBV DNA, ALT elevation, and moderate to severe hepatic inflammation; HBeAg can be present or absent (positive anti-HBe); and 3) *inactive*, characterized by the absence of HBeAg and presence of anti-HBe, low or undetectable levels of HBV viremia, normal ALT, and minimal hepatic inflammation.[8] The immune tolerant phase has been considered a period of minimal or no disease progression, though recent studies indicate that histological activity and increased risk of hepatocellular carcinoma may occur.[23] Fibrosis progression primarily occurs during the immune active phase; however, the presence and severity of fibrosis in the immune active and inactive phases is variable, as patients can transition between these phases. Although the course of chronic HBV infection varies widely, potential long-term sequelae include cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[24] Death from cirrhosis or hepatocellular carcinoma is thought to occur in 15 to 25 percent of those chronically infected with HBV. Increased viral load is associated with greater risk of cirrhosis, hepatocellular carcinoma, and liver-related mortality.[25,26] Reactivation of HBV, or the abrupt increase in HBV activity in persons with inactive or resolved HBV, can also occur.[11] Reactivation may be spontaneous, but is more commonly associated with use of immunosuppressive agents; reactivation can also occur in patients receiving direct-acting antiviral therapy for hepatitis C virus (HCV) infection.[27-29] Clinically, the severity of reactivation ranges from mild to severe, fulminant or even fatal hepatitis. Chronically infected persons are a reservoir for person-to-person transmission of HBV infection. Presence of hepatitis D virus coinfection can impact the clinical course of HBV infection and inform treatment choices.[8]

Risk Factors

People born in countries with an HBV prevalence of 2 percent or greater account for 47 to 95 percent of the chronically infected population in the United States, although marked decreases in prevalence have been seen among younger persons born in these countries due to universal immunization programs.[17,18,30,31] In 2015, the prevalence of HBV infection was highest in Africa (6.1%) and in the Western Pacific region (6.2% in countries including China, the Philippines, and Vietnam), and lowest in Europe (1.6%) and the Americas (0.7%).[31] Persons at higher risk for acute HBV infection in the United States include men, those age 30 to 49 years, and in recent years, non-Hispanic white persons.[12] Risk factors for HBV infection include working in healthcare, having household contacts or sex partners with HBV infection (prevalence of chronic infection, 3% to 20%), HCV-positive status (1.3% to 5.8%), male sexual activity with other males (1.1% to 2.3%), injection drug use (2.7% to 11%), and HIV-positive status (6% to 15%).[10,12,22,32-37] Settings with high proportions of persons at risk for HBV infection include sexually transmitted infection clinics, HIV testing and treatment centers, health care settings that target services toward persons who inject drugs (PWID) and men who have sex with men

(MSM), correctional facilities, hemodialysis facilities, and institutions and nonresidential daycare centers for developmentally disabled persons.[6]

Rationale for Screening/Screening Strategies

Identification of asymptomatic persons with chronic HBV infection through screening may identify those who would benefit from earlier evaluation and management of their disease. In 2016, an estimated 90 percent of HBsAg-positive individuals globally remained undiagnosed.[38] In the United States, estimates of the proportion of persons with HBV infection unaware of their infection status range from one-third to two-thirds.[22] Identification of asymptomatic chronic HBV infection could also lead to reductions in behaviors associated with more rapid progression of liver disease or interventions to decrease transmission of HBV, and identify close contacts who might also benefit from testing.[38-40] Screening could also identify persons with evidence of HBV exposure (positive anti-HBc) who could benefit from education regarding risk of reactivation, and those who could benefit from HBV vaccination (e.g., those never exposed to HBV or those who are isolated anti-HBc positive and immunocompromised).

Interventions/Treatment

Vaccination

Screening could identify persons without prior evidence of HBV exposure (anti-HBs and anti-HBc negative), who could benefit from vaccination to protect against future infection. In persons with isolated anti-HBc positivity, vaccination is recommended in persons from low endemicity areas or those who are immunocompromised.[8] In the United States, current policies are for universal vaccination of all infants at birth, catch-up vaccination of adolescents, and vaccination of high-risk adults.[41] In persons not at increased risk of HBV infection, HBV serologic testing prior to vaccination is not required. HBV vaccines in the United States contain between 10 to 40 micrograms of HBsAg protein/mL for adolescents and adults, and before 2017 involved at least three intramuscular doses administered at 0, 1, and 6 months.[6,10] Vaccination with the three dose vaccine results in greater than 90 percent protective antibody response after the third dose in adults and greater than 95 percent in adolescents, although protective anti-HBs titers may be attained in some persons after one or two doses.[6,10] By the end of 2017, 187 countries had introduced nationwide HBV vaccine for infants, with 105 countries targeting vaccination of all newborns.[42] In 2015, global coverage with the third infant dose of HBV vaccine reached 84 percent, and prevalence of chronic infection in children under 5 years of age dropped to 1.3 percent, compared with about 4.7 percent before vaccination programs began.[31,43] In November 2017, the U.S. Food and Drug Administration (FDA) approved a two-dose HBV vaccine[44] for use in adults based on three trials showing comparable serologic outcomes to three-dose vaccines through up to 28 weeks.[45] Studies of the two-dose vaccine were not designed to assess effects on risk of HBV acquisition, though vaccine-induced seroprotection is considered a surrogate of clinical protection.[46]

Treatment

Drugs for HBV infection are broadly categorized as interferons or nucleoside/nucleotide analogs.[8,30,47,48] The interferons affect viral replication as well as immune modulation.[8,9] Nucleoside/nucleotide analogues (lamivudine, adefovir, entecavir, and others) compete with binding sites on the HBV reverse transcriptase. As of October 2017, seven antiviral drugs had been approved by the FDA for treatment of chronic HBV infection: interferon alfa-2b, pegylated interferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine, tenofovir disoproxil fumarate (TDF); and the most recently approved medication (in 2016), tenofovir alafenamide (TAF).[49,50] TAF is a prodrug of tenofovir with improved kidney and bone safety parameters compared with TDF. The American Association for the Study of Liver Diseases (AASLD) recommends pegylated interferon, entecavir, and TDF as preferred initial therapy for immune-active chronic HBV;[8] TAF was recently added to the preferred list.[8] Telbivudine is no longer manufactured in the United States, though it is available in other countries.

Cure rates with current antiviral therapies are low,[51] and other therapies have been studied, but remain investigational.[52] A number of combination therapies have also been evaluated but are not FDA approved and not recommended as first-line treatment due to unclear advantages over monotherapy in most patients, particularly in those at low risk for developing drug resistance.[8] The choice of antiviral medication varies according to patient characteristics and disease activity. Factors that affect the decision to treat include the HBV DNA level, serum transaminase levels, and HBeAg status.[8] Biopsy may be performed in some patients to establish the degree of liver inflammation and fibrosis, which also affect treatment, surveillance and hepatocellular carcinoma screening decision-making.[8] Noninvasive alternatives to biopsy for assessing degree of hepatic fibrosis include imaging with transient elastography and various blood tests.[53-56] The goal of treatment is to achieve sustained suppression of HBV replication and remission of liver disease in order to prevent cirrhosis, hepatic failure, and hepatocellular carcinoma.[30,47] The recommended duration of treatment varies depending on the HBeAg status, presence of cirrhosis, duration of HBV DNA suppression, and choice of medication.[8,22] Many patients remain on antiviral treatment indefinitely, with the exception of interferon-based therapy, which is usually recommended for a defined duration of treatment, in part due to limited tolerability and immunomodulatory effects of interferons which may result in a sustained response.[8] Other treatments in patients with chronic HBV infection could include counseling or education to potentially reduce behaviors associated with accelerated progression of liver disease (such as alcohol use) or transmission, or surveillance with imaging tests to identify hepatocellular carcinoma,[8] though the effectiveness of such surveillance on improving clinical outcomes is uncertain.[57] Low rates of linkage and retention in treatment and use of antiviral therapy are barriers to optimal care of persons with HBV infection.[58]

Current Clinical Practice/Recommendations of Other Groups

Screening for HBV infection is usually performed by testing for HBsAg and anti-HBs.[8] Testing for anti-HBc is not routinely recommended by AASLD[8] but is recommended by the American College of Physicians (ACP)/CDC;[59] it indicates prior HBV exposure status (anti-HBc does not develop after vaccination) and can help determine a patient's risk for reactivation (e.g., in persons being considered for HCV therapy or immunosuppressive treatment). New rapid tests for

HBsAg have recently been developed, but no rapid test has been approved by the FDA.[60-63] The CDC recommends that FDA-approved tests be used to screen for HBsAg and a confirmatory test performed for initially reactive results.[22] In persons with serologic findings suggesting chronic infection, followup includes quantitative testing for HBV viremia, presence of HBeAg, and liver transaminase levels. Current U.S. screening practices for HBV and rates of HBV testing are largely unreported. One study of over one million Americans with access to private health care found that about 20 percent were tested for HBV over a median of more than 7 years and 1.4 percent tested positive for HBV infection.[64] Based on national HBV prevalence data, it was estimated that 20 to 50 percent of expected HBV infections were not identified in this cohort. Guidelines generally recommend that screening be targeted to populations and persons at increased risk for chronic HBV infection, including persons born in high-prevalence countries.[8,59] However, some studies indicate that target populations are not being provided with screening and/or vaccination despite having contact with their clinician.[65-67] HBV screening best practice advice from the ACP/CDC[59] and recommendations from AASLD[8] are shown in **Table 2**.

Both the ACP/CDC best practice advice and AASLD guideline also recommend screening of persons who engage in behaviors associated with increased risk for HBV, including men who have sex with men, persons who inject drugs, HIV-positive persons, and household contacts or sexual partners of persons with HBV infection, inmates of correctional facilities, persons with HCV infection, and persons with end-stage kidney disease.[59] AASLD also recommends screening of persons with multiple sex partners or those seeking evaluation or treatment for a sexually transmitted infection, residents and staff of facilities for the developmentally disabled, and travelers to HBV endemic countries.[8] Both AASLD and earlier (2008) CDC guidelines recommend screening of U.S. born persons not vaccinated as infants whose parents were born in regions with an eight percent or greater prevalence; the CDC guideline also recommends screening needle-sharing contacts of injection drug users.[8,22] The National Academies of Science, Engineering, and Medicine National Strategy cites the USPSTF recommendation on screening as an essential component of its National Strategy for Elimination of Hepatitis B and C.[68]

Internationally, the World Health Organization (WHO) recommends HBV testing in the general population when the prevalence is 2 percent or greater and in higher-risk populations.[69] The United Kingdom's National Institute for Clinical Excellence recommends HBV testing in higher-risk populations and is generally consistent with the USPSTF recommendation.[70]

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[71] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created an analytic framework with the key questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**).

Key Questions

1. What are the benefits of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?
2. What are the harms of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults (e.g., labeling or anxiety)?
3. What is the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV screening strategies (e.g., universal vs. targeted screening or screening strategies based on alternative risk factors)?
4. How effective is antiviral treatment in improving intermediate outcomes among nonpregnant adolescents and adults with chronic HBV infection, including virologic or histologic improvement, clearance of HBeAg (as indicated by loss of HBeAg or acquisition of anti-HBe), or clearance of HBsAg (as indicated by loss of HBsAg or acquisition of anti-HBs)?*
5. How effective is antiviral treatment in improving health outcomes among nonpregnant adolescents and adults with chronic HBV infection?*
6. What are the harms associated with antiviral treatment in nonpregnant adolescents and adults with chronic HBV infection?*
7. What is the association between improvements in intermediate outcomes as a result of antiviral treatment of chronic HBV infection and reduction in risk of HBV-related adverse health outcomes?

*Subpopulations of interest for key questions 4, 5, and 6 include those defined by age, race/ethnicity, sex, injection drug use status, HBV genotype, HBeAg status, fibrosis stage, alanine transaminase level, presence of nonalcoholic steatohepatitis, HBV DNA level, and hepatitis D virus status.

Contextual Questions

Contextual Question were also requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology:

1. What are the effects of different risk- or prevalence-based methods for screening for HBV infection in modeling studies?
2. What is the accuracy of tools for identifying persons with chronic HBV infection?
3. In persons with serologic evidence of HBV infection (positive test results for anti-HBc or for HBsAg), what is the likelihood of reactivation following exposure to

immunosuppressant therapy, and what is the effectiveness of interventions to improve clinical outcomes associated with reactivation?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews and Ovid MEDLINE (2014 to August 2019), and clinicaltrials.gov for relevant studies and systematic reviews. Search strategies are available in **Appendix A1.** We also reviewed reference lists of relevant articles; studies from the prior USPSTF review[3,72] meeting inclusion criteria were carried forward. Ongoing surveillance was conducted to identify major studies published since August 2019 that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on July 24, 2020 and identified no studies affecting review conclusions.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on the basis of prespecified inclusion and exclusion criteria developed for each key question (**Appendix A2**). For Key Questions on screening, randomized trials and cohort studies on benefits or harms of screening versus no screening or on the yield (sensitivity and number needed to screen to identify one HBV-infected person) were included. We also included cross-sectional studies on the yield of screening. For Key Questions related to treatment, randomized trials of patients that compared monotherapy with an FDA-approved medication versus placebo or no treatment and reported clinical outcomes (including mortality, cirrhosis, hepatocellular cancer, quality of life, HBV transmission, extrahepatic outcomes, or harms) or intermediate outcomes (virologic improvement, histologic improvement, biochemical improvement [improvement in alanine aminotransferase levels], HBeAg clearance [loss of HBeAg or acquisition of anti-HBe], or HBsAg clearance [loss of HBsAg or acquisition of anti-HBs]) were included. FDA-approved antiviral therapies classified as either preferred/first-line or nonpreferred in recent HBV guidelines were included (**Table 3**).[8,49] Preferred antiviral therapies are entecavir, TDF, TAF, pegylated interferon (adults), and nonpegylated interferon (children); nonpreferred therapies are adefovir, lamivudine, and telbivudine. Because few placebo controlled trials evaluated preferred antiviral therapies, we also included randomized trials of preferred versus nonpreferred therapies. Studies of treatment were excluded if they evaluated non–FDA-approved or combination therapies. In adults, nonpegylated interferon has been supplanted by pegylated interferon and is no longer available in the United States; however, we included trials of nonpegylated interferon because evidence from placebo-controlled and head-to-head trials of pegylated interferon was sparse. Long-term (≥1 year), large (n>1,000) cohort studies of antiviral treatment versus no treatment that reported clinical outcomes and controlled for potential confounders were also included. We also included cohort studies that reported adjusted risk estimates for the association between achieving an intermediate outcome following antiviral treatment (e.g., clearance of HBeAg or HBV DNA from serum, normalization of serum transaminases, histological improvement, or a composite intermediate outcome) and long-term clinical outcomes (mortality, hepatocellular carcinoma, or cirrhosis). In order to increase the

applicability of the evidence to populations likely to be identified by screening, we excluded trials of antiviral therapy in which greater than 20 percent of the population was treatment experienced (nonresponders to prior antiviral therapy or patients with virological relapse) or had cirrhosis at baseline. For cohort studies, we permitted studies in which up to 30 percent of patients had cirrhosis, if fibrosis stage was controlled for in the analysis. We excluded studies of patients with HIV or HCV coinfection, patients on hemodialysis, and transplant patients; management of these conditions is considered outside the scope of screening by the USPSTF.

For Key Questions related to screening, inclusion was restricted to the United States and other low prevalence settings in which the epidemiology and management of HBV infection are similar to those in the United States. For treatment, studies from any country were eligible for inclusion.

The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists the included studies, and **Appendix A5** lists the excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we created data abstraction forms to summarize characteristics of study populations, interventions, comparators, outcomes study designs, settings, and methods. One investigator conducted data abstraction, which was reviewed for completeness and accuracy by another team member. Predefined criteria were used to assess the quality of individual controlled trials and observational studies by using criteria developed by the USPSTF; studies were rated as "good," "fair," or "poor" per USPSTF criteria, depending on the seriousness of the methodological shortcomings (**Appendix A6**).[71] For each study, quality assessment was performed by two team members. Disagreements were resolved by consensus.

Data Synthesis

To summarize evidence on effects of antiviral therapy versus placebo and preferred versus nonpreferred antiviral therapies, meta-analysis was conducted on intermediate outcomes (HBeAg loss, HBeAg seroconversion, HBsAg loss, HBsAg seroconversion, HBV DNA loss [virological suppression], ALT normalization, histological improvement, and composite outcomes [HBeAg loss plus HBV DNA loss, or HBV DNA loss plus ALT normalization]), clinical outcomes (mortality, cirrhosis, hepatocellular carcinoma), and harms (serious adverse events, withdrawal due to adverse events, any adverse events, gastrointestinal adverse events, and kidney adverse events) using a random effects (profile likelihood) model in Stata/IC 14.2 (StataCorp LP, College Station, TX). When the profile likelihood model did not converge, the Dersimonian-Laird model was used instead. For placebo-controlled trials, data from all antiviral drugs were pooled, though analyses were stratified by individual drug. For head-to-head comparisons, each drug-drug comparison was pooled separately. Stratified analyses were conducted based on study quality, geographic setting (low prevalence, high prevalence, or mixed/other), duration of followup (<52 weeks versus ≥52 weeks), HBeAg status, immune tolerant (based on high HBV

DNA level, normal or minimally elevated AST level, and minimal or no histological activity) or immune active status, and cirrhosis (excluded or included some [up to 20% of sample] with baseline cirrhosis) when there were at least five trials, and a test for subgroup differences (interaction) performed. Statistical heterogeneity was assessed using the I^2 statistic. Graphical and statistical tests for small sample effects were not conducted due to fewer than 10 trials for most analyses and clinical heterogeneity (due to differences in the drugs evaluated and populations [e.g., HBeAg status]) in analyses with more than 10 trials.[73]

For all Key Questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[71] Evidence was rated "good", "fair", or "poor" based on study quality, consistency of results between studies, precision of estimates, risk of reporting bias, applicability, and other study limitations.[71] A summary of evidence table was developed to assess the overall quality of evidence for each Key Question using the approach described in the USPSTF Procedure Manual.[71]

Expert Review and Public Comment

The draft Research Plan was posted for comment on the USPSTF Web site from November 29, 2018 through January 2, 2019. In response to public comments, the USPSTF revised the Research Plan by adding extrahepatic manifestations as a health outcome, removing harms of liver biopsies as a key question, and adding cohort studies of treatment versus no treatment for long-term clinical outcomes.

A draft version of this report was reviewed by content experts (**Appendix A7**), representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report. Reviewers suggested edits for clarity; some publications were suggested but did not meet inclusion criteria. The draft report was also posted for public comment from 5/5/20 to 6/1/20 and one person responded. In response, to the Recommendations of Other Groups section, we revised the text to include details about the 2008 CDC hepatitis B screening recommendations. No other changes were necessary.

Chapter 3. Results

A total of 6,272 new references from electronic database searches and manual searches of recently published studies were reviewed, and 506 full-text papers were evaluated for inclusion. Across all KQs, 30 RCTs[74-102] (N=7,099), 17 cohort studies[103-119] (N=56,029), and three retrospective studies addressing the yield of alternative strategies (N=31,040)[120-122] were included. Twenty-two studies[88-91,98-110,117-119,121,122] were new for this update, and 28 studies[74-87,92-97,111-116,120] were carried forward from the previous review. Included studies and quality ratings are described in **Appendix B**.

Key Question 1. What Are the Benefits of Screening for HBV Infection in Asymptomatic, Nonpregnant Adolescents and Adults on Morbidity, Mortality, and Disease Transmission?

As in the prior USPSTF review, no study compared clinical outcomes between individuals screened and not screened for HBV infection.

Key Question 2. What Are the Harms of Screening for HBV Infection in Asymptomatic, Nonpregnant Adolescents and Adults (e.g., Labeling or Anxiety)?

As in the prior USPSTF review, no study compared harms between individuals screened and not screened for HBV infection.

Key Question 3. What Is the Yield (Number of New Diagnoses per Tests Performed) and Sensitivity of Alternative HBV Screening Strategies (e.g., Universal vs. Targeted Screening or Screening Strategies Based on Alternative Risk Factors)?

Summary

Three European studies (N=30,040) found that screening strategies that targeted persons with a variety of risk factors (ever having immigrated from high prevalence countries, other demographic risk factors, and behavioral risk factors) would identify nearly all cases of HBV infection while screening about two-thirds of the population; numbers needed to screen to identify one HBV infection ranged from 32 to 148. Screening only immigrants from high prevalence (≥2%) countries was more efficient (number needed to screen 19 to 71) and identified 85 to 99 percent of patients with HBV infection in higher prevalence clinical settings, but missed about two-thirds of HBV infections in a study conducted in primary care practices.

Evidence

The prior USPSTF review included one fair-quality (n=6,194) retrospective study that found that a strategy of screening persons in France at a sexually transmitted infection clinic born in countries with higher (≥2%) chronic HBV prevalence, men, and unemployed persons would identify 98 percent (48/49) of HBV infections while testing about two-thirds of the population, for a number needed to screen to identify one case of HBV infection of 82 (**Appendix B Tables 1-3**).[120] Strategies that involved screening persons born in higher prevalence countries and replaced male sex or employment status with behavioral risk factors would have resulted in higher proportions of patients, no increase in sensitivity, and numbers needed to screen similar to screening the whole population (~126). Screening only patients born in higher prevalence (≥2%) countries would have resulted in testing of 12 percent of patients, a sensitivity of 85 percent, and a number needed to screen to identify one case of HBV infection of 19.

Two new, fair-quality studies on the yield of alternative screening strategies were identified for this update (**Appendix B Tables 1-3**).[121,122] Both studies were conducted in Europe and applied screening strategies retrospectively.

A French study (n=3,929) performed HBV screening in 10 centers, including settings with higher HBV prevalence (clinics focusing on sexually transmitted infection testing, immigrants, persons with low socioeconomic status, or incarcerated individuals). It found that 2.2 percent of participants had active HBV infection (based on a positive test for HBsAg), 13 percent had resolved HBV infection, 3.3 percent had isolated anti-HBc, 44 percent had been vaccinated, and 38 percent were non-immunized. In this population, 44 percent of patients were born in a country with HBV prevalence ≥2 percent, 46 percent had more than one sexual partner in the past 12 months, 23 percent had no healthcare or healthcare assistance, 11 percent were MSM, and 0.6 percent were intravenous drug users. A strategy of HBV screening based on the physicians' judgment that testing was needed would identify 87 percent (74/85) of HBV infections while testing about two-thirds of the population, for a number needed to screen to identify one case of HBV infection of 35. A strategy of HBV screening based on the 2008 CDC HBV screening recommendations[22] would have identified all infections and was slightly more efficient; in this strategy; about 7 percent of the population would be screened, resulting in a number needed to screen of 32. Screening only persons from countries with HBV prevalence ≥2% was the most efficient strategy: it would have identified almost all infections (99%, or 84/85) while screening 44 percent of the population, resulting in a number needed to screen of 20.

A German study (n=20,917) evaluated a series of screening strategies based on a 16-item questionnaire adapted from the German HBV[123] and HCV[124] guidelines. The sample consisted of patients in private primary care practices with an HBsAg prevalence of 0.52 percent.[122] Screening all persons in the cohort would have resulted in a number needed to screen to detect one HBsAg positive unaware of their status of 224. A strategy of screening persons with a positive response to at least one of the HBV-related items in the questionnaire would have identified 67 percent (62/93) cases while testing 44 percent of the population, for a number needed to screen of 148. A strategy of screening only persons with an immigration background or hepatitis positive household member would have identified 37 percent (34 of 93) cases while screening 12 percent of the population, for a number needed to screen of 77. Screening only

persons with an immigration background would have slightly lower sensitivity (30%), but would also be slightly more efficient (number needed to screen 71).

Key Question 4. How Effective Is Antiviral Treatment in Improving Intermediate Outcomes Among Nonpregnant Adolescents and Adults With Chronic HBV Infection, Including Virologic or Histologic Improvement, Clearance of HBeAg (as Indicated by Loss of HBeAg or Acquisition of Anti-HBe), or Clearance of HBsAg (as Indicated by Loss of HBsAg or Acquisition of Anti-HBs)?

Summary

As in the prior USPSTF review, antiviral therapy was associated with increased likelihood of achieving intermediate outcomes versus placebo:

- HBeAg loss: 6 trials, N=1,121, relative risk (RR) 1.91, 95% confidence interval (CI) 1.46 to 2.81, I^2=15%; absolute risk difference (ARD) 14%, 95% CI 5.8% to 23%
- HBeAg seroconversion: 4 trials, N=1,104, RR 2.11, 95% CI 1.30 to 3.55, I^2=0%; ARD 6.2%, 95% CI 2.4% to 10.5%
- HBsAg loss: 3 trials, N=714, RR 4.63, 95% CI 1.10 to 19.55, I^2=70%; ARD 8.2%, 95% CI -2.6% to 18.9%
- Virological suppression: 13 trials, N=2,522, RR 4.39, 95% CI 2.61 to 7.39, I^2=86%; ARD 39%, 95% CI 24% to 53%
- ALT normalization: 11 trials, N=2,044, RR 2.62, 95% CI 2.22 to 3.10, I^2=0%; ARD 32%, 95% CI 27% to 37%
- Histological improvement: 6 trials, N =1,057, RR 2.00, 95% CI 1.63 to 2.41, I^2=0%; ARD 28%, 95% CI 22% to 34%
- Composite of virological suppression plus ALT normalization: 3 trials, N=286, RR 6.30, 95% CI 3.06 to 13.11, I^2=0%; ARD 48%, 95% CI 29% to 61%
- Composite of HBeAg loss/seroconversion plus virological suppression: 2 trials of lamivudine, N=391, RR 3.18, 95% CI 1.11 to 9.11, I^2=0%; ARD 9.2%, 95% CI -0.2% to 16%; and 2 trials of interferon, N=232, RR 2.18, 95% CI 1.10 to 4.78; ARD 23%, 95% CI 8% to 37%

As in the prior USPSTF review, preferred antiviral therapies (entecavir, TDF, pegylated interferon) were associated with greater likelihood of achieving some intermediate outcomes versus nonpreferred therapies in head-to-head comparisons. Analyses were limited by small numbers of trials, with imprecise estimates for some outcomes. Evidence was most robust for effects of entecavir versus lamivudine on virological suppression (6 trials, N=2,115, RR 1.70, 95% CI 1.38 to 2.13, I^2=81%; ARD 30%, 95% CI 17% to 43%) and ALT normalization (6 trials, N=2,079, RR 1.13, 95% CI 1.08 to 1.27, I^2=0%; ARD 12%, 95% CI 4.2% to 22%). One trial found pegylated interferon alfa-2a associated with increased likelihood of achieving virological,

biochemical, and histological outcomes versus lamivudine 24 weeks following the completion of 48 weeks of therapy. Three trials found TDF probably associated with increased likelihood of virological suppression versus adefovir (N=1,150, RR 2.32, 95% CI 0.96 to 6.10, I^2=97%); estimates for other intermediate outcomes were imprecise or indicated no differences.

Evidence

Antiviral Therapy vs. Placebo or No Treatment

The prior USPSTF review found antiviral therapy more effective than placebo or no treatment in achieving HBeAg loss or seroconversion (10 trials; RR, 2.1; 95% CI, 1.6 to 2.9; I^2=4%), HBsAg loss or seroconversion (12 trials; RR, 2.4; 95% CI, 1.2 to 4.9; I^2=0%), ALT normalization (12 trials; RR, 2.5; 95% CI, 2.1 to 3.0; I^2=27%), reduction in HBV DNA (nine trials; RR, 7.2; 95% CI, 3.2 to 16; I^2=58%), and histological improvement (seven trials; RR, 2.1; 95% CI, 1.8 to 2.6; I^2=0%). The prior USPSTF review included trials in which more than 20 percent of patients had cirrhosis at baseline,[125-129] patients had previously received antiviral therapy,[130-132] or that were rated poor-quality;[133-135] these trials were excluded for this update.

Eighteen trials (N=2,972) comparing antiviral therapy to placebo or no treatment were included in this update (**Appendix B Tables 4-5**).[74-91] Fourteen trials were included in the prior USPSTF review and four trials[88-91] were added for this update. One trial evaluated entecavir,[90] six trials non-pegylated interferon,[80,81,83,84,88,89] three trials adefovir,[77,82,91] and eight trials lamivudine;[74-76,78,79,85-87] no placebo-controlled trials of pegylated interferon, tenofovir (TDF or TAF), or telbivudine met inclusion criteria. The number of participants in the 18 trials ranged from 42 to 526. All trials included only adults, with mean ages ranging from 24 to 46 years. Most participants were male (54% to 100%). Of 11 studies reporting baseline HBeAg status, in eight trials more than 95 percent of patients were HBeAg-positive,[78,79,82-84,86-88] in two studies 6 percent or less of patients were HBeAg-positive,[75,85] and one study included 38 percent HBeAg-positive patients.[90] One trial excluded patients with cirrhosis;[83] in the other 17 trials, the proportion with cirrhosis was ≤20 percent. Eleven trials excluded patients with decompensated liver disease.[75,78,80,81,84-87,89-91] Although the trials did not classify patients as having “immune active” or “immune tolerant” HBV infection, two trials appeared to focus on immune tolerant patients, based on high HBV DNA level, normal or minimally elevated AST, and minimal histological activity.[86,90] In the other trials, patients had characteristics consistent with immune active disease.

The duration of followup ranged from 1.8 to 86 months. Six studies were conducted in the United States, Canada, Europe, Australia, or New Zealand,[76,80,83-85,88] seven were conducted in Asia,[75,78,79,81,87,90,91] and five were multinational or conducted in other countries.[74,77,82,86,89]

All trials were rated fair-quality (**Appendix B Table 6**). Frequent methodological limitations were unclear reporting of randomization, allocation concealment, and blinding methods.

HBeAg Loss or Seroconversion

In patients with HBeAg-positive HBV infection, antiviral therapy was associated with increased likelihood of HBeAg loss versus placebo or no antiviral therapy (6 trials, N=1,121, RR 1.91, 95% CI 1.46 to 2.81, I^2=15%; ARD 14%, 95% CI 5.8% to 23%)[76,82,83,87-89] (**Figure 2**). Effects favored antiviral therapy for each individual drug. Lamivudine was evaluated in two trials (N=515, RR 2.06, 95% CI 0.94 to 4.93, I^2=0%),[76,87] adefovir in one trial (N=332, RR 2.27, 95% CI 1.35 to 3.83),[82] nonpegylated interferon alfa-2a in two trials (N=210, RR 2.61, 95% CI 1.15 to 5.47, I^2=0%),[88,89] and nonpegylated interferon alfa-2b in one trial (N=64, RR 1.48, 95% CI 1.10 to 2.00).[83] There were no interactions between geographic region, prior antiviral treatment status, or followup duration and effects on HBeAg loss (**Table 4**). All trials were rated fair-quality.

Antiviral therapy was also associated with increased likelihood of HBeAg seroconversion, though fewer trials (four) evaluated this outcome (N=1,104, RR 2.11, 95% CI 1.30 to 3.55, I^2=0%; ARD 6.2%, 95% CI 2.4% to 10%) (**Figure 3**).[76,82,86,87] Lamivudine was evaluated in three trials (N=607, RR 1.98, 95% CI 0.99 to 4.65, I^2=0%)[76,86,87] and adefovir in one trial (N=497, RR 2.29, 95% CI 1.14 to 4.58).[82]

HBsAg Loss or Seroconversion

Antiviral therapy was associated with increased likelihood of HBsAg loss versus placebo or no antiviral therapy (three trials, N=714, RR 4.63, 95% CI 1.10 to 19.55, I^2=70%; ARD 8.2%, 95% CI -2.6% to 19%) (**Figure 4**).[83,85,91] Adefovir was evaluated in one trial (RR 12.58, 95% CI 5.93 to 26.71)[91] and nonpegylated interferon-alfa in one trial (RR 3.76, 95% CI 1.17 to 12.06);[83] the third trial evaluated lamivudine but only reported one case of HBsAg loss (RR 0.36, 95% CI 0.01 to 8.55).[85]

Effects of antiviral therapy versus placebo or no antiviral therapy on likelihood of HBsAg seroconversion was only reported in one trial, which reported no cases.[85]

Virological Suppression

Antiviral therapy was associated with increased likelihood of HBV DNA suppression versus placebo (13 trials, N=2,522, RR 4.39, 95% CI 2.61 to 7.39, I^2=86%; ARD 39%, 95% CI 24% to 53%) (**Figure 5**).[75-78,82,83,85-91] HBV DNA suppression was defined as less than 500 IU/mL (one trial), less than 400 copies/mL (two trials), less than 100 copies/mL (1 trial), or less than 1 to less than 2.5 pg/mL (five trials); four trials[83,88-90] did not report criteria for HBV DNA suppression. Statistical heterogeneity was present in the overall analysis, but not in analyses of the individual drugs, each of which favored antiviral therapy. Lamivudine was evaluated in six trials (N=1.159, RR 3.98, 95% CI 3.07 to 5.17, I^2=12%),[75,76,78,85-87] adefovir in three trials (N=1,048, RR 19.22, 95% CI 10.98 to 33.67, I^2=0%),[77,82,91] entecavir in one trial (N=41, RR 31.50, 95% CI 2.02 to 492.36),[90] nonpegylated interferon alfa-2a in two trials (N=210, RR 1.88, 95% CI 1.25 to 2.82, I^2=0%),[88,89] and nonpegylated interferon alfa-2b in one trial (N=64, RR 1.36, 95% CI 0.96 to 1.92).[83] Results also consistently favored antiviral therapy in stratified analyses based on geographic region, HBeAg status, prior antiviral treatment status, and duration of followup, though some statistically significant interactions were observed (**Table 4**). Effects on HBV DNA

suppression were stronger in trials conducted in Asia (five trials, RR 7.06, 95% CI 3.43 to 15.93, I^2=72%)[75,78,87,90,91] than in trials conducted in the United States, Canada, Europe, Australia, or New Zealand (4 trials, RR 2.32, 95% CI 1.39 to 4.10, I^2=62%; p for interaction <0.005).[76,77,82,83] Effects were also stronger in trials with followup less than 52 weeks (four trials, RR 5.65, 95% CI 3.14 to 48.74, I^2=36%)[77,82,87,91] than in trials greater than or equal to 52 weeks (nine trials, RR 3.50, 95% CI 1.88 to 6.94, I^2=85%, p for interaction<0.005).[75,76,78,83,85,86,88-90] Although there was an interaction between HBeAg status and greater effects on HBV DNA suppression, only one trial excluded HBeAg-positive patients (**Table 4**). Effects were similar in trials that were restricted to treatment-naïve patients and trials that included some treatment-experienced patients or that did not report prior treatment status. Antiviral therapy was associated with increased likelihood of HBV DNA suppression in trials of immune tolerant patients (two trials, RR 8.81, 95% CI 0.75 to 103.94, I^2=39%)[86,90] and trials of immune active patients (11 trials, RR 4.17, 95% CI 2.46 to 7.97, I^2=88%; p for interaction=0.13), though the estimate for immune tolerant patients was very imprecise and not statistically significant. All of the trials were rated fair-quality.

ALT Normalization

Antiviral therapy was associated with increased likelihood of ALT normalization (11 trials, N=2,044, RR 2.62, 95% CI 2.22 to 3.10, I^2=0%; ARD 24%, 95% CI 7.8% to 39%) (**Figure 6**).[74-78,81-83,87,88,91] Effects favored antiviral therapy for each individual drug. Lamivudine was evaluated in five trials (N=752, RR 1.88, 95% CI 1.10 to 3.20, I^2=0%),[74-76,78,87] adefovir in three trials (N=1,033, RR 3.04, 95% CI 2.32 to 3.96, I^2=0%),[77,82,91] and nonpegylated interferon alfa-2a in two trials (N=195, RR 2.44, 95% CI 1.29 to 4.62, I^2=0%),[81,88] and nonpegylated interferon alfa-2b in one trial (N=64, RR 1.88, 95% CI 1.10 to 3.20).[83] There were no interactions between geographic region, restriction to treatment-naïve patients, or followup duration and effects of antiviral treatment on likelihood of ALT normalization (**Table 4**). One trial[77] excluded HBeAg-positive patients; effects on likelihood of ALT normalization (RR 2.51, 95% CI 1.66 to 3.81) were very similar to the overall estimate.

Histological Improvement

Antiviral therapy was associated with increased likelihood of histological improvement versus placebo or no therapy (six trials, N=1,057, RR 2.00, 95% CI 1.63 to 2.41, I^2=0%; ARD 28%, 95% CI 22% to 34%) (**Figure 7**).[75-78,82,90] In all trials, histological improvement was defined as ≥2 point improvement in the Knodell score (scale 0 to 22). Effects favored antiviral therapy for lamivudine (three trials, N=511, RR 2.29, 95% CI 1.66 to 3.26, I^2=0%)[75,76,78] and adefovir (two trials, N=507, RR 2.02, 95% CI 1.51 to 2.65, I^2=0%);[77,82] the estimate for entecavir was imprecise (one trial, N=39, RR 0.86, 95% CI 0.40 to 1.82).[90]

Composite Intermediate Outcomes

Antiviral therapy was associated with increased likelihood of the composite outcome of HBV DNA suppression plus ALT normalization versus placebo or no therapy (three trials, N=286, RR 6.30, 95% CI 3.06 to 13.11, I^2=0%; ARD 48%, 95% CI 29% to 61%)[75,80,85] (**Figure 8**). Two

trials evaluated lamivudine (N=244, RR 6.98, 95% CI 2.85 to 20.01, I^2=0%)[75,85] and one trial evaluated nonpegylated interferon alfa-2b (RR 4.00, 95% CI 0.96 to 16.66).[80]

Antiviral therapy was also associated with increased likelihood of the composite outcome of HBeAg loss or seroconversion plus HBV DNA suppression versus placebo or no therapy (four trials, N=623, RR 2.36, 95% CI 1.44 to 4.28, I^2=0%; ARD 12%, 95% CI 4.8% to 24%) (**Figure 9**).[78,81,86,89] Two trials evaluated nonpegylated interferon alfa-2a (N=232, RR 2.18, 95% CI 1.10 to 4.78, I^2=0%)[81,89] and two trials evaluated lamivudine (N=391, RR 3.18, 95% CI 1.11 to 9.11, I^2=0%).[78,86]

Subgroups

Effects of HBeAg status and inclusion of some patients with cirrhosis at baseline were evaluated in stratified analyses across trials, as described above. Two trials enrolled only patients with normal ALT values, and results were consistent with those of other trials.[86,90] There was insufficient evidence to evaluate how effects of antiviral therapies varied within studies according to demographic (age, sex, race) and other clinical factors (HBV DNA level, injection drug use status, HBV genotype, ALT level, presence of nonalcoholic steatohepatitis, or hepatitis D virus status). Few trials reported how effects of antiviral therapies varied according to these factors, with one trial reporting no effect of HBV genotype[91] and two that did not report statistical analyses for subgroup differences.[78,89] Some factors (e.g., injection drug use status and presence of nonalcoholic steatohepatitis) were not reported by the trials.

Preferred vs. Nonpreferred Regimens

The prior USPSTF review found the preferred antiviral therapies entecavir (four trials) and pegylated interferon alfa-2a (two trials) associated with greater likelihood of achieving some intermediate outcomes (virological improvement, histological improvement) versus the nonpreferred antiviral therapy lamivudine, though comparisons were limited by small numbers of trials. Estimates for effects of TDF versus adefovir on intermediate outcomes were imprecise, based on two trials.

Twelve head-to-head trials (reported in 11 publications; N=4,127) of preferred (entecavir, TDF, or pegylated interferon alfa-2a) versus nonpreferred (lamivudine, telbivudine, or adefovir) antiviral regimens for HBV infection were included in this update (**Appendix B Tables 7-8**).[92-102] Seven trials were included in the prior USPSTF review and five trials were added for this update. Sample sizes ranged from 44 to 715. All trials only enrolled adults. Between 55 and 83 percent of patients were men. In six trials, all or most of patients were HBeAg-positive,[92,95-97,100,102] and in two trials, few to no patients were HBeAg-positive;[93,96] one trial did not report HBeAg status.[99] Of five studies reporting cirrhosis at baseline, prevalence ranged from 7 to 20 percent.

Six trials compared entecavir versus lamivudine,[92-94,97,99,101] two trials entecavir versus telbivudine,[100,102] three trials (reported in two publications) TDF versus adefovir,[96,98] and one trial pegylated interferon alfa-2a versus lamivudine.[95] No trial evaluated TAF (FDA-approved in 2016). Duration of followup ranged from 3.7 to 22 months. Two multinational trials were

conducted in the United States, Europe, and other areas with low HBV prevalence,[96] six trials were conducted in Asia,[97-102] and four multinational trials were conducted in high and low HBV prevalence settings (e.g., Asia and the United States or Europe).[92-95] Five trials were rated good-quality[92,93,95,98,101] and the others were rated fair-quality. Methodological limitations in the fair-quality trials included unclear or no blinding of outcome assessors, care providers, and patients in most studies; attrition did not differ between groups for all studies (**Appendix B Table 6**).

HBeAg Loss or Seroconversion

Three trials compared effects of preferred versus nonpreferred antiviral therapies on likelihood of HBeAg loss.[94,95,98] Each evaluated a different drug comparison; though results favored preferred antiviral drugs, estimates were imprecise. One trial (n=202) compared TDF versus adefovir (18% vs. 10%, RR 1.73, 95% CI 0.84 to 3.56)[98] and one trial (n=543) pegylated interferon alfa-2a versus lamivudine (27% vs. 20%, RR 1.38 95% CI 1.04 to 1.84 at end of treatment at 48 weeks and 32% vs. 19%, RR 1.64, 95% CI 1.23 to 2.18 at 24 weeks following the end of treatment).[95] A third, smaller (n=69) trial evaluated entecavir versus lamivudine, but there were only 2 cases of HBeAg loss (both in the lamivudine arm).[94]

Seven trials evaluated effects of preferred versus nonpreferred antiviral therapies on likelihood of HBeAg seroconversion (**Figure 10**).[94-97,101,102,136] One trial found pegylated interferon alfa-2a associated with increased likelihood of HBeAg seroconversion versus lamivudine at the end of treatment at 48 weeks (N=543, 27% vs. 20%, RR 1.31, 95% CI 0.97 to 1.79)[95] and at 24 weeks following the end of treatment (32% vs. 19%, RR 1.68, 95% CI 1.24 to 2.27). Although estimates favored entecavir over lamivudine at 22 to 96 weeks (five trials, N=1,266, RR 1.19, 95% CI 0.87 to 1.49, I^2=0%)[94,97,101,136] and TDF over adefovir at 48 weeks (one trial, N=233, RR 1.20, 95% CI 0.68 to 2.11)[96] differences were not statistically significant. In one trial, entecavir was associated with decreased likelihood of HBeAg seroconversion versus telbivudine at 24 weeks, but the estimate was imprecise and not statistically significant (one trial, N=131, RR 0.55, 95% CI 0.26 to 1.16).[102]

HBsAg Loss or Seroconversion

Three trials evaluated effects of preferred versus nonpreferred antiviral therapies on likelihood of HBsAg loss or seroconversion.[92,95,96] Each evaluated a different antiviral therapy comparison. Although results favored the preferred antiviral therapies, estimates were imprecise. One trial (n=709) compared entecavir versus lamivudine (RR 1.8, 95% CI 0.9 to 3.9 for HBsAg loss),[92] one trial (n=240) TDF versus adefovir (RR 5.74, 95% CI 0.32 to 102.59 for HBsAg loss),[96] and one trial (n=543) pegylated interferon alfa-2a versus lamivudine (RR 17, 95% CI 1.0 to 294 for HBsAg seroconversion at 72 weeks, 24 weeks following the completion of therapy).[95] Two other trials (N=481) reported no cases of HBsAg loss with either TDF or adefovir.[96,98]

Virological Suppression

Nine trials compared effects of preferred versus nonpreferred antiviral therapy on likelihood of HBV DNA suppression.[93-99,136] Virological suppression was defined as less than 300 copies/mL

in three trials and less than 400 copies/mL in three trials; two trials did not define criteria for virological suppression.

Entecavir was associated with increased likelihood of HBV DNA suppression versus lamivudine at 22 to 96 weeks (six trials, N=2,115, RR 1.70, 95% CI 1.38 to 2.13, I^2=81%; ARD 30%, 95% CI 17% to 43%) (**Figure 11**).[93,94,97,99,101,136] Although statistical heterogeneity was present, estimates favored entecavir in all trials (RRs ranged from 1.25 to 2.08). There was no interaction between HBeAg status and likelihood of virological suppression (HBeAg-negative: 1 trial, RR 1.95, 95% CI 1.51 to 2.54 versus HBeAg-positive/mixed: five trials, RR 1.66, 95% CI 1.28 to 2.16 I^2=0%; p for interaction=0.60), though stratification by HBeAg status eliminated statistical heterogeneity. There was also no interaction between duration of followup and likelihood of virological suppression (**Table 5**).

Results favored TDF over adefovir for likelihood of HBV DNA suppression at 48 weeks, though the difference was not statistically significant (three trials, N=1,150, RR 2.32, 95% CI 0.96 to 6.10, I^2=92%) (**Figure 11**).[96,98] Statistical heterogeneity was also present in this analysis, but estimates favored tenofovir in all trials (RR ranged from 1.47 to 5.71).

One trial found pegylated interferon alfa-2a associated with decreased likelihood of HBV DNA suppression versus lamivudine at the end of treatment at 48 weeks (N=543, 25% vs. 40%, RR 0.63, 95% CI 0.49 to 0.81), but increased likelihood 24 weeks following the end of treatment (14% vs. 5%, RR 2.80, 95% CI 1.55 to 5.03). There was no difference between entecavir versus telbivudine in likelihood of HBV DNA suppression (two trials, N=175, RR 0.89, 95% CI 0.59 to 3.44, I^2=0%).[100,102]

Across preferred versus nonpreferred antiviral therapy comparisons, there were no interactions between HBeAg status or duration of followup and likelihood of virological suppression (**Table 5**).

ALT Normalization

Entecavir was associated with increased likelihood of ALT normalization versus lamivudine at 22 to 96 weeks (six trials, N=2,079, RR 1.13, 95% CI 1.08 to 1.27, I^2=0%; ARD 12%, 95% CI 4.2% to 22%) (**Figure 12**).[85,93,94,99,136] There was no statistical heterogeneity and estimates favored entecavir in all trials (RR ranged from 1.10 to 1.70). There was an interaction between HBeAg status and likelihood of ALT normalization (HBeAg-negative: one trial, RR 1.70, 95% CI 1.31 to 2.19 versus HBeAg-positive/mixed: five trials, RR 1.12, 95% CI 1.07 to 1.17, I^2=0%; p for interaction=0.035). There was no interaction between duration of followup and likelihood of ALT normalization (**Table 5**).

There was no difference between tenofovir versus adefovir in likelihood of ALT normalization at 48 weeks (three trials, N=1,122, RR 1.03, 95% CI 0.96 to 1.18, I^2=0%).[96,98] One trial found pegylated interferon alfa-2a associated with decreased likelihood of ALT normalization versus lamivudine at the end of treatment at 48 weeks (N=543, 39% vs. 62%, RR 0.63, 95% CI 0.53 to 0.75)[95] but greater likelihood 24 weeks following the end of treatment (41% vs. 28%, RR 1.47,

95% CI 1.15 to 1.86). One trial found no difference between entecavir versus telbivudine in likelihood of ALT normalization at 48 weeks (N=131, RR 0.95, 95% CI 0.78 to 1.15).[102]

Histological Improvement

Entecavir was associated with increased likelihood of histological improvement versus lamivudine at 52 or 96 weeks (two trials, N=1211, RR 1.16, 95% CI 1.06 to 1.27, I^2=0%; ARD 9.8%, 95% CI 3.7% to 16%) (**Figure 13**).[93,136]

One trial (n=512) found no difference between tenofovir versus adefovir in likelihood of histological improvement at 48 weeks (RR 1.02, 95% CI 0.79 to 1.31)[98] and one trial (n=543) found no difference between pegylated interferon alfa-2a versus lamivudine in likelihood of histologic improvement at 72 weeks (24 weeks after the end of treatment; RR 1.10, 95% CI 0.88 to 1.38).[95]

Key Question 5. How Effective Is Antiviral Treatment in Improving Health Outcomes Among Nonpregnant Adolescents and Adults With Chronic HBV Infection?

Summary

As in the prior USPSTF review, evidence from randomized trials on effects of antiviral therapy versus placebo or no treatment on clinical outcomes was limited due to small numbers of trials, few events, and insufficient duration of followup. Antiviral therapy was associated with decreased risk of mortality, based on three trials of interferon with a total of 8 deaths (N=349, RR 0.15, 95% CI 0.03 to 0.69, I^2=0%; ARD -0.3%, 95% CI -1.7% to 0.8%). Estimates for incident cirrhosis (two trials, N=165, RR 0.72, 95% CI 0.29 to 1.77, I^2=0%)[81,83] and hepatocellular carcinoma (four trials, N=343, RR 0.60, 95% CI 0.16 to 2.33, I^2=20%)[75,80,81,83] favored antiviral therapy over placebo or no therapy, but differences were not statistically significant. In seven cohort studies with longer-term (2.7 to 8.9 years) followup, antiviral therapy was consistently associated with decreased risk of hepatocellular carcinoma versus no antiviral therapy (adjusted hazard ratios [HRs] ranged from 0.24 to 0.64). One cohort study found antiviral therapy associated with decreased risk of mortality after 8.25 years (adjusted HR 0.58, 95% CI 0.43 to 0.79).[108] Data from head-to-head trials of preferred versus nonpreferred antiviral therapy were insufficient to evaluate effects on clinical outcomes.

Evidence

Antiviral Therapy vs. Placebo or No Treatment

The prior USPSTF report found antiviral therapy might be associated with reduced risk of incident cirrhosis (three trials; RR, 0.70; 95% CI, 0.33 to 1.46; I^2=0%), hepatocellular carcinoma (five trials; RR, 0.57; 95% CI, 0.32 to 1.04; I^2=2%), and mortality (five trials; RR, 0.55; 95% CI, 0.18 to 1.71; I^2=43%) versus placebo or no therapy. However, none of the differences was

statistically significant, estimates were imprecise, and some trials had relatively short duration of followup. The prior USPSTF review included trials in which more than 20 percent of patients had cirrhosis had baseline,[125-129,137-142] trials of treatment-experienced patients,[130-132] and poor-quality trials;[133-135] these trials were excluded for this update.

Seven randomized trials (N=1,042) of antiviral therapy versus placebo or no treatment (see Key Question 4 for more detailed description of trials) that reported effects on clinical outcomes were included in this update (**Appendix B Tables 4-5**).[75,76,78,80,81,83,89] All but one[89] of these trials were included in the prior USPSTF report. None of the trials reported effects on quality of life, risk of HBV disease transmission, or extrahepatic outcomes. Four trials evaluated nonpegylated interferon,[80,81,83,89] and three trials lamivudine;[75,76,78] all of the trials evaluated adults. The trials were generally not designed to evaluated effects on clinical outcomes and generally reported small numbers of events. There were a total of 23 cases of incident cirrhosis in two trials,[81,83] 13 cases of hepatocellular carcinoma in four trials,[75,80,81,83] and eight deaths in three trials[81,83,89] (two other trials that reported mortality recorded no deaths).[76,78] The duration of followup ranged from 11 to 86 months. All of the trials were rated fair-quality (**Appendix B Table 6**).

Antiviral therapy was associated with decreased risk of mortality versus placebo or no therapy (three trials, N=349, RR 0.15, 95% CI 0.03 to 0.69, I^2=0%; ARD -0.3%, 95% CI -1.7% to 0.8%) (**Figure 14**); all of the trials reporting mortality evaluated nonpegylated interferon.[81,83,89] Pooled estimates for incident cirrhosis (two trials, N=165, RR 0.72, 95% CI 0.29 to 1.77, I^2=0%)[81,83] (**Figure 15**) and hepatocellular carcinoma (four trials, N=343, RR 0.60, 95% CI 0.16 to 2.33, I^2=20%) (**Figure 16**)[75,80,81,83] favored antiviral therapy over placebo or no therapy, but differences were not statistically significant.

Seven cohort studies (N=~50,912) evaluated effects of antiviral therapy versus no therapy on mortality or hepatocellular carcinoma after controlling for potential confounders (**Appendix B Tables 9-11**).[103-109] Cohort studies on effects of antiviral therapy on clinical outcomes were not included in the prior USPSTF review. Sample sizes ranged from 632 to 43,190 and the duration of followup ranged from 2.7 to 8.9 years. The proportion of patients with cirrhosis at baseline ranged from 13 to 29 percent. All studies were conducted in Asia except for two[103,104] which evaluated U.S. cohorts. Three of the Asian studies appeared to examine overlapping populations from Taiwan's National Health Insurance Research Database.[106,108,109] One study focused on patients who received entecavir,[105] a preferred antiviral and one study focused on lamivudine,[107] a nonpreferred antiviral; in the other studies, the antiviral drugs varied. All of the studies were rated fair-quality. Methodological limitations included unclear blinding of data analysts, unclear percentages of those with missing data or lost to followup, and failure to adjust for key confounders. Studies typically adjusted for age, sex, fibrosis stage; some studies also adjusted for HBV DNA level, ALT level, or medical comorbidities.

Antiviral therapy was consistently associated with decreased risk of hepatocellular carcinoma. Two studies of U.S. cohorts found antiviral therapy associated with decreased risk of hepatocellular carcinoma after a median 5.2 years (adjusted HR 0.39, 95% CI 0.27 to 0.56)[103] or after a median of 8.9 years (adjusted HR 0.24, 95% CI 0.15 to 0.39). U.S. patients found receipt of various antivirals associated with decreased risk of hepatocellular carcinoma after a median of 8.9 years (adjusted HR 0.24, 95% CI to 0.10 to 0.58).[104] Results were similar in five studies

conducted in Asian populations (adjusted HRs ranged from 0.37 to 0.64 at 2.7 to 5.3 years followup).[105-109] A study conducted on Taiwan's National Health Insurance Research Database found antiviral therapy associated with decreased risk of mortality (adjusted HR 0.58, 95% CI 0.43 to 0.79).[108]

Preferred vs. Nonpreferred Regimens

The prior USPSTF report found too few clinical events in head-to-head trials of entecavir or pegylated interferon alfa-2a versus lamivudine to determine effects on clinical outcomes. For this update, nine trials (reported in eight publications; N=3,767) evaluated effects of preferred versus nonpreferred antiviral therapy (see Key Question 4 for description of trials) on clinical outcomes (mortality, cirrhosis, hepatocellular carcinoma);[92,93,95-97,99,101] six trials were carried forward from the prior report[92,93,95-97] and three were new[98,99,101] (**Appendix B Tables 7-8**). Five trials compared entecavir versus lamivudine,[92,93,97,99,101] three trials TDF versus adefovir,[96,98] and one trial pegylated interferon alfa-2a versus lamivudine.[95] The duration of followup ranged from 11 to 22 months. Five trials were rated good-quality[92,93,95,98,101] and the remainder fair-quality (**Appendix B Table 6**).

The trials were not designed to evaluate clinical outcomes, with small numbers of events reported. For entecavir versus lamivudine, there were a total of nine deaths in four trials[92,93,97,99] and two cases of hepatocellular carcinoma in 3 trials;[92,93,97] cirrhosis was not reported. For comparisons of pegylated interferon versus lamivudine[95] and tenofovir versus adefovir,[98] there was one death each; cirrhosis and hepatocellular carcinoma were not reported. In a pooled analysis, there was no difference between entecavir versus lamivudine in risk of mortality, but the estimate was very imprecise (three trials, N=1,467, RR 1.19, 95% CI 0.28 to 5.12, I^2=10%) (**Figure 17**).[93,99,136]

Key Question 6. What Are the Harms Associated With Antiviral Treatment in Nonpregnant Adolescents and Adults With Chronic HBV Infection?

Summary

As in the prior USPSTF review, antiviral therapy was associated with no differences versus placebo in risk of serious adverse events or any adverse event. Antiviral therapy was associated with increased risk of study withdrawal due to adverse events (three trials, N=496, RR 4.44, 95% CI 0.95 to 20.77, I^2=0%),[80,82,85] with the risk highest in a trial of nonpegylated interferon. Estimates for gastrointestinal and kidney adverse events were imprecise.

In head-to-head trials, pegylated interferon was associated with increased risk of any adverse event (one trial, N=543, RR 1.58, 95% CI 1.41 to 1.78) versus lamivudine and is probably associated with increased risk of withdrawal due to adverse events, though the difference was not statistically significant (one trial, N=543, RR 4.01, 95% CI 0.86 to 18.73).[95] TDF was associated

with increased risk of nausea versus adefovir (RR 3.36, 95% CI 1.45 to 7.81). For other head-to-head comparisons and harms, there were no differences or imprecise estimates.

One cohort study found no association between TDF or entecavir versus no antiviral therapy and risk of osteopenia or osteoporosis; it was not designed to evaluated risk of fracture.

Evidence

Antiviral Therapy vs. Placebo or No Treatment

The prior USPSTF review found no differences between antiviral therapy versus placebo or no therapy in risk of serious adverse events or any adverse events. Antiviral therapy was associated with more withdrawals due to adverse events than placebo or no treatment (nine trials; RR, 3.97; 95% CI, 1.4 to 11; I^2=0%).

Twelve trials of antiviral therapy versus placebo or no treatment (see Key Question 4 for study details) that reported harms were included in this update (**Appendix B Tables 4-5**).[75-80,82,85-89] All trials but two[88,89] were included in the prior USPSTF report. Three trials evaluated pegylated interferon,[80,88,89] two trials evaluated adefovir,[77,82] and the other trials evaluated lamivudine. Followup ranged from 1.8 to 30 months. All of the trials were rated fair-quality (**Appendix B Table 6**).

One new cohort study (n=1,224) evaluated risk of incident osteopenia or osteoporosis in patients with chronic HBV infection on TDF, entecavir, or no therapy. The study was rated fair-quality, due in part to differences between groups in duration of followup (**Appendix B Tables 9-11**).

Serious Adverse Events

There was no difference between antiviral therapy versus placebo or no antiviral therapy in risk of serious adverse events (four trials, N=802, RR 0.92, 95% CI 0.45 to 1.85, I^2=0%) (**Figure 18**).[75,77,78,85] Rates of serious adverse events on antiviral therapy ranged from 1.8 to 14.6 percent. Lamivudine was evaluated in three trials and adefovir in one trial.

Withdrawal Due to Adverse Events

Antiviral therapy was associated with increased risk of withdrawal due to adverse events versus placebo or no antiviral therapy, but the estimate was very imprecise and the difference was not statistically significant (three trials, N=505, RR 4.44, 95% CI 0.95 to 20.77, I^2=0%) (**Figure 19**).[80,82,85] Rates of withdrawal due to adverse events on antiviral therapy were 24 percent in one trial of interferon alfa-2b and less than 2 percent in one trial each of adefovir or lamivudine. The risk of withdrawal due to adverse events was higher in the trial of interferon alfa-2b (RR 11.00, 95% CI 0.65 to 187.17)[80] than in the trial of adefovir (RR 2.93, 95% 0.31 to 27.88)[82] or lamivudine (RR 3.25, 95% CI 0.13 to 78.18).[85] One trial of interferon reported no withdrawals due to adverse events in either group.[88]

Any Adverse Event

There was no difference between antiviral therapy versus placebo or no therapy in risk of any adverse event (five trials, N=1,290, RR 1.01, 95% CI 0.90 to 1.11, I^2=0%) (**Figure 20**).[77,78,85,87,89] Rates of any adverse event ranged from 42 to 97 percent. The risk of any adverse event was substantially higher in one trial of interferon alfa-2a (RR 107.14, 95% CI 6.78 to 1,694.36)[89] than in trials of lamivudine (three trials, RR 0.99, 95% CI 0.80 to 1.12, I^2=0%)[78,85,87] or adefovir (one trial, RR 1.04, 95% CI 0.87 to 1.24).[77]

Gastrointestinal Adverse Events

There was no difference between antiviral therapy versus placebo or no antiviral therapy in risk of nausea (three trials, RR 0.80, 95% CI 0.48 to 2.10, I^2=0%) (**Figure 21**).[82,85,87] Two trials evaluated lamivudine and one trial evaluated adefovir.

Antiviral therapy might be associated with increased risk of diarrhea versus placebo or no antiviral therapy, but the estimate was imprecise and the difference was not statistically significant (four trials, RR 1.50, 95% CI 0.87 to 2.46, I^2=0%) (**Figure 22**).[76,82,85,87] Three trials reporting diarrhea evaluated lamivudine and one trial evaluated adefovir.

Kidney Adverse Events

There was no statistically significant difference between antiviral therapy versus placebo or no antiviral therapy in risk of creatinine elevation versus placebo or no antiviral therapy, though the estimate favored placebo (three trials, RR 1.27, 95% CI 0.31 to 3.55, I^2=0%) (**Figure 23**).[75,76,78] All of the trials evaluated lamivudine.

Bone Adverse Events

A cohort study (n=1,224) compared risk of incident osteopenia or osteoporosis in patients with chronic HBV infection on TDF (median followup 48 months), entecavir (median 67 months), or no therapy (median 24 months).[110] The study was conducted in the United States in Asian patients. Neither TDF nor entecavir was associated with increased risk of osteopenia or osteoporosis compared with no therapy, though estimates were imprecise (adjusted HR 0.74, 95% CI 0.34 to 1.59 and 0.98, 95% CI 0.51 to 1.90, respectively). The study was not designed to assess risk of fractures.

Preferred vs. Nonpreferred Regimens

The prior USPSTF review found pegylated interferon alfa-2a was associated with greater risk of serious adverse events (RR, 2.1; 95% CI, 1.0 to 4.5; I^2=0%), withdrawals due to adverse events (RR, 7.6; 95% CI, 1.1 to 52; I^2=38%), and any adverse event (RR, 1.7; 95% CI, 1.5 to 2.0; I^2=55%) versus lamivudine. There were no differences between entecavir and lamivudine (three trials) or between tenofovir and adefovir (two trials).

Twelve head-to-head trials (reported in 11 publications) of preferred versus nonpreferred therapies that reported harms were included in this update (see Key Question 4 for study details) (**Appendix B Tables 7-8**).[92-102] Seven trials were included in the prior USPSTF review, and five trials were added for this update.[98-102] Six trials compared entecavir versus lamivudine,[92-94,97,99,101] two compared entecavir to telbivudine,[100,102] three trials compared TDF versus adefovir,[96,98] and one trial compared pegylated interferon versus lamivudine.[95] The duration of followup ranged from 3.7 to 22 months. Five trials were rated good-quality[92,93,95,98,101] and the others fair-quality (**Appendix B Table 6**).

Serious Adverse Events

Entecavir might be associated with decreased risk of serious adverse events versus lamivudine, but the difference was not statistically significant (four trials, N=1,986, RR 0.78, 95% CI 0.54 to 1.07, I^2=0%) (**Figure 24**).[93,99,101,136] Results were similar for tenofovir versus adefovir (two trials, N=1,150, RR 0.84, 95% CI 0.22 to 1.81, I^2=0%).[96,98]

One trial (n=543) found that pegylated interferon alfa-2a might be associated with increased risk of serious adverse events versus lamivudine, but the difference was not statistically significant (RR 2.41, 95% CI 0.86 to 6.74).[95]

Withdrawal Due to Adverse Events

There was no difference between entecavir versus lamivudine in likelihood of withdrawal from study due to adverse events, but the estimate was imprecise (five trials, N=2,073, RR 0.50, 95% CI 0.18 to 1.15, I^2=0%) (**Figure 25**).[93,94,99,101,136] There was no difference between tenofovir versus adefovir in likelihood of withdrawal due to adverse events, though the estimate was imprecise (two trials, N=1,150, RR 1.03, 95% CI 0.28 to 3.79, I^2=0%).[96,98]

One trial (n=543) found pegylated interferon alfa-2a associated with substantially increased likelihood of withdrawal due to adverse events versus lamivudine, though the difference was not statistically significant (RR 4.01, 95% CI 0.86 to 18.73).[95]

Any Adverse Event

There were no differences between entecavir versus lamivudine (five trials, N=2,073, RR 1.02, 95% CI 0.96 to 1.08, I^2=0%;[93,94,99,101,136] or tenofovir versus adefovir (two trials, N=1,150, RR 1.03, 95% CI 0.92 to 1.23, I^2=0%; **Figure 26**)[96,98] in risk of any adverse event. In one trial (n=543), pegylated interferon alfa-2a was associated with increased risk of any adverse event versus lamivudine (RR 1.58, 95% CI 1.41 to 1.78)[95] and in one small trial (n=44) entecavir was associated with increased risk of any adverse event versus telbivudine, but the difference was not statistically significant (RR 1.58, 95% CI 0.86 to 2.91).[100]

Other Adverse Events

Harms were combined from two trials of TDF versus adefovir reported in the same publication; the trials differed primarily in enrollment of HBeAg-positive or –negative patients.[96] At 48

weeks, only one case of serum creatinine increase ≥0.5 mg/dL was reported (0% vs. 0.5%, RR 0.17, 95% CI 0.007 to 4.12), with no cases of creatinine clearance less than 50 mL/min. TDF was associated with increased risk of nausea (9.4% vs. 2.8%, RR 3.36, 95% CI 1.45 to 7.81) and might be associated with increased risk of diarrhea (6.6% vs. 5.1%, RR 1.28, 95% CI 0.65 to 2.53), though the difference was not statistically significant, and a small trial (n=42) found no difference in diarrhea between entecavir and lamivudine (28.6% vs. 33.3%).[97] One trial reported no difference between entecavir versus lamivudine in likelihood of creatinine increase, with few events recorded (3.6% vs. 0%).[99]

Key Question 7. What Is the Association Between Improvements in Intermediate Outcomes as a Result of Antiviral Treatment of Chronic HBV Infection and Reduction in Risk of HBV-Related Adverse Health Outcomes?

Summary

As in the prior USPSTF review, there were consistent associations between various intermediate outcomes (virological remission, biochemical remission, histological improvement, HBeAg loss, or a composite intermediate outcome) and clinical outcomes (death, hepatocellular carcinoma, cirrhosis, or a composite clinical outcome), based on nine observational studies. However, variability in patient populations (e.g., HBeAg status, viral load, or AST levels), the intermediate and clinical outcomes evaluated, and presence of some methodological limitations make it difficult to draw strong conclusions. In some studies, estimates were imprecise and associations were not statistically significant.

Evidence

The prior USPSTF review included 10 studies that found an association between various intermediate outcomes (virological remission, biochemical remission, histological improvement, HBeAg loss, or a composite intermediate outcome) and clinical outcomes (death, hepatocellular carcinoma, or a composite clinical outcome). However, results were not statistically significant in all studies and variability in patient populations (e.g., HBeAg status and prevalence of cirrhosis at baseline, intermediate and clinical outcomes evaluated, and methodological limitations (including failure to control for key potential confounders: age, sex, fibrosis stage, HBV DNA level, and HBeAg status) made it difficult to draw strong conclusions. The prior USPSTF review included studies on the association between intermediate and clinical outcomes in which more than 30 percent of patients had cirrhosis at baseline;[138-141] these studies were excluded for this update.

Nine studies (N=3,893) on the association between improvement in intermediate outcomes following antiviral therapy for chronic HBV infection and clinical outcomes were included for this update (**Table 6 and Appendix B Tables 12-13**). Six studies[111-116] were included in the prior USPSTF report and three studies[117-119] were added for this update. Sample sizes ranged from 63 to 1,531 patients, and duration of followup from 3.2 to 9.9 years. The studies varied in the

intermediate outcomes that were evaluated. Four studies evaluated virological response (loss of HBV DNA or sustainability of HBV DNA loss),[111,116,117,119] one study evaluated biochemical remission (normalization of serum transaminase levels),[115] one study evaluated HBeAg clearance,[114] one study evaluated HBeAg seroconversion,[118] one study evaluated histological response (improvement in biopsy findings),[112] and one study evaluated a composite intermediate outcome (virological response plus HBeAg clearance).[113] The clinical outcomes also varied. One study evaluated death,[113] four studies hepatocellular carcinoma,[116-119] one study cirrhosis,[118] and the remainder various composite clinical outcomes (2 or more of the following: death, liver transplantation, cirrhosis, or complications of cirrhosis).[111-115,117] Four studies focused on HBeAg-positive patients, three studies focused on HBeAg-negative patients and the remainder included mixed populations of HBeAg-positive and negative. The antiviral treatment was lamivudine in one study, interferon in six studies, and entecavir in 2 studies. One study excluded patients with cirrhosis, and in the other studies, the proportion of patients with cirrhosis ranged from 8 to 27 percent.

Six studies were conducted in the United States or Europe and three studies were conducted in Asia. All studies were rated fair-quality (**Appendix B Table 14**). Methodological shortcomings included unclear blinding status of outcome assessors and failure to report loss to followup; some studies did not control for five key confounders (age, sex, fibrosis stage, HBV DNA level, HBeAg status) or it was unclear whether the adjustments were made for these specific analyses.[112,113,115,117-119]

As in the prior USPSTF review, the variability in patient populations (e.g., HBeAg status and prevalence of cirrhosis at baseline), intermediate and clinical outcomes evaluated, and methodological limitations makes it difficult to draw strong conclusions regarding the association between achieving intermediate outcomes after antiviral treatment and improvement in clinical outcomes (**Table 6**). However, across intermediate and clinical outcome comparisons, estimates of risk consistently favored achieving the intermediate outcomes, although results were not always statistically significant.

Mortality

One study (n=103) of HBeAg-positive patients with elevated AST and/or ALT found achieving a composite intermediate outcome (sustained HBV DNA loss and HBeAg clearance) with antiviral therapy associated with decreased risk of death (adjusted HR, 0.59; 95% CI, 0.20 to 1.67).[113] The mean duration of followup was 6.2 years.

Hepatocellular Carcinoma

Four studies evaluated the association between achieving intermediate outcomes following antiviral therapy and risk of hepatocellular carcinoma.[116-119] In three studies, the intermediate outcome was virological remission and in the fourth it was HBeAg seroconversion.

Studies suggest that achieving virological remission might reduce risk of hepatocellular carcinoma, but estimates varied and were not statistically significant in two of the three studies. One study (n=233) of HBeAg-positive patients found HBeAg seroconversion associated with

decreased risk of hepatocellular carcinoma at a median duration of followup of 6.8 years (adjusted HR, 0.13, 95% CI 0.08 to 0.57).[118] A study (n=744) of patients with chronic HBV infection (HBeAg status not reported) found a virological response (HBV DNA <80 IU/mL) associated with a slightly decreased risk of hepatocellular carcinoma that was not statistically significant (adjusted HR 0.87, 95% CI 0.17 to 4.58).[117] The third study (n=818) of HBeAg-negative patients with elevated ALT or HBV DNA greater than 2000 IU/mL found virological remission (HBV DNA <200 IU/mL) associated with a reduction in risk of hepatocellular carcinoma that was not statistically significant at mean followup of 4.7 years (adjusted HR 0.77, 95% CI 0.35 to 1.69).[116]

One study (n=1,531) of patients with HBV infection (30% HBeAg-positive) found sustained (≥24 months) virological remission associated with decreased risk of hepatocellular carcinoma versus remission sustained for less than 24 months (adjusted HR 0.3, 95% CI 0.1 to 0.6).[119] In this study, 31 percent of patients had received prior antiviral therapy; results were similar in the subgroup of treatment-naïve patients (adjusted HR 0.4, 95% CI 0.2 to 0.7).

Cirrhosis

One study (n=233) of HBeAg-positive patients found HBeAg seroconversion associated with decreased risk of cirrhosis (adjusted HR 0.41, 95% CI 0.32 to 0.88).[118] The median duration of followup was 6.8 years.

Composite Clinical Outcomes

Six studies evaluated the association between various intermediate outcomes (virological response, ALT normalization, HBeAg loss, histological response, or a composite intermediate outcomes) and effects on composite clinical outcomes.[111-115,117] Despite heterogeneity in patient populations and the intermediate and composite clinical outcomes evaluated, there was a consistent association between achieving the intermediate outcomes and decreased risk of the composite outcome, though some differences were not statistically significant.

Two studies evaluated the association between achieving a virological response and risk of a composite clinical outcome.[111,117] One study (n=744) of patients with chronic HBV infection (HBeAg status not reported) found a virological response (HBV DNA <80 IU/mL) associated with decreased risk of a clinical event (hepatocellular carcinoma, liver decompensation, or death) that was not statistically significant at median followup of 3.2 years (adjusted HR 0.70, 95% CI 0.28 to 1.77).[117] A small study (n=63) of HBeAg-negative patients with HBV infection found a virological response (HBV DNA <10,000 copies/mL) associated with decreased risk of a disease complication (not defined) at 6 years (adjusted HR 0.24, 95% CI 0.06 to 0.96).[111]

The other studies each looked at a different intermediate outcome. One study (n=89) of HBeAg-positive patients with HBV infection found a histological response (improvement of 2 points or more on the Histological Activity Index) following antiviral therapy associated with decreased risk of liver complications that was not statistically significant at median followup of 9.9 years (adjusted HR 0.62, 95% CI 0.06 to 6.9).[112] A study (n=103) of HBeAg-positive patients with elevated AST and/or ALT found achieving a composite intermediate outcome (sustained HBV

DNA loss and HBeAg clearance) associated with decreased risk of death or a liver-related complication (variceal hemorrhage, ascites, or encephalopathy) at median followup of 6.2 years (adjusted HR, 0.07; 95% CI, 0.02 to 0.33).[113] A study (n=103) of HBeAg-positive patients with elevated ALT found HBeAg loss associated with decreased risk of liver complications (death, liver transplantation, decompensated cirrhosis, or esophageal varices) at mean followup of 4.2 years (adjusted HR 0.06, 95% CI 0.01 to 0.61).[114] The fourth study (n=209) evaluated HBeAg-negative patients with elevated ALT; it found normalization of ALT associated with decreased risk of the composite outcomes of death or liver transplantation (adjusted HR 0.48, 95% CI 0.23 to 1.0) or severe clinical complications, defined as death, liver transplantation, liver decompensation, or hepatocellular carcinoma at mean followup of 6 years (adjusted HR 0.53, 95% CI 0.29 to 0.91).[115]

Contextual Question 1. What Are the Effects of Different Risk- or Prevalence-Based Methods for Screening for HBV Infection in Modeling Studies?

Two studies modeled the incremental cost-effectiveness of alternative HBV screening strategies in U.S. settings.[143,144] One study focused on screening in six higher-risk populations: foreign-born Asian/Pacific Islanders (based case HBV prevalence 7.9%), Africa-born black persons (9.7%), incarcerated persons (1.4%), refugees (6.3%), PWID (11.8%), and MSM (2.3%).[144] In each population, three strategies were compared to no screening: 1) screen for HBV infection and treat infected persons ("treatment only"); 2) screen for HBV susceptibility and vaccinate susceptible ("vaccinate only"); and 3) screen for HBV infection and susceptibility and treat or vaccinate as appropriate ("inclusive"). The screening strategies were evaluated using a lifetime Markov model and assumed treatment with tenofovir (not specified if TDF or TAF, though both are preferred antivirals in HBV treatment guidelines).[145] Across populations, the vaccinate-only strategy was associated with incremental cost-effectiveness ratios (ICERs) of less than $14,000 per quality-adjusted life year (QALY) gained or was dominant (less expensive and more effective), compared with no screening. The treatment only strategy was associated with ICERs of $17,000 to $26,000 per QALY gained, compared with the vaccinate only strategy. The inclusive strategy dominated (resulted in cost savings and health gains) the treatment only strategy in most populations. The exception was Asian/Pacific Islanders, in which the inclusive strategy was associated with an ICER of $18,378/QALY compared with treatment only. The inclusive strategy was also directly compared to no screening, with ICERs that ranged from $3,000 to $18,000 per QALY gained. In one-way sensitivity analyses, factors with the greatest impact on ICER estimates were age, discount rate, tenofovir cost, health state utilities, and rate of disease progression. However, in all populations, the ICER of the inclusive strategy remained less than $50,000 per QALY gained across all uncertainty ranges. In multivariate analyses, at a willingness-to-pay threshold of $50,000 per QALY gained, the inclusive strategy was cost-effective in 61 to 97 percent of simulations across all populations, and was usually the preferred strategy.

Another study modeled the cost-effectiveness of screening in a setting with an HBV infection prevalence of 2 percent.[143] Screening strategies were compared with no screening in a Markov model, with differences in strategies according to the antiviral therapy used followed screening:

1) pegylated interferon alfa-2a, 2) low-cost nucleoside or nucleotide agent with a higher rate of developing viral resistance for 48 weeks, 3) prolonged treatment with low-cost, high-resistance nucleoside or nucleotide, or 4) prolonged treatment with a high-cost, low-resistance nucleoside or nucleotide. The strategy involving prolonged treatment with a low-cost, high-resistance nucleoside or nucleotide assumed use of salvage therapy with a high-cost, low-resistance nucleoside or nucleotide in persons who developed resistance. Versus no screening, this strategy was associated with an ICER of $29,232 per QALY gained; this strategy was associated with a lower ICER (versus no screening) than screening followed by treatment with the same regimen for 48 weeks and dominated strategies involving treatment with pegylated interferon or a high-cost, low-resistance nucleoside or nucleotide (the ICER for this strategy was $43,500/QALY versus no screening). In probabilistic sensitivity analysis, the low-cost, high-resistance nucleoside or nucleotide strategy was preferred 80 percent of the time and the high-cost, low-resistance nucleoside or nucleotide strategy was preferred 20 percent of the time. In deterministic sensitivity analysis, the ICER of the low-cost, high-resistance nucleoside or nucleotide strategy remained less than $50,000/QALY when the prevalence of HBV infection was as low as 0.3 percent (similar to the prevalence of HBV infection in the general U.S. population).

Contextual Question 2. What Is the Accuracy of Tools for Identifying Persons With Chronic HBV Infection?

No study evaluated the accuracy of tools for identifying persons with chronic HBV infection. Although the CDC has developed a "Hepatitis Risk Assessment Tool," it has not undergone formal validation. The tool was designed as a self-administered tool to help individuals determine whether they should be vaccinated or tested for viral hepatitis, according to CDC criteria (**Appendix C Table 1**).[146,147]

Contextual Question 3. In Persons With Serologic Evidence of HBV Infection (HBsAg-Positive/Anti-HBc-Positive or HBsAg-Negative/Anti-HBc-Positive), What Is the Likelihood of Reactivation Following Exposure to Immunosuppressant Therapy, and What Is the Effectiveness of Interventions to Improve Clinical Outcomes Associated With Reactivation?

Screening could identify persons with serologic evidence of HBV infection (HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive) who might benefit from interventions to prevent or treat HBV reactivation when receiving immunosuppressant drugs. HBV reactivation has primarily been described in persons with chronic conditions such as cancer or an autoimmune disorder. Management of such conditions, including assessment of HBV status,[8,148] is generally considered outside the scope of the USPSTF. Of more relevance to screening is the prevalence of reactivation among persons without conditions warranting HBV screening who receive immunosuppressant therapy for acute conditions (e.g., gout, asthma) in primary care settings. We identified no study on the likelihood of HBV reactivation in anti-HBc-

positive patients exposed to immunosuppressant therapy in primary care settings or among patients exposed to immunosuppressant therapy for treatment of an acute medical condition.

In persons with chronic conditions, the major factors affecting risk of reactivation are the patient's HBsAg status and the type of immunosuppressant drugs used. A systematic review commissioned by the American Gastroenterological Association summarized the evidence on risk of reactivation for different immunosuppressant drugs in anti-HBc-positive patients (**Appendix C Table 2**).[149] Risk was classified as high (>10%), moderate (1% to 10%), and low (<1%). High risk scenarios were HBsAg-positive or -negative persons who received B cell-depleting agents (e.g., rituximab and ofatumumab) and HBsAg-positive patients who received anthracycline derivatives (e.g., doxorubicin and epirubicin) or moderate/high dose corticosteroid therapy for ≥4 weeks. Moderate risk scenarios were HBsAg-positive or –negative persons who received tumor necrosis factor-alpha inhibitors (e.g., etanercept, adalumumab, certolizumab, or infliximab), other cytokine inhibitors and integrin inhibitors (e.g., abatacept, ustekinumab, natalizumab, or vedolizumab), or tyrosine kinase inhibitors (e.g., imatinib, nilotinib); other moderate risk scenarios were low-dose corticosteroid therapy for ≥4 weeks in HBsAg-positive persons or moderate/dose corticosteroid therapy for ≥4 weeks in HBsAg-negative persons. Low risk scenarios were use of traditional immunosuppressive agents (e.g., azathioprine, 6-mercaptupurine, or methotrexate), intra-articular corticosteroids, corticosteroid therapy for ≤1 week, or low-dose corticosteroid therapy for ≥4 weeks in HBsAg-negative persons.

In persons at higher risk for reactivation due to receipt of immunosuppressant therapy, prophylactic antiviral therapy appears to be effective for reducing risk. The systematic review found antiviral treatment in anti-HBc-positive patients associated with decreased of HBV reactivation (five trials, RR 0.13, 95% CI 0.06 to 0.30, I^2=0%) and HBV hepatitis flare (five trials, RR 0.16, 95% CI 0.06 to 0.42, I^2=0%) versus no prophylaxis.[149] Four trials in the meta-analysis evaluated lamivudine and one trial evaluated entecavir.

HBV reactivation also occurs in persons with HCV co-infection treated with direct acting antiviral (DAA) therapy, with risk varying according to HBsAg status. A recent systematic review of 17 studies found the proportion who experienced HBV reactivation with DAA therapy was 24 percent (95% CI 19 to 30%) among HBsAg-positive/anti-HBc-positive patients and 1.4 percent (95% CI 0.8 to 2.4%) among HBsAg-negative/anti-HBc-positive patients.[29] Rates of HBV reactivation related hepatitis were 9 percent (95% CI 5% to 16%) and 0.5 percent (95% CI 0.0% to 1.2%), respectively.

Chapter 4. Discussion

Summary of Review Findings

As in the 2014 USPSTF review,[72] we found no direct evidence on effects of screening for HBV infection versus no screening on clinical outcomes. The evidence reviewed in this update is summarized in **Table 7**. This report differs from the USPSTF review by focusing on evidence from populations more relevant for screening, by restricting to trials in which few (<20%) or no patients had cirrhosis at baseline and excluding trials of treatment-experienced patients. In addition, in accordance with USPSTF procedures,[71] poor-quality trials included in the prior USPSTF review were excluded. Despite these differences, the main findings of this review are consistent with the prior USPSTF review.

The USPSTF previously determined that HBV screening tests (based on interpretation of serologic markers) are accurate (sensitivity and specificity greater than 98%).[21] Evidence on the sensitivity and yield of different HBV screening strategies is available from three studies.[120-122] These studies found that screening strategies that focused on patients with risk factors (immigration from high prevalence country, other demographic risk factors, and/or behavioral risk factors) would identify nearly all cases of HBV infection while screening about two-thirds of the population. The number needed to screen to identify one HBV infection ranged from 32 to 148, depending in part on the prevalence of HBV infection in the population studied. A more focused strategy of only screening immigrants from high prevalence countries would be more efficient (number needed to screen 16 to 71), but missed about two-thirds of infected persons in one study conducted in primary care practices.[122] A limitation of these studies is that the screening strategies were retrospectively applied. In addition, the studies were conducted in Europe and some evaluated high HBV prevalence populations, which might limit applicability to primary care settings in the United States.

As in the previous USPSTF review, randomized trials found antiviral therapy to be more effective than placebo or no treatment for achieving various intermediate outcomes, including HBeAg loss (RR 1.91, 95% CI 1.46 to 2.81), HBeAg seroconversion (RR 2.11, 95% CI 1.30 to 3.55), HBsAg loss (RR 4.63, 95% CI 1.10 to 19.55), ALT normalization (RR 2.62, 95% CI 2.22 to 3.10), HBV DNA suppression (RR 4.39, 95% CI 2.61 to 7.39), histological improvement (RR 2.00, 95% CI 1.63 to 2.41), and composite intermediate outcomes (HBeAg loss/seroconversion plus DNA suppression: RR 2.36, 95% CI 1.44 to 4.28, I^2=0% and DNA suppression plus ALT normalization: RR 6.30, 95% CI 3.06 to 13.11, I^2=0%). The numbers needed to treat to achieve one intermediate outcome ranged from 2.6 for HBV DNA suppression to 17 for HBeAg seroconversion. Results were generally consistent when analyses were stratified by individual drug, though some estimates were imprecise and not statistically significant. Although this update focused on FDA-approved antiviral therapies, almost all of the trials evaluated therapies classified as nonpreferred in current guidelines (lamivudine, adefovir, nonpegylated interferon).[8] There were no placebo-controlled trials of pegylated interferon, though some extrapolation from trials of nonpegylated interferon may be justified: pegylation increases the half-life of interferon and for HCV infection, pegylated interferon has been shown to be more effective than nonpegylated interferon.[150] The effectiveness of preferred antiviral therapies is also supported by

head-to-head trials, which found entecavir, TDF, and pegylated interferon associated with greater or similar likelihood of achieving various intermediate outcomes versus nonpreferred therapies. One trial found pegylated interferon associated with increased likelihood of achieving intermediate outcomes versus lamivudine 6 months following the completion of 48 weeks of therapy, a consideration for patients who may wish to avoid indefinite antiviral therapy.[95] Effects of antiviral therapies were generally consistent when trials were stratified according to HBeAg status or whether some patients with cirrhosis were included. The trials focused on treatment of patients with immune active HBV infection, with very little data on effectiveness of antiviral therapy in the immune tolerant phase. There was insufficient evidence to determine how effects of antiviral therapies varied according to demographic and other clinical factors: the trials did not evaluate these factors and some factors (injection drug use status, HBV genotype, presence of nonalcoholic steatohepatitis, presence of hepatitis D virus) were not reported.

As in the prior USPSTF review, antiviral therapy was not associated with an increased risk of serious adverse events or experiencing any adverse event versus placebo. Antiviral therapy was associated with an increased risk of withdrawal due to adverse events (RR 4.44, 95% CI 0.95 to 20.77, I^2=0%)[80,82,85]; the risk of withdrawal due to adverse events was greatest with interferon. In head-to-head comparisons, pegylated interferon alfa-2a was associated with increased risk of serious adverse events and withdrawal due to adverse events versus lamivudine, consistent with the known high prevalence of adverse events with interferon-based therapies. Data on risks of kidney and bone adverse events, were limited but did not indicate increased risk. TDF has been associated with bone and kidney toxicities in some conditions (e.g., HIV infection),[151] but limited evidence in patients with HBV infection found few cases and no increase in risk. In general, adverse events associated with antiviral therapy, including interferon-based therapies, are self-limited and resolve following discontinuation of the drug.

Data from randomized trials on effects of antiviral therapy versus placebo or no therapy on clinical outcomes remains sparse. The trials were not designed to assess these outcomes, due to small sample sizes and insufficient duration of followup. Although antiviral therapy was associated with decreased risk of mortality, the estimate was based on three trials of nonpegylated interferon with a total of eight deaths. Antiviral therapy might be associated with decreased risk of cirrhosis and hepatocellular carcinoma, but estimates were imprecise and not statistically significant. To further inform conclusions regarding effects of antiviral therapy on clinical outcomes, this update included longer-term cohort studies of antiviral therapy versus no antiviral therapy that controlled for potential confounders. There was a consistent association between receipt of antiviral therapy and decreased risk of hepatocellular carcinoma; evidence on effects on risk of cirrhosis and mortality was sparse but also indicated decreased risk. Most of the cohort studies were conducted in Asia, which might limit applicability to U.S. primary care settings. However, studies conducted in the United States reported findings consistent with the Asian studies. Head-to-head trials of preferred versus nonpreferred antiviral therapy were not designed to assess clinical outcomes and were underpowered, with imprecise estimates. No trial evaluated effects of antiviral therapy on quality of life, risk of HBV transmission, or extrahepatic manifestations of HBV infection.

Understanding the degree to which improvements in intermediate outcomes are associated with mortality, hepatocellular carcinoma, or cirrhosis could be helpful for interpreting the effects of

antiviral therapies on clinical outcomes through an indirect pathway. As in the prior USPSTF review, observational studies generally found an association between achieving an intermediate outcome (HBeAg loss or seroconversion, ALT normalization, HBV DNA suppression, or a composite intermediate outcome) and reduced risk of mortality, hepatocellular carcinoma, cirrhosis, or a composite clinical outcome. However, results were not statistically significant in all studies. In addition, differences across studies in the intermediate and clinical outcomes evaluated, variability in patient populations (e.g., with regard to HBeAg status, ALT levels, or HBV DNA levels) and methodological limitations preclude strong conclusions.

Limitations

This review has several limitations. We excluded non-English language studies. We did not search for studies published only as abstracts and could not formally assess for publication bias with graphical or statistical methods due to small numbers of studies for each comparison and outcome.[73] Evidence from placebo-controlled trials of preferred antiviral therapy was limited; therefore, we also included head-to-head trials of preferred versus nonpreferred antiviral therapy. No trial evaluated the preferred antiviral TAF, which was FDA-approved for treatment of chronic HBV infection in 2016 and may have fewer kidney and bone toxicities compared with TDF.[152] There were no trials of telbivudine, which is FDA-approved but a non-preferred antiviral. However, this drug is no longer manufactured in the United States, though it is available in other countries. We excluded studies included in the prior USPSTF review in which greater than 20 percent of patients had cirrhosis, greater than 20 percent of patients were treatment-experienced, or that were rated poor-quality, reducing the evidence base available for this update. However, these exclusions strengthened the quality and applicability of the reviewed evidence to populations identified by screening, and overall conclusions were similar to the prior USPSTF review.

We included observational studies to evaluate the association between antiviral therapy versus no antiviral therapy and long-term clinical outcomes because randomized trials were not designed to assess these outcomes. We also included observational studies on the association between achieving an intermediate outcome after antiviral therapy and clinical outcomes, because it is not possible to randomize patients' response to therapy.[153] We focused on studies that controlled for potential confounders, in order to reduce potential effects from confounding.

Another limitation is that we included studies conducted in countries where the prevalence, characteristics (e.g., likelihood of HBeAg-negative chronic HBV infection), and natural history of HBV infection may differ from in the United States. Including such evidence might reduce the applicability of the reviewed evidence to screening in the United States. However, findings were similar when trials were stratified according to whether they were conducted in low or high HBV prevalence settings, and for studies conducted in Asia and the United States.

This update did not address effectiveness of vaccinations or the effectiveness of education or behavior change counseling. The prior USPSTF review found HBV vaccination in high risk persons with evidence of HBV immunity associated with decreased risk of HBV acquisition based on serologic and biochemical markers, but no evidence on clinical outcomes.[72] It also

identified no trials on the effectiveness of education or behavior change counseling in patients with chronic HBV infection for reducing transmission or improving health outcomes. A literature scan during the work plan development phase of this report and input from expert Key Informants identified no new evidence to address these areas. We also did not include evidence on the effectiveness of surveillance for hepatocellular carcinoma in patients with HBV infection, which reported mixed results.[154,155] Hepatocellular carcinoma surveillance was considered to be outside the scope of screening.

Emerging Issues/Next Steps

Trends in the epidemiology of HBV infection are likely to inform future assessments of screening. Symptomatic acute HBV infections in the United States declined approximately 85 percent from the early 1990s to 2009 following the adoption of universal infant vaccination and catch-up vaccinations for children and adolescents,[156,157] with substantial reductions in prevalence among U.S. children and adolescents. Further declines in HBV prevalence in the United States have been offset by immigration from places where HBV infection remains endemic, such as Asia and Africa.[16] Foreign-born persons are estimated to account for approximately 95 percent of newly reported HBV infections in the United States, a factor potentially informing future screening strategies.

Among currently approved drugs for treatment of HBV infection, entecavir and tenofovir (TDF or TAF) have potent antiviral activity, appear to have low rates of drug resistance, and are better tolerated than pegylated interferon alfa-2a, but data on their effects on clinical outcomes remain extremely limited. TAF, which was FDA-approved in 2016, may be associated with fewer kidney adverse effects than TDF, but data on effects on intermediate and clinical outcomes are lacking. Although a number of combination antiviral therapies have been evaluated for management of HBV infection, none has been proven to be superior to monotherapy for achieving intermediate or clinical outcomes and avoiding drug resistance.[158] However, research on combination therapies and new investigational agents, including drugs with novel viral targets,[159,160] is ongoing.

HBV reactivation has become increasingly recognized as a clinical issue in persons previously exposed to HBV.[28] Screening could identify patients with evidence of past HBV infection but without current active disease who could benefit from interventions to prevent reactivation. To date, evidence on the prevalence and prevention of HBV reactivation has focused on patients with cancer or autoimmune conditions undergoing immunosuppressant therapy, or patients with HCV infection receiving antiviral therapy. The USPSTF generally considers management of such chronic conditions (including testing for HBV infection) to be outside the scope of screening. However, some evidence indicates that HBV testing rates are low in persons with cancer undergoing chemotherapy, highlighting a potential practice gap.[161,162] Of greater relevance to evaluating benefits of screening would be data on the prevalence and severity of HBV reactivation in primary care settings in persons treated for acute conditions; such data are currently not available.

Relevance for Priority Populations

HBV infection is more prevalent in the United States among persons originating from countries with higher prevalence. WHO regions with prevalence greater than 2 percent are the African Region (6.1%), Eastern Mediterranean (3.3%), South-East Asia (2.0%), and Western Pacific (6.2%).[31] About half of prevalent U.S. cases of chronic infection are in non-Hispanic Asians, a group representing 5 to 6 percent of the U.S. population.[19] Challenges in screening immigrant populations include language barriers, lack of access to healthcare, stigma associated with HBV infection, and lack of knowledge.[163,164]

Data indicate that the prevalence of HBV infection has declined in adolescents, due to implementation of universal HBV vaccination. However, there has been little change in prevalence among adults age 50 years or older. No randomized trial that met inclusion criteria evaluated antiviral therapy in adolescents. Nonpegylated interferon was the first antiviral therapy approved for treatment of chronic HBV infection in children. Pegylated interferon alfa-2a is approved for use in children ages 3 years and older, entecavir is approved in children ages 2 years and older, and TDF is approved in adolescents ages 12 years and older. Lamivudine and adefovir are now rarely used in adolescents, due to limited efficacy and high rates of viral resistance. Trials did not evaluate how effects of antiviral therapies varied according to age, race, or sex.

Future Research

Research gaps limit full understanding of the benefits and harms of screening for HBV infection. Studies that compare clinical outcomes in patients screened and not screened for HBV infection would provide the most direct evidence but would require large sample sizes and long duration of followup. Studies would not necessarily need to be randomized trials; well-conducted observational studies (prospective or retrospective) that control for potential confounders could also be informative. Studies that compare different screening strategies would be helpful for understanding the feasibility and outcomes of alternative screening approaches (e.g., strategies that focus on persons originating from high-prevalence countries versus more generalized screening strategies).

Research is also needed on long-term clinical outcomes associated with use of preferred antiviral therapies for chronic HBV infection. Studies are needed to evaluate the most recently approved antiviral drug, TAF, and to determine whether it carries advantages with regard to adverse kidney and bone effects versus TDF or other antivirals. Studies that evaluate whether receipt of antiviral therapy is associated with decreased risk of HBV transmission (as has been shown for HIV infection)[165] would be useful for identifying additional public health benefits of screening and subsequent treatment; studies are also needed on the effects of antiviral therapies on quality of life and extrahepatic manifestations of HBV infection. Almost all trials have focused on treatment of patients with immune active HBV infection; studies are needed on the effects of treatment during the immune tolerant phase, including risk of hepatocellular carcinoma.[23] Evidence from observational studies on the association between achieving intermediate outcomes and clinical outcomes would be strengthened by improved standardization of the

intermediate and clinical outcomes evaluated. Such studies should be designed and analyzed to account for important confounders. Pre-exposure prophylaxis with antiviral therapy to prevent HBV infection is a preventive strategy beyond the scope of this report, but may warrant additional research.[166]

Conclusions

There was no direct evidence for the clinical benefits and harms of HBV screening versus no screening. Antiviral therapy for chronic HBV infection was associated with improved intermediate outcomes and may improve clinical outcomes. Research is needed to clarify effects of screening and subsequent interventions on clinical outcomes and to identify optimal screening strategies.

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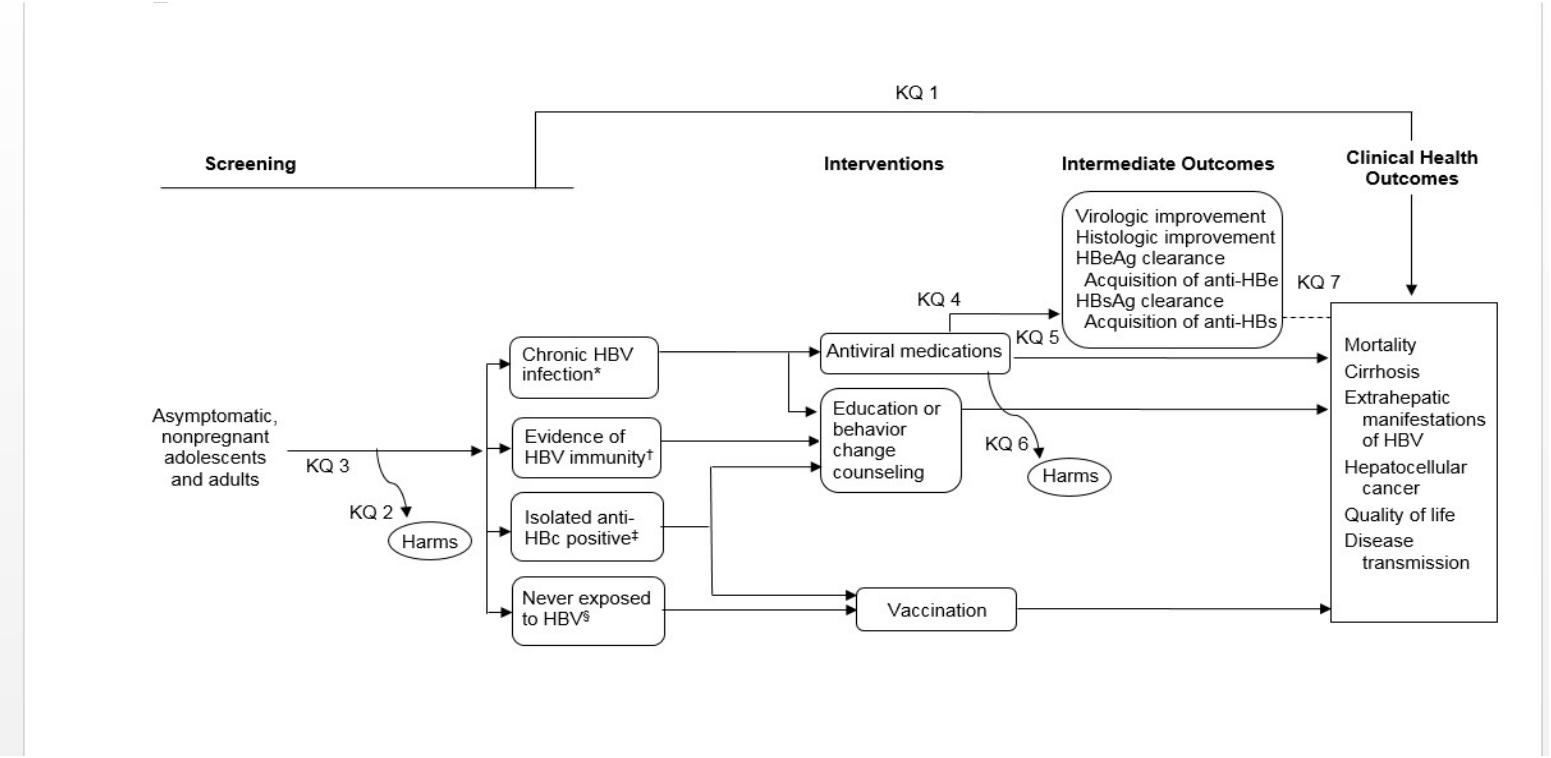
Figure 1. Analytic Framework and Key Questions

Analytic Framework



Note: "Screening" is defined as testing for anti-HBs and HBsAg, with or without testing for anti-HBc.
* "Chronic HBV infection" is defined by a positive HBsAg test result. Chronic HBV infection should be staged by assessment for hepatitis fibrosis/inflammation, HBV viral load, HBeAg status, anti-HBe status, and liver function tests. Appropriate interventions depend on disease stage.
† "Evidence of HBV immunity" is defined as positive anti-HBs, negative HBsAg, and positive (cleared infection) or negative (seroprotection due to vaccination) anti-HBc test results. Patients who have positive anti-HBc test results may benefit from education regarding risk of reactivation.
‡ "Isolated anti-HBc positive" is defined as positive anti-HBc test results but negative anti-HBs and HBsAg test results and indicates prior HBV exposure or false positive test. Patients who have positive isolated anti-HBc test results may benefit from education regarding risk of reactivation and if immunocompromised, HBV DNA testing. HBV vaccination is recommended for patients with positive isolated anti-HBc test results who are from countries with low prevalence of HBV infection (such as the United States) or who are immunocompromised.
§ "Never exposed to HBV" is defined as negative anti-HBs, anti-HBc, and HBsAg test results.

Abbreviations: anti-HBc = antibody to the hepatitis B core antigen; anti-HBe = antibody to the hepatitis B e antigen; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; KQ = key question.

Figure 1. Analytic Framework and Key Questions

Key Questions

1. What are the benefits of screening for hepatitis B virus (HBV) infection in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?
2. What are the harms of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults (e.g., labeling or anxiety)?
3. What is the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV screening strategies (e.g., universal vs. targeted screening or screening strategies based on alternative risk factors)?
4. How effective is antiviral treatment in improving intermediate outcomes among nonpregnant adolescents and adults with chronic HBV infection, including virologic or histologic improvement, clearance of hepatitis B e-antigen (HBeAg) (as indicated by loss of HBeAg or acquisition of the antibody to HBeAg [anti-HBe]), or clearance of hepatitis B surface antigen (HBsAg) (as indicated by loss of HBsAg or acquisition of hepatitis B surface antibody [anti-HBs])?*
5. How effective is antiviral treatment in improving health outcomes among nonpregnant adolescents and adults with chronic HBV infection?*
6. What are the harms associated with antiviral treatment in nonpregnant adolescents and adults with chronic HBV infection?*
7. What is the association between improvements in intermediate outcomes as a result of antiviral treatment of chronic HBV infection and reduction in risk of HBV-related adverse health outcomes?

*Subpopulations of interest for key questions 4, 5, and 6 include those defined by age, race/ethnicity, sex, injection drug use status, HBV genotype, HBeAg status, fibrosis stage, alanine transaminase level, presence of nonalcoholic steatohepatitis, HBV deoxyribonucleic acid (DNA) level, and hepatitis D virus status.

Figure 2. Antiviral Treatment vs. Placebo or No Treatment – HBeAg Loss

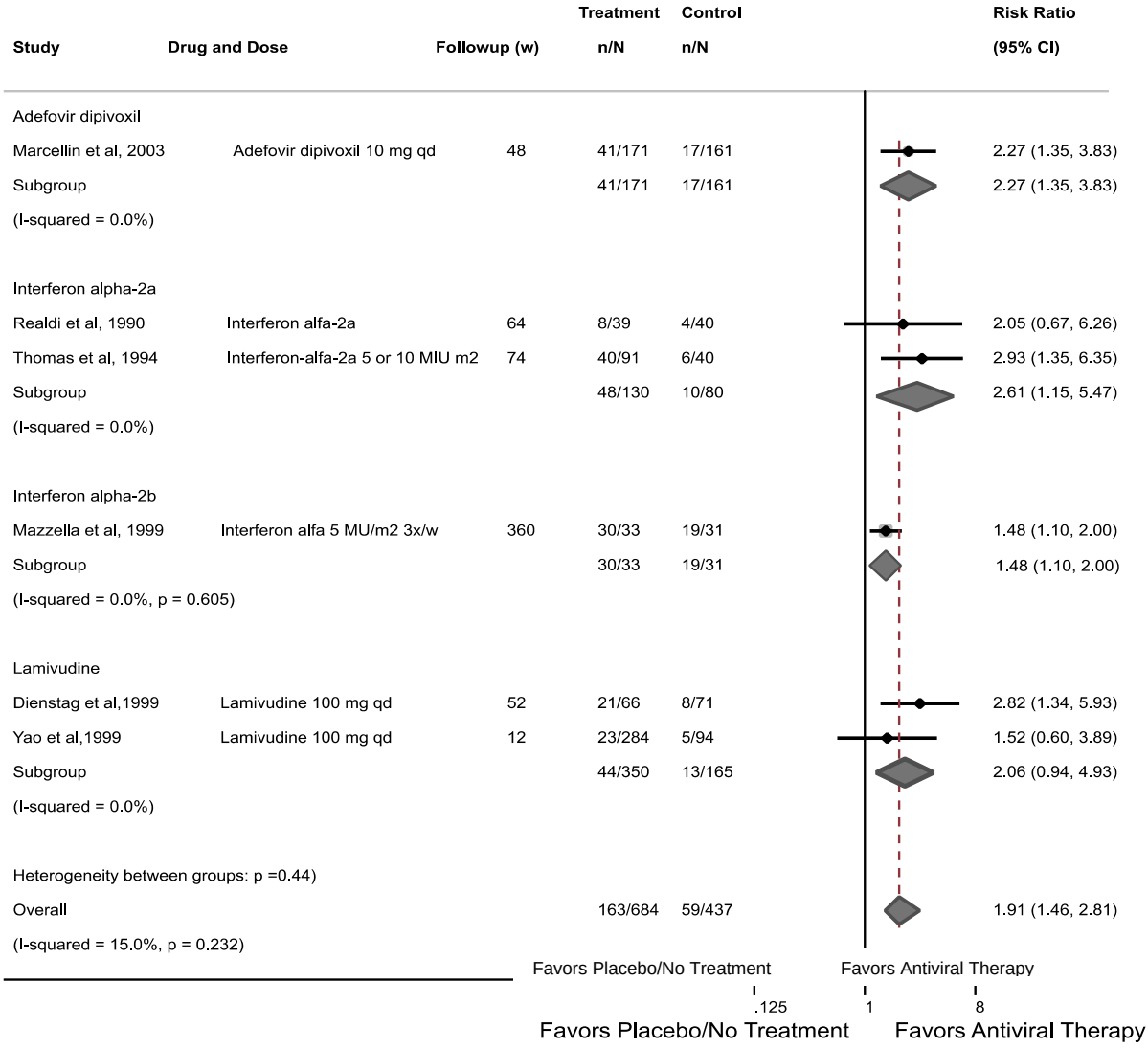


Figure 3. Antiviral Treatment vs. Placebo or No Treatment – HBeAg Seroconversion

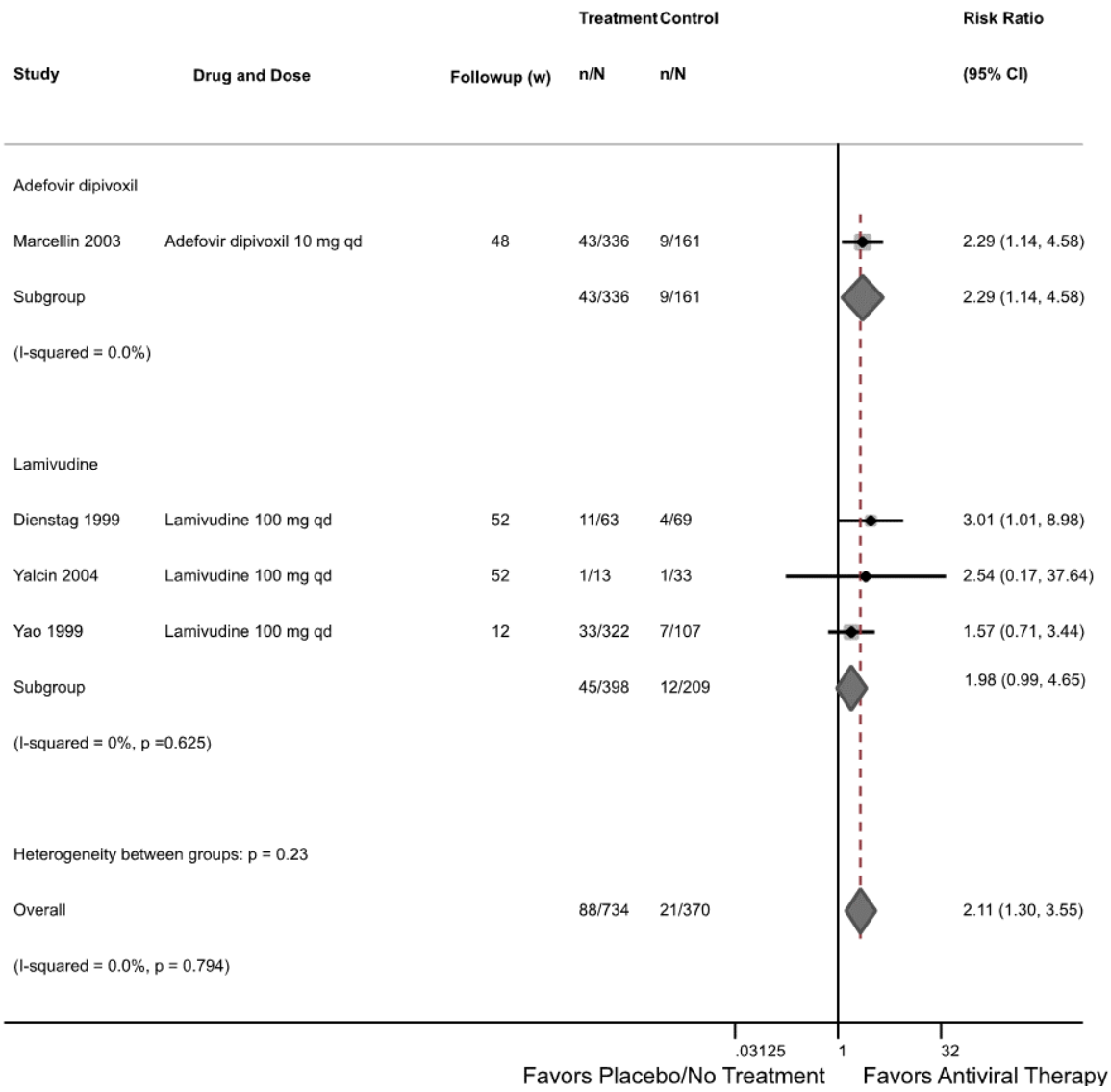


Figure 4. Antiviral Treatment vs. Placebo or No Treatment – HBsAg Loss

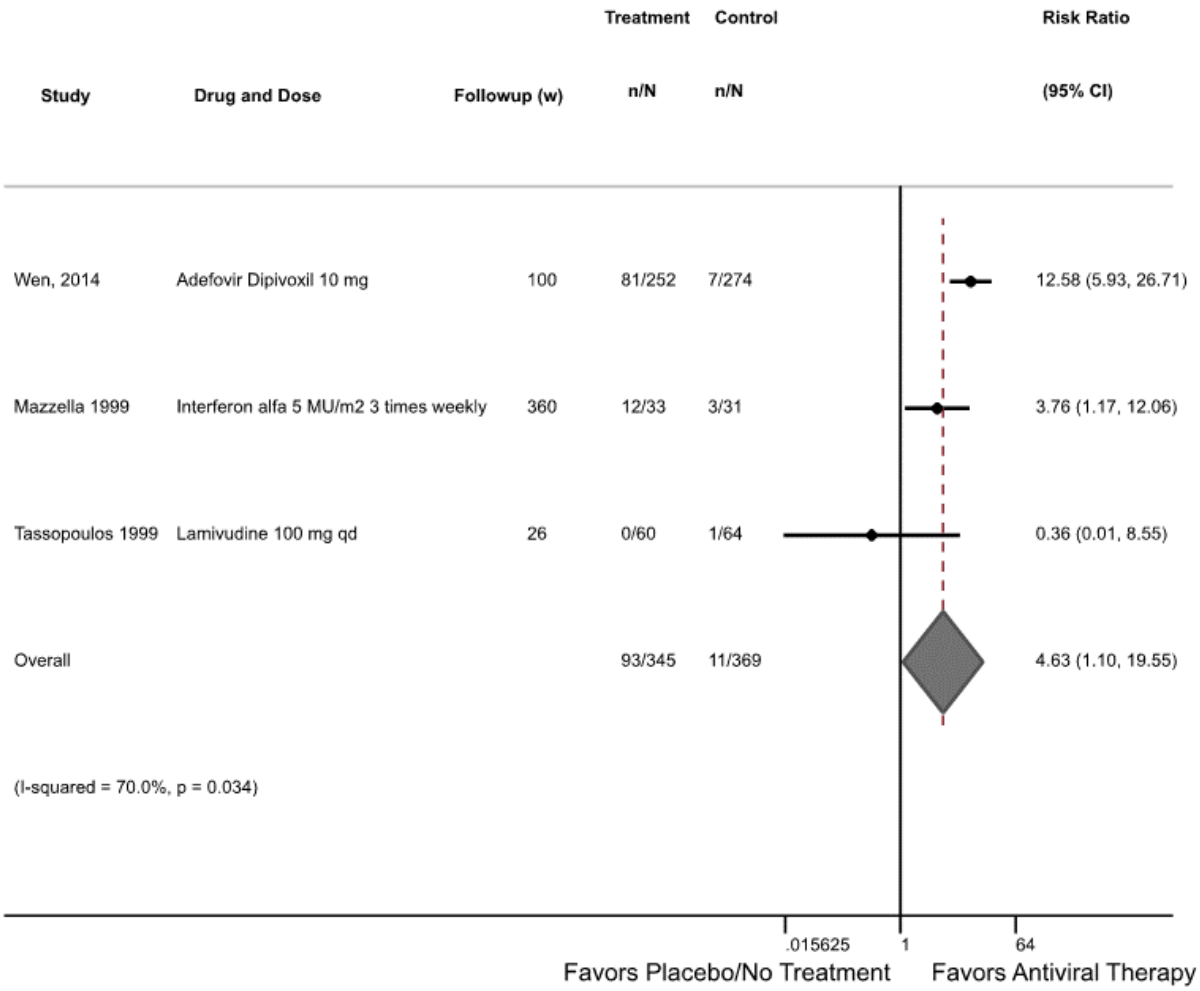
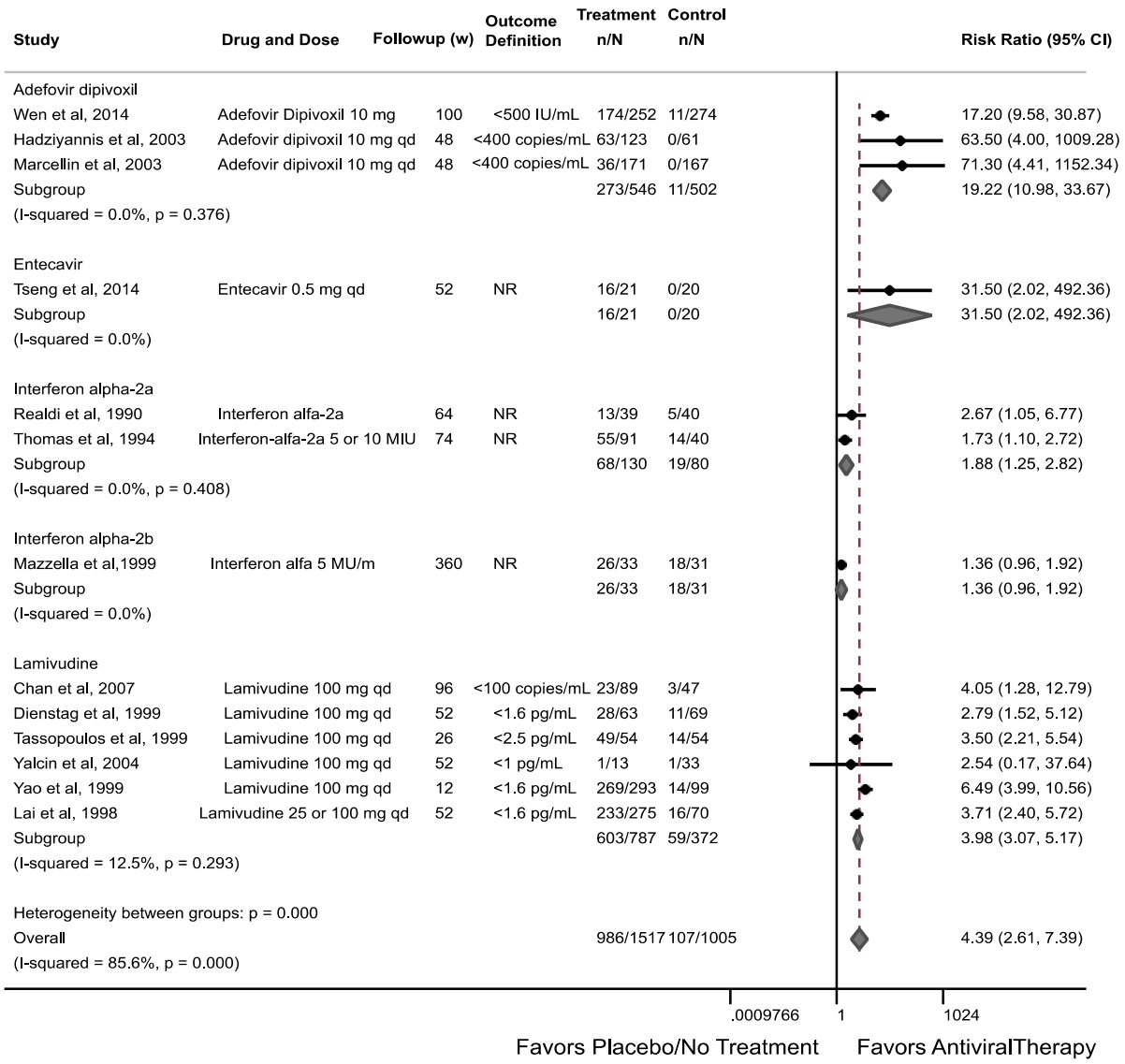


Figure 5. Antiviral Treatment vs. Placebo or No Treatment – HBV DNA Loss/Virological Suppression



Abbreviation: NR = not reported.

Figure 6. Antiviral Treatment vs. Placebo or No Treatment – ALT Normalization

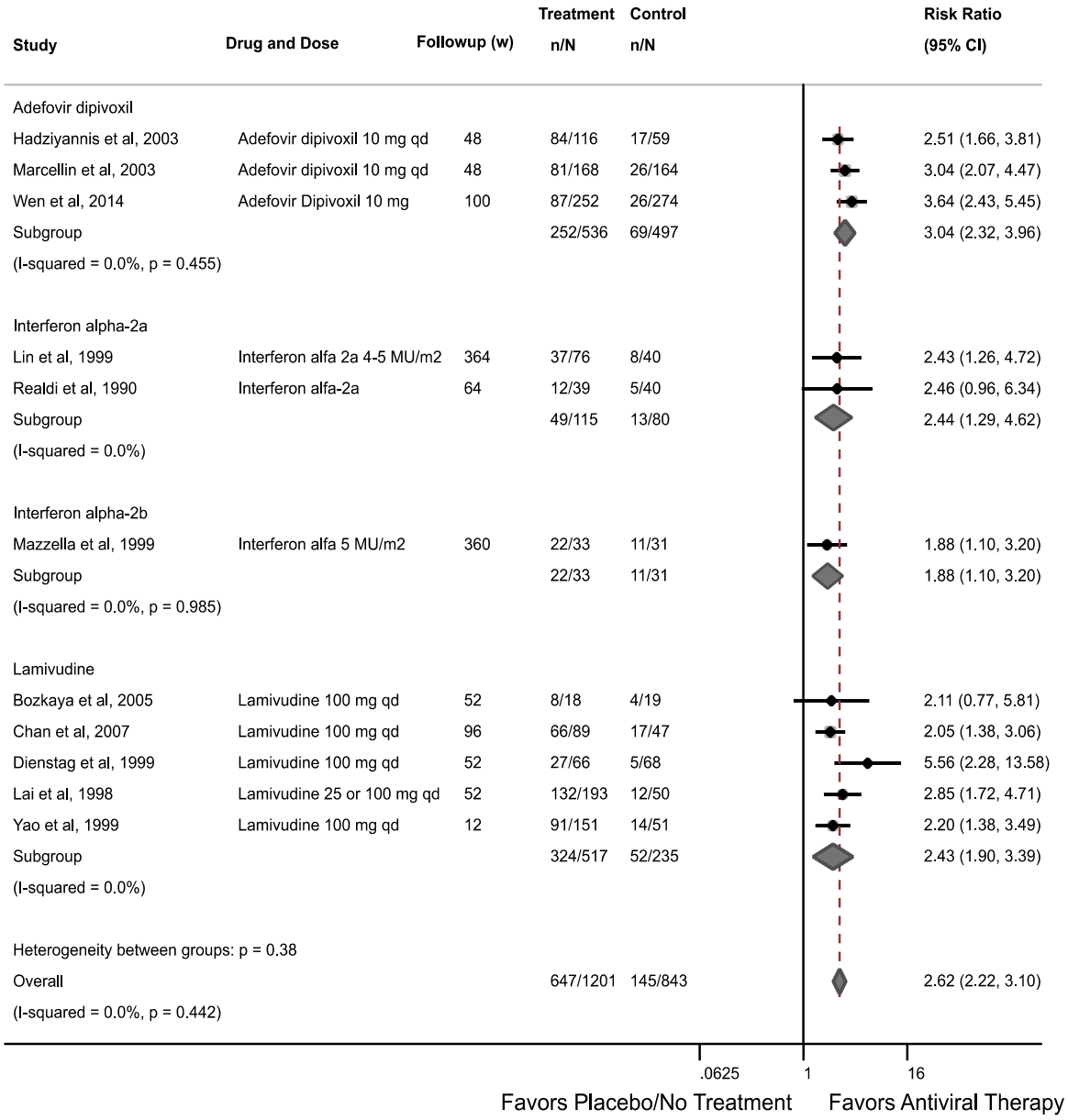
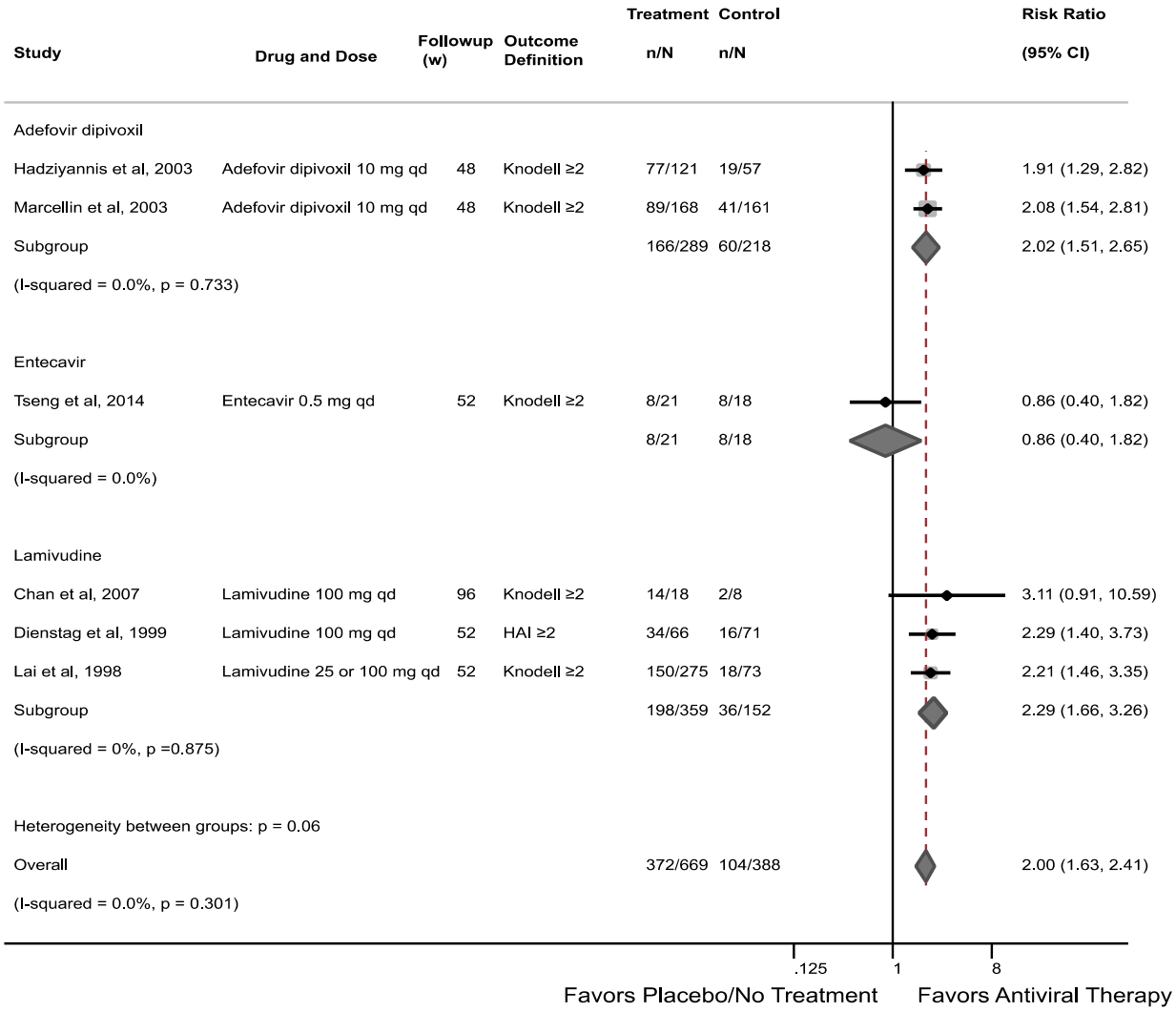
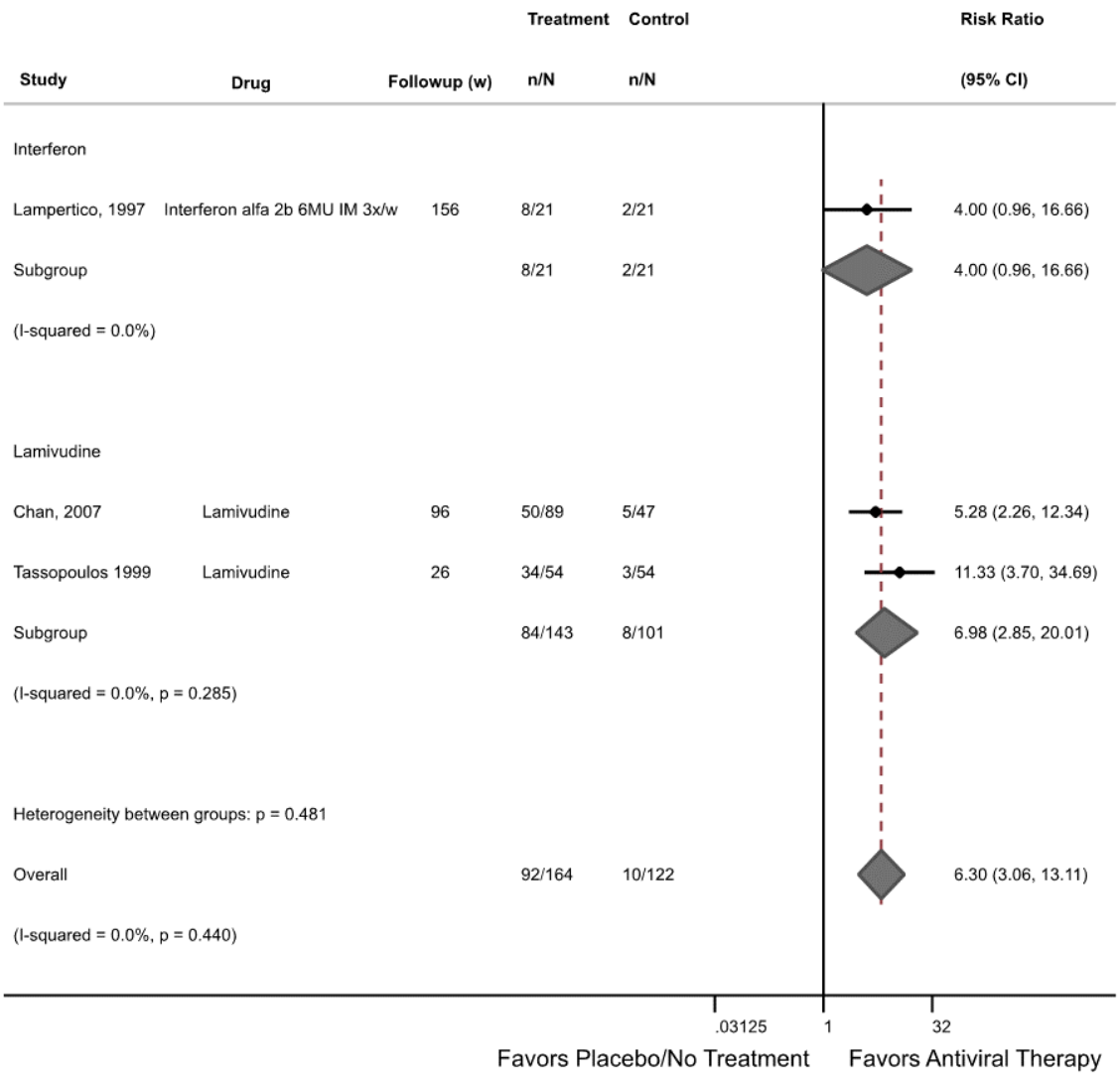


Figure 7. Antiviral Treatment vs. Placebo or No Treatment – Histologic Improvement



Abbreviation: HAI = histology activity index.

Figure 8. Antiviral Treatment vs. Placebo or No Treatment – HBV DNA Loss + ALT Normalization



Abbreviation: IM = intramuscular.

Figure 9. Antiviral Treatment vs. Placebo or No Treatment – HBV DNA Loss + HBeAg Loss

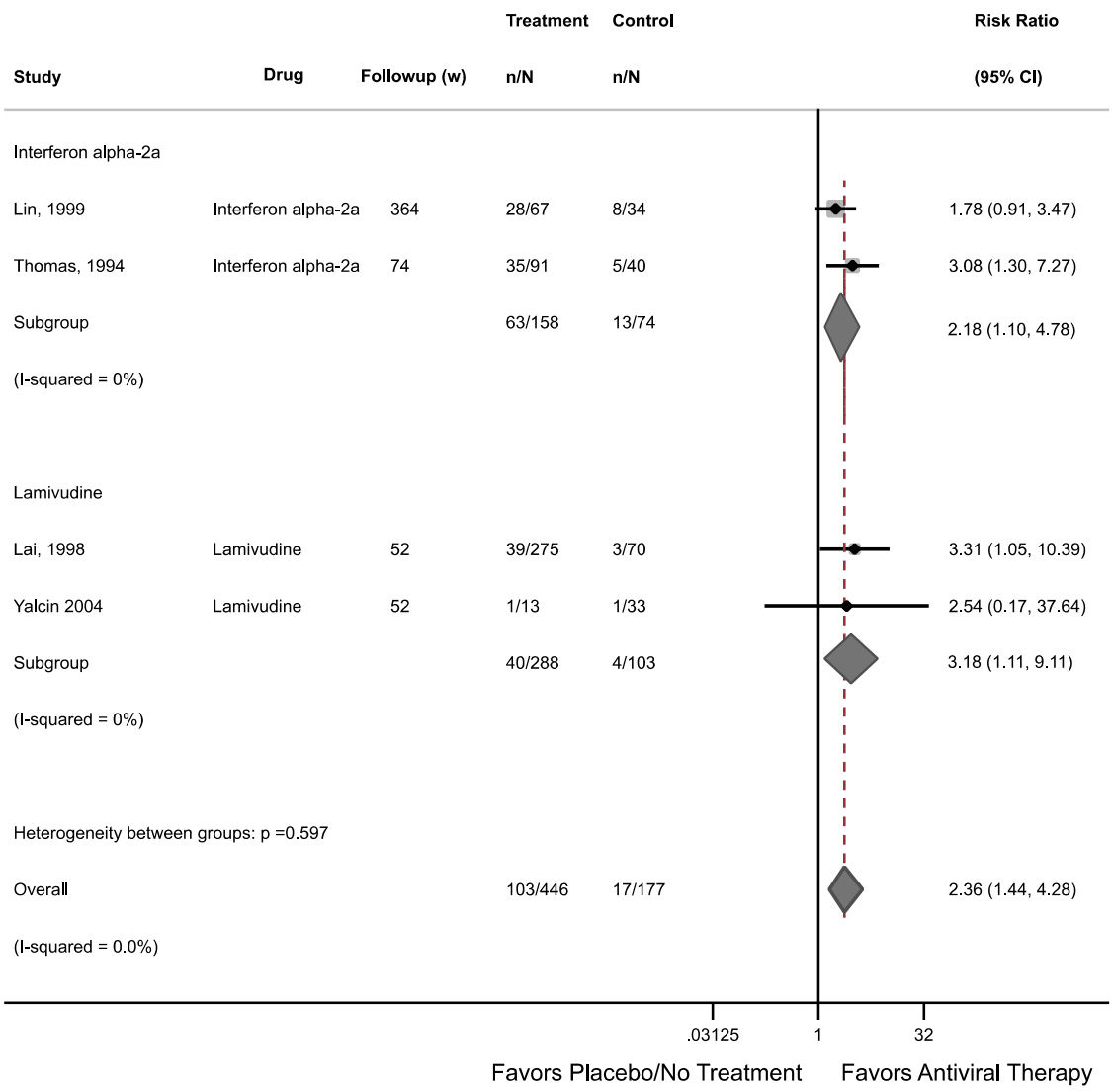


Figure 10. Preferred vs. Nonpreferred Treatment – HBeAg Seroconversion

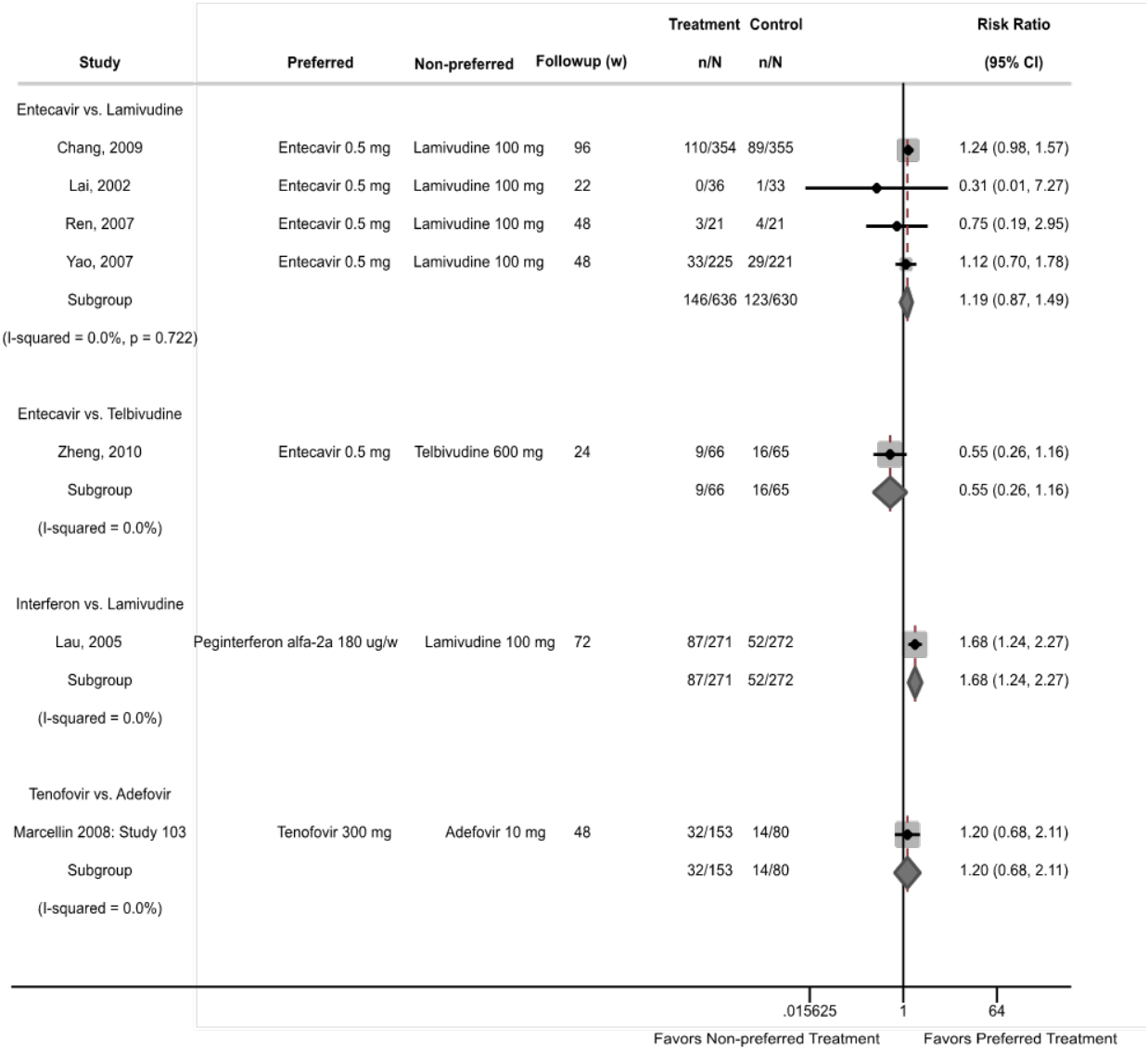
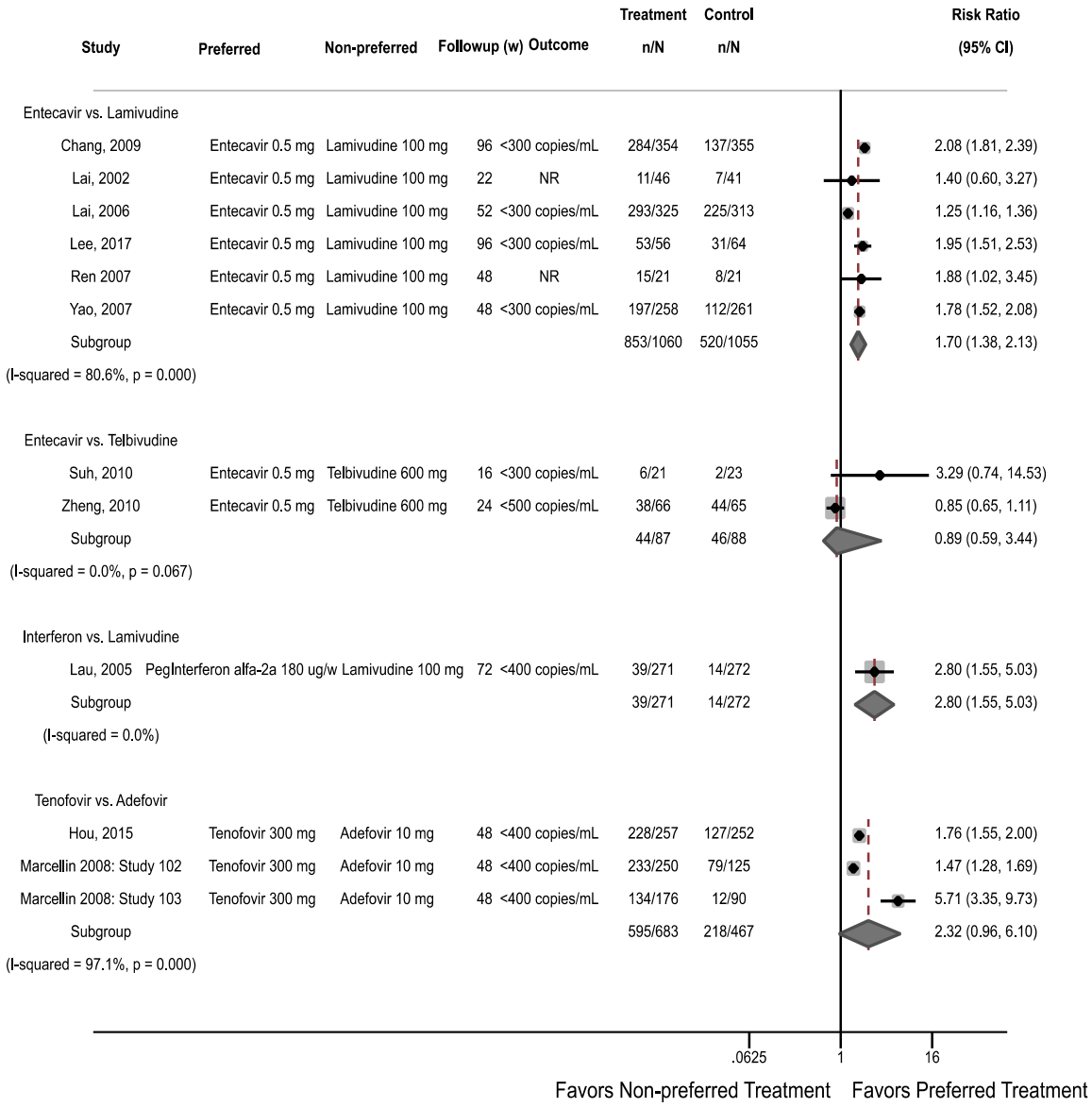


Figure 11. Preferred vs. Nonpreferred Treatment – HBV DNA Loss/Suppression



Abbreviation: NR = not reported.

Figure 12. Preferred vs. Nonpreferred Treatment – ALT Normalization

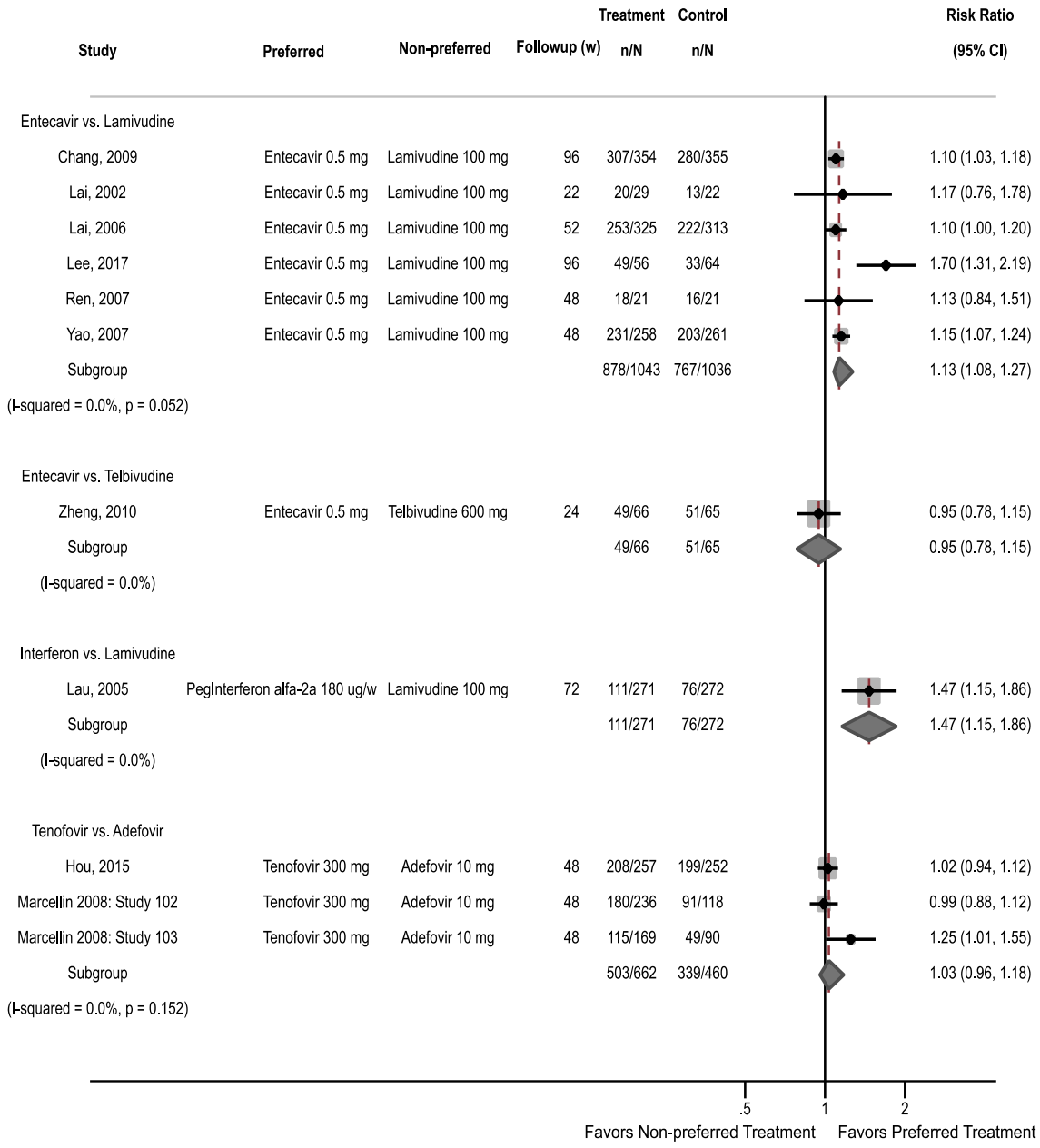


Figure 13. Entecavir vs. Lamivudine – Histologic Improvement

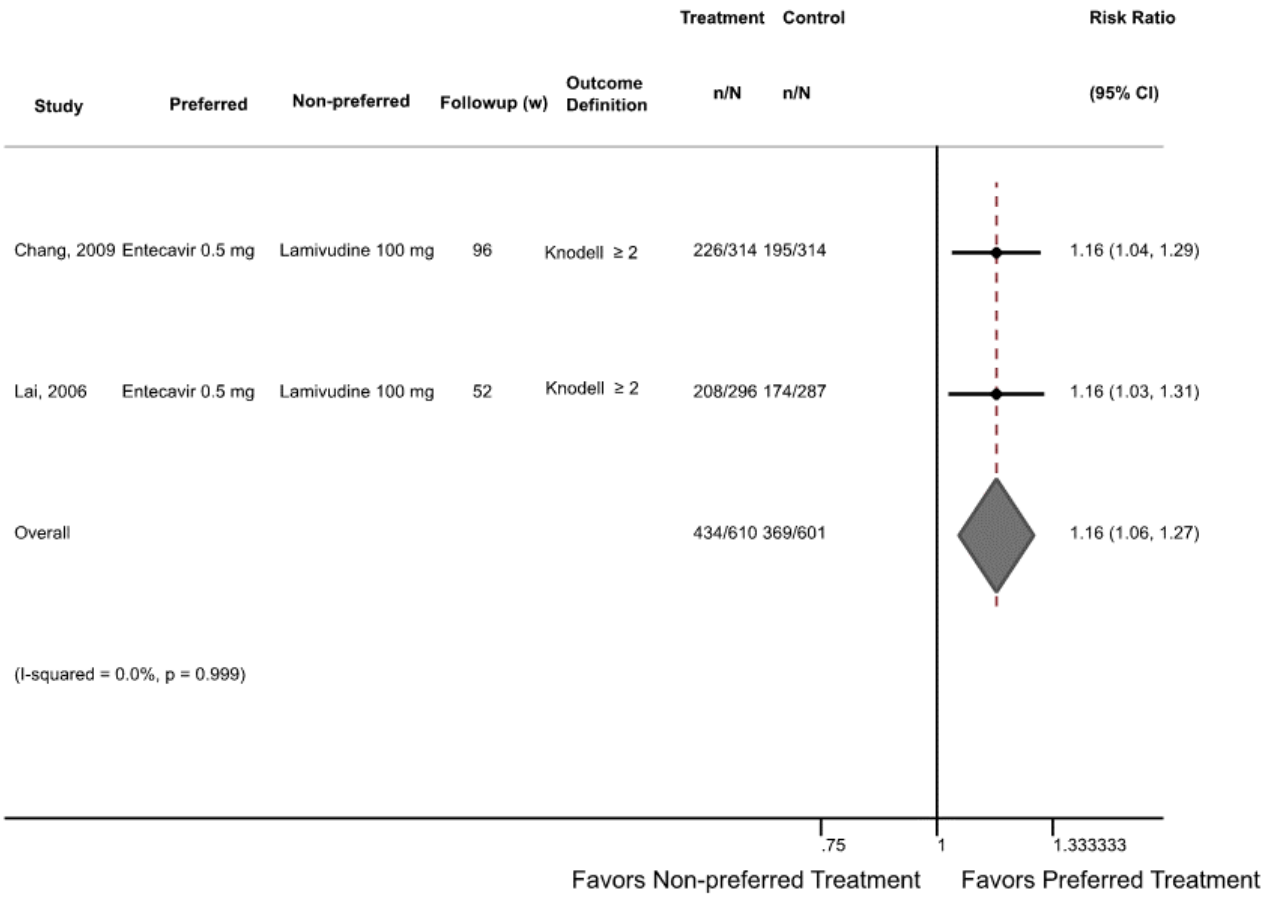


Figure 14. Antiviral Treatment vs. Placebo or No Treatment – Mortality

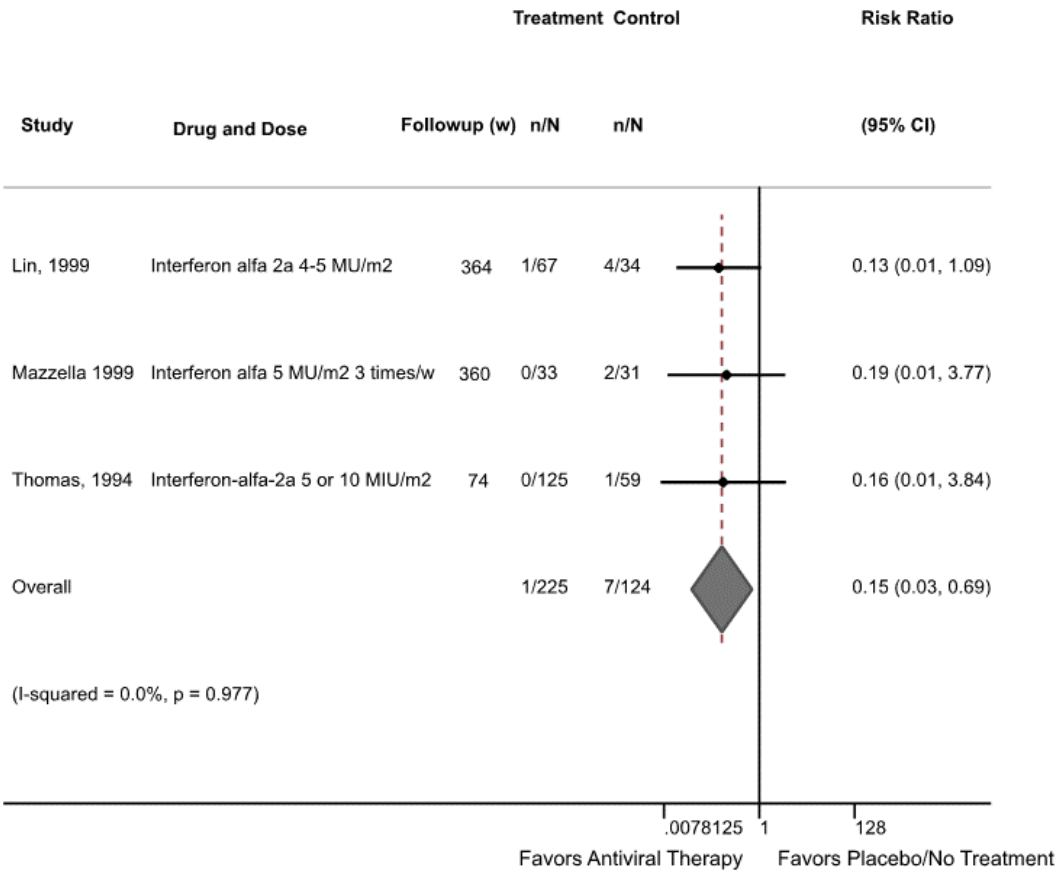


Figure 15. Antiviral Treatment vs. Placebo or No Treatment – Incident Cirrhosis

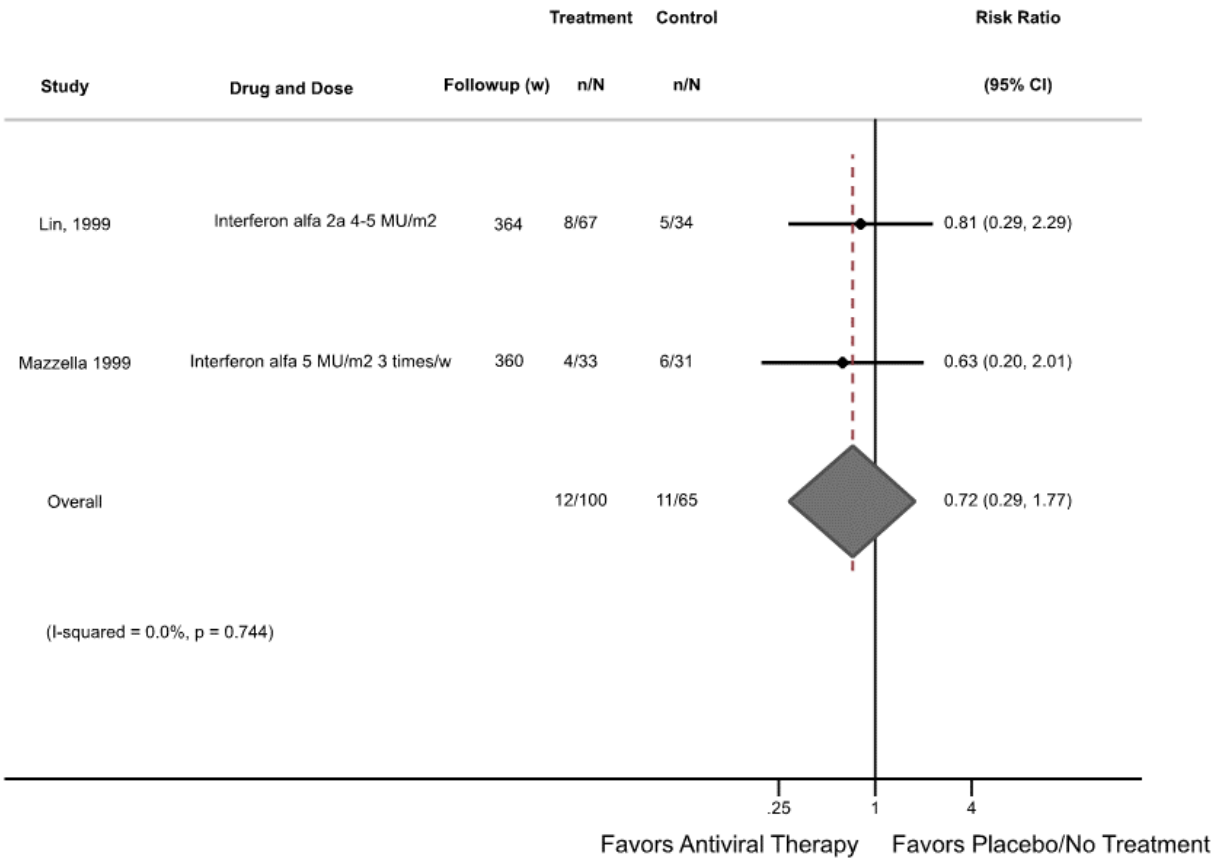
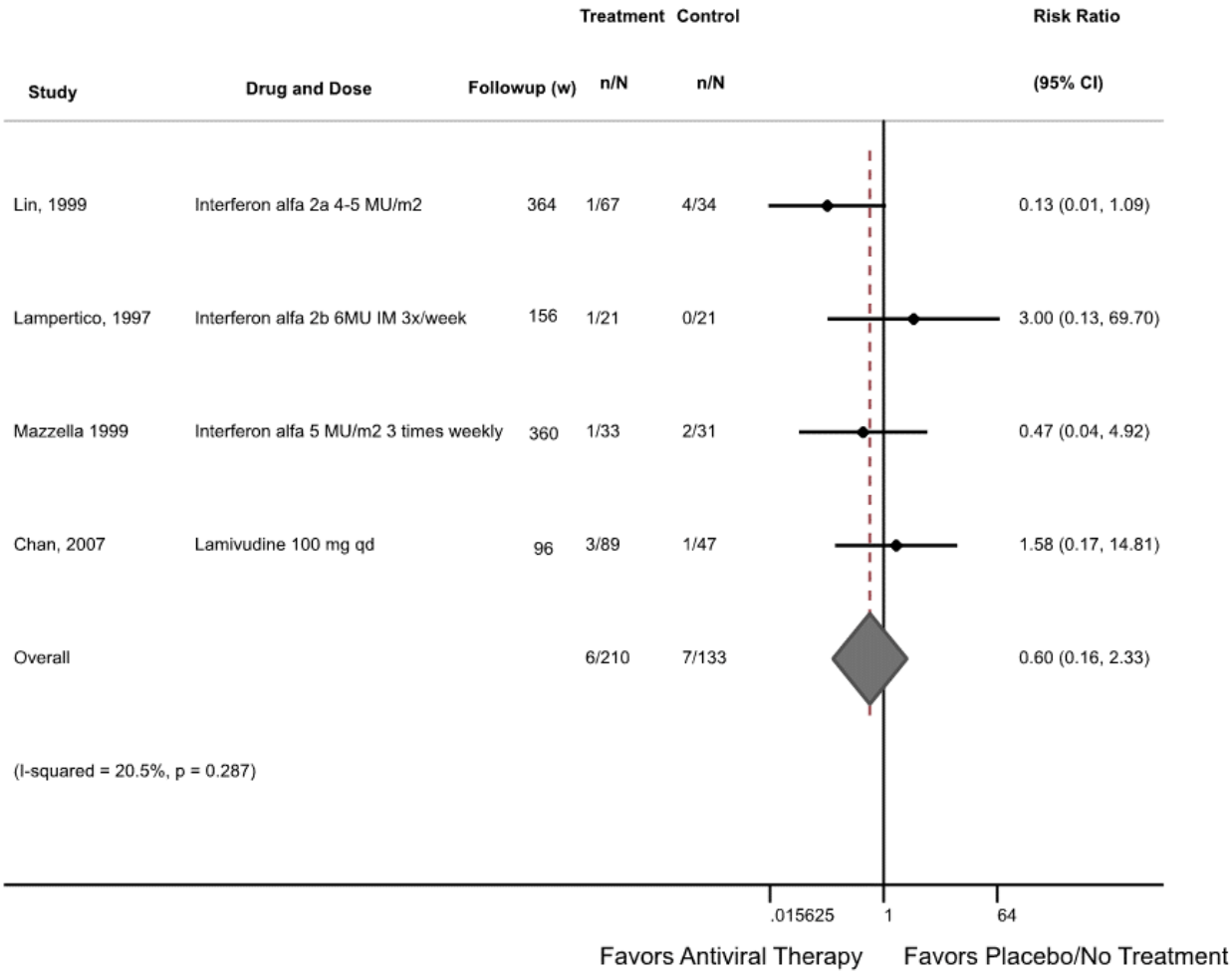


Figure 16. Antiviral Treatment vs. Placebo or No Treatment – Hepatocellular Carcinoma



Abbreviation: IM = intramuscular.

Figure 17. Preferred vs. Nonpreferred Treatment – Mortality

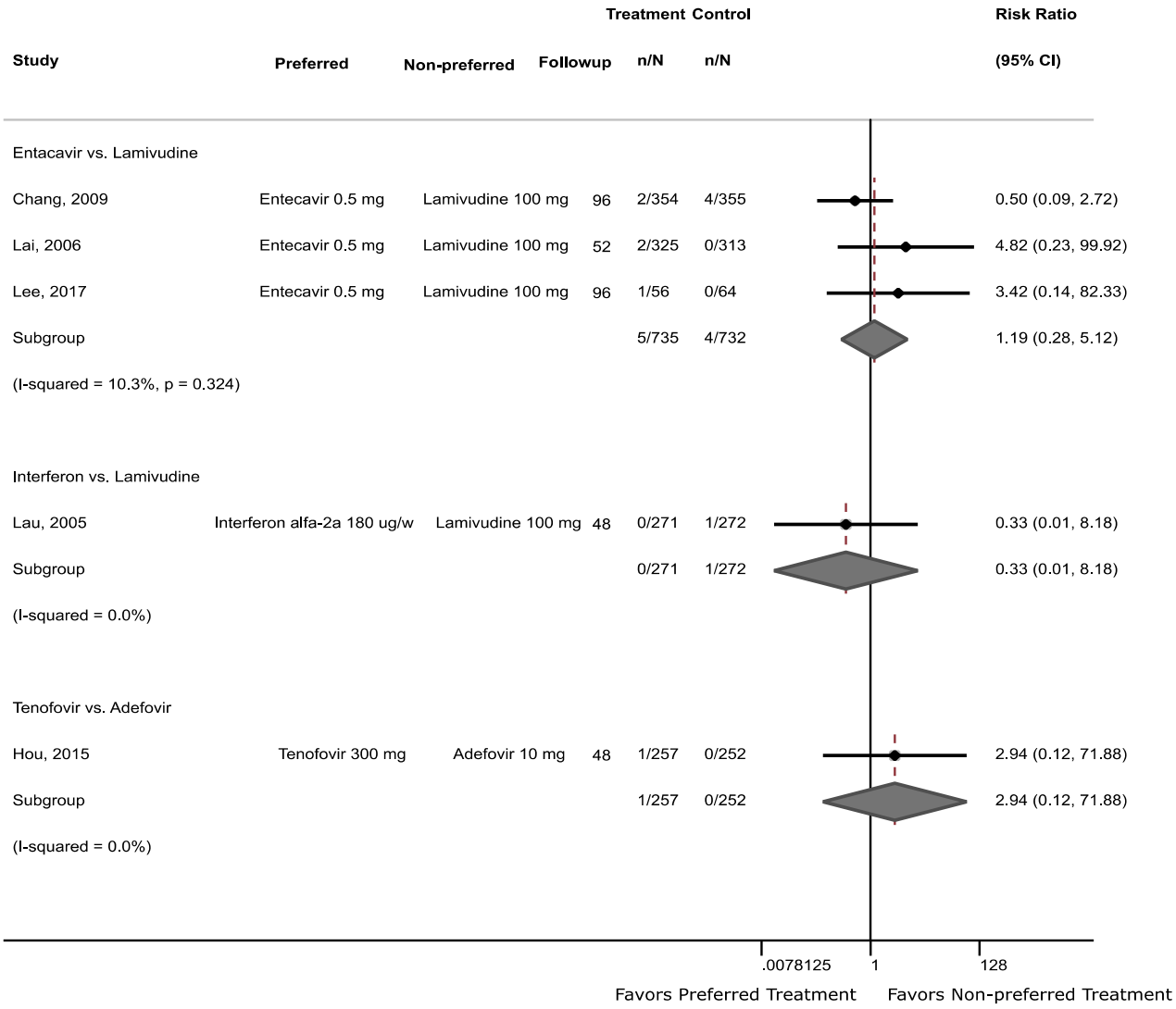


Figure 18. Antiviral Treatment vs. Placebo or No Treatment – Serious Adverse Effects

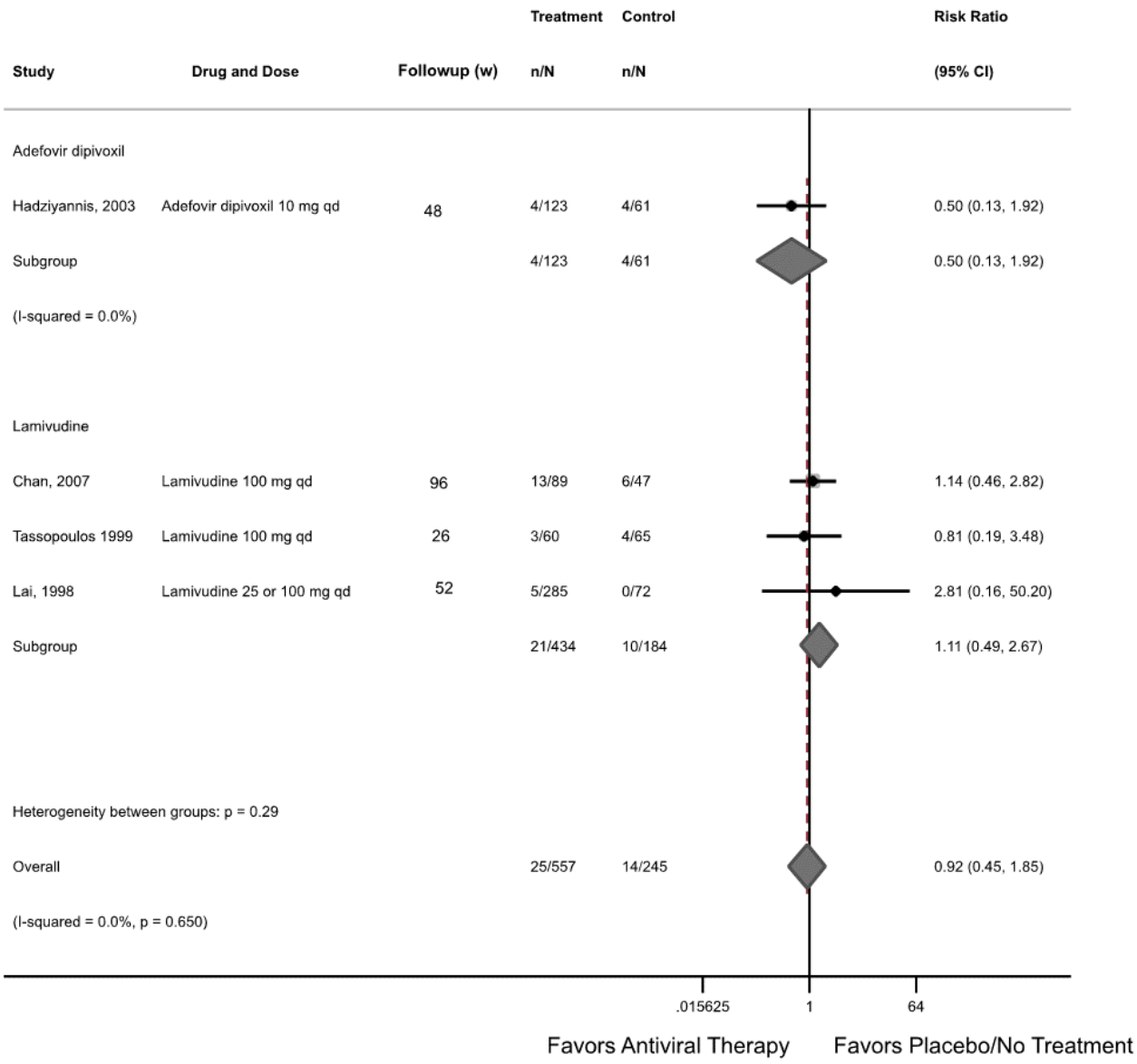
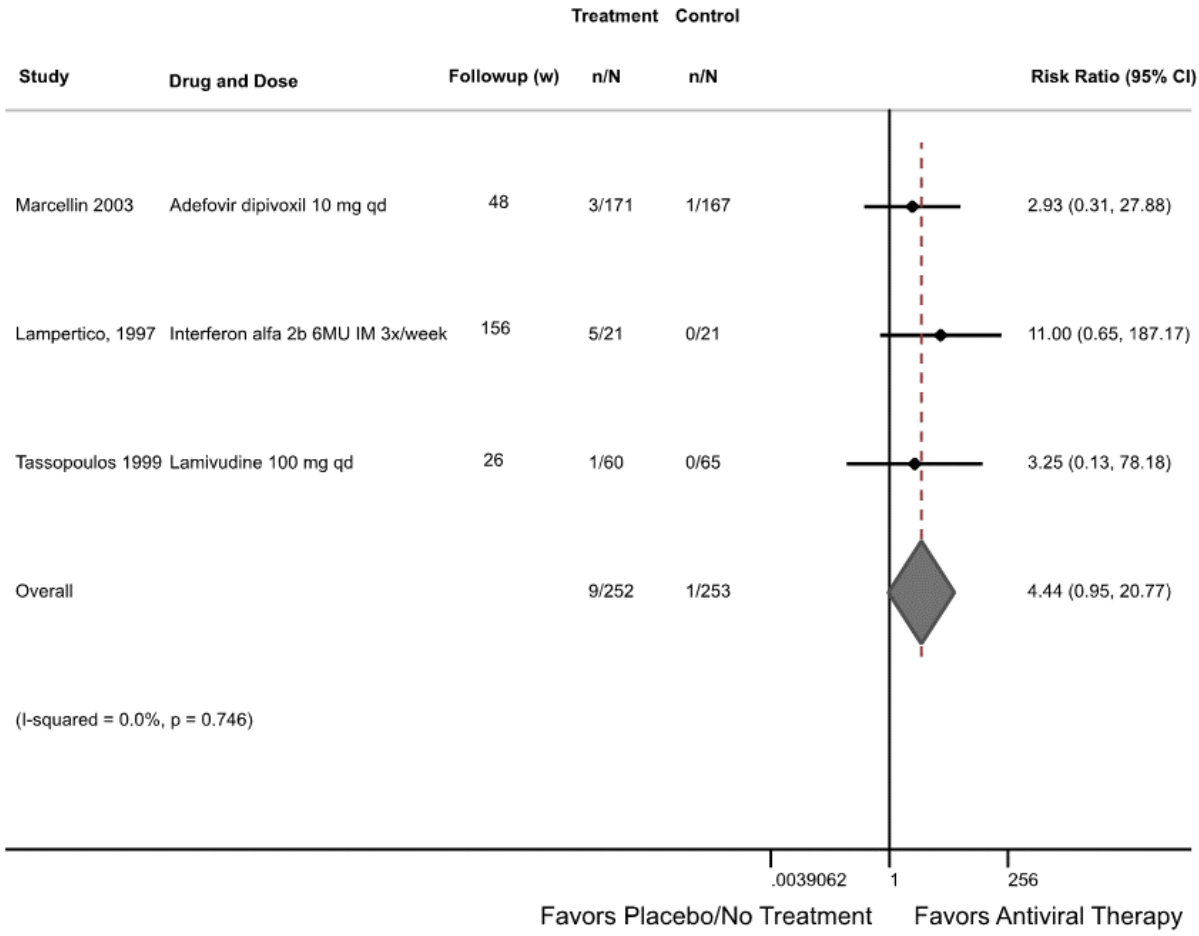


Figure 19. Antiviral Treatment vs. Placebo or No Treatment – Withdrawals Due to Adverse Effects



Abbreviation: IM = intramuscular.

Figure 20. Antiviral Treatment vs. Placebo or No Treatment – Any Adverse Effects

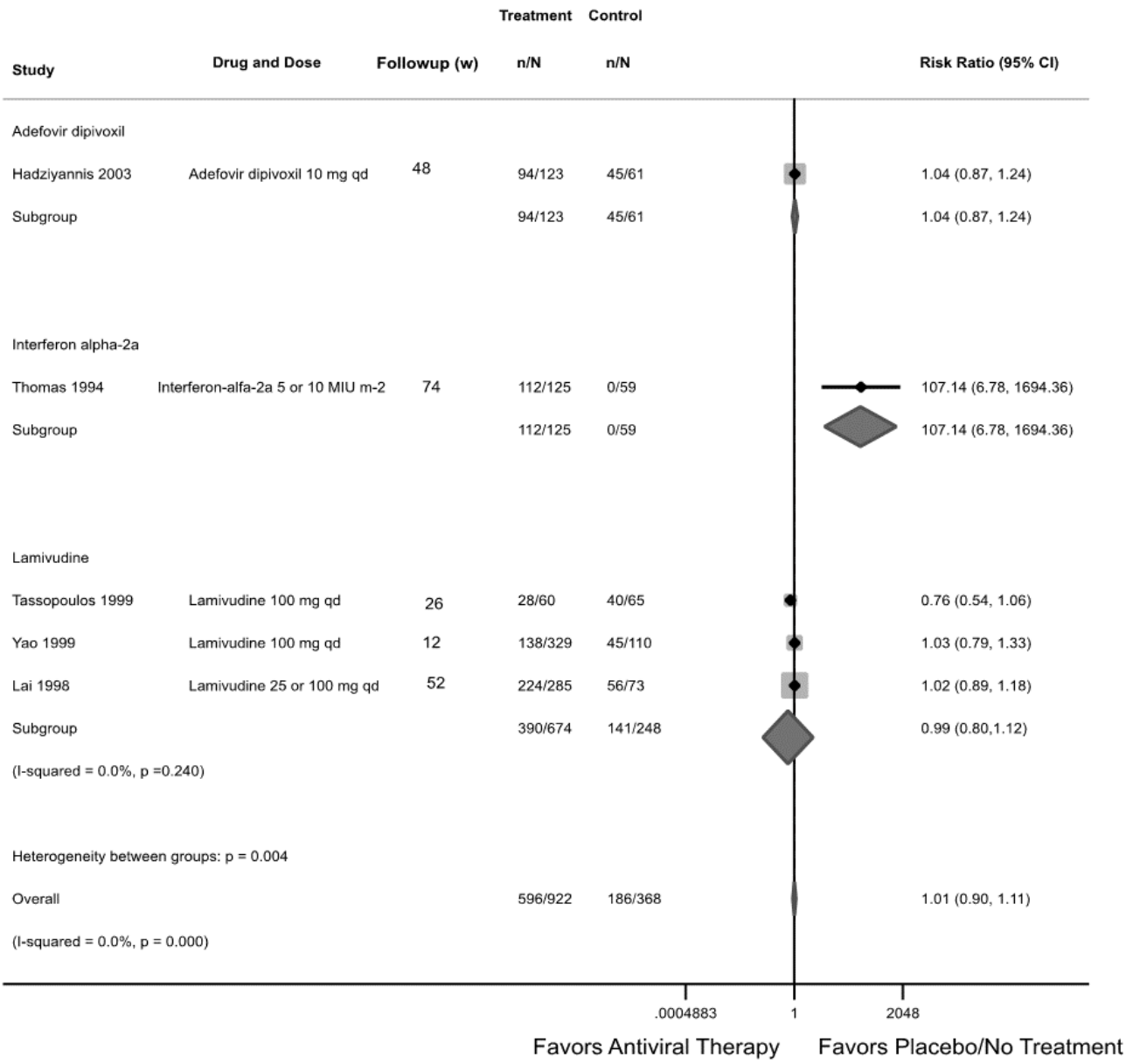


Figure 21. Antiviral Treatment vs. Placebo or No Treatment – Nausea

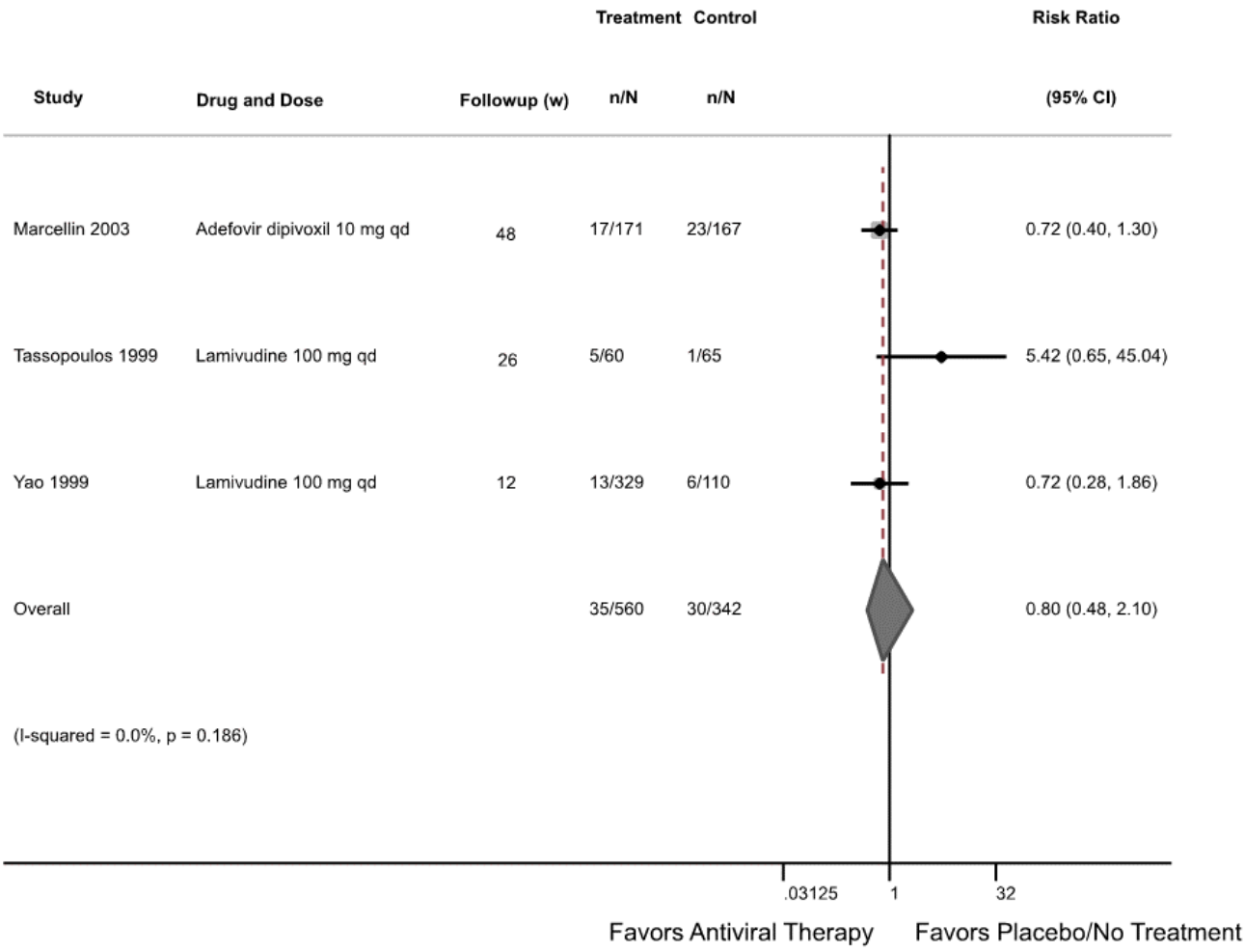


Figure 22. Antiviral Treatment vs. Placebo or No Treatment – Diarrhea

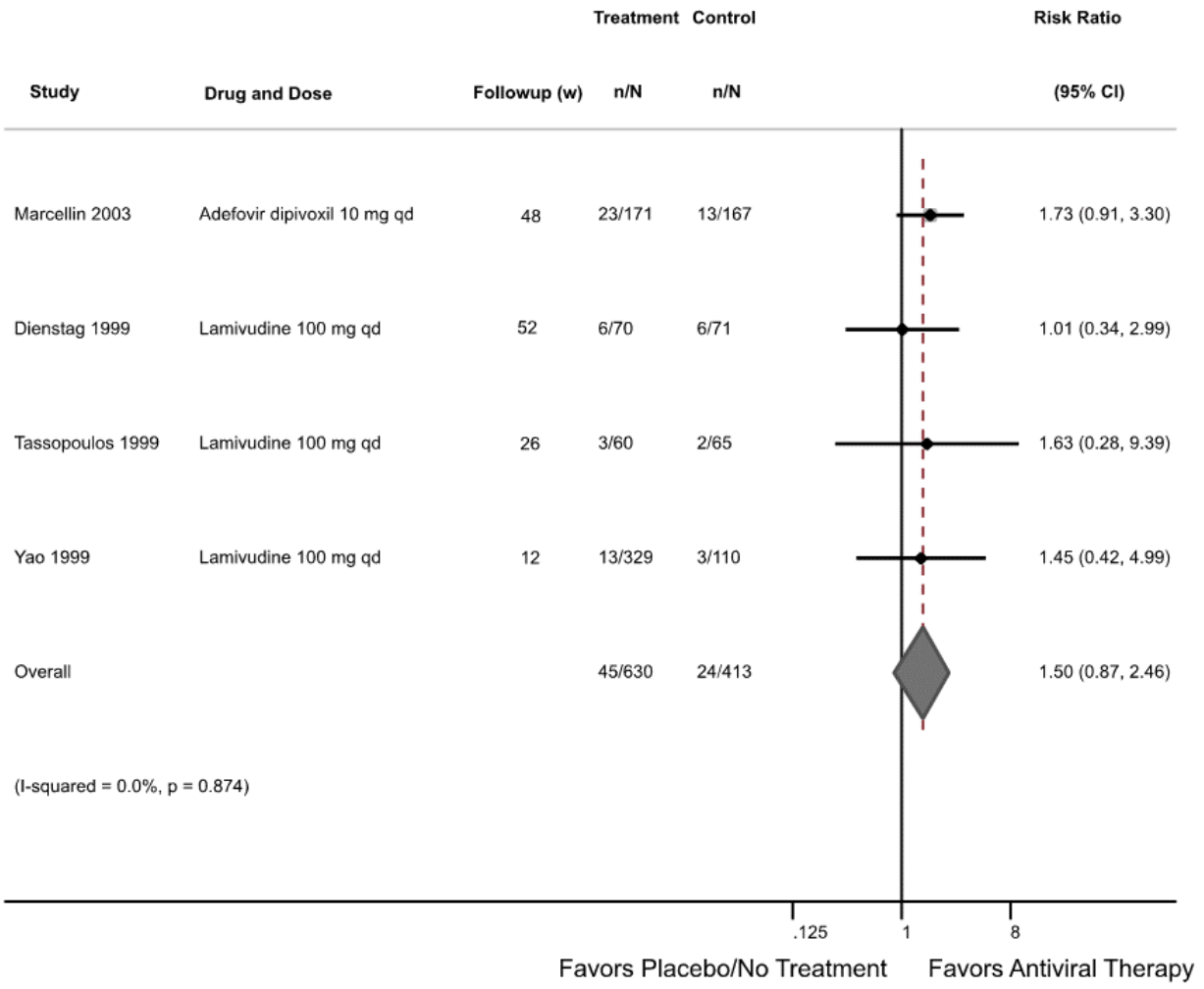
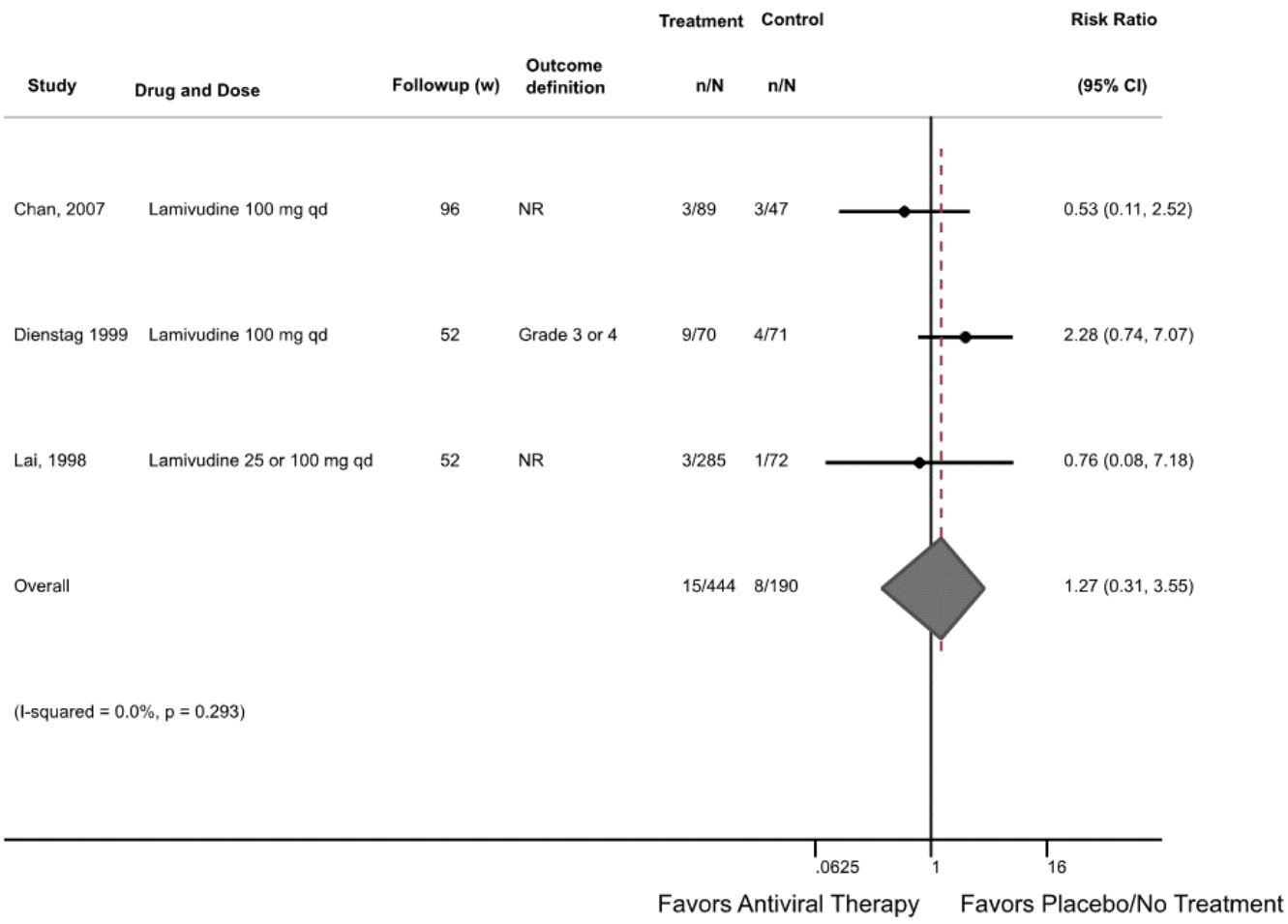


Figure 23. Antiviral Treatment vs. Placebo or No Treatment – Elevated Creatinine



Abbreviation: NR = not reported.

Figure 24. Preferred vs. Nonpreferred Treatment – Serious Adverse Effects

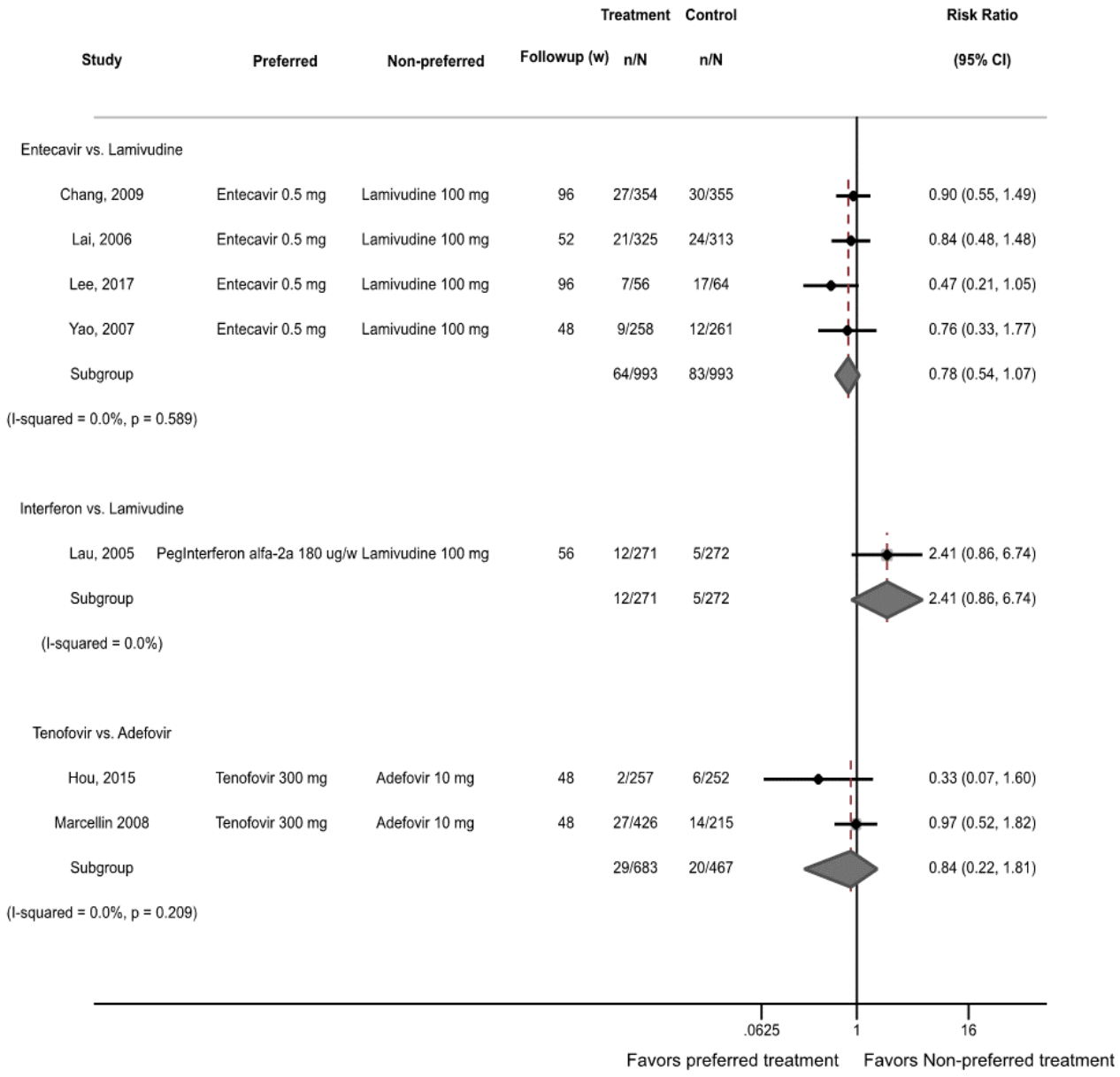


Figure 25. Preferred vs. Nonpreferred Treatment – Withdrawals Due to Adverse Effects

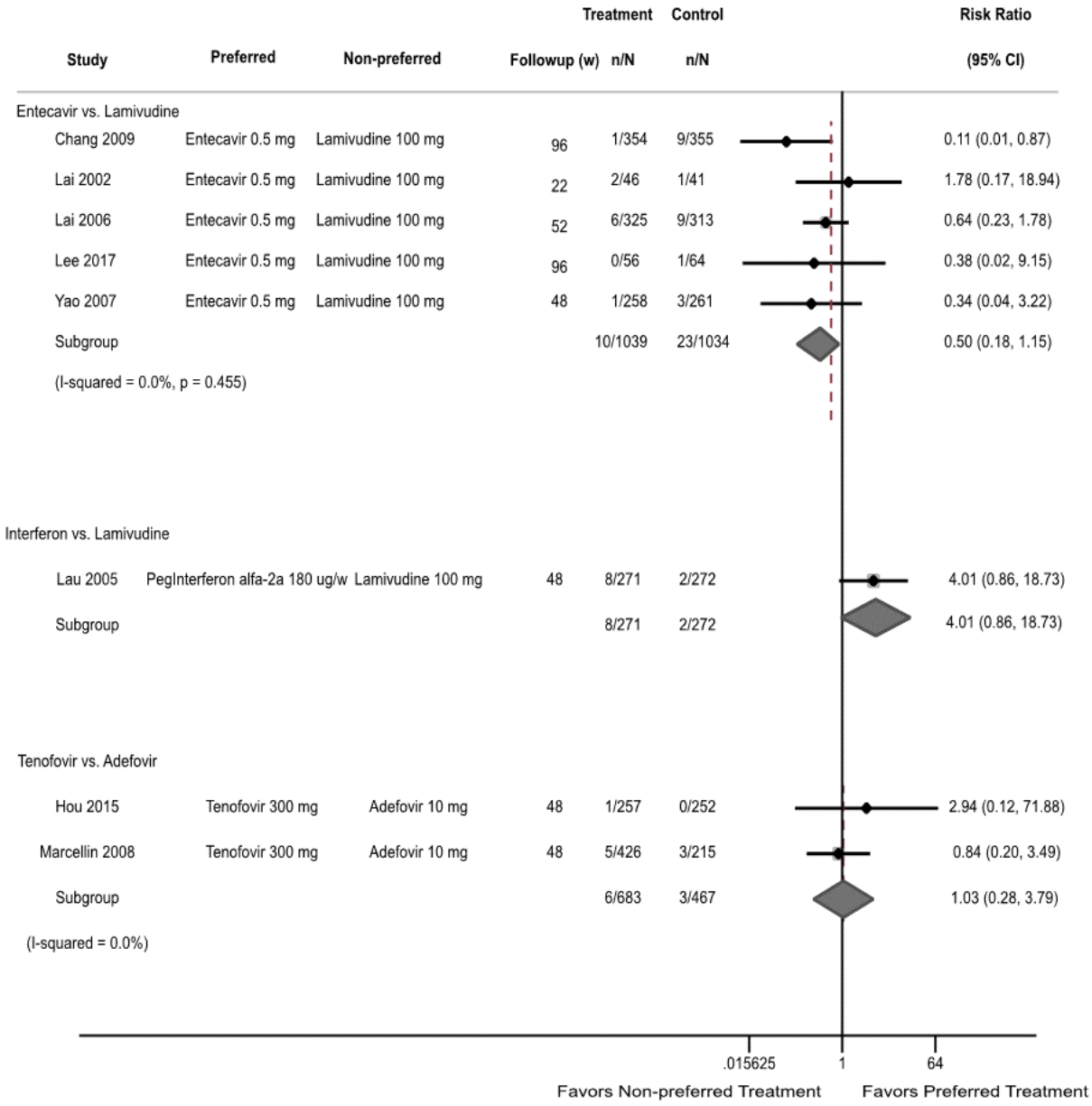


Figure 26. Preferred vs. Nonpreferred Treatment – Any Adverse Effects

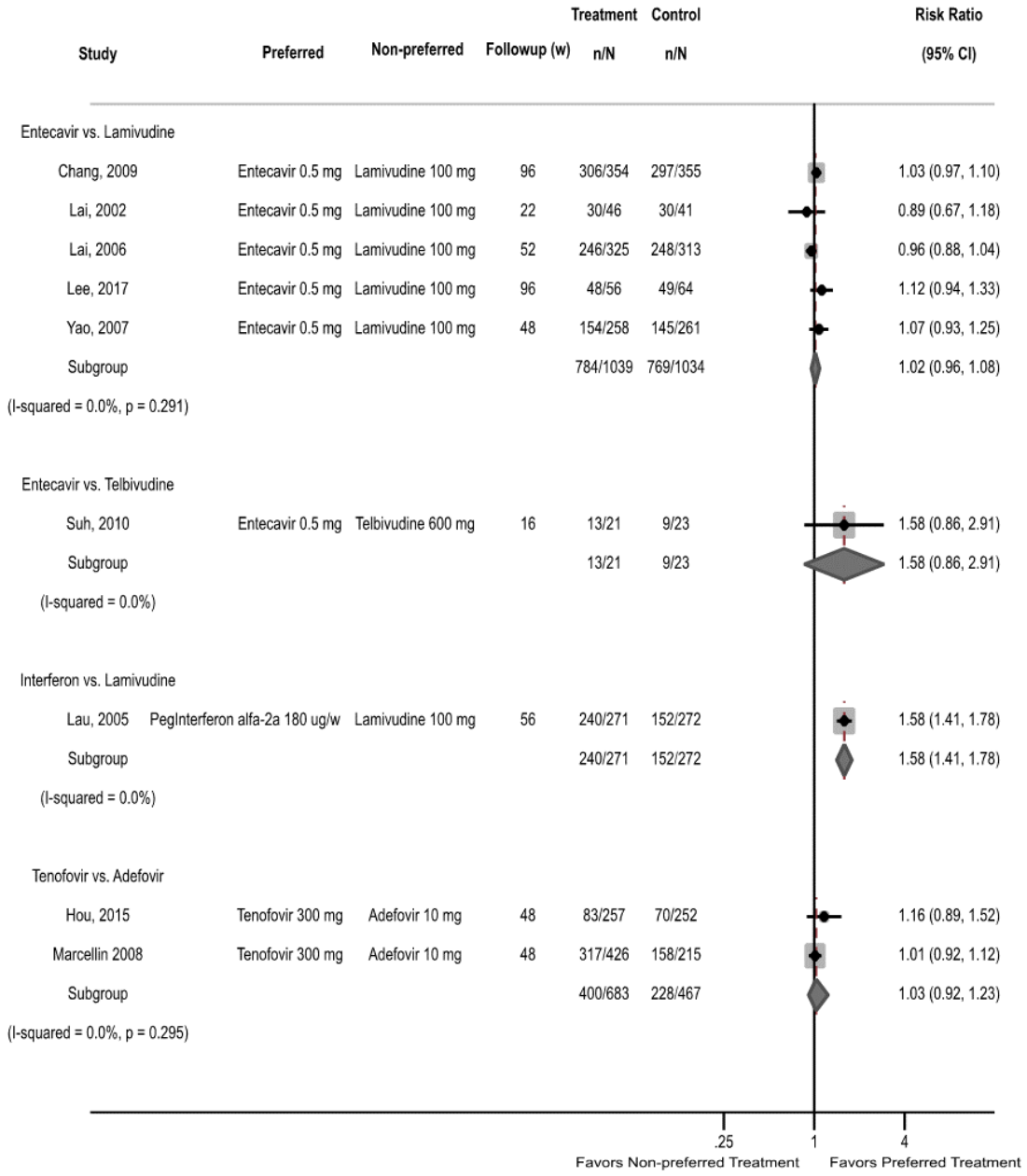


Table 1. Interpretation of Screening Tests for HBV Infection

Screening Test Results			Interpretation	Management	Vaccinate?
HBsAg	Anti-HBc	Anti-HBs			
+	+	-	Chronic HBV infection	Additional testing and management needed	No
-	+	+	Past HBV infection, resolved	No further management unless immunocompromised or undergoing chemotherapy or immunosuppressive therapy	No
-	+	-	Past HBV infection, resolved or false-positive ("isolated anti-HBc"*)	HBV DNA testing if immunocompromised patient	Yes, if not from area of intermediate or high endemicity
-	-	+	Immune due to HBV vaccination	No further testing	No
-	-	-	Uninfected and not immune	No further testing	Yes

Source: American Association for the Study of Liver Diseases 2018.[8]
*May be seen in persons with HIV infection coinfected with hepatitis C virus infection.[167]

Abbreviations: anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to HBsAg; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

Table 2. HBV Screening Recommendations From the CDC and AASLD

Risk factor	Chronic HBV prevalence	AASLD, 2018[8]	ACP/CDC, 2017[59]
Persons born in region with ≥2% HBV prevalence	4.5% to 10.3%	✓	✓
Men who have sex with men	1.1% to 2.3% (7% for persons with HIV)	✓	✓
U.S. born persons, not vaccinated as infant, parent born in region with ≥8% HBV prevalence	Not available	✓	-
Persons who inject drugs	3% to 20%	✓	✓
Persons with HIV	6% to 14%	✓	✓
Household contact or sexual partner of person with HBV infection	3% to 20%	✓	✓
Inmates of correctional facilities	1% to 3.7%	✓	✓
Persons with hepatitis C virus infection	1.4%	✓	✓
Multiple sexual partners or seeking evaluation or treatment for sexually transmitted infections	Not available	✓	-
Unvaccinated persons with diabetes, ages 19 to 59 years	<1%	✓	-
Persons with end-stage renal disease	2.8%	✓	✓

Abbreviations: AASLD = American Association for the Study of Liver Diseases; ACP = American College of Physicians; CDC = Centers for Disease Control and Prevention; HBV = hepatitis B virus.

Table 3. HBV Treatment Recommendations From the AASLD

Category	Drug	Dose in Adults*	Use in Children*
Preferred	Peg-IFN-α-2a (adult) IFN-a-2b (children)	180 mcg weekly	≥1 year dose: 6 million IU/m^2 3 times weekly†
	Entecavir	0.5 mg daily	≥2 years dose: weight-based to 10 to 30 kg; above 30 kg: 0.5 mg daily‡
	Tenofovir dipovoxil fumarate	300 mg daily	≥12 years
	Tenofovir alafenamide	25 mg daily	-
Nonpreferred	Lamivudine	100 mg daily	≥2 years dose: 3 mg/kg daily to max 100 mg
	Adefovir	10 mg daily	≥12 years
	Telbivudine	600 mg daily	-

Source: American Association for the Study of Liver Diseases.[8]
*****Dose adjustments are needed in patients with renal dysfunction.
†Peg-IFN-α-2a is not approved for children with chronic HBV, 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 is 1 mg daily if the patient is lamivudine experienced or if they have decompensated cirrhosis.

Abbreviations: AASLD = American Association for the Study of Liver Diseases; HBV = hepatitis B virus; IFN = interferon.

Table 4. Antiviral Treatment vs. Placebo or No Treatment on Intermediate Outcomes - Subgroup Analyses

Intermediate outcome Subgroup analysis	Number of trials*	Relative risk (95% CI)	I^2	$P_{Interaction}$
HBeAg loss				
Geographic region: • Low-prevalence (US, Canada, Europe, Australia, etc.)	3	1.59 (1.20 to 2.10)	0%	0.16
• High-prevalence (Asia)	1	1.52 (0.60 to 3.89)	--	--
• Mixed prevalence/other	2	2.46 (1.61 to 3.78)	0%	--
Treatment status: • Naive	2	2.94 (1.07 to 8.09)	0%	0.28
• Naïve and non-naive/NR	5	1.74 (1.38 to 2.20)	0%	--
Followup duration: • <52 weeks	2	2.07 (1.31 to 3.26)	0%	1.00
• ≥52 weeks	5	1.71 (1.32 to 2.22)	0%	--
Drug: • Adefovir dipivoxil	1	2.27 (1.35 to 3.83)	0%	0.44
• Interferon alpha-2a	2	2.61 (1.15 to 5.47)	0%	--
• Interferon alpha-2b	1	1.48 (1.10 to 2.00)	0%	--
• Lamivudine	2	2.06 (0.94 to 4.93)	0%	--
DNA loss				
Geographic region: • Low-prevalence (US, Canada, Europe, Australia, etc.)	4	2.32 (1.39 to 4.10)	62%	0.000
• High-prevalence (Asia)	5	7.06 (3.42 TO 15.93)	72%	--
• Mixed prevalence/other	4	2.09 (0.22 TO 164.21)	0%	--
HBeAg • Negative	1	63.50 (4.00 to 1009.28)	NA	0.001
• Positive, mixed, or not reported	12	4.01 (2.43 to 7.19)	84%	--
Treatment status: • Naive	2	2.78 (1.08 to 6.92)	0%	1.00
• Naïve and non-naive/NR	11	4.77 (2.66 to 10.34)	88%	--
Followup duration: • <52 weeks	4	5.65 (3.14 to 48.75)	36%	0.000
• ≥52 weeks	9	3.50 (1.88 to 6.94)	85%	--
Immune tolerant: • Yes	2	8.81 (0.75 to 103.94)	39%	0.13
• No	11	4.17 (2.46 to 7.97)	88%	--
Drug: • Adefovir dipivoxil	3	19.22 (10.98 to 33.67)	0%	0.000
• Entecavir	1	31.50 (2.02 to 492.36)	0%	--
• Interferon alpha-2a	2	1.88 (1.25 to 2.82)	0%	--
• Interferon alpha-2b	1	1.36 (0.96 to 1.92)	0%	--
• Lamivudine	6	3.98 (3.07 to 5.17)	12.5%	--

Table 4. Antiviral Treatment vs. Placebo or No Treatment on Intermediate Outcomes - Subgroup Analyses

Intermediate outcome Subgroup analysis	Number of trials*	Relative risk (95% CI)	I^2	$P_{Interaction}$
ALT normalization				
Geographic region: • Low-prevalence (US, Canada, Europe, Australia, etc.)	3	2.76 (1.44 to 5.27)	52%	1.00
• High-prevalence (Asia)	5	2.60 (2.07 to 3.26)	15%	--
• Mixed prevalence/other	3	2.73 (2.08 to 3.58)	0%	--
HBeAg • Negative	1	2.51 (1.66 to 3.81)	0%	0.88
• Positive, mixed, or not reported	10	2.64 (2.22 to 3.14)	7%	--
Treatment status: • Naive	2	3.53 (1.37 to 9.12)	50%	0.32
• Naïve and non-naive/NR	9	2.58 (2.20 to 3.02)	0%	--
Followup duration: • <52 weeks	3	2.61 (2.05 to 3.33)	0%	1.00
• ≥52 weeks	8	2.64 (2.10 to 3.31)	18%	--
Drug: • Adefovir dipivoxil	3	3.04 (2.32 to 3.96)	0%	0.38
• Interferon alpha-2a	2	2.44 (1.29 to 4.62)	0%	--
• Interferon alpha-2b	1	1.88 (1.10 to 3.20)	0%	--
• Lamivudine	5	2.43 (1.90 to 3.39)	%	--

*Trials with poolable data.

Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; DNA = deoxyribonucleic acid; HbeAg = antibody to hepatitis B e-antigen; NR = not reported.

Table 5. Entecavir vs. Lamivudine on Intermediate Outcomes – Subgroup Analyses

Intermediate outcome Subgroup analysis	Number of trials*	Relative risk (95% CI)	I^2	$P_{Interaction}$
ALT normalization				
HBeAg: • Excluded	1	1.70 (1.31 to 2.19)	--	0.035
• Not excluded	5	1.12 (1.07 to 1.17)	0%	--
Followup duration: • <52 weeks	3	1.15 (1.04 to 1.27)	0%	0.72
• ≥52 weeks	3	1.12 (0.90 to 1.77)	0%	--
DNA loss				
HBeAg: • Excluded	1	1.95 (1.51 to 2.54)	--	0.60
• Not excluded	5	1.66 (1.28 to 2.16)	0%	--
Followup duration: • <52 weeks	3	1.77 (1.42 to 2.18)	0%	0.92
• ≥52 weeks	3	1.69 (1.17 to 2.50)	91%	--

*Trials with poolable data.
Note: RR>1.00 favored entecavir.

Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; DNA = deoxyribonucleic acid; HBeAg = antibody to hepatitis B e-antigen.

Table 6. Associations Between Intermediate Outcomes and Health Outcomes

Intermediate Outcomes	Health Outcomes			
	Cirrhosis	Death	HCC	Composite Outcome
ALT normalization	-	-	-	1 study Death or liver transplantation aHR, 0.48 (95% CI, 0.23 to 1.0)*[115] Severe clinical complications (death, liver decompensation [ascites, variceal bleeding, hepatic encephalopathy], and HCC) aHR 0.53 (95% CI, 0.29 to 0.91)*[115]
Composite intermediate outcome (Sustained loss of HBV DNA and clearance of HBeAg within 1 year of starting treatment)[113]	-	1 study aHR, 0.59 (95% CI, 0.20 to 1.67)[113]	-	1 study Death or liver-related complication (variceal hemorrhage, ascites, encephalopathy): aHR, 0.07 (95% CI, 0.02 to 0.33)[113]
HBeAg loss	-	-	-	1 study Liver complications (death; need for liver transplantation; development of ascites, jaundice, or hepatic encephalopathy; occurrence of or bleeding from esophageal varices): aHR, 0.06 (95% CI, 0.01 to 0.61)[114]
HBeAg seroconversion	1 study aHR 0.41 (95% CI, 0.32 to 0.88)[118]	-	1 study aHR 0.13 (95% CI, 0.08 to 0.57)[118]	-
Histological response	-	-	-	1 study Liver complications (HBV-related decompensated liver cirrhosis or HCC): aHR, 0.62 (95% CI, 0.06 to 6.9)[112]
Virological response	-	-	3 studies aHR, 0.77 (95% CI, 0.35 to 1.69)*[116] aHR 0.87 (95% CI, 0.17 to 4.58)[117] aHR 0.3 (95% CI 0.1, to 0.6)[119]	2 studies Death or disease complication (not defined): aHR, 0.24 (95% CI, 0.06 to 0.96)*[111] Clinical event (composite endpoint of development of HCC, liver decompensation, or death): aHR 0.70 (95% CI, 0.28 to 1.77)[117]

- = No studies examined the association.
*Study performed in HBeAg-negative patients.
Note: Studies examined association of achieving intermediate outcomes and decreased risk of health outcomes.

Abbreviations: aHR = adjusted hazard ratio; ALT = alanine aminotransferase; CI = confidence interval; DNA = deoxyribonucleic acid; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma.

Table 7. Summary of Evidence

Key Question	Studies Observations (N) Study designs	Summary of Findings	Consistency and Precision	Other Limitations	EPC Assessment of Strength of evidence	Applicability
1. What are the benefits of **screening** for HBV infection in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?	No studies	No evidence	N/A	No studies	No evidence	N/A
2. What are the **harms** of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults (e.g., labeling or anxiety)?	No studies	No evidence	N/A	No studies	No evidence	N/A
3. What is the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV **screening strategies** (e.g., universal vs. targeted screening or screening strategies based on alternative risk factors)?	Prior report: 1 retrospective study[120] (N=6,194) Update: 2 retrospective studies[121,122] (N=24,846)	Three European studies found that screening strategies that targeted persons with a variety of risk factors (immigration from high prevalence risk factors, other demographic risk factors, and behavioral risk factors) would identify nearly all cases of HBV infection while screening about two-thirds of the population; numbers needed to screen to identify one HBV infection ranged from 32 to 148. Screening only immigrants from high prevalence (≥2%) countries was more efficient (number needed to screen 19 to 71) and identified 85% to 99% of patients with HBV infection in higher prevalence clinical settings, but missed about two-thirds of HBV infections in a study conducted in primary care practices.	Consistent Precise	Studies applied screening strategies retrospectively	Moderate	Some studies included patients in high-prevalence settings; all studies were conducted in Europe

Table 7. Summary of Evidence

Key Question	Studies Observations (N) Study designs	Summary of Findings	Consistency and Precision	Other Limitations	EPC Assessment of Strength of evidence	Applicability
4. How effective is antiviral treatment in improving **intermediate outcomes** among nonpregnant adolescents and adults with chronic HBV infection, including virologic or histologic improvement, clearance of HBeAg (as indicated by loss of HBeAg or acquisition of the anti-HBe), or clearance of HBsAg (as indicated by loss of HBsAg or acquisition of anti-HBs)?	*Treatment vs. placebo/no treatment* Prior report: 14 trials[74-87] (N=2,148) Update: 4 trials[88-91] (N=824) *Preferred vs. nonpreferred* Prior report: 7 trials[92-97] (N=2,793) Update: 5 trials[98-102] (N=1,334)	Antiviral treatment vs. placebo or no treatment: • HBeAg loss: 6 trials, N=1,121, RR 1.91, 95% CI 1.46 to 2.81, I^2=15%) • HBeAg seroconversion: 4 trials, N=1,104, RR 2.11, 95% CI 1.30 to 3.55, I^2=0%) • HBsAg loss: 3 trials, N=714, RR 4.63, 95% CI 1.10 to 19.55, I^2=70%) • Virological suppression: 13 trials, N=2,522, RR 4.39, 95% CI 2.61 to 7.39, I^2=86%) • ALT normalization: 11 trials, N=2,044, RR 2.62, 95% CI 2.22 to 3.10, I^2=0% • Histological improvement: 6 trials, N =1,057, RR 2.00, 95% CI 1.63 to 2.41, I^2=0% Entecavir was associated with increased likelihood of achieving intermediate outcomes vs. lamivudine (6 trials) and pegylated interferon associated with increased likelihood of intermediate outcomes vs. lamivudine (1 trial); TDF was associated with increased likelihood of virological suppression vs. adefovir (3 trials)	Consistency was high for antiviral therapies and for entecavir vs. lamivudine and TDF vs. adefovir; it could not be assessed for pegylated interferon vs. lamivudine (1 trial) Precision was high for antiviral therapy vs. placebo and entecavir vs. lamivudine; some imprecision for TDF vs. adefovir and pegylated interferon vs. lamivudine	Study duration and patient characteristics varied widely; few good quality studies; almost all placebo-controlled trials evaluated nonpreferred antiviral therapies; no trials of tenofovir alafenamide	Moderate for antiviral therapy vs. placebo, entecavir vs. lamivudine, and pegylated interferon vs. adefovir; low for TDF vs. adefovir	About half the studies conducted outside of the U.S. or other low prevalence settings; about one-third enrolled HBeAg-negative patients; no trial enrolled adolescents; inclusion restricted to studies in which <20% of patients had cirrhosis at baseline or were treatment-experienced

Table 7. Summary of Evidence

Key Question	Studies Observations (N) Study designs	Summary of Findings	Consistency and Precision	Other Limitations	EPC Assessment of Strength of evidence	Applicability
5. How effective is antiviral treatment in improving **health outcomes** among nonpregnant adolescents and adults with chronic HBV infection?	*Treatment vs. placebo/no treatment* Prior report: 6 trials[75,76,78,80,81,83] (N=866) Update: 1 RCT[89] (N=176) and 7 cohort studies[103-109] (N=~50,912; 3 studies likely examined overlapping populations) *Preferred vs. nonpreferred* Prior report: 6 trials[92,93,95-97] (N=2,608) Update: 3 trials[98,99,101] (N=1,159)	Antiviral therapy vs. placebo or no treatment: Incident cirrhosis: 2 trials; RR, 0.72; 95% CI, 0.29 to 1.77; I^2=0% Hepatocellular carcinoma: 4 trials; RR, 0.60; 95% CI, 0.16 to 2.33; I^2=20% Mortality: 3 trials; RR, 0.15; 95% CI, 0.03 to 0.69; I^2=0%) Seven cohort studies with longer-term (2.7 to 8.9 years) followup found antiviral therapy consistently associated with decreased risk of hepatocellular carcinoma vs. no antiviral therapy (adjusted HRs ranged from 0.24 to 0.64) Data from head-to-head trials of preferred vs. nonpreferred antiviral therapy were insufficient to evaluate effects on clinical outcomes	Consistent Some imprecision (RCTs)	RCTs were not designed to assess clinical outcomes and reported few events; most studies rated fair-quality, heterogeneity in patient populations and settings; observational studies for long-term clinical outcomes susceptible to residual confounding	Low	About half the studies conducted outside of the U.S. or other low-prevalence settings; about one-third of studies enrolled HBeAg-negative patients; inclusion restricted to studies in which <20% of patients had cirrhosis at baseline or were treatment-experienced; most studies evaluated nonpreferred outcomes

Table 7. Summary of Evidence

Key Question	Studies Observations (N) Study designs	Summary of Findings	Consistency and Precision	Other Limitations	EPC Assessment of Strength of evidence	Applicability
6. What are the **harms** associated with antiviral treatment in nonpregnant adolescents and adults with chronic HBV infection?	*Treatment vs. placebo/no treatment* Prior report: 10 trials[75-80,82,85-87] (N=1,851) Update: 2 RCTs[88,89] (N=255) and 1 cohort study[110] (N=1,224) *Preferred vs. nonpreferred* Prior report: 7 trials[92-97] (N=2,774) Update: 5 trials[98-102] (N=1,334)	Antiviral therapy vs. placebo or no therapy: • Serious adverse events: 4 trials, N=802, RR 0.92, 95% CI 0.45 to 1.85, I^2=0%[75,77,78,85] • Withdrawal due to adverse events: 3 trials, N=496, RR 4.44, 95% CI 0.95 to 20.77, I^2=0%[80,82,85] • Any adverse event: 5 trials, N=1,290, RR 1.01, 95% CI 0.90 to 1.11, I^2=0% • Nausea: 3 trials, RR 0.80, 95% CI 0.48 to 2.10, I^2=0% • Diarrhea: 4 trials, RR 1.50, 95% CI 0.87 to 2.46, I^2=0% • Kidney adverse events: 3 trials, RR 1.27, 95% CI 0.31 to 3.55, I^2=0%[75,76,78] One cohort study found no association between TDF or entecavir versus no antiviral therapy and risk of osteopenia or osteoporosis In head-to-head trials, pegylated interferon was associated with increased risk of any adverse event (1 trial, N=543, RR 1.58, 95% CI 1.41 to 1.78) vs. lamivudine and is probably associated with increased risk of withdrawal due to adverse events (1 trial, N=543, RR 4.01, 95% CI 0.86 to 18.73).[95] TDF was associated with increased risk of nausea vs. adefovir (RR 3.36, 95% CI 1.45 to 7.81).	Consistency was high. Some imprecision present	See Key Question 4. In addition, no study evaluated tenofovir alafenamide, which may be associated with fewer kidney adverse effects	Moderate	See Key Question 4.

Table 7. Summary of Evidence

Key Question	Studies Observations (N) Study designs	Summary of Findings	Consistency and Precision	Other Limitations	EPC Assessment of Strength of evidence	Applicability
7. What is the **association** between improvements in intermediate outcomes as a result of antiviral treatment of chronic HBV infection and reduction in risk of HBV-related adverse health outcomes?	Prior report: 6 observational studies[111-116] (N=1,385) Update: 3 observational studies[117-119] (N=2,508)	Nine cohort studies found consistent associations between achieving or not achieving various intermediate outcomes (virological remission, biochemical remission, histological improvement, HBeAg loss, or a composite intermediate outcome) and decreased adverse health outcomes (death, hepatocellular carcinoma, cirrhosis, or a composite clinical outcome). However, variability in patient populations, the intermediate and clinical outcomes evaluated, and presence of methodological limitations make it difficult to draw strong conclusions. In some studies, estimates were imprecise and associations were not statistically significant.	Consistency was high. Some imprecision in individual study estimates	High variability in patient characteristics and outcomes evaluated; all studies were rated fair-quality; all studies were observational studies and susceptible to residual confounding	Moderate	Inclusion restricted to studies that adjusted for baseline fibrosis stage and fewer than 30% of patients had cirrhosis at baseline; most studies conducted in Asia (though U.S. studies reported consistent findings); few studies focused on use of current preferred antiviral therapies

Abbreviations: ALT = alanine aminotransferase; anti-HBe = antibody to HBeAg; anti-HBs = hepatitis B surface antibody; CI = confidence interval; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HR = hazard ratio; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; TDF = tenofovir disoproxil fumarate; U.S. = United States.

Appendix A1. Search Strategies

Key Questions 1-2

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

1. exp Hepatitis B/
2. exp Hepatitis B Antigens/
3. Hepatitis B virus/
4. ("hepatitis b" or hbv).ti,ab,kf.
5. or/1-4
6. Mass Screening/
7. screen*.ti,ab,kf.
8. 6 or 7
9. 5 and 8
10. exp cohort studies/
11. cohort$.tw.
12. controlled clinical trial.pt.
13. epidemiologic methods/
14. limit 13 to yr=1966-1989
15. exp case-control studies/
16. (case$ and control$).tw.
17. or/10-12,14-16
18. randomized controlled trial.pt.
19. (random* or placebo* or control* or trial or blind*).ti,ab.
20. (animals not humans).sh.
21. (comment or editorial or meta-analysis or practice-guideline or review or letter).pt.
22. (18 or 19) not (20 or 21)
23. review.pt.
24. (medline or medlars or embase or pubmed or cochrane).tw,sh.
25. (scisearch or psychinfo or psycinfo).tw,sh.
26. (psychlit or psyclit).tw,sh.
27. cinahl.tw,sh.
28. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
29. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
30. (pooling or pooled or mantel haenszel).tw,sh.
31. (peto or dersimonian or der simonian or fixed effect).tw,sh.
32. or/24-31
33. 23 and 32
34. meta-analysis.pt.
35. meta-analysis.sh.
36. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
37. (systematic$ adj5 review$).tw,sh.
38. (systematic$ adj5 overview$).tw,sh.
39. (quantitativ$ adj5 review$).tw,sh.
40. (quantitativ$ adj5 overview$).tw,sh.
41. (quantitativ$ adj5 synthesis$).tw,sh.
42. (methodologic$ adj5 review$).tw,sh.
43. (methodologic$ adj5 overview$).tw,sh.
44. (integrative research review$ or research integration).tw.
45. or/34-44
46. 33 or 45
47. 17 or 22 or 46
48. 9 and 47
49. (2013 jul $ or 2013 aug $ or 2013 sep $ or 2013 oct $ or 2013 nov $ or 2013 dec $).dp.
50. ("2013 07 $" or "2013 08 $" or "2013 09 $" or 2013 10 $ or 2013 11 $ or 2013 12 $).dp.
51. 48 and (49 or 50)

52. limit 48 to yr="2014 - 2019"
53. 51 or 52
54. limit 53 to english language

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1. exp Hepatitis B/
2. exp Hepatitis B Antigens/
3. Hepatitis B virus/
4. ("hepatitis b" or hbv).ti,ab,kf.
5. or/1-4
6. Mass Screening/
7. screen*.ti,ab,kf.
8. 6 or 7
9. 5 and 8
10. limit 9 to yr="2013 - 2019"

Key Question 3

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
1. exp Hepatitis B/
2. Hepatitis B virus/
3. ("hepatitis b" or hbv).ti,ab,kf.
4. mass screening/
5. screen*.ti,ab,kf.
6. exp "Sensitivity and Specificity"/
7. (accuracy or sensitivity or specificity).ti,ab,kf.
8. (screen* adj5 (strateg* or method* or algorithm* or risk)).ti,ab,kf.
9. (1 or 2 or 3) and (4 or 5) and (6 or 7 or 8)
10. (2013 jul $ or 2013 aug $ or 2013 sep $ or 2013 oct $ or 2013 nov $ or 2013 dec $).dp.
11. ("2013 07 $" or "2013 08 $" or "2013 09 $" or 2013 10 $ or 2013 11 $ or 2013 12 $).dp.
12. 9 and (10 or 11)
13. limit 9 to yr="2014 - 2019"
14. limit 13 to english language

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1. exp Hepatitis B/
2. Hepatitis B virus/
3. ("hepatitis b" or hbv).ti,ab,kf.
4. mass screening/
5. screen*.ti,ab,kf.
6. exp "Sensitivity and Specificity"/
7. (accuracy or sensitivity or specificity).ti,ab,kf.
8. (screen* adj5 (strateg* or method* or algorithm* or risk)).ti,ab,kf.
9. (1 or 2 or 3) and (4 or 5) and (6 or 7 or 8)
10. limit 9 to yr="2013 - 2019"

Key Questions 4-6

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
1. exp Hepatitis B/dt, pc, th [Drug Therapy, Prevention & Control, Therapy]
2. Hepatitis B virus/de [Drug Effects]
3. ("hepatitis b" or hbv).ti,ab,kf.

Appendix A1. Search Strategies

4. (interferon or "alfa 2a" or "alfa 2b" or entecavir or tenofovir or lamivudine or adefovir or telbivudine).ti,ab,kf,hw.
5. 1 or 2
6. 4 and
7. 3 and 4
8. 6 or 7
9. Treatment Outcome/
10. limit 8 to "therapy (best balance of sensitivity and specificity)"
11. (8 and 9) or 10
12. exp cohort studies/
13. cohort$.tw.
14. controlled clinical trial.pt.
15. epidemiologic methods/
16. limit 15 to yr=1966-1989
17. exp case-control studies/
18. (case$ and control$).tw.
19. or/12-14,16-18
20. randomized controlled trial.pt.
21. (random* or placebo* or control* or trial or blind*).ti,ab.
22. (animals not humans).sh.
23. (comment or editorial or meta-analysis or practice-guideline or review or letter).pt.
24. (20 or 21) not (22 or 23)
25. review.pt.
26. (medline or medlars or embase or pubmed or cochrane).tw,sh.
27. (scisearch or psychinfo or psycinfo).tw,sh.
28. (psychlit or psyclit).tw,sh.
29. cinahl.tw,sh.
30. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
31. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
32. (pooling or pooled or mantel haenszel).tw,sh.
33. (peto or dersimonian or der simonian or fixed effect).tw,sh.
34. or/26-33
35. 25 and 34
36. meta-analysis.pt.
37. meta-analysis.sh.
38. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
39. (systematic$ adj5 review$).tw,sh.
40. (systematic$ adj5 overview$).tw,sh.
41. (quantitativ$ adj5 review$).tw,sh.
42. (quantitativ$ adj5 overview$).tw,sh.
43. (quantitativ$ adj5 synthesis$).tw,sh.
44. (methodologic$ adj5 review$).tw,sh.
45. (methodologic$ adj5 overview$).tw,sh.
46. (integrative research review$ or research integration).tw.
47. or/36-46
48. 35 or 47
49. 19 or 24 or 48
50. 8 and 49
51. 10 or 11 or 50
52. limit 51 to english language
53. (2013 jul $ or 2013 aug $ or 2013 sep $ or 2013 oct $ or 2013 nov $ or 2013 dec $).dp.
54. ("2013 07 $" or "2013 08 $" or "2013 09 $" or 2013 10 $ or 2013 11 $ or 2013 12 $).dp.
55. 52 and (53 or 54)
56. limit 52 to yr="2014 - 2019"
57. 55 or 56

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1. exp Hepatitis B/
2. Hepatitis B virus/
3. ("hepatitis b" or hbv).ti,ab.
4. 1 or 2 or 3
5. (interferon or "alfa 2a" or "alfa 2b" or entecavir or tenofovir or lamivudine or adefovir or telbivudine).ti,ab.
6. 4 and 5
7. limit 6 to english language
8. limit 7 to yr="2013 - 2019"
9. limit 7 to medline records
10. 8 not 9

Key Question 7

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
1. ("hepatitis b" or hbv).ti,ab,kf.
2. (mortality or cirrhosis or "hepatocellular cancer" or "hepatocellular carcinoma" or "quality of life" or extrahepatic).ti,ab,kf.
3. transmission.ti,ab,kf.
4. 1 and (2 or 3)
5. 4 and (association or relation* or clinical or outcome*).ti,ab,kf.
6. limit 5 to english language
7. (2013 jul $ or 2013 aug $ or 2013 sep $ or 2013 oct $ or 2013 nov $ or 2013 dec $).dp.
8. ("2013 07 $" or "2013 08 $" or "2013 09 $" or 2013 10 $ or 2013 11 $ or 2013 12 $).dp.
9. 6 and (7 or 8)
10. limit 6 to yr="2014 - 2019"
11. 9 or 10

Database: Ovid MEDLINE(R)
1. exp Hepatitis B/
2. exp Hepatitis B Antigens/
3. Hepatitis B virus/
4. ("hepatitis b" or hbv).ti,ab,kf.
5. or/1-4
6. disease-free survival/ or treatment outcome/
7. exp survival analysis/
8. (mortality or cirrhosis or "hepatocellular cancer" or "hepatocellular carcinoma" or "quality of life" or extrahepatic).ti,ab,kf,hw.
9. Carcinoma, Hepatocellular/
10. transmission.ti,ab.
11. tm.fs.
12. 5 and (6 or 7)
13. 12 and (8 or 9 or 10 or 11)
14. (2013 jul $ or 2013 aug $ or 2013 sep $ or 2013 oct $ or 2013 nov $ or 2013 dec $).dp.
15. ("2013 07 $" or "2013 08 $" or "2013 09 $" or 2013 10 $ or 2013 11 $ or 2013 12 $).dp.
16. limit 13 to yr="2014 - 2019"
17. 15 or 16
18. limit 17 to english language
19. 18 not (case series or case reports or editorial or comment).pt.

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1. exp Hepatitis B/
2. exp Hepatitis B Antigens/
3. Hepatitis B virus/
4. ("hepatitis b" or hbv).ti,ab,kf.

5. or/1-4
6. disease-free survival/ or treatment outcome/
7. exp survival analysis/
8. (mortality or cirrhosis or "hepatocellular cancer" or "hepatocellular carcinoma" or "quality of life" or extrahepatic).ti,ab,kf,hw.
9. Carcinoma, Hepatocellular/
10. transmission.ti,ab.
11. tm.fs.
12. 5 and (6 or 7 or 8 or 9 or 10 or 11)
13. limit 12 to yr="2013 - 2019"
14. limit 12 to medline records
15. 13 not 14

All Key Questions

Database: EBM Reviews - Cochrane Database of Systematic Reviews

1. ("hepatitis b" or hbv).ti.
2. limit 1 to full systematic reviews
3. limit 1 to full systematic reviews

Appendix A2. Inclusion and Exclusion Criteria

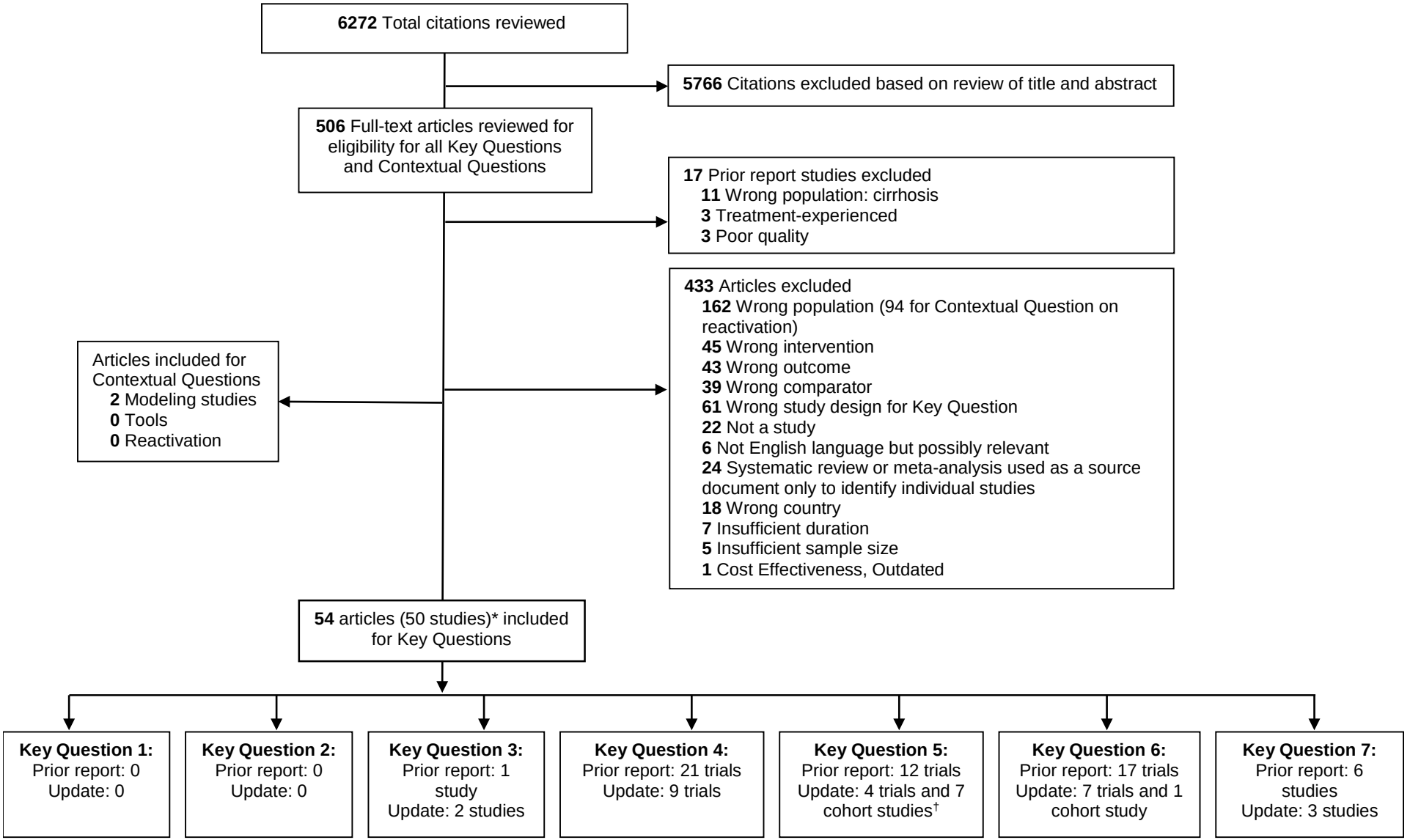
	Included	Excluded
Definition of Disease	Chronic HBV infection, defined as detectable HBsAg in blood for >6 months	Acute HBV infection
Populations	**KQs 1–3:** Nonpregnant adolescents (ages 13 to <18 years) and adults (age ≥18 years) with no signs or symptoms of HBV infection **KQs 4–7:** Nonpregnant adolescents and adults with chronic HBV infection	**KQs 1–3:** Symptomatic patients, children age <13 years, pregnant women, persons living with HIV or hepatitis C virus infection, persons who have been previously treated for HBV infection, and other special populations (e.g., persons undergoing hemodialysis or an organ transplant)
Interventions	**KQs 1–3:** Screening, including alternative screening strategies (KQ 3) **KQs 4–7:** Antiviral treatments approved by the FDA for patients who have never been treated for HBV infection. Therapies will be classified as: • **Preferred:** Pegylated interferon (adults), nonpegylated interferon (adolescents ages 13 to 17 years), entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide • **Nonpreferred:** Lamivudine, adefovir, and telbivudine	**KQs 4–7:** Antiviral treatments not approved by the FDA; combination therapy
Comparators	**KQs 1, 2:** No screening **KQ 3:** One screening strategy vs. an alternative screening strategy **KQs 4–6:** No treatment; preferred vs. nonpreferred antiviral therapies **KQ 7:** Effects on intermediate outcomes (HBV DNA level, HBeAg status, HBsAg status, alanine aminotransferase level, fibrosis) as a result of antiviral therapy vs. no effects on intermediate outcomes	
Outcomes	**KQs 1, 5, 7:** • Mortality • Cirrhosis • Hepatocellular cancer • Quality of life • Disease transmission • Extrahepatic outcomes (e.g., polyarteritis nodosa, membranous nephropathy, membranoproliferative glomerulonephritis) **KQ 2:** Labeling, anxiety, and stigma **KQ 3:** Yield (number of new diagnoses per number of persons screened) and sensitivity (number of diagnoses of HBV infection per number of total HBV diagnoses) **KQ 4:** • Virologic improvement • Histologic improvement • HBeAg clearance (loss of HBeAg or acquisition of anti-HBe) • HBsAg clearance (loss of HBsAg or acquisition of anti-HBs) **KQ 6:** • Harms of antiviral medications • Withdrawals due to adverse events • Serious adverse events	**KQ 4:** Drug resistance; development of virus mutations or antibodies to drugs
Setting	**All KQs:** Primary care and primary care–referable settings (e.g., correctional settings, community care settings serving persons who inject drugs, men who have sex with men, or persons with sexually transmitted diseases) **KQs 1–3:** United States and countries with similar HBV prevalence **KQs 4–7:** All countries	

Appendix A2. Inclusion and Exclusion Criteria

	Included	Excluded
Study Designs	**KQs 1–3:** Randomized, controlled trials; cohort studies; and case-control studies; cross-sectional studies (KQ 3 only) **KQs 4–6:** Randomized, placebo-controlled trials; head-to-head trials of preferred vs. nonpreferred antiviral therapies approved by the FDA **KQ 5:** Cohort studies for long-term (>5 years) clinical outcomes that report adjusted risk estimates **KQ 6**: All of the above study designs, plus cohort studies of harms not adequately evaluated in randomized trials **KQ 7:** Cohort studies examining the association between intermediate and clinical outcomes after antiviral treatment that report adjusted risk estimates	**KQs 1–3:** Uncontrolled studies (e.g., case studies, treatment series)

Abbreviations: anti-HBe = antibody to the hepatitis B e-antigen; anti-HBs = hepatitis B surface antibody; DNA = deoxyribonucleic acid; FDA = U.S. Food and Drug Administration; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; KQ = key question.

Appendix A3. Literature Flow Diagram



*Some included studies overlap among the Key Questions.
†Some cohort studies included overlapping populations from the same database.

Appendix A4. Included Studies

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Appendix A5. Excluded Studies with Reasons for Exclusion

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Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis b infection. *J Hepatol*. 2015;62(3):533-40. doi: 10.1016/j.jhep.2014.10.035. PMID: 25450717. Excluded: wrong comparator.

Aggeletopoulou I, Davoulou P, Konstantakis C, et al. Response to hepatitis B vaccination in patients with liver cirrhosis. *Rev Med Virol*. 2017;27(6):11. doi: 10.1002/rmv.1942. PMID: 28905444. Excluded: wrong intervention: vaccine.

Aghoram R, Cai P, Dickinson JA. Alpha-foetoprotein and/or liver ultrasonography for screening of hepatocellular carcinoma in patients with chronic hepatitis B. *Cochrane Database Syst Rev*. 2012 (9) PMID: 22972059. Excluded: wrong intervention.

Ajayi T, Luu H, Saberi B, et al. Role of nucleoside/nucleotide analogues and low-dose hepatitis B immune globulin in prophylaxis of hepatitis B recurrence among cadaveric liver transplant recipients. *Turk J Gastroenterol*. 2018;29(1):61-6. doi: 10.5152/tjg.2018.17595. PMID: 29391309. Excluded: wrong population – excluded for reactivation CQ.

Akuta N, Suzuki F, Suzuki Y, et al. Favorable efficacy of long-term lamivudine therapy in patients with chronic hepatitis B: an 8-year follow-up study. *J Med Virol*. 2005;75(4):491-8. doi: 10.1002/jmv.20305. PMID: 15714490. Excluded: wrong population.

Alavian SM, Haghbin H. Relative importance of hepatitis b and c viruses in hepatocellular carcinoma in EMRO countries and the middle east: a systematic review. *Hepat Mon*. 2016;16(3):e35106. doi: 10.5812/hepatmon.35106. PMID: 27226803. Excluded: wrong outcome.

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Ali HY. Trial of lamivudine in hepatitis B surface antigen carriers with persistent hepatitis B core IgM antibody. *Saudi Med J*. 2003;24(9):996-9. PMID: 19746176. Excluded: poor quality.

Aljumah AA, Bin Selayem NA, Al-Howti SY, et al. Clinical and virological outcomes of entecavir therapy in patients with chronic hepatitis B: a real life experience. *J Infect Chemother*. 2019;25(1):12-6. doi: 10.1016/j.jiac.2018.09.014. PMID: 30366861. Excluded: wrong study design for key question.

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Anderson MG, Harrison TJ, Alexander G, et al. Randomised controlled trial of lymphoblastoid interferon for chronic active hepatitis B. *Gut*. 1987;28(5):619-22. PMID: 3297940. Excluded: wrong population.

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Arends P, Rijckborst V, Zondervan PE, et al. Loss of intrahepatic HBsAg expression predicts sustained response to peginterferon and is reflected by pronounced serum HBsAg decline. *J Viral Hepat*. 2014;21(12):897-904. doi: 10.1111/jvh.12218. PMID: 24444353. Excluded: wrong outcome.

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Armbruster B, Brandeau ML. Cost-effective control of chronic viral diseases: finding the optimal level of screening and contact tracing. *Math Biosci*. 2010;224(1):35-42. doi: 10.1016/j.mbs.2009.12.006. PMID: 20043926. Excluded: wrong outcome.

Atay K, Hatemi I, Canbakan B, et al. Five-year results of oral antiviral therapy in HBeAg-negative chronic hepatitis B. *Turk J Gastroenterol*. 2016;27(3):279-83. doi: 10.5152/tjg.2016.16085. PMID: 27210786. Excluded: wrong study design for key question.

Bakker M, Bunge EM, Marano C, et al. Immunogenicity, effectiveness and safety of combined hepatitis A and B vaccine: a systematic literature review. *Expert Rev Vaccines*. 2016;15(7):829-51. doi: 10.1586/14760584.2016.1150182. PMID: 26840060. Excluded: wrong intervention: vaccine.

Barbosa JR, Cortes VF, Portilho MM, et al. Performance of point of care assays for hepatitis B and C viruses in chronic kidney disease patients. *J Clin Pathol*. 2018;71(10):879-84. doi: 10.1136/jclinpath-2018-205024. PMID: 29730611. Excluded: wrong intervention.

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Buti M, Fung S, Gane E, et al. Long-term clinical outcomes in cirrhotic chronic hepatitis B patients treated with tenofovir disoproxil fumarate for up to 5 years. *Hepatol Int*. 2015;9(2):243-50. doi: 10.1007/s12072-015-9614-4. PMID: 25788199. Excluded: wrong population – cirrhosis.

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Cai Q, Chen K, Chen J, et al. The effect of prophylactic lamivudine plus adefovir therapy compared with lamivudine alone in preventing hepatitis B reactivation in lymphoma patients with high baseline HBV DNA during chemotherapy. *PLoS One*. 2016;11(10):e0164210. doi: 10.1371/journal.pone.0164210. PMID: 27711135. Excluded: wrong population – excluded for reactivation CQ.

Cannizzaro MV, Franceschini C, Esposito M, et al. Hepatitis B reactivation in psoriasis patients treated with anti-TNF agents: prevention and management. *Psoriasis (Aukl).* 2017;7:35-40. doi: 10.2147/PTT.S108209. PMID: 29387606. Excluded: wrong population – excluded for reactivation CQ.

Cannizzo ES, Tincati C, Binda F, et al. Unconventional T cells in chronic hepatitis B patients on long-term suppressive therapy with tenofovir followed by a Peg-IFN add-on strategy: a randomized study. *J Viral Hepat*. 2018;25(4):381-90. doi: 10.1111/jvh.12820. PMID: 29091327. Excluded: wrong intervention.

Cantini F, Boccia S, Goletti D, et al. HBV reactivation in patients treated with antitumor necrosis factor-alpha (TNF-alpha) agents for rheumatic and dermatologic conditions: a systematic review and meta-analysis. *Int J Rheumatol*. 2014;2014:926836. doi: 10.1155/2014/926836. PMID: 25114684. Excluded: wrong population – excluded for reactivation CQ.

Carroll MB, Forgione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol*. 2010;29(9):1021-9. doi: 10.1007/s10067-010-1523-2. PMID: 20556450. Excluded: wrong population – excluded for reactivation CQ.

Castelli R, Ferraris L, Pantaleo G, et al. High rate of hepatitis B viral breakthrough in elderly non-Hodgkin lymphomas patients treated with rituximab based chemotherapy. *Dig Liver Dis*. 2016;48(11):1394-7. doi: 10.1016/j.dld.2016.08.113. PMID: 27590841. Excluded: wrong population – excluded for reactivation CQ.

Caviglia GP, Olivero A, Ngatchou D, et al. Long-term results of chronic hepatitis B antiviral treatment with nucleos(t)ide analogues: a single center experience. *Minerva Gastroenterol Dietol*. 2019;65(1):77-8. doi: 10.23736/S1121-421X.18.02517-5. PMID: 30037184. Excluded: wrong study design for key question.

Centers for Disease Control and Prevention. Surveillance for viral hepatitis-United States, 2015. 2015. https://www.cdc.gov/hepatitis/statistics/2015surveillance/Commentary.htm#Ref02. Accessed August 21,

2019. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Chan HL, Chan CK, Hui AJ, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. *Gastroenterology*. 2014;146(5):1240-8. doi: 10.1053/j.gastro.2014.01.044. PMID: 24462735. Excluded: wrong intervention.

Chan HL, Chen YC, Gane EJ, et al. Randomized clinical trial: efficacy and safety of telbivudine and lamivudine in treatment-naive patients with HBV-related decompensated cirrhosis. *J Viral Hepat*. 2012;19(10):732-43. doi: 10.1111/j.1365-2893.2012.01600.x. PMID: 22967105. Excluded: wrong comparator.

Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1(3):185-95. doi: 10.1016/S2468-1253(16)30024-3. PMID: 28404091. Excluded: wrong comparator.

Chan HL, Shaikh J, Gupta S, et al. Renal function in nucleos(t)ide analog-treated patients with chronic hepatitis B: a systematic literature review and network meta-analysis. *Adv Ther*. 2016;33(5):862-75. doi: 10.1007/s12325-016-0337-2. PMID: 27146675. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

Chan HY, Lim YS, Seto WK, et al. Three year efficacy and safety of tenofovir alafenamide (TAF) compared to tenofovir disoproxil fumarate (TDF) in HBeAgnegative and HBeAg-positive patients with chronic hepatitis B. *Hepatol Int*. 2019;13. Excluded: wrong comparator.

Chang JJ, Mohtashemi N, Bhattacharya D. Significance and management of isolated hepatitis B core antibody (Anti-HBc) in HIV and HCV: strategies in the DAA era. *Curr HIV/AIDS Rep*. 2018;15(2):172-81. doi: 10.1007/s11904-018-0379-y. PMID: 29572624. Excluded: wrong population – excluded for reactivation CQ.

Chang ML, Liaw YF, Hadziyannis SJ. Systematic review: cessation of long-term nucleos(t)ide analogue therapy in patients with hepatitis B e antigen-negative chronic hepatitis B. *Aliment Pharmacol Ther*. 2015;42(3):243-57. doi: 10.1111/apt.13272. PMID: 26151841. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

Chang TT, Lai CL, Kew Yoon S, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology*. 2010;51(2):422-30. doi: 10.1002/hep.23327. PMID: 20049753. Excluded: wrong population.

Chang TT, Liaw YF, Wu SS, 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(3):886-93. doi: 10.1002/hep.23785. PMID: 20683932. Excluded: wrong study design for key question.

Chang Y, Choe WH, Sinn DH, et al. Nucleos(t)ide analogue treatment for patients with hepatitis B virus (HBV) e antigen-positive chronic HBV genotype C infection: a nationwide, multicenter, retrospective study. *J Infect Dis*. 2017;216(11):1407-14. doi: 10.1093/infdis/jix506. PMID: 29029102. Excluded: wrong population.

Charuworn P, Hengen PN, Aguilar Schall R, et al. Baseline interpatient hepatitis B viral diversity differentiates HBsAg outcomes in patients treated with tenofovir disoproxil fumarate. *J Hepatol*. 2015;62(5):1033-9. doi: 10.1016/j.jhep.2014.12.008. PMID: 25514556. Excluded: wrong outcome.

Chen CH, Hung CH, Wang JH, et al. Long-term incidence and predictors of hepatitis B surface antigen loss after discontinuing nucleoside analogues in noncirrhotic chronic hepatitis B patients. *Clin Microbiol Infect*. 2018;24(9):997-1003. doi: 10.1016/j.cmi.2017.12.013. PMID: 29288020. Excluded: wrong comparator.

Chen G, Liu H, Hu ZQ, et al. A new scheme with infusion of hepatitis B immunoglobulin combined with entecavir for prophylaxis of hepatitis B virus recurrence among liver transplant recipients. *Eur J Gastroenterol Hepatol.* 2015;27(8):901-6. doi: 10.1097/MEG.0000000000000388. PMID: 26011237. Excluded: wrong population.

Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis. *Hepatology*. 2017;66(1):13-26. doi: 10.1002/hep.29109. PMID: 28195337. Excluded: wrong population - excluded for reactivation CQ.

Chen LF, Mo YQ, Jing J, et al. Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. *Int J Rheum Dis*. 2017;20(7):859-69. doi: 10.1111/1756-185X.13010. PMID: 28160426. Excluded: wrong population – excluded for reactivation CQ.

Appendix A5. Excluded Studies with Reasons for Exclusion

Chen WC, Cheng JS, Chiang PH, et al. A comparison of entecavir and lamivudine for the prophylaxis of hepatitis B virus reactivation in solid tumor patients undergoing systemic cytotoxic chemotherapy. *PLoS One*. 2015;10(6):e0131545. doi: 10.1371/journal.pone.0131545. PMID: 26121480. Excluded: wrong population – excluded for reactivation CQ.

Chen X, Chen X, Chen W, et al. Extended peginterferon alfa-2a (Pegasys) therapy in Chinese patients with HBeAg-negative chronic hepatitis B. *J Med Virol*. 2014;86(10):1705-13. doi: 10.1002/jmv.24013. PMID: 24980710. Excluded: wrong comparator.

Cheng J, Hou J, Ding H, et al. Validation of ten noninvasive diagnostic models for prediction of liver fibrosis in patients with chronic hepatitis B. *PLoS One*. 2015;10(12)doi: 10.1371/journal.pone.0144425. PMID: 26709706. Excluded: wrong outcome.

Cheng J, Wang Y, Hou J, et al. Peginterferon alfa-2b in the treatment of Chinese patients with HBeAg-positive chronic hepatitis B: a randomized trial. *J Clin Virol.* 2014;61(4):509-16. doi: 10.1016/j.jcv.2014.08.008. PMID: 25200354. Excluded: wrong comparator.

Cheng Y, Yan ML, Wang L, et al. Effect of entecavir and adefovir dipivoxil on thyroid function and liver function in patients with decompensated hepatitis B cirrhosis. *World Chin J Dig*. 2018;26(5):311-7. doi: 10.11569/wcjd.v26.i5.311. Excluded: not English language but possibly relevant.

Chi H, Hansen BE, Guo S, et al. Pegylated interferon Alfa-2b add-on treatment in hepatitis B virus envelope antigen-positive chronic hepatitis B patients treated with nucleos(t)ide analogue: a randomized, controlled trial (PEGON). *J Infect Dis*. 2017;215(7):1085-93. doi: 10.1093/infdis/jix024. PMID: 28329061. Excluded: wrong intervention.

Chiang HH, Lee CM, Hu TH, et al. A combination of the on-treatment FIB-4 and alpha-foetoprotein predicts clinical outcomes in cirrhotic patients receiving entecavir. *Liver Int*. 2018;38(11):1997-2005. doi: 10.1111/liv.13889. PMID: 29797410. Excluded: wrong population – cirrhosis.

Chisenga CC, Musukuma K, Chilengi R, et al. Field performance of the determine HBsAg point-of-care test for diagnosis of hepatitis B virus co-infection among HIV patients in Zambia. *J Clin Virol*. 2018;98:5-7. doi: 10.1016/j.jcv.2017.11.005. PMID: 29175231. Excluded: wrong population – comorbid HIV or HCV.

Cholongitas E, Haidich AB, Apostolidou-Kiouti F, et al. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. *Ann Gastroenterol*. 2018;31(4):480-90. doi: 10.20524/aog.2018.0266. PMID: 29991894. Excluded: wrong population – excluded for reactivation CQ.

Choudhary NS, Saraf N, Saigal S, et al. Low-dose short-term hepatitis B immunoglobulin with high genetic barrier antivirals: the ideal post-transplant hepatitis B virus prophylaxis? *Transpl Infect Dis*. 2015;17(3):329-33. doi: 10.1111/tid.12369. PMID: 25682715. Excluded: wrong population – cirrhosis.

Coluccio C, Begini P, Marzano A, et al. Hepatitis B in patients with hematological diseases: an update. *World J Hepatol*. 2017;9(25):1043-53. doi: 10.4254/wjh.v9.i25.1043. PMID: 28951776. Excluded: wrong population – excluded for reactivation CQ.

Crespo J, Esteban R, Torres C, et al. Cost-effectiveness of a hepatitis B virus screening strategy to prevent reactivation in patients with hematologic neoplasms. *Rev Esp Enferm Dig*. 2017;109(9):619-26. doi: 10.17235/reed.2017.4693/2016. PMID: 28648087. Excluded: wrong population.

Cruz HM, Scalioni LP, Paula VS, et al. Poor sensitivity of rapid tests for the detection of antibodies to the hepatitis B virus: implications for field studies. *Mem Inst Oswaldo Cruz*. 2017;112(3):209-13. doi: 10.1590/0074-02760160394. PMID: 28146158. Excluded: wrong country.

Cunha-Silva M, Marinho FRT, Oliveira PF, et al. Retrospective analysis of hepatitis B virus chronic infection in 247 patients: clinical stages, response to treatment and poor prognostic factors. *Braz J Infect Dis.* 2017;21(4):441-7. doi: 10.1016/j.bjid.2017.03.019. PMID: 28554002. Excluded: wrong population – cirrhosis.

Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naive patients with chronic hepatitis B. *Value Health*. 2010;13(8):934-45. doi: 10.1111/j.1524-4733.2010.00777.x. PMID: 20825624. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

Day FL, Karnon J, Rischin D. Cost-effectiveness of universal hepatitis B virus screening in patients beginning chemotherapy for solid tumors. *J Clin*

Oncol. 2011;29(24):3270-7. doi: 10.1200/JCO.2011.35.1635. PMID: 21788556. Excluded: wrong population.

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de Niet A, Jansen L, Stelma F, et al. Peg-interferon plus nucleotide analogue treatment versus no treatment in patients with chronic hepatitis B with a low viral load: a randomised controlled, open-label trial. *Lancet Gastroenterol Hepatol*. 2017;2(8):576-84. doi: 10.1016/S2468-1253(17)30083-3. PMID: 28522204. Excluded: wrong intervention.

Di Marco V, Lo Iacono O, Camma C, et al. The long-term course of chronic hepatitis B. *Hepatology*. 1999;30(1):257-64. doi: 10.1002/hep.510300109. PMID: 10385664. Excluded: sample size for cohort less than 1,000.

Di Marco V, Marzano A, Lampertico P, et al. Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. *Hepatology*. 2004;40(4):883-91. PMID: 15382125. Excluded: wrong population – cirrhosis.

Ding Y, Lou J, Chen H, et al. Tolerability, pharmacokinetics and antiviral activity of rHSA/IFNalpha2a for the treatment of chronic hepatitis B infection. *Br J Clin Pharmacol*. 2017;83(5):1056-71. doi: 10.1111/bcp.13184. PMID: 27862178. Excluded: wrong comparator.

Ding Y, Zhang H, Li X, et al. Safety, pharmacokinetics and pharmacogenetics of a single ascending dose of pradefovir, a novel liver-targeting, anti-hepatitis B virus drug, in healthy Chinese subjects. *Hepatol Int*. 2017;11(4):390-400. doi: 10.1007/s12072-017-9797-y. PMID: 28560658. Excluded: wrong intervention.

Dong HJ, Ni LN, Sheng GF, et al. Risk of hepatitis B virus (HBV) reactivation in non-hodgkin lymphoma patients receiving rituximab-chemotherapy: a meta-analysis. *J Clin Virol*. 2013;57(3):209-14. doi: 10.1016/j.jcv.2013.03.010. PMID: 23562041. Excluded: wrong population – excluded for reactivation CQ.

Dong J, Wu Y, Zhu H, et al. A pilot study on screening blood donors with individual-donation nucleic acid testing in China. *Blood Transfus*. 2014;12(2):172-9. doi: 10.2450/2013.0095-13. PMID: 24333061. Excluded: wrong country.

El Kassas M, Shimakawa Y, Ali-Eldin Z, et al. Risk of hepatitis B virus reactivation with direct-acting antivirals against hepatitis C virus: a cohort study from Egypt and meta-analysis of published data. *Liver Int*. 2018;38(12):2159-69. doi: 10.1111/liv.13874. PMID: 29738637. Excluded: wrong population – excluded for reactivation CQ.

Embree J, Law B, Voloshen T, et al. Immunogenicity, safety, and antibody persistence at 3, 5, and 10 years postvaccination in adolescents randomized to booster immunization with a combined tetanus, diphtheria, 5-component acellular pertussis, and inactivated poliomyelitis vaccine administered with a hepatitis B virus vaccine concurrently or 1 month apart. *Clin Vaccine Immunol*. 2015;22(3):282-90. doi: 10.1128/CVI.00682-14. PMID: 25540274. Excluded: wrong intervention.

Eun JR, Lee HJ, Lee SH, et al. The effect of lamivudine and adefovir dipivoxil on preventing hepatocellular carcinoma in hepatitis B virus-related liver cirrhosis. *Hepatology*. 2007;46(4):664A-5A. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol*. 2011;22(5):1170-80. doi: 10.1093/annonc/mdq583. PMID: 21115603. Excluded: wrong population – excluded for reactivation CQ.

Fang J, Li W, Tan Z, et al. Comparison of prednisolone and lamivudine combined therapy with prednisolone monotherapy on carriers of hepatitis B virus with IgA nephropathy: a prospective cohort study. *Int Urol Nephrol*. 2014;46(1):49-56. doi: 10.1007/s11255-013-0480-5. PMID: 23756850. Excluded: wrong comparator.

Fattovich G, Giustina G, Realdi G, et al. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alfa. European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology*. 1997;26(5):1338-42. PMID: 9362381. Excluded: wrong population – cirrhosis.

Feld JJ, Terrault NA, Lin HS, et al. Entecavir and peginterferon alfa-2a in adults with hepatitis B e antigen-positive immune-tolerant chronic hepatitis B virus infection. *Hepatology*. 2019;69(6):2338-48. doi: 10.1002/hep.30417. PMID: 30549279. Excluded: wrong intervention: nonFDA approved drug.

Fernandez I, Loinaz C, Hernandez O, et al. Tenofovir/entecavir monotherapy after hepatitis B immunoglobulin withdrawal is safe and effective in the prevention of hepatitis B in liver transplant recipients. *Transpl Infect Dis*. 2015;17(5):695-701. doi: 10.1111/tid.12434. PMID: 26257166. Excluded: wrong population.

Flanagan S, Kunkel J, Appleby V, et al. Case finding and therapy for chronic viral hepatitis in primary care (HepFREE): a cluster-randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2019;4(1):32-44. doi: 10.1016/S2468-1253(18)30318-2. PMID: 30477810. Excluded: wrong outcome.

Franzeck FC, Ngwale R, Msongole B, et al. Viral hepatitis and rapid diagnostic test based screening for HBsAg in HIV-infected patients in rural Tanzania. *PLoS One*. 2013;8(3) PMID: 23469281. Excluded: wrong population – comorbid HIV or HCV.

Fung J, Wong T, Chok K, et al. Oral nucleos(t)ide analogs alone after liver transplantation in chronic hepatitis B with preexisting rt204 mutation. *Transplantation*. 2017;101(10):2391-8. doi: 10.1097/TP.0000000000001883. PMID: 28731907. Excluded: wrong population.

Fung S, Gordon SC, Krastev Z, et al. Tenofovir disoproxil fumarate in Asian or Pacific Islander chronic hepatitis B patients with high viral load (>= 9 log10 copies/ml). *Liver Int.* 2015;35(2):422-8. doi: 10.1111/liv.12694. PMID: 25277773. Excluded: wrong study design for key question.

Furukawa EN, Yamashita S, Maeyama K, et al. Clinical course of hepatitis B surface antigen positive subjects following screening: a retrospective observational study from April 2008 to January 2013. *Hepatol Res*. 2016;46(7):678-85. doi: 10.1111/hepr.12608. PMID: 26492344. Excluded: wrong outcome.

Gaia S, Marzano A, Smedile A, et al. Four years of treatment with lamivudine: clinical and virological evaluations in HBe antigen-negative chronic hepatitis B. *Aliment Pharmacol Ther*. 2004;20(3):281-7. doi: 10.1111/j.1365-2036.2004.02073.x. PMID: 15274664. Excluded: wrong comparator.

Gane EJ, Wang Y, Liaw YF, et al. Efficacy and safety of prolonged 3-year telbivudine treatment in patients with chronic hepatitis B. *Liver Int*. 2011;31(5):676-84. doi: 10.1111/j.1478-3231.2011.02490.x. PMID: 21457439. Excluded: wrong population.

Gao YJ, Zhang M, Jin B, et al. Clinical-pathological analysis of hepatitis B virus recurrence after liver transplantation in Chinese patients. *J Gastroenterol Hepatol*. 2014;29(3):554-60. doi: 10.1111/jgh.12404. PMID: 24117714. Excluded: wrong population.

Garg H, Sarin SK, Kumar M, et al. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology*. 2011;53(3):774-80. doi: 10.1002/hep.24109. PMID: 21294143. Excluded: wrong population – excluded for reactivation CQ.

Geng L, Lin BY, Shen T, et al. Anti-virus prophylaxis withdrawal may be feasible in liver transplant recipients whose serum HBeAg and HBV DNA are negative. *Hepatobiliary Pancreat Dis Int*. 2016;15(3):316-8. PMID: 27298109. Excluded: wrong population.

Gentile G, Andreoni M, Antonelli G, et al. Screening, monitoring, prevention, prophylaxis and therapy for hepatitis B virus reactivation in patients with haematologic malignancies and patients who underwent haematologic stem cell transplantation: a systematic review. *Clin Microbiol Infect*. 2017;23(12):916-23. doi: 10.1016/j.cmi.2017.06.024. PMID: 28668465. Excluded: wrong population – excluded for reactivation CQ.

Geue C, Wu O, Xin Y, et al. Cost-effectiveness of HBV and HCV screening strategies - a systematic review of existing modelling techniques. *PLoS One*. 2015;10(12):e0145022. doi: 10.1371/journal.pone.0145022. PMID: 26689908. Excluded: wrong outcome.

Gisbert JP, Chaparro M, Esteve M. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2011;33(6):619-33. PMID: 21416659. Excluded: wrong population – excluded for reactivation CQ.

Gong WF, Zhong JH, Lu SD, et al. Effects of antiviral therapy on post-hepatectomy HBV reactivation and liver function in HBV DNA-negative patients with HBV-related hepatocellular carcinoma. *Oncotarget*. 2017;8(9):15047-56. PMID: 28122361. Excluded: wrong population.

Govan L, Wu O, Xin Y, et al. Comparative effectiveness of antiviral treatment for hepatitis B: a systematic review and Bayesian network meta-analysis. *Eur J Gastroenterol Hepatol*. 2015;27(8):882-94. doi: 10.1097/MEG.0000000000000376. PMID: 25919772. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

Guarino M, Picardi M, Vitello A, et al. Viral outcome in patients with occult HBV infection or HCV-Ab positivity treated for lymphoma. *Ann Hepatol*. 2017;16(2):198-206. doi: 10.5604/16652681.1231567. PMID: 28233742. Excluded: wrong population – excluded for reactivation CQ.

Guner R, Kocak Tufan Z, Yilmaz GR, et al. Tenofovir disoproxil fumarate may not cause renal and bone toxicity in chronic hepatitis B patients: a retrospective cross-sectional study. *Turk J Med Sci*. 2019;49(1):451-2. doi: 10.3906/sag-1805-233. PMID: 30761830. Excluded: wrong study design for key question.

Guzelbulut F, Ovunc AO, Oetinkaya ZA, et al. Comparison of the efficacy of entecavir and tenofovir in chronic hepatitis B. *Hepatogastroenterology*. 2012;59(114):477-80. doi: 10.5754/hge11426. PMID: 21940383. Excluded: wrong outcome.

Hadziyannis S, Bramou T, Makris A, et al. Interferon alfa-2b treatment of HBeAg negative/serum HBV DNA positive chronic active hepatitis type B. *J Hepatol*. 1990;11 Suppl 1:S133-6. PMID: 2079571. Excluded: wrong population – cirrhosis.

Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology*. 2006;131(6):1743-51. doi: 10.1053/j.gastro.2006.09.020. PMID: 17087951. Excluded: wrong population.

Hahne SJ, Veldhuijzen IK, Wiessing L, et al. Infection with hepatitis B and C virus in Europe: a systematic review of prevalence and cost-effectiveness of screening. *BMC Infect Dis*. 2013;13:181. doi: 10.1186/1471-2334-13-181. PMID: 23597411. Excluded: wrong country.

Hakim GD, Akarsu M, Karademir S, et al. The efficacy and safety of tenofovir in the prevention of hepatitis B virus recurrence following liver transplantation. *Turk J Gastroenterol*. 2014;25(6):685-9. doi: 10.5152/tjg.2014.5819. PMID: 25599782. Excluded: wrong population.

Han M, Jiang J, Hou J, et al. Sustained immune control in HBeAg-positive patients who switched from entecavir therapy to pegylated interferon-alpha2a: 1 year follow-up of the OSST study. *Antivir Ther*. 2016;21(4):337-44. doi: 10.3851/IMP3019. PMID: 26734984. Excluded: wrong comparator.

Han Y, Zeng A, Liao H, et al. The efficacy and safety comparison between tenofovir and entecavir in treatment of chronic hepatitis B and HBV related cirrhosis: a systematic review and meta-analysis. *Int Immunopharmacol*. 2017;42:168-75. doi: 10.1016/j.intimp.2016.11.022. PMID: 27915131. Excluded: systematic review or meta-analysis used as a source document only to identify individual studies.

Hardtke S, Wedemeyer H, Caruntu FA, et al. Frequency, severity and impact of Peg-IFNa-associated flares in HDV infection: results from the HIDIT-II study. *J Hepatol*. 2019;70(1):e466. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Hay AE, Meyer RM. Hepatitis B, rituximab, screening, and prophylaxis: effectiveness and cost effectiveness. *J Clin Oncol*. 2012;30(26):3155-7. doi: 10.1200/JCO.2012.43.7509. PMID: 22891267. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

He LT, Ye XG, Zhou XY. Effect of switching from treatment with nucleos(t)ide analogs to pegylated interferon alpha-2a on virological and serological responses in chronic hepatitis B patients. *World J Gastroenterol.* 2016;22(46):10210-8. doi: 10.3748/wjg.v22.i46.10210. PMID: 28028369. Excluded: wrong population.

Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology*. 2011;140(1):132-43. doi: 10.1053/j.gastro.2010.10.011. PMID: 20955704. Excluded: wrong study design for key question.

Hepatitis B Foundation. Hepatitis C coinfection. http://www.hepb.org/what-is-hepatitis-b/hepatitis-c-co-infection/. Accessed January 2, 2019. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Hepatitis B Foundation. HIV/AIDS coinfection. http://www.hepb.org/what-is-hepatitis-b/hivaids-co-infection/. Accessed January 2, 2019. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.

Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size

- Reliable screening test

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has a fatal flaw, such as: Uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Source: U.S. Preventive Services Task Force Procedure Manual. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes.

Appendix A7. Expert Reviewers of the Draft Report

- Erin Abramsohn, MPH, DrPH, Centers for Disease Control and Prevention
- Jennifer Fuld, PhD, Centers for Disease Control and Prevention
- David E. Kaplan, MD, MSc, FACP, FAASLD, Perelman School of Medicine, University of Pennsylvania, Department of Medicine, Division of Gastroenterology and Hepatology
- Bill G. Kapogiannis, MD, Eunice Kennedy Shriver National Institute of Child Health and Development, National Institutes of Health
- Rajen Koshy, PhD, National Institute of Allergy and Infectious Diseases
- Rebecca L. Morgan, MPH, PhD, McMaster University
- John W. Ward, MD, Coalition for Global Hepatitis Elimination, Task Force for Global Health

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings.

Appendix B Table 1. HBV Screening Strategies – Study Characteristics

Author, year Study name From prior report or update	Study design	Setting Country Study period	N	Baseline characteristics	Screening strategies	Funding source	Quality
Bottero 2014[121] OPTISCREEN-B From update	Cross-sectional, substudy	10 healthcare centers Paris, France September 2010 to August 2011	Screened for eligibility: 5,393 Included in study: 3,997 Included in primary analysis: 3,929	Age, median: 33 years Male: 55.9% HBV prevalence of birth country: 56.2% low (<2.0%), 20.5% intermediate (2.0 to 8.0%), high 23.3% (>8.0%) Intravenous drug use: 0.6% Men who have sex with men: 10.6%	A. Previous HBV-testing B. Physician's decision to screen C. 2008 CDC HBV screening recommendations[22] (Testing recommended for pregnant women, infants born to HBsAg-positive mothers, household contacts and sex partners of HBV-infected persons, populations with and persons born in countries with HBsAg prevalence of ≥2%, persons who are the source of blood or body fluid exposures that might warrant postexposure prophylaxis, persons infected with HIV, men who have sex with mean, and persons who inject drugs) D. Persons from countries with high prevalence (≥2%) of HBV	Agence Nationale de Recherchesur le Sida et les Hepatites virales, Gilead Sciences and Roche	Fair
Spenatto 2013[120] From prior report	Cross-sectional	1 sexually transmitted disease clinic France January 2009 to June 2009	Screened=6,194 183 patients (1 HBV case) did not have information on country of birth	Age: 62% 20 to 29 years Male: 44% High endemic area (prevalence >8%) country of birth: 7.2% Self-reported injection drug use: 0.7%	A. Screen all B. Screening those born in moderate or high prevalence (>2%) country C. Same as B, plus men and unemployed D. Screen those born in moderate or high prevalence country, transfusion history or blood contacts, tattoos, body piercing, more than two sexual partners during the last year, hepatitis among sexual partners or household members, or intravenous or intranasal drug use; no screening for patients who reported prior HBV vaccination E. Same as D, except prior vaccination history not considered	NR	Fair
Wolffram 2015[122] From update	Cross-sectional Screening strategies were hypothetically applied after the data was collected, so these are proposed strategies	51 private primary care practices Germany January 2012 to June 2013	Screened=21,008	Non-HBV/HCV vs. HBsAg positive Age: 57.5 vs. 52.3 years Male: 43.9% vs. 54.5% Intravenous drug use: 0.1% vs. 0.9% Blood transfusion before 1992: 5.8% vs. 4.1% Immigration: 10.0% vs. 35.6% Infection in household: 4.0% vs. 11.0% Elevated ALT: 13.2% vs. 21.8%	Screening strategies for HBsAg positive patients, based on identified risk factors A. Male, immigrant, and someone with hepatitis in the household B. Male, with either immigration background or someone with hepatitis in the household C. Male, with immigration background D. Elevated ALT values E. German HBV guidelines HBV questionnaire* added to Check-Up 35+[†] and the following 3 risk factors were associated with HBsAg positivity via stepwise logistic regression: Immigration: OR 4.4 (95% CI, 2.9 to 6.7) Infection in household: OR 2.5 (95% CI, 1.2 to 4.5) Male: OR 1.6 (95% CI, 1.1 to 2.4)	Gilead, Janssen	Fair

Appendix B Table 1. HBV Screening Strategies – Study Characteristics

Author, year Study name From prior report or update	Study design	Setting Country Study period	N	Baseline characteristics	Screening strategies	Funding source	Quality
Wolffram 2015[122] (continued)	See Wolfram 2015	See Wolfram 2015	Screened=20,864	See Wolfram 2015	Screening strategies for previously unknown HBsAg positive patients according to German guideline adapted questions[123] A. Total cohort B. Positive answer to at least either one of the HBV related questions C. Positive answer to at least either one of the HBV related questions **or** elevated serum ALT D. Positive answer to at least either one of the HBV related questions excluding the question for elevated ALT values E. Positive answer to at least either one of the HBV related questions excluding the question for ALT values **or** elevated serum ALT F. Presence of elevated serum ALT levels G. Immigration background **or** hepatitis positive household member H. Immigration background **or** hepatitis positive house member **or** elevated serum ALT I. Immigration background	See Wolfram 2015	See Wolfram 2015

*Questionnaire covered 12 yes/no questions with risk scenarios for HBV or HCV adapted for the German guidelines which should prompt a screening if positively answered; with the addition of 4 questions on piercings, tattoos, previous surgery, or travel to countries with high HBV and HCV prevalence.
†Standard preventive medical examination for patients at least 35 years of age.

Abbreviations: ALT = alanine aminotransferase; CDC = Centers for Disease Control and Prevention; CI = confidence interval; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; NR= not reported; OPTISCREEN-B = study name is a not an acronym; OR = odds ratio.

Appendix B Table 2. HBV Screening Strategies – Results

Author, year Study name From prior report or update	Screening strategies	HBV prevalence, HBsAg positive	Proportion screened	Sensitivity	Specificity	AUROC	NNS to identify 1 case of HBV infection
Bottero 2014[121] OPTISCREEN-B From update	A. Previous HBV-testing B. Physician's decision to screen C. 2008 CDC HBV screening recommendations[22] D. Persons from countries with high prevalence (≥2%) of HBV	2.2% (85/3,929) Resolved HBV infection: 13.4% (528/3,929) anti-HBcAb: 3.3% (131/3,929)	A. 30.5% (1,199/3,929) B. 66.6% (2,615/3,929) C. 69.6% (2,735/3,929) D. 43.8% (1,721/3,929)	A. 36.5% (95% CI, 26.3% to 47.6%) B. 87.1% (95% CI, 78.0% to 93.4%) C. 100% (95% CI, 95.8% to 100%) p<0.0001 D. 99% (84/85)	A. 69.6 B. 33.9 C. 31.1% (95% CI, 29.6% to 32.6%) D. 47% (2207/3844)	A. 0.53 (95% CI, 0.48 to 0.58) B. 0.61 (95% CI, 0.57 to 0.64) C. 0.66 (95% CI, 0.65 to 0.66)	D. 20
Spenatto 2013[120] From prior report	A. Screen all B. Screening those born in moderate or high prevalence (>2%) country C. Same as B, plus men and unemployed D. Screen those born in moderate or high prevalence country, transfusion history or blood contacts, tattoos, body piercing, more than two sexual partners during the last year, hepatitis among sexual partners or household members, or intravenous or intranasal drug use; no screening for patients who reported prior HBV vaccination E. Same as D, except prior vaccination history not considered	0.8% (49/6,194) anti-HBc positive: 4.4% (275/6,194)	A: 100% (6,194/6,194) B: 12% (761/6,011) C: 64% (3,949/6,194) D: 73% (4,504/6,194) E: 84% (5,205/6,194)	A: 100% (49/49) B: 85% (41/48) C: 98% (48/49) D: 84% (41/49) E: 94% (46/49)	A: 0% (0/6,145) B: 88% (5,243/5,963) C: 37% (2,244/6,145) D: 27% (1,682/6,145) E: 16% (986/6,145)	C. 0.92	A: 126 B: 19 C: 82 D: 110 E: 113

Appendix B Table 2. HBV Screening Strategies – Results

Author, year Study name From prior report or update	Screening strategies	HBV prevalence, HBsAg positive	Proportion screened	Sensitivity	Specificity	AUROC	NNS to identify 1 case of HBV infection
Wolffram 2015[122] From update	Screening strategies for HBsAg positive patients, based on identified risk factors A. Male, immigrant, and someone with hepatitis in the household B. Male, with either immigration background or someone with hepatitis in the household C. Male, with immigration background D. Elevated ALT values E. German HBV guidelines HBV questionnaire* added to Check-Up 35+[†] and the following 3 risk factors were associated with HBsAg positivity via stepwise logistic regression: Immigration: OR 4.4 (95% CI, 2.9 to 6.7) Infection in household: OR 2.5 (95% CI, 1.2 to 4.5) Male: OR 1.6 (95% CI, 1.1 to 2.4) *Continued on next page-*	Total: 0.52% (110/21,008) A. Unclear B. 2.0% (23/1,169), identified 21% of all HBsAg positive patients C. 2.1% (20/948),identified 18% of all HBsAg positive patients D. 0.8% (24/2,835), 22% of all HBsAg positive patients E. 0.45% (93/20,864), 84.5% of all HBsAg positive patients	A. 0.30% (62/21,008) B. 5.56% (1,169/21,008) C. 4.51% (948/21,008) D. 13.5% (2,835/21,008) E. 99.3% (20,864/21,008)	NR	NR	NR	NR

Appendix B Table 2. HBV Screening Strategies – Results

Author, year Study name From prior report or update	Screening strategies	HBV prevalence, HBsAg positive	Proportion screened	Sensitivity	Specificity	AUROC	NNS to identify 1 case of HBV infection
Wolffram 2015[122] (continued)	Screening strategies for previously unknown HBsAg positive patients according to German guideline adapted questions[123] A. Total cohort B. Positive answer to at least either one of the HBV related questions C. Positive answer to at least either one of the HBV related questions **or** elevated serum ALT D. Positive answer to at least either one of the HBV related questions excluding the question for elevated ALT values E. Positive answer to at least either one of the HBV related questions excluding the question for ALT values **or** elevated serum ALT F. Presence of elevated serum ALT levels G. Immigration background **or** hepatitis positive household member H. Immigration background **or** hepatitis positive house member **or** elevated serum ALT I. Immigration background	Total: A. 0.45% (93/20,864) B. 0.67% C. 0.66% D. 0.69% E. 0.65% F. 0.71% G. 1.3% H. 0.91% I. 1.4%	A. 100% (20,864/20,864) B. 44.1% (9,198/20,864) C. 50.2% (10,467/20,864) D. 39.1% (8,147/20,864) E. 46.6% (9,719/20,864) F. 13.4% (2,799/20,864) G. 12.5% (2,603/20,864) H. 23.8% (4,970/20,864) I. 9.5% (1,976/20,864)	NR	NR	NR	A. 224 B. 148 C. 152 D. 145 E. 154 F. 140 G. 77 H. 116 I. 71

*Questionnaire covered 12 yes/no questions with risk scenarios for HBV or HCV adapted for the German guidelines which should prompt a screening if positively answered; with the addition of 4 questions on piercings, tattoos, previous surgery, r travel to countries with high HBV and HCV prevalence.
†Standard preventive medical examination for patients at least 35 years of age.

Abbreviations: ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; anti-HBcAb = antibodies to hepatitis B surface and core antigens; AUROC = area under the receiver operating characteristics; CDC = Centers for Disease Control and Prevention; CI = confidence interval; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NNS = number needed to screen; NPV = negative predictive value; NR = not reported; OPTISCREEN-B = study name is a not an acronym; OR = odds ratio; PPV = positive predictive value.

Appendix B Table 3. HBV Screening Strategies – Quality Assessment

Study, Year From prior report or update	Did the Study Attempt to Enroll All (or a Random Sample of) Patients Meeting Inclusion Criteria, or a Random Sample (Inception Cohort)?	Did the Study Evaluate a Representative Spectrum?	Did the Study Report the Proportion of Eligible Patients Who Met Inclusion Criteria Who Underwent Screening?	Was There a High Rate of Nonscreening Among Eligible Patients?	Did the Study Describe Methods for Ascertaining Risk Factors?	Did the Study Prospectively Compare Different Predefined Screening Strategies?	Quality
Bottero 2014[121] From update	Yes	Yes	No	Unclear	Yes	Yes	Fair
Spenatto 2013[120] From prior report	Yes	Yes	Yes	No (19%)	Yes	No	Fair
Wolffram 2015[122] From update	Yes	Yes	No	Unclear	Yes	No	Fair

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Bozkaya 2005[74] Fair From prior report	Non-RCT	1 site Turkey	1 year treatment; 6 months post-treatment followup (for those in treatment group) Mean followup: NR	A: Lamivudine 100 mg daily (n=18) B: Untreated group with raised ALT (n=19) C: Untreated group with normal ALT (n=18)	A vs. B vs. C Age, mean: 32 vs. 39 vs. 38 years Male: 94% vs. 68% vs. 17% Race: NR Serology: HBV DNA, median (range): 1.2 x 10^3 (1 x 10^2 to 9.7 x 10^4) vs. 4.2 x 10^3 (1 x 10^2 to 3.6 x 10^5) vs. 2.5 x 10^3 (1 x 10^2 to 5.2 x 10^5) copies/mL ALT, median (range): 64 (38 to 186) vs. 48 (35 to 168) vs. 17 (11 to 30) IU/L Histopathology: HAI (Knodell score) median (range): 4.5 (1.0 to 16.0) vs. 4.0 (1.0 to 8.0) vs. 2.0 (1.0 to 4.0) Fibrosis (Knodell fibrosis score ≥1) : 33% vs. 24% vs. 0% Cirrhosis: NR Prior HBV treatment: No patients	ALT >1 x ULN (groups A and B); undetectable HBV DNA by hybrid capture assay during monthly/bi-monthly assessments during year prior to entry into study; alcohol intake absent or <20 g per week; body mass index <30 kg/m^2	Presence of non-alcoholic steatohepatitis and significant liver steatosis; high body mass index; high alcohol intake; drug-related toxicity	Screened: 390 Eligible: 55 Enrolled: 55 Analyzed: 55	NR	NR

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Chan 2007[75] Fair From prior report	RCT	8 sites China	24 months of treatment; 6 months followup Mean followup: NR	A. Lamivudine 100 mg daily (n=89) B. Placebo (n=47)	A vs. B Age, mean: 39 vs. 39 years Male: 84% vs. 83% Race: NR Serology: HBV DNA, mean: 5.7 vs. 5.6 log copies/mL HBeAg positive: 6% vs. 6% Anti-HBe positive: 94% vs. 96% ALT, mean: 2.1 vs. 2.6 x ULN Histopathology (reported for n=52 vs. 28 patients): Necroinflammatory score, median (Knodell 0 to 18): 5 vs. 5 Fibrosis score, median (Ishak 0 to 6): 2 vs. 2 Cirrhosis: 16% overall (histology not reported for 42%) Prior HBV treatment: NR, but allowed (see eligibility criteria)	Age >18 years; positive HBsAg for >6 months prior to screening; detectable HBV DNA by non-PCR based assay; significantly increased ALT levels (ALT 1.5 to 10 times ULN on >2 occasions in the previous 6 months or ALT above ULN with >1 flare-up of ALT >200 IU/L in past 12 months); liver biopsy in past 12 months showing evidence of active hepatitis; once PCR-based HBV DNA assay was available, inclusion modified to HBV DNA >100,000 copies/mL	Hepatocellular carcinoma; ALT >10 times ULN at screening; decompensated liver disease; complications of liver cirrhosis; coinfection with HCV, HDV, or HIV; serious medical or psychiatric illness; use of immunosuppressive or immunomodulatory therapy within the previous 6 months; treatment with antiviral agent within the previous 6 months; history of hypersensitivity to nucleoside analogues; serum creatinine >1.5 times ULN; anti-nuclear antibody titer >1:160; serum amylase or lipase level >2 times ULN, hemoglobin <11 g/dL; white cell count $<3x10^9$/L; platelet count $<100x10^9$/L; pregnant or lactating women	Screened: 443 Eligible: 139 Enrolled: 139 Analyzed: 136	Withdrawals during treatment: 18% (25/136) Withdrawals post-treatment:18 % (19/105) Post-randomization exclusions: 2.2% (3/139) Missing data: 6.6% (9/136)	Glaxo-SmithKline

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Dienstag 1999[76] Fair From prior report	RCT	34 sites United States	Study duration: 68 weeks Treatment duration: 52 weeks Post-treatment followup: 16 weeks	A. Lamivudine 100 mg daily (n=66) B. Placebo (n=71)	A vs. B Age, median: 40 vs. 38 years Male: 86% vs. 80% Race: 59% vs. 56% white, 24% vs. 17% Asian, 15% vs. 18% black Serology: HBV DNA, median serum : 102.2 vs. 56.5 pg/mL ALT, median serum: 125 vs. 135 IU/L Bilirubin, median serum: 0.7 vs. 07 mg/dL Albumin, median serum: 3.9 vs. 3.8 g/dL Histopathology: Median HAI (Knodell score): 10 vs. 11 Cirrhosis: 6% vs. 14% Prior HBV treatment: None	Age ≥18 years; detectable serum HBsAg for at least 6 months, serum HBeAg for at least 1 month, and ALT levels 1.3 to 10 times ULN for at least 3 months; evidence of chronic hepatitis on liver biopsy; and detectable levels of HBV DNA	Previous antiviral therapy for HBV; any treatment with antiviral drugs, immunomodulatory drugs, or corticosteroids within the previous 6 months; bilirubin level >2.5 mg/dL; prothrombin time more than 3 seconds longer than normal; albumin level of less than 3.5 g/dL; history of ascites, variceal hemorrhage, or hepatic encephalopathy; co-infection with HCV, HDV, or HIV; a nuclear antibody titer of more than 1:160; a creatine level of more than 1.5 mg/dL; a hemoglobin level of less than 11 g/dL; a white-cell count of less than 3,000 cells/mm^3; a neutrophil count of less than 1500 cells/mm^3; a platelet count of less than 100,000 cells/mm^3; presence of a confounding illness or other type of liver disease; pregnant or breastfeeding	Screened: 217 Eligible: NR Enrolled: 143 Analyzed: 137 *143 enrolled but 6 excluded at the baseline visit because they did not have 6 months of serum HBsAg*	Withdrawals: 6 (2 patients withdrew before receiving treatment, 4 others excluded because they did not meet inclusion criteria)	Glaxo Wellcome; Hepatitis Research Fund of Massachusetts General Hospital; National Institutes of Health Clinical Research Center

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Hadziyannis 2003[77] Fair From prior report	RCT	32 sites; Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore	48 weeks duration and followup; safety analysis included all events that occurred within 30 days of drug discontinuation	A. Adefovir 10 mg daily (n=123) B. Placebo (n=62)	A vs. B Age, mean: 46 vs. 45 years Male: 83% vs. 82% Race: 67% vs. 66% white; 4% vs. 2% black; 29% vs. 33% Asian Serology: HBV DNA, mean: 6.9 vs. 6.9 log copies/mL ALT x ULN, mean: 3.5 vs. 3.6 Histopathology: Knodell necroinflammatory activity score, mean: 7.7 vs. 7.1 Knodell fibrosis score, mean: 1.9 vs. 1.8 Cirrhosis: 11% vs. 10% Prior HBV treatment: Prior interferon alfa treatment: 39% vs. 46% Prior lamivudine treatment: 8% vs. 7% Prior famciclovir treatment: 6% vs. 11% Note: some patients had received more than one medication	Age 16 to 65 years of age with HBeAg negative chronic HBV and compensated liver disease. Chronic HBV defined as HBsAg for at least 6 months, undetectable HBeAg, detectable anti-HBe, HBV DNA of at least 10^5 copies/mL, ALT between 1.5 and 15x ULN. Total bilirubin no more than 2.5 mg/dL; prothrombin time no more than 1 second above normal range; albumin at least 3 g/dL; creatinine no more than 1.5 mg/dL; adequate blood count.	Coexisting serious medical or psychiatric illness, immune globulin, interferon, or other immune or cytokine based therapies with possible activity against HBV disease within 6 months before screening; organ or bone marrow transplantation; recent treatment with systemic corticosteroids, immunosuppressants, or chemotherapeutic agents; serum AFP of at least 50 ng/mL, evidence of a hepatic mass, liver disease not due to HBV, prior therapy for more than 12 weeks with a nucleoside or nucleotide analogue with activity against HBV, seropositivity for HIV, HCV, or HDV	Screened: 391 Eligible: 235 Enrolled: 185 Analyzed: 178 for histologic outcomes Note: one patient in group B never received treatment and was excluded, baseline n=123 in group A, 61 in group B	Withdrawals: 2.4% (3/123) vs. 1.6% (1/61) Loss to followup: 0.8% (1/123) vs. 0% (0/61)	Gilead Sciences

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Lai 1997[79] Fair From prior report	RCT	Single site Hong Kong	Treatment duration: 4 weeks Post-treatment followup: 4 weeks	A. Lamivudine 25 mg daily (n=12) B. Lamivudine 100 mg daily (n=12) C. Lamivudine 300 mg daily (n=12) D. Placebo (n=6)	A vs. B vs. C vs. D Age, mean: 33 vs. 33 vs. 34 vs. 26 years Male: 58% vs. 58% vs. 75% vs. 67% Race: 100% Asian Serology: Mean HBV DNA: 91.3 vs. 94.5 vs. 103.0 vs. 67.1 pg/mL HBsAg positive: 100% vs. 100% vs. 100% vs. 100% HBeAg positive: 100% vs. 100% vs. 100% vs. 100% ALT, median: 37.5 vs. 29.5 vs. 38.0 vs. 28.5 IU/L Histopathology: NR Prior HBV treatment: NR	Chronic HBsAg carriers; HBV DNA levels >10 pg/mL for at least 3 months; stable serum ALT and AST levels of less than 2 times ULN range for at least 3 months; no antiviral, investigational, or biological modifier drugs in the past 6 months; no evidence of liver decompensation, renal impairment, or pancytopenia; tested negative for antibodies against HCV, HDV, and HIV	NR	Screened: NR Eligible: NR Enrolled: 42 Analyzed: 42	None	NR

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Lai 1998[78] Fair From prior report	RCT	Multiple sites (number NR) Hong Kong, Taiwan, Singapore	Study duration: 52 weeks Median followup: 365 days, range 2 to 409 days	A. Lamivudine 25 mg daily (n=142) B. Lamivudine 100 mg daily (n=143) C. Placebo (n=73)	A vs. B vs. C Age, median: 33 vs. 31 vs. 29 years Male: 73% vs. 74% vs. 72% Race: 100% Asian Serology: HBV DNA, median serum: 70.7 vs. 74.2 vs. 99.4 pg/mL (A vs. C, p=0.04, B vs. C, p=0.08) HBsAg positive: 100% vs. 100% vs. 100% HBeAg positive: 100% vs. 100% vs. 99% Anti-HBeAg positive: 0% vs. 4% vs. 3% ALT, median: 1.4 vs. 1.5 vs. 1.5 x ULN Histopathology: Knodell (histologic activity) score, mean: 9 vs. 8 vs. 8 Cirrhosis: 5% overall (individual groups NR)	Aged 16 to 70 years; detectable serum HBsAg and HBeAg for at least the previous 6 months; serum HBV DNA levels of at least 5 pg/mL; ALT levels <10 times the ULN for at least the previous 3 months	HCV, HDV, or HIV infection; decompensated liver disease; evidence of autoimmune hepatitis; received an investigational drug in the previous 30 days; received any antiviral, immunomodulator, cytotoxic agents, or corticosteroids in the previous 6 months; or received lamivudine in the previous 3 months	Screened: NR Eligible: NR Enrolled: 358 Analyzed: 357 Note: 1 patient in placebo group excluded due to no evidence of HBsAg for 6 months prior to enrollment	A vs. B vs. C Withdrawals: 6% (8/142) vs. 3% (4/143) vs. 4% (3/73)	Glaxo Wellcome Research and Developme nt

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Lampertico 1997[80] Fair From prior report	Open label RCT	Single site Italy	Study duration: 3 years (2 years treatment + 1 year followup) Mean duration of followup: 22 months	A. Interferon alfa 2b 6 MU intramuscular injection 3x/week (n=21) B. No treatment (n=21)	A vs. B Age, mean: 44 vs. 47 years Male: 80% vs. 90% Race: NR Serology: HBV DNA positive: 67% vs. 67% HBcAg, tissue: 82% vs. 81% IgM anti-HBc: 95% vs. 100% ALT, mean: 140 vs. 173 U/L Histopathology: HAI, median: 10 vs. 10 Cirrhosis: 19% vs. 14%	Age 18 to 65 years; chronic active HBV, with or without cirrhosis; HBsAg and anti-HBe in serum for ≥1 year; serum ALT >2x ULN; detectable serum HBV DNA in year preceding study	HCV, HDV or HIV positive; pregnant or lactating; drug abuse; alcoholism; antiviral or immunosuppressive therapy in 12 months preceding study; platelet counts <100,000/mL; white blood cell counts <3,000/mL; serum markers of autoimmunity; renal failure; history of hepatic decompensation; other serious medical illness	Screened: NR Eligible: NR Enrolled: 42 Analyzed: unclear	Withdrawals: 6/42 (14%) Loss to followup: 3/42 (7%)	Istituto Superiore di Sanità (Italian National Health Service)
Lin 1999[81] Fair From prior report *Additional publication: Liaw 1994[168]*	RCT	Single site China	18 weeks treatment + mean 7 years followup (range 1 to 11 years)	A. Interferon alfa 2a 4 to 5 MU/m^2 (n=67) B. Placebo (n=34)	A vs. B Age, mean: 32 vs. 32 years Male: 100% (both groups) Race: 100% Chinese (both groups) Serology: HBV DNA, pg/mL: ≤200: 18% vs. 18% 201 to 500: 22% vs. 12% 501 to 1,000: 7% vs. 18% >1,000: 52% vs. 53% ALT, mean: 227 vs. 256 U/L AFP, mean: 9 vs. 11 ng/mL Histopathology: Cirrhosis: 10% vs. 15%	Age 16 to 65 years; heterosexual male; HBsAg and HBeAg positive; elevated ALT (<40 U/L); liver biopsy within 3 months of study entry showing chronic active hepatitis or chronic lobular hepatitis; presence of serum HBV DNA	Immunosuppressive or antiviral therapy use; HDV infection; intravenous drug abuse; decompensated liver disease; other serious medical illness; AFP >100 ng/mL	Screened: NR Eligible: NR Enrolled: 120 Analyzed: 101	NR	The Prosperous Foundation (Taipei, Taiwan)

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Marcellin 2003[82] Fair From prior report	RCT	78 sites North America, Europe, Australia, and Southeast Asia	48 weeks duration and followup; safety analysis included all events that occurred within 30 days of drug discontinuation	A. Adefovir 10 mg daily (n=172) B. Placebo (n=170) *Excluding adefovir 30 mg daily (n=173); FDA-approved dose is 10 mg*	A vs. B Age, mean: 34 vs. 37 years Male: 76% vs. 71.3% Race: 35.1% vs. 35.9% white, 4.7% vs. 1.8% black, 59.6% vs. 60.5% Asian, 0.6% vs. 1.8% other Serology: HBV DNA, mean: 8.25 vs. 8.12 log copies/mL HBeAg positive: 100% ALT, mean: 3.4 vs. 3.4 times ULN Histopathology: Total Knodell score, mean: 9.01 vs. 9.65 Knodell necroinflammatory score, mean: 7.37 vs. 7.83 Knodell fibrosis score, mean: 1.64 vs. 1.83 Prior interferon alfa treatment (all groups): 24.9% (123/494)	Age 16 to 65 years with HBeAg positive chronic HBV and compensated liver disease. Chronic HBV defined as presence of serum HBsAg for at least 6 months, serum HBV DNA of at least 1 million copies per mL, and serum ALT 1.2 to 10 x ULN. Prothrombin time no more than 1 second above normal range, serum albumin greater than 3 g/dL, total bilirubin level no more than 2.5 mg/dL, serum creatinine level of no more than 1.5 mg/dL, adequate blood count. Negative pregnancy test and contraception use for women.	Coexisting serious medical or psychiatric illness; immune globulin, interferon, or other immune or cytokine based therapies with possible activity against HBV disease within 6 months before screening, organ or bone marrow transplantation, recent treatment with systemic corticosteroids, immunosuppressants, or chemotherapeutic agents; serum AFP level of at least 50 ng/mL, evidence of hepatic mass, liver disease not due to HBV, prior therapy for more than 12 weeks with a nucleoside or nucleotide analogue with activity against HBV, seropositivity for HIV or HCV or HDV.	Screened: NR Eligible: NR Enrolled: 342 Analyzed: 329 for histologic outcomes Note: 4 patients (1 in group A, 3 in group B) took no study medications and were excluded after randomization, baseline n=171 in group A, 167 in group B	A vs. B Withdrawals: 7.0% (12/171) vs. 7.8% (13/167) Loss to followup for baseline biopsies: 1.8% (3/171) vs. 3.6% (6/167) Loss to followup for total group: Unclear	Gilead Sciences

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Mazzella 1999[83] Fair From prior report	RCT	Number of sites NR Italy	6 months treatment 7.2 years mean followup	A. Interferon alfa, 5 MU/m^2 3 times weekly for 6 months, mean total dose 648 MU (n=33) B. No treatment (n=31)	A vs. B Age, mean: 36.3 vs. 40.6 years Male: 75.8 vs. 80.6% Race: NR Serology: HBsAg and HBeAg: 100% positive ALT, mean: 106 vs. 144 U/L Histopathology: Cirrhosis: 0% (both groups) Prior HBV treatment: NR	HBsAg, HBeAg and HBV DNA positive; elevated ALT; histologic evidence of chronic active or persistent hepatitis	Age <18 or >65 years; pregnancy; histologically proven cirrhosis; HDV or HIV antibodies; history of drug abuse	Screened: NR Eligible: NR Enrolled: 64 Analyzed: 64	NR	NR
Muller 1990[84] Fair From prior report	RCT	Unclear (likely single site) Germany	Study duration: 4 months Duration of followup: range 10 to 28 months (including treatment period)	A. Interferon alfa 2b 3 MU subcutaneous 3x/week (n=30) B. No treatment (n=28)	A vs. B Age: mean NR, range 18 to 65 years Male: 79.3% Race: NR Serology: HBsAg positive: 100% HBeAg positive: 96.4% vs. 96.3% of completers (n=55) ALT: NR Histopathology: Cirrhosis: 5.2% Prior HBV treatment: NR	Age 18 to 65 years; HBsAg and HBV DNA positive for ≥6 months	HDV or HIV positive; decompensated cirrhosis; chronic renal insufficiency; use of hemodialysis or immunosuppressive agents; previous organ transplantation; poor physical condition	Screened: NR Eligible: NR Enrolled: 58 Analyzed: 55	Withdrawals: 5.2% (3/58) Loss to followup: none reported	NR

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Realdi 1990[88] Fair From update	RCT	Multicenter (number of sites NR) Italy	4 month treatment with 16 months followup	A. Interferon alfa-2a 4.5 MU thrice weekly (n=39) B. No treatment (n=40)	Age, mean: 33 vs. 31 years Male: 64% vs. 74% Race: NR (set in Italy) Serology: HBV DNA 1+: 36% vs. 28% HBV DNA 2+: 18% vs. 38% HBV DNA 3+: 26% vs. 28% HBV DNA 4+: 21% vs. 8% HBeAg positive: 100% vs. 100% HBsAg positive: 100% vs. 100% ALT, mean x ULN: 4.8 vs. 4.0 Active cirrhosis: 18% vs. 15% Fibrosis: 1.5 vs. 1.5	Male and female, HBsAg, HBeAg, HBV DNA positive for at least 12 months, abnormal ALT; chronic hepatitis on biopsy within 6 months of entry	HDV or HIV coinfection	Screened: NR Eligible: NR Enrolled (randomized): 82 Analyzed: 79	Withdrawals: 3, 3.7% Loss to followup: 0	NR

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Tassopoulos 1999[85] Fair From prior report	RCT	Unclear (authors from North America and Europe)	A vs. B Followed for up to 52 weeks (unblinding at week 26 and further participation based on week 24 sera results) Median exposure (range): 366 (55 to 425) vs.189 (11 to 257) days	A. Lamivudine 100 mg daily (n=60) B. Placebo (n=64) *Note: Comparison data only available up to week 26*	A vs. B Age, median: 42 vs. 44 years Male: 83.3% vs. 76.6% Race: NR Serology: HBV DNA positive: 91.7% vs. 85.9% HBV DNA, median: 255.0 vs. 95.5 pg/mL HBsAg positive: 100% vs. 100% HBeAg negative: 98.3% vs. 98.4% Anti-HBeAg positive: 98.3% vs. 100% Abnormal ALT: 96.7% vs. 95.3% ALT x ULN, median: 3.2 vs. 3.3 Histopathology: Knodell necro-inflammatory score, median: 5 vs. 7 Cirrhosis: 13.3% vs. 15.6% (calculated from n's reported in table; reported %'s are 14% and 18%) Prior HBV treatment: NR, but allowed (see eligibility criteria)	Men and women 16 to 70 years of age with detectable HBsAg, detectable anti-HBeAg, and undetectable HBeAg at screening and for 6 months prior to screening; serum HBV DNA >2.5 pg/mL at screening, presence of HBV DNA in serum for 3 months before screening; ALT 1.5 to 10 times ULN at screening and at least once >3 months before screening with no value falling in reference range during intervening period	HCV, HDV, HIV positive; presence of decompensated liver disease; evidence of autoimmune hepatitis; interferon treatment within previous 6 months	Screened: 260 Eligible: 125 Enrolled: 125 Analyzed: 124	A vs. B Withdrawals: 11.7% (7/60) vs. 6.3% (4/64)	Glaxo Wellcome Research and Develop-ment

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Thomas 1994[89] Fair From update	RCT	6 countries (United Kingdom, Hong Kong, Spain, Australia, Argentina, Switzerland based on author locations)	24 weeks duration and 12 month followup post-treatment	A. Interferon-α2a 2.5 MIU thrice weekly (n=45) B. Interferon-α2a 5 MIU thrice weekly (n=47) C. Interferon-α2a 10 MIU thrice weekly (n=44) D. No treatment (n=40)	Age: NR Male: 89% vs. 83% vs. 98% vs. 88% Europid: 58% vs. 57% vs. 68% vs. 72% Chinese: 36% vs. 37% vs. 27% vs. 25% Black: 6% vs. 6% vs. 5% vs. 3% With cirrhosis: 9% vs. 15% vs. 34% vs. 25% HIV positive: 9% vs. 2% vs. 9% vs. 7% ALT ratio to ULN ≤1: 18% vs. 20% vs. 14% vs. 30% ALT ratio to ULN >1 to 3: 47% vs. 50% vs. 43% vs. 42% ALT ratio to ULN >3 to 5: 22% vs. 11% vs. 18% vs. 15% ALT ratio to ULN >5: 13% vs. 19% vs. 25% vs. 13%	Male and female 18 to 65 with histological diagnosis of chronic active hepatitis, with or without cirrhosis	Minimal hepatitis, chronic persistent hepatitis, decompensated cirrhosis, HCC, previously received interferon-α, pregnant	Screened: NR Eligible: 191 Enrolled (randomized): NR Analyzed: 176	Withdrawals: NR Loss to followup: NR	NR

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Tseng 2014[90] Fair From update	RCT	5 sites Taiwan	52 weeks duration and followup	A. Entecavir 0.5 mg daily (n=22) B. Placebo (n=20)	Age, mean: 45 vs. 42 years Male: 59% vs. 55% Race: NR (set in Taiwan) Serology: HBV DNA, mean, log_{10} copies/mL: 6.0 vs. 6.3 HBeAg positive: 32% vs. 45% Anti-HBe positive: 64% vs. 45% ALT, mean x ULN: 0.6 vs. 0.6 Histopathology: Knodell score, mean total: 5.1 vs. 6.7 Knodell score, mean necroinflammatory: 3.1 vs. 4.6 Knodell score, mean fibrosis: 1.1 vs. 2.0 Prior HBV treatment: None	Male and female 18 to 65 with chronic HBV; detectable HBsAg for ≥24 weeks, or for <24 weeks and negative for IgM anti-HBc and chronic HBV confirmed by biopsy; at least 2 ALT <ULN within 1 year that were ≥3 months apart; normal ALT at screening; HBV DNA $\geq 10^4$ copies/mL by PCR; Knodell score ≥4 within a year of randomization; and negative pregnancy test for women with childbearing potential	Coinfection with HIV, HCV, HDV or other liver disease including alcoholic, autoimmune, or biliary; decompensated liver disease; therapy with agents active against HBV within 24 weeks of randomization; more than 12 weeks of therapy with nucleoside or nucleotide agents active against HBV; prior entecavir; allergy to nucleoside analogs; hemoglobin, platelets, or neutrophils below specific thresholds; creatinine or anti-nuclear antibody titer above specified thresholds	Screened: 380 Eligible: 95 Enrolled (randomized): 43 Analyzed: 39	Withdrawals: 9% (4/43) Loss to followup: NR	Bristol Myers Squibb and the Department of Health, Taiwan
Wen 2014[91] Fair From update	RCT	1 site China	48 weeks duration and 1 year followup	A. Adefovir dipivoxil 10 mg daily (n=252) B. Placebo (n=274)	Age, mean: 38 vs, 37 Male: 73% vs. 70% Race: NR (set in China) HBV DNA level of 10^4 to 10^7 IU/mL ALT: 80 to 400 U/mL	Male and female 18 to 65 with HBsAg positive for at least 6 months	Coinfection with HIV, HCV, HDV, positive results for autoantibody, decompensated hepatosis, hyperthyroidism, psychosis, pregnancy	Screened: NR Eligible: NR Enrolled (randomized): 526 Analyzed: NR	Withdrawals: NR Loss to followup: NR	Non-profit

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Yalcin 2004[86] Fair From prior report	RCT	One site Turkey	Duration: 12 months Active treatment: 12 weeks	A. Lamivudine 100 mg daily (n=13) B. Control (n=33)	A vs. B Age, mean: 23.3 vs. 24.8 years Male: 53.8% vs. 54.5% Race: NR Serology: HBV DNA, median: 4,116 vs. 4,094 pg/mL HBsAg positive: 100% in both groups HBeAg positive: 100% in both groups ALT, median: 27 vs. 30 IU/L Histopathology: Knodell inflammation score, median: 1.0 vs. 2.0 Knodell fibrosis score, median: 0 in both groups Prior HBV treatment: 0% vs. 0% (ineligible)	Adult patients with no previous antiretroviral treatment; HBsAg positive for >6 months; positive HBeAg; serum HBV DNA >1 pg/mL; persistently normal ALT values on at least 3 occasions in the previous 6 months; histological evidence of absent or minimal changes in liver biopsy; negative urine or serum pregnancy test for women of childbearing age; all men with partners of childbearing age and premenopausal women required to use reliable contraception during study and 6 months after treatment completion	Previously treated with interferon or antiviral or immunosuppressive medications; positive for antibody to HDV, HCV, HIV and pregnancy; with decompensated liver disease; with medical condition associated with chronic liver disease other than viral hepatitis; alcohol and/or drug abuse within 1 year of study entry	Screened: 53 Eligible: 46 Enrolled: 46 Analyzed: 46	Withdrawals: 2.2% (1/46), NR by group Loss to followup NR	NR

Appendix B Table 4. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Yao 1999[87] Fair From prior report *Additional publications :Yao 2000[169] and Yao 2009[170]*	RCT	Multiple sites (number NR) China	Blinded treatment duration: 12 weeks Open-label treatment: 9 months	A. Lamivudine 100 mg daily (n=329) B. Placebo (n=110) *N=429 for efficacy, 439 for harms*	A vs. B Age: 32.2 vs. 30.8 years *(unclear if this is mean or median)* Male: 74.2% vs. 69.2% Race: NR, conducted in China Serology: HBV DNA, median: 66.4 vs. 60.4 pg/mL HBsAg positive: 100% HBeAg positive: 100% ALT, median: 1.0 (range 0.3 to 6.7) vs. 1.0 (range 0.2 to 17.3) x ULN Histopathology: NR Prior HBV treatment: NR	Aged 16 to 65 years; HBeAg and HBsAg positive in the 6 months prior to screening; detectable HBV DNA at screening; ALT levels <10 x ULN at screening	HCV, HDV, or HIV infection; decompensated liver disease; evidence of autoimmune or hereditary liver disease; bone marrow depression; serious concurrent illness; alcoholism; drug abuse; elevated creatinine concentration >1.5 x ULN; had received antiviral or cytotoxic agents, corticosteroids, or immunomodulators in the previous 6 months; history of hypersensitivity to nucleoside analogs; pregnancy or lactation; females of childbearing age not using contraceptives	Screened: 440 Eligible: 429 Enrolled: 429 Analyzed: 429	A vs. B Withdrawals: 2.8% (9/322) vs. 1.9% (2/107)	NR

Abbreviations: AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e-antigen; anti-HBeAg = antibody to hepatitis B e antigen; DNA = deoxyribonucleic acid; FDA = U.S. Food and Drug Administration; HAI = histology activity index; HBcAg = hepatitis B core antigen; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; IgM = immunoglobulin M; NR = not reported; PCR = polymerase chain reaction; RCT = randomized controlled trial; U = units; ULN = upper limit of normal.

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Bozkaya 2005[74] From prior report	A: Lamivudine 100 mg daily (n=18) B: Untreated group with raised ALT (n=19) C: Untreated group with normal ALT (n=18)	Screened: 390 Eligible: 55 Enrolled: 55 Analyzed: 55	N/A	A vs. B vs. C Month 12 ALT normalization A vs. B (group C had normal ALT at baseline): 44% (8/18) vs. 21% (4/19); RR 2.1 (95% CI, 0.7 to 5.8)	NR	NR
Chan 2007[75] From prior report	A. Lamivudine 100 mg daily (n=89) B. Placebo (n=47)	Screened: 443 Eligible: 139 Enrolled: 139 Analyzed: 136	OR adjusted for baseline HBV DNA and ALT levels	A vs. B Month 24 Complete response: 56% (50/89) vs. 11% (5/47); adjusted OR 10.8 (95% CI, 3.8 to 30.2) HBV <10,000 copies/mL: 58% (52/89) vs. 19% (9/47); RR 3.1 (95% CI, 1.7 to 5.6) HBV undetectable: 26% (23/89) vs. 6% (3/47); RR 4.1 (95% CI, 1.3 to 12.8) HBsAg loss: 0 vs. 0 ALT normalization: 74% (66/89) vs. 36% (17/47); RR 2.1 (95% CI, 1.4 to 3.1) Month 30 Complete response: 26% (23/89) vs. 19% (9/47); RR 1.4 (95% CI, 0.7 to 2.7) HBV <10,000 copies/mL: 33% (29/89) vs. 26% (12/47); RR 1.3 (95% CI, 0.7 to 2.3) HBV undetectable: 10% (9/89) vs. 2% (1/47); RR 4.8 (95% CI, 0.6 to 36.4) HBsAg loss: 1% (1/89) vs. 0% (0/47); RR 1.6 (95% CI, 0.07 to 38.5) ALT normalization: 60% (53/89) vs. 38% (18/47); RR 1.6 (95% CI, 1.0 to 2.3) Necroinflammatory improvement (Knodell ≥2 points): 78% (14/18) vs. 25% (2/8); RR 3.1 (95% CI, 0.9 to 10.6) Fibrosis improvement (Ishak ≥2 points): 33% (6/18) vs. 0% (0/8); RR 6.2 (95% CI, 0.4 to 97.7) Complete response =HBV DNA <10,000 copies/mL + ALT normalization; HBV by PCR, detection limit <100 copies/mL	A vs. B Mortality: NR HCC: 3.4% (3/89) vs. 2.1% (1/47); RR 1.6 (95% CI, 0.2 to 14.8) Note: Study not powered to detect effect of lamivudine on prevention of HCC	A vs. B Serious adverse events15% (13/89) vs. 13% (6/47) RR 1.1 (95% CI, 0.5 to 2.8)

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Dienstag 1999[76] From prior report	A. Lamivudine 100 mg daily (n=66) B. Placebo (n=71)	Screened: 217 Eligible: NR Enrolled: 143 Analyzed: 137 *143 enrolled but 6 excluded at the baseline visit because they did not have 6 months of serum HBsAg*	Adjustments for ORs: ALT, HBV DNA, HAI (Knodell score), race, age, sex, weight, and the presence of cirrhosis	A vs. B 1 year results (end of treatment): HBV DNA loss: 44% (28/63) vs. 16% (11/69); RR 2.79 (95% CI, 1.52 to 5.12) HBeAg seroconversion: 17% (11/63) vs. 6% (4/69); RR 3.01 (95% CI, 1.01 to 8.98) HBeAg loss: 32% (21/66) vs. 11% (8/71); RR 2.82 (95% CI, 1.34 to 5.93) ALT normalization: 41% (27/66) vs. 7% (5/68); RR 5.56 (95% CI, 2.28 to 13.58) Histologic improvement (≥2 points on HAI): 52% (34/66) vs. 23% (16/71); RR 2.29 (95% CI, 1.40 to 3.73) 16 month results (4 months post-treatment): HBsAg loss: 2% (1/66) vs. 0% (0/71); RR 3.22 (95% CI, 0.13 to 77.78) HBeAg seroconversion: 17% (11/63) vs. 9% (6/69); RR 2.01 (95% CI, 0.79 to 5.11) HBeAg loss: 29% (19/66) vs. 15% (11/71); RR 1.86 (95% CI, 0.96 to 3.60) Time point NR: Likelihood of histologic response: adjusted OR 7.5, (95% CI, 2.7 to 20.9) Likelihood of HBeAg seroconversion: adjusted OR 9.7 (95% CI, 1.7 to 56.1) Seroconversion =HBV DNA loss + HBeAg loss + anti-HBe development; HBV DNA by hybridization, detection limit 1.6 pg/mL	Mortality: None	A vs. B Serious adverse events 0% (0/66) vs. 0% (0/71) RR 1.1 (95% CI, 0.0 to 53) (inferred)
Hadziyannis 2003[77] From prior report	A. Adefovir 10 mg daily (n=123) B. Placebo (n=62)	Screened: 391 Eligible: 235 Enrolled: 185 Analyzed: 178 for histologic outcomes *Note: 1 patient in group B never received treatment and was excluded, baseline n=123 in group A, 61 in group B*	N/A	A vs. B Histologic improvement: 64% (77/121) vs. 33% (19/57); RR 1.9 (95% CI, 1.3 to 2.8) HBV DNA undetectable: 51% (63/123) vs. 0% (0/61); RR 64 (95% CI, 4.0 to 1,009) ALT normalization: 72% (84/116) vs. 29% (17/59); RR 2.5 (95% CI, 1.7 to 3.8) Histologic improvement =≥2 point reduction in Knodell necro-inflammatory score with no increase in Knodell fibrosis score; HBV DNA by PCR, detection limit 400 copies/mL	NR	A vs. B Serious adverse events 3% (4/123) vs. 7% (4/61) RR 0.5 (95% CI, 0.1 to 1.9) Withdrawal due to adverse events: 0% (0/123) vs. 0% (0/61) RR 0.5 (95% CI, 0.0 to 25) Any adverse events: 76% (94/123) vs. 74% (45/61) RR 1.0 (95% CI, 0.9 to 1.2) *Note: any adverse event refers to those reported by at least 5% of patients in group A*

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Lai 1997[79] From prior report	A. Lamivudine 25 mg daily (n=12) B. Lamivudine 100 mg daily (n=12) C. Lamivudine 300 mg daily (n=12) D. Placebo (n=6)	Screened: NR Eligible: NR Enrolled: 42 Analyzed: 42	N/A	(A+ B + C) vs. D HBV DNA: >90% decrease vs. no significant change HBeAg loss: 0/36 vs. 0/6 ALT: no change with treatment HBV DNA: Abbott assay, method and detection limit NR	NR	A vs. B Serious adverse events: 0% (0/36) vs. 0% (0/6) RR 0.2 (95% CI, 0.0 to 8.8)
Lai 1998[78] From prior report	A. Lamivudine 25 mg daily (n=142) B. Lamivudine 100 mg daily (n=143) C. Placebo (n=73)	Screened: NR Eligible: NR Enrolled: 358 Analyzed: 357 *Note: 1 patient in placebo group excluded due to no evidence of HBsAg for 6 months prior to enrollment*	N/A	A vs. B vs. C HBeAg seroconversion and HBV DNA undetectable: 13% (17/135) vs. 16% (22/140) vs. 4% (3/70); RR of A vs. C: 2.94 (95% CI, 0.89 to 9.69); RR of B vs. C: 3.67 (95% CI, 1.14 to 11.83) Sustained ALT response: 65% (64/98) vs. 72% (68/95) vs. 24% (12/50); RR of A vs. C: 2.72 (95% CI, 1.63 to 4.55); RR of B vs. C: 2.98 (95% CI, 1.79 to 4.96) Histologic improvement: 49% (70/142) vs. 56% (80/143) vs. 25% (18/73); RR of A vs. C: 2.00 (95% CI, 1.29 to 3.09); RR of B vs. C: 2.27 (95% CI, 1.48 to 3.48) Treated vs. untreated HBeAg seroconversion and HBV DNA undetectable: 14.2% (39/275) vs. 4% (3/70); RR 3.31 (95% CI, 1.05 to 10.40) Sustained ALT response: 68.4% (132/193) vs. 24% (12/50); RR 2.85 (95% CI, 1.72 to 4.71) Histologic improvement: 52.6% (150/285) vs. 25% (18/73); RR 2.13 (95% CI, 1.41 to 3.24) HBV DNA by hybridization, detection limit 1.6 pg/mL; seroconversion =loss of antigen and development of antibody; sustained ALT response =2 consecutive normal values with no 2 consecutive abnormal values, or 1 normal value at 52 weeks; histologic improvement =≥2 point decrease in Knodell necroinflammatory score	Mortality: None	A + B vs. C Serious adverse events 1.8% (5/285) vs. 0% (0/73) RR 2.9 (95% CI, 0.2 to 51) Any adverse event 78.6% (224/285) vs. 77% (56/73) RR 1.0 (95% CI, 0.9 to 1.2) (combined treatment arms)

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Lampertico 1997[80] From prior report	A. Interferon alfa 2b 6 MU intramuscular injection 3x/week (n=21) B. No treatment (n=21)	Screened: NR Eligible: NR Enrolled: 42 Analyzed: unclear	N/A	A vs. B 2-year outcomes (end of treatment) HBsAg loss: 0/21 vs. 0/21 Loss of HBV DNA + ALT normalization: 38% (8/21) vs. 10% (2/21); RR 4.0 (95% CI, 0.96 to 17) HAI (Knodell score) improvement (paired biopsy data available for 13 treated and 13 untreated patients): 33% (7/21) vs. 10% (2/21); RR 3.5 (95% CI 0.82 to 15); 3-year outcomes (post treatment) Loss of HBsAg: 10% (2/21) vs. 0% (0/21); RR 5 (95% CI, 0.25 to 98) Loss of HBV DNA + ALT normalization: 29% (6/21) vs. 0% (0/21); RR 13 (95% CI, 0.78 to 217) Loss of HBsAg and/or HBV DNA: 33% (7/21) vs. 0% (0/21); RR 15 (95% CI, 0.91 to 247) HBV DNA by hybridization, detection limit 1 pg/mL	A vs. B HCC: 4.8% (1/21) vs. 0% (0/21); RR 3 (95% CI, 0.13 to 70)	A vs. B Withdrawals due to adverse events: 4% (5/21) vs. 0% (0/21) RR 11 (95% CI, 0.65 to 187)
Lin 1999[81] From prior report *Additional publication: Liaw 1994*[168]	A. Interferon alfa 2a 4 to 5 MU/m^2 (n=67) B. Placebo (n=34)	Screened: NR Eligible: NR Enrolled: 120 Analyzed: 101	Age, baseline ALT, baseline HBV DNA, preexisting cirrhosis, AFP level, duration of HBV, treatment regimen	A vs. B. ALT normalization: 48.7% (37/76) vs. 20% (8/40), RR 2.43 (95% CI, 1.26 to 4.72) Composite outcome (HBeAg + HBV DNA loss): 13.2% (10/76) vs. 0% (0/40), RR 11.18 (95% CI, 0.67 to 186) HbeAg seroconversion: 42% (28/67) vs. 24% (8/34) Seroclearance: 62% (41/67) vs. 67% (23/34) HbsAg loss: 0% (0/67) vs. 0% (0/34)	A vs. B Mortality: 1.5% (1/67) vs. 12% (4/34); RR 0.13 (95% CI, 0.01 to 1.09) HCC: 1.5% (1/67) vs. 12% (4/34); RR 0.13 (95% CI, 0.01 to 1.09) Incident cirrhosis: 12% (8/67) vs. 15% (5/34); RR 0.81 (95% CI, 0.29 to 2.29)	NR

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Marcellin 2003[82] From prior report	A. Adefovir 10 mg daily (n=172) B. Placebo (n=170) Excluding adefovir 30 mg daily (n=173); FDA-approved dose is 10 mg	Screened: NR Eligible: NR Enrolled: 342 Analyzed: 329 for histologic outcomes *Note: 4 patients (1 in group A, 3 in group B) took no study medications and were excluded after randomization, baseline n=171 in group A, 167 in group B*	Adjustments made for 7 geographic regions	A vs. B HBV DNA undetectable: 21.1% (36/171) vs. 0% (0/167); RR 71.30 (95% CI, 4.41 to 1,152.4) HBeAg loss: 24.0% (41/171) vs. 10.6% (17/161); RR 2.27 (95% CI, 1.35 to 3.83); HBeAg seroconversion: 11.7% (20/171) vs. 5.6% (9/161); RR 2.09 (95% CI, 0.98 to 4.46) ALT normalization: 48.2% (81/168) vs. 15.9% (26/164); RR 3.04 (95% CI, 2.07 to 4.47) Histologic improvement (unassessable data: 1 to 2%, missing data: 9 to 10%): 53.0% (89/168) vs. 25.5% (41/161); adjusted RR 2.08 (95% CI, 1.54 to 2.81) HBV DNA by PCR, detection limit 400 copies/mL; seroconversion =loss of antigen and development of antibody; histologic improvement =≥2 point decrease in Knodell necroinflammatory score without increase in Knodell fibrosis score	NR	A vs. B Overall adverse events: NR Serious adverse events: NR (severe only) Withdrawal due to adverse events: 1.83% (3/171) vs. 0.6% (1/167) Diarrhea: 13.5% (23/171) vs. 7.8% (13/167) Nausea: 9.9% (17/171) vs. 13.8% (23/167) *Note: n values calculated from proportions provided by study, based on the number of participants at baseline* *Combined treatment arms*
Mazzella 1999[83] From prior report	A. Interferon alfa, 5 MU/m^2 3 times weekly for 6 months, mean total dose 648 MU (n=33) B. No treatment (n=31)	Screened: NR Eligible: NR Enrolled: 64 Analyzed: 64	N/A	A vs. B HBV DNA loss: 78.8% (26/33) vs. 58.1% (18/31); RR 1.36 (95% CI, 0.96 to 1.92) HBsAg loss: 36.4% (12/33) vs. 9.7% (3/31); RR 3.76 (95% CI, 1.17 to 12.06) HBeAg loss: 90.9% (30/33) vs. 61.3% (19/31); RR 1.48 (95% CI, 1.10 to 2.00) ALT normalization: 66.7% (22/33) vs. 35.5% (11/31); RR 1.88 (95% CI, 1.10 to 3.20) *Definition of HBV DNA loss unclear; detection limit reported for PCR, but data in Table 2 from hybridization assay*	A vs. B Mortality: 0% (0/33) vs. 6.5% 2/31; RR 0.19 (95% CI, 0.01 to 3.77) HCC: 3.0% (1/33) vs. 6.5% (2/31) ; RR 0.47 (95% CI, 0.04 to 4.92) Incident cirrhosis: 12.1% (4/33) vs. 19.4% (6/31); RR 0.63 (95% CI, 0.2 to 2.01)	NR
Muller 1990[84] From prior report	A. Interferon alfa 2b 3 MU subcutaneous 3x/week (n=30) B. No treatment (n=28)	Screened: NR Eligible: NR Enrolled: 58 Analyzed: 55	N/A	A vs. B Complete response: 3.6% (1/28) vs. 0% (0/27); RR 2.90 (95% CI, 0.12 to 68.15) Partial response: 28.6% (8/28) vs. 0% (0/27); RR 16.41 (95% CI, 0.99 to 271.15) HBV DNA by hybridization, detection limit NR; complete response =elimination of HBsAg, HBeAg, and HBV DNA and normalization of ALT; partial response =elimination of HBeAg and HBV DNA and normalization of ALT while HBsAg persisted	NR	Interferon alfa 2b (no results presented for untreated group) Withdrawals due to adverse events: 3.3% (1/30)

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Realdi 1990[88] From update	A. Interferon alfa-2a 4.5 MU thrice weekly (n=39) B. No treatment (n=40)	Screened: NR Eligible: NR Enrolled (randomized): 82 Analyzed: 79	N/A	A vs. B End of treatment: HBV DNA negative: 13/39 (33%) vs. 5/40 (12.5%) HBeAg negative: 8/39 (20.5%) vs. 4/40 (10%) ALT normal: 12/39 (31%) vs. 5/40 (12.5%) End of followup: HBV DNA negative: 16/39 (41%) vs. 10/40 (25%) HBeAg negative: 13/39 (33%) vs. 6/40 (15%) ALT normal: 23/39 (59%) vs. 14/40 (35%) Liver biopsy fibrosis score: 1.3 vs. 1.1	NR	Side effects of interferon mild (41%) or moderate (51%); no mention of harms in nontreated group; no specific harms mentioned Withdrawals due to adverse events: 0% (0/39) vs. 0% (0/40)
Tassopoulos 1999[85] From prior report	A. Lamivudine 100 mg daily (n=60) B. Placebo (n=64) *Note: Comparison data only available up to week 26*	Screened: 260 Eligible: 125 Enrolled: 125 Analyzed: 124	N/A	A vs. B Week 24 Complete response: 63.0% (34/54) vs. 5.6% (3/54); RR 11.33 (95% CI, 3.70 to 34.69) Partial response: 27.8% (15/54) vs. 20.4% (11/54); RR 1.36 (95% CI, 0.69 to 2.69) HBsAg loss: 0% (0/60) vs. 1.6% (1/64); RR 0.36 (95% CI, 0.015 to 8.55) HBsAg seroconversion: 0 vs. 0 DNA by hybridization, detection limit 2.5 pg/mL; complete response =HBV DNA loss + ALT normalization; partial response =HBV DNA loss without ALT normalization	NR	A vs. B Any adverse events 46.7% (28/60) vs. 61.5% (40/65) RR 0.76 (95% CI, 0.54 to 1.06) Serious adverse events 5.0% (3/60) vs. 6.2% (4/65) RR 0.81 (95% CI, 0.19 to 3.48) Withdrawal due to adverse events 1.7% (1/60) vs. 0% (0/65) RR 3.25 (95% CI, 0.13 to 78.18) Diarrhea 5.0% (3/60) vs. 3.1% (2/65) RR 1.63 (95% CI, 0.28 to 9.39) Nausea and vomiting (5/60) vs. (1/65) RR 5.42 (95% CI, 0.65 to 45.05)

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Thomas 1994[89] From update	A. Interferon-α2a 2.5 MIU thrice weekly B. Interferon-α2a 5 MIU thrice weekly C. Interferon α2a 10 MIU thrice weekly D. No treatment	Screened: NR Eligible: 191 Enrolled (randomized): NR Analyzed: 176	N/A	A vs. B vs. C vs. D HBV DNA clearance: 67% (30/45) vs. 60% (28/47) vs. 61% (27/44) vs. 35% (14/40) HBeAg clearance: 33% (15/45) vs. 38% (18/47) vs. 50% (22/44) vs. 15% (6/40) Response: 33% vs. 34% vs. 43% vs. 13% Response =complete response + partial response; complete response =suppression of all signs of viral replication and seroconversion from HBeAg and HBsAg and significant improvement of necroinflammatory lesions on followup biopsy; partial response =suppression of signs of viral replication and seroconversion from HBe to anti-HBe with persistence of HBsAG and some signs of improvement in necroinflammatory lesions	NR	Only provided for interferon groups
Tseng 2014[90] From update	A. Entecavir 0.5 mg daily (n=22) B. Placebo (n=21)	Screened: 380 Eligible: 95 Enrolled (randomized): 43 Analyzed: 42 (39 for biopsy)	N/A	A vs. B HBV DNA loss: 73% (16/21) vs. 0% (0/18); RR 28.5 (95% CI, 1.8 to 444) HBeAg loss (of those HBeAg positive at baseline): 29% (2/7) vs. 0% (0/8); RR 5.6 (95% CI, 0.31 to 101) HBeAg seroconversion (of those HBeAg positive at baseline): 29% (2/7) vs. 0% (0/8); RR 5.6 (95% CI, 0.31 to 101) HbsAg loss: 0 vs. 0 HbsAg seroconversion: 0 vs. 0 ALT, mean x ULN: 0.5 (SD 0.2) vs. 0.6 (SD 0.2), p=0.009 Histologic improvement: 38% (8/21) vs. 44% (8/18); RR 0.86 (95% CI, 0.40 to 1.8) HBV DNA by PCR, detection limit 60 IU/mL; seroconversion not defined	NR	NR

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Wen 2014[91] From update	A. Adefovir dipivoxil 10 mg daily (n=252) B. Placebo (n=274)	Screened: NR Eligible: NR Enrolled (randomized): 526 Analyzed: NR	N/A but analyzed results for genotypes B and C separately	A vs. B (see figure 2 for all values; estimated) HBV DNA <500IU/mL at 3, 6, 12 months favors A, p≤0.05 HBV DNA decline rate (>3lg IU/mL) at 3, 6, 12 months favor A, p≤0.05 ALT normalization rate at 3, 6, 12 months favors A, p≤0.05 HBeAg seroclearance rate at 3, 6, 12 months favors A, p≤0.05 HBeAg seroconversion rate at 3, 6, 12 months favors A, p≤0.05 HBV DNA level at 3, 6 months no difference between groups, p>0.05 HBV DNA level at 12 months favors A in genotype B only, p≤0.05	NR	NR
Yalcin 2004[86] From prior report	A. Lamivudine 100 mg daily (n=13) B. Control (n=33)	Screened: 53 Eligible: 46 Enrolled: 46 Analyzed: 46	N/A	A vs. B Month 3 (on treatment) Transient loss of HBV DNA: 100% (13/13) vs. 0% (0/33); RR 65.57 (95% CI, 4.18 to 1029.05) Month 12 (treatment plus post-treatment followup) Loss of HBV DNA: 7.7% (1/13) vs. 3.0% (1/33); RR 2.54 (95% CI, 0.17 to 37.64) Loss of HBsAg: 0/13 vs. 0/33; RR 2.43 (95% CI, 0.051 to 116.46) HBeAg seroconversion: 7.7% (1/13) vs. 3.0% (1/33); RR 2.54 (95% CI, 0.17 to 37.64) HBeAg seroconversion + HBV DNA loss (At 12 months, or SVR): 7.7% (1/13) vs. 3.0% (1/33); RR 2.54 (95% CI, 0.17 to 37.64) HBV DNA by hybridization, detection limit 1 pg/mL; seroconversion =loss of antigen and development of antibody	NR	A vs. B Serious adverse events: 0% (0/13) vs. 0% (0/33) RR 2.43 (95% CI, 0.051 to 116.46) Any adverse events, withdrawals due to adverse events, specific adverse events: NR

Appendix B Table 5. Trials of HBV Antiviral Treatment vs. Placebo or No Treatment – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Yao 1999[87] From prior report *Additional publications:Yao 2000[169] and Yao 2009[170]*	A. Lamivudine 100 mg daily (n=322) B. Placebo (n=107) *N=429 for efficacy, 439 for harms*	Screened: 440 Eligible: 429 Enrolled: 429 Analyzed: 429	N/A	A vs. B Cumulative undetectable HBV DNA at week 12: 92.2% (270/293) vs. 14.1% (14/99); RR 6.52 (95% CI, 4.01 to 10.56) Sustained undetectable HBV DNA at week 12: 78.2% (229/293) vs. 11.1% (11/99); RR 7.03 (95% CI, 4.02 to 12.32) HBeAg loss: 8.1% (23/284) vs. 5.3% (5/94); RR 1.52 (95% CI, 0.60 to 3.89) Anti-HBe development: 10.2% (29/284) vs. 6.4% (6/94); RR 1.60 (95% CI, 0.69 to 3.73) HBeAg seroconversion: 5.3% (15/284) vs. 4.3% (4/94); RR 1.24 (95% CI, 0.42 to 3.65) Sustained ALT response : 60.3% (91/151) vs. 27.5% (14/51); RR 2.20 (95% CI, 1.38 to 3.49) HBV DNA by hybridization, detection limit 1.6 pg/mL; seroconversion not defined; sustained ALT response =value at or below ULN with no subsequent increases above ULN	NR	A vs. B Any adverse events: 41.9% (138/329) vs. 40.9% (45/110) RR 1.03 (95% CI, 0.79 to 1.33) Serious adverse events: NR Withdrawal due to adverse events: 0% (0/329) vs. 0% (0/110) RR 0.34 (95% CI, 0.007 to 16.85) Diarrhea: 4.0% (13/329) vs. 2.7% (3/110) RR 1.45 (95% CI, 0.42 to 4.99) Nausea, vomiting: 4.0% (13/329) vs. 5.5% (6/110); RR 0.72 (95% CI, 0.28 to 1.86)

Abbreviations: AFP = alpha-fetoprotein; ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e-antigen; CI = confidence interval; DNA = deoxyribonucleic acid; FDA = U.S. Food and Drug Administration; HAI = histology activity index; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; N/A = not applicable; NR = not reported; OR = odds ratio; PCR = polymerase chain reaction; RR = relative risk; SD = standard deviation; SVR = sustained virologic response; ULN = upper limit of normal.

Appendix B Table 6. Trials of HBV Antiviral Treatment – Quality Assessment

Author, year From prior report or update	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and with-drawals reported?	Loss to followup: differential/ high?	Analyze people in the groups in which they were randomized?	Quality
Bozkaya 2005[74] From prior report	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	No/No	Yes	Fair
Chan 2007[75] From prior report	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/No	Yes	Fair
Chang 2006[92]; Gish 2007[171]; Chang 2009[136] From prior report	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Dienstag 1999[76] From prior report	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Fair
Hadziyannis 2003[77] From prior report	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Hou 2015[98] From update	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Good
Lai 1997[79] From prior report	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Fair
Lai 1998[78] From prior report	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Fair
Lai 2002[94] From prior report	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Lai 2006[93] From prior report	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Lampertico 1997[80] From prior report	Yes	Yes	Yes	Yes	No	No	No	Yes	Unclear	Yes	Fair
Lau 2005[95] From prior report	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Lee 2017[99] From update	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/Yes	Yes	Fair
Lin 1999[81], Liaw 1994[168] From prior report	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Marcellin 2003[82] From prior report	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Unclear	Fair
Marcellin 2008[96] (2 studies in article) From prior report	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No/No	Yes	Fair
Mazzella 1999[83] From prior report	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Muller 1990[84] From prior report	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Realdi 1990[88] From update	Unclear	Unclear	No	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Ren 2007[97] From prior report	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair

Appendix B Table 6. Trials of HBV Antiviral Treatment – Quality Assessment

Author, year From prior report or update	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and with-drawals reported?	Loss to followup: differential/ high?	Analyze people in the groups in which they were randomized?	Quality
Suh 2010[100] From update	Unclear	Unclear	No	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
Tassopoulos 1999[85] From prior report	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Thomas 1994[89] From update	Unclear	Unclear	Unclear	Yes	Unclear	No	No	Yes	Unclear/No	Yes	Fair
Tseng 2014[90] From update	Unclear	Unclear	No	Yes	Yes	Unclear	Unclear	Yes	No/No	Yes	Fair
Wen 2014[91] From update	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	No	Unclear	Unclear	Fair
Yalcin 2004[86] From prior report	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Yao 1999[87], Yao 2000[169], Yao 2009[170] From prior report	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Fair
Yao, 2007[101] From update	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Good
Zheng, 2010[102] From update	Yes	Unclear	Unclear	Yes	Yes	No	No	Yes	No/No	Yes	Fair

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Chang 2006[92]; Gish 2007[171]; Chang 2009[136] Good From prior report	RCT	137 centers North America, Asia, Australia, South America	96 weeks (52 weeks treatment + additional 44 weeks for partial responders; results for responders, partial responders and non-responders included in results)	A. Entecavir 0.5 mg daily (n=354) B. Lamivudine 100 mg daily (n=355)	A vs. B Age, mean: 35 vs. 35 years Male: 77% vs. 74% Race: Asian: 58% vs. 57% White: 40% vs. 40% Black: 2% vs. 2% Other: <1% vs. 1% Serology: HBV DNA: 2.56 vs. 2.61 MEq/mL, 9.62 vs. 9.69 log copies/mL HBeAg positive: 98% vs. 99% Anti-HBe negative: 97% vs. 97% ALT, mean: 140.5 vs. 146.3 IU/L Histopathology: Knodell necroinflammatory score, mean (for n=659 with biopsy specimens): 7.8 vs. 7.7 Ishak fibrosis score, mean (n=659): 2.3 vs. 2.3 Cirrhosis: 8% vs. 8% Prior interferon treatment: 13% vs. 13% Prior lamivudine treatment: 3% vs. 3%	Age ≥16 years, HBeAg positive, compensated liver function, serum HBsAg present for at least 24 weeks prior to screening, evidence of chronic HBV per liver biopsy, evidence of HBV DNA at least 4 weeks prior to screening, ALT 1.3 to 10x ULN	HCV, HDV or HIV coinfection, other liver disease, use of antiviral agents within 24 weeks of randomization, prior lamivudine use lasting >12 weeks, AFP >100 mg/mL, history of ascites requiring diuretics or paracentesis, previous entecavir treatment	Screened: 1,056 Eligible: NR Enrolled: 715 Analyzed: 709	Withdrawals: unclear; 10/715 (1%) withdrew due to adverse events Loss to follow up: 54/715 (8%)	Bristol Myers Squibb

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Hou 2015[98] Good From update	RCT	22 sites China	48 weeks duration with open label after week 48 to week 240	A. Tenofovir disoproxil fumarate 300 mg daily (n=257) B. Adefovir dipivoxil 10 mg daily (n=252)	Age, mean: 36 vs. 36 Male: 83% vs. 83% Race: Asian-East Asian Heritage: 100% vs. 100% HBV DNA log_{10} copies/mL: 7.6 vs. 7.7 HBeAg-positive: 40% vs. 39% HBV genotype B: 47% vs. 47% HBV genotype C: 51% vs. 51% ALT: 159.7 vs. 142.6	Male and female aged 18 to 69 with HBV DNA ≥10^5 copies/mL and elevated ALT, HBsAg-positive for >6 months	HCC, decompensated liver disease, liver transplantation, autoimmune hepatitis or other hepatitis, HIV	Screened: 969 Eligible: NR Enrolled (randomized): 512 Analyzed: 509	Withdrawals: 12 Loss to followup: 2	Industry
Lai 2002[94] Fair From prior report	RCT	39 centers Australia, Belgium, Canada, France, Germany, Hong Kong, Israel, Italy, Malaysia, the Netherlands, the Philippines, Poland, Russia, Singapore, Thailand	22 weeks (22 weeks treatment + 2 weeks post-treatment)	A. Entecavir 0.5 mg daily (n=46) B. Lamivudine 100 mg daily (n=41) *Dose ranging study; results for 0.01 and 0.1 mg not abstracted*	A vs. B Age, median: 31 vs. 29 years Male: 65% vs. 85% Race: Asian/Pacific Islander: 50% vs. 56% White: 35% vs. 39% Other: 15% vs. 5% Serology: HBV DNA, mean: 8.1 vs. 8.0 log_{10} copies/mL HBsAg positive: 100% HBeAg positive: 78% vs. 80% ALT, median serum: 80.0 vs. 65.0 IU/L Histopathology: NR Prior interferon treatment: 24% vs. 20% Prior lamivudine treatment: 0% vs. 2.4%	Age ≥16 years, HBsAg positive, HBeAg positive or HBeAg negative and anti-HBe positive, HBV DNA >40 MEq/mL, ALT <10x ULN, compensated liver disease	Pregnancy, previous use of immunosuppressive therapy or antiviral therapy within 24 weeks of randomization, HIV, HCV or HDV infection, serious medical illness, pancytopenia, alcohol or drug abuse	Screened: 431 Eligible: NR Enrolled: 185 Analyzed: 169 (87 A vs. B)	Withdrawals: 8/185 (4%) Loss to followup: None reported	NR

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Lai 2006[93] Good From prior report	RCT	146 centers Europe, Middle East, Asia, Australia, North America, South America	52 weeks (time on treatment; responders followed for 24 weeks post-treatment, partial responders given an additional 44 weeks of treatment); mean followup 56 weeks	A. Entecavir 0.5 mg daily (n=325) B. Lamivudine 100 mg daily (n=313)	A vs. B Age, mean: 44 vs. 44 years Male: 76% vs. 75% Race: White: 59% vs. 56% Asian: 38% vs. 41% Black: 2% vs. 2% Other: <1% vs. <1% Serology: HBV DNA, mean: 1.2 vs. 1.2 MEq/mL, 7.6 vs. 7.6 log_{10} copies/mL HBeAg positive: 1% vs. 1% Anti-HBe positive: 99% vs. 100% ALT, mean: 141 vs. 143 IU/L Histopathology: Knodell necroinflammatory score, mean (for n=596 patients with biopsy specimens): 8.0 vs. 7.7 Ishak fibrosis score, mean (n=596): 2.4 vs. 2.5 Cirrhosis: 5% vs. 10% Prior HBV treatment: 15% vs. 14%	Age ≥16 years, HBeAg negative, compensated liver function, serum HBsAg present for at least 24 weeks prior to screening, evidence of chronic HBV per liver biopsy, evidence of HBV DNA at least 4 weeks prior to screening, ALT 1.3 to 10 x ULN	HCV, HDV or HIV coinfection, other liver disease, use of antiviral agents within 24 weeks of randomization, prior lamivudine use lasting >12 weeks, AFP >100 ng/mL, history of ascites requiring diuretics or paracentesis, previous entecavir treatment	Screened: 1,468 Eligible: 694 Enrolled: 648 Analyzed: 638	Withdrawals: 31/638 (5%) Loss to followup: None reported	Bristol Myers Squibb

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Lau 2005[95] Good From prior report	RCT	67 centers 16 countries in Asia, Australasia, Europe, North America, South America	72 weeks (48 weeks treatment + 24 weeks followup)	A. Pegylated interferon alfa 2a 180 µg per week + placebo (n=271) B. Lamivudine (100 mg) (n=272) *n=543 (excluding 271 patients randomized to peg interferon + lamivudine combination therapy)*	Age, mean: 32.5 vs. 31.6 years Male: 79% vs. 79% Race: Asian: 87% vs. 85% White: 9% vs. 12% Black: 1% vs. 1% Other: 2% vs. 2% Serology: HBV DNA, mean: 9.9 vs. 10.1 $\log_{10}$ copies/mL HBsAg positive: 100% HBeAg positive: 100% ALT, mean: 114.6 vs. 102.3 IU/L Histopathology: Bridging fibrosis or cirrhosis: 18% vs. 17% Prior interferon treatment: 11% vs. 12% Prior lamivudine treatment: 11% vs. 15%	HBsAg positive for at least 6 months, anti-HBs negative, HBeAg positive, HBV DNA >500,000 copies/mL, ALT >1 and <10x ULN, chronic HBV confirmed by liver biopsy	Decompensated liver disease, coexisting serious medical or psychiatric illness, neutrophil count <1500/mL^3, platelet count <90,000/mL^3, creatinine >1.5x ULN, history of alcohol or drug abuse, HIV, HCV or HDV coinfection, HBV treatment within 6 months of study	Screened: NR Eligible: NR Enrolled: n=543 (excluding 271 patients randomized to peg interferon + lamivudine combination therapy) Analyzed: 543	Withdrawals: 70/543 (13%) Loss to followup: NR	Roche Pharmac-euticals

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Lee 2017[99] Fair From update	RCT	16 sites South Korea	96 weeks duration with open label after week 96 to week 240	A. Entecavir 0.5 mg once daily B. Lamivudine 100 mg once daily	Age, mean: 46 vs. 49 Male: 84% vs. 75% Race: NR (set in South Korea) HBV DNA log_{10} copies/mL: 6.1 vs. 5.8 ALT: 111 vs. 94 Prior interferon: 3.6% vs. 0%	Male and female 17 years and up who were HBeAg-negative, antiHBe-positive for ≥ 6 months; naïve to long-term nucleos(t)ide analogue treatment; compensated liver function, HBV DNA ≥ 10^5 copies, international normalized ratio ≤ 1.5, albumin ≥ 3 g/dL, bilirubin ≤ 2.5 mg/dL	Interferon treatment within 24 weeks of randomization, HIV, HCV, HDV, HCC, pregnancy	Screened: 200 Eligible: 122 Enrolled (randomized): 122 Analyzed: 106 (double-blind treatment period) Analyzed: 61 (open-label extension	Double-blind period: Withdrawals: 14 Loss to followup: 2 Open-label extension: Withdrawals: 28 Loss to followup: 3 Did not participate: 14	Industry

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Marcellin 2008[96] Fair Study 102 (HBeAg negative at baseline) From prior report	RCT	106 centers 15 countries in Europe, North America, Australia and New Zealand	48 weeks (time on treatment)	A. Tenofovir disoproxil fumarate 300 mg daily (n=250) B. Adefovir dipivoxil 10 mg daily (n=125)	Age, mean: 44 vs. 43 years Male: 77.2% vs. 77.6% Race: White: 64.4% vs. 64.5% Asian: 25.2% vs. 24.0% Black: 3.2% vs. 3.2% Other: 7.2% vs. 8.0% Serology: HBV DNA, mean: 6.86 vs. 6.98 log_{10} copies/mL HBsAg positive: 100% HBeAg positive: 0% ALT, mean: 127.5 vs. 163.6 IU/mL Histopathology: Knodell necroinflammatory score, mean: 7.8 vs. 7.9 Knodell fibrosis score, mean: 2.3 vs. 2.4 Cirrhosis: 18.8% vs. 20.0% Prior treatment with lamivudine or emtricitabine: 17.2% vs. 18.4% Prior treatment with interferon: 16.8% vs. 18.4%	Age 18 to 69 years, compensated liver disease, Knodell necroinflammatory score ≥3 (scale 0 to 18, higher score=more severe hepatitis), HBsAg positive for at least 6 months before screening, ALT >1 to <10x ULN, HBV DNA $>10^5$ copies/mL, <12 weeks treatment with any nucleoside or nucleotide or use of lamivudine or emtricitabine for at least 12 weeks	HIV, HCV or HDV infection, evidence of HCC, creatinine clearance <70 mL/minute, hemoglobin <8 g/dL, neutrophil count $<1000/mL^3$, liver decompensation or failure	Screened: 846 Eligible: 382 Enrolled: 375 Analyzed: 375	Withdrawals: 10/375 (2.7%) Loss to followup: 1/375 (0.3%)	Gilead Sciences

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Marcellin 2008[96] Fair Study 103 (HBeAg positive at baseline) From prior report	RCT	106 centers 15 countries in Europe, North America, Australia and New Zealand	48 weeks (time on treatment)	A. Tenofovir disoproxil fumarate 300 mg daily (n=176) B. Adefovir dipivoxil 10 mg daily (n=90)	Age, mean: 34 vs. 34 years Male: 67.6% vs. 71.1% White: 52.3% vs. 51.1% Asian: 36.4% vs. 35.6% Black: 7.4% vs. 5.6% Other: 4.0% vs. 7.8% Serology: HBV DNA, mean: 8.64 vs. 8.88 $\log_{10}$ copies/mL HBsAg positive: 100% HBeAg positive: 100% ALT, mean: 142 vs. 155 IU/mL Histopathology: Knodell necroinflammatory score, mean: 8.3 vs. 8.3 Knodell fibrosis score, mean: 2.3 vs. 2.4 Cirrhosis: 19.8% vs. 19.5% Prior treatment with lamivudine or emtricitabine: 4.5% vs. 1.1% Prior treatment with interferon: 17.0% vs. 14.4%	Age 18 to 69 years, compensated liver disease, Knodell necroinflammatory score ≥3 (scale 0 to 18, higher score=more severe hepatitis), HBsAg positive for at least 6 months before screening, ALT >2 to <10x ULN, HBV DNA >10^6 copies/mL, <12 weeks treatment with any nucleoside or nucleotide	HIV, HCV or HDV infection, evidence of HCC, creatinine clearance <70 mL/minute, hemoglobin <8 g/dL, neutrophil count <1000/mL^3, liver decompensation or failure	Screened: 603 Eligible: 272 Enrolled: 266 Analyzed: 266	Withdrawals: 15/266 (5.6%) Loss to followup: noted but number NR	Gilead Sciences

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Ren 2007[97] Fair From prior report	RCT	Single center China	48 weeks (time on treatment)	A. Entecavir 0.5 mg daily (n=21) B. Lamivudine 100 mg daily (n=21) *n=42 (excluding 19 patients who previously failed lamivudine treatment and were switched to entecavir)*	A vs. B Age, mean: 33 vs. 31 years Male: 57.1% vs. 52.4% Race: NR, conducted in China Serology: HBV DNA, mean: 8.52 vs. 8.49 log_{10} copies/mL HBsAg positive: 100% HBeAg positive: 100% ALT, mean: 211 vs. 202 IU/L Histopathology: NR Prior HBV treatment: 100%	Age 19 to 68 years, HBeAg positive chronic HBV, compensated liver function, serum bilirubin ≤2.5 mg/dL, prothrombin time not more than 3 seconds longer than normal, serum albumin at least 3 g/dL, no history of variceal bleeding or hepatic encephalopathy, detectable HBsAg, HBV DNA positive, serum ALT 1.3 to 10 X ULN	HIV, HCV or HDV infection, other liver disease, use of interferon, thymosin or HBV antivirals within 24 weeks of randomization, prior lamivudine therapy lasting more than 12 weeks, AFP >100 ng/mL, history of ascites requiring diuretics or paracentesis, previous treatment with entecavir or adefovir	Screened: NR Eligible: NR Enrolled: 61 Analyzed: unclear of efficacy, 61 for harms	Withdrawals: 1.6% (1/61) Loss to followup: None reported	NR
Suh 2010[100] Fair From update	RCT	Multicenter, number NR South Korea	16 weeks (12 weeks' treatment)	A. Entecavir 0.5 mg daily (n=21) B. Telbivudine 600 mg daily (n=23)	A vs. B Age, mean: 33 vs. 36 years Male: 57.1% vs. 78.3% Race: 100% South Korean Serology: HBV DNA, mean: 9.72 vs. 10.29 log_{10} copies/mL ALT, mean: 170.2 vs. 163.1 IU/L Histopathology: NR Prior HBV treatment: not reported	Age ≥18 years, HBeAg+ compensated chronic HBV. detectable HBsAg for ≥24 weeks, HBV DNA ≥7 log_{10} copies/ml, ALT 1.3 to 10.0x ULN, and evidence of chronic liver inflammation.	HCV, HDV, or HIV infection; interferon or other immunomodulatory agents within 12 months; any previous treatment with oral nucleoside or nucleotide analog agents; conditions requiring systemic corticosteroids or hepatotoxic or nephrotoxic medications	Screened: NR Eligible: NR Enrolled (randomized): 44 Analyzed: 44	Withdrawals: 0% (0/44) Loss to followup: None reported	Novartis Pharma

Appendix B Table 7. Trials of HBV Preferred vs. Non-Preferred Treatments – Study Characteristics

Author, year Quality From prior report or update	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline characteristics	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (number, %) Loss to followup (number, %)	Funding source
Yao 2007[101] Good From update	RCT	26 centers China	Treatment 48 to 96 weeks based on response; mean treatment 51.1 vs. 50.5 weeks	A. Entecavir 0.5 mg daily (n=261) B. Lamivudine 100 mg daily (n=264)	A vs. B Age, mean: 30 vs. 30 years Male: 82% vs. 83% HBV DNA, mean: 8.64 vs. 8.48 log_{10} copies/mL HBeAg+: 87% vs. 85% ALT, mean: 196 vs. 198 U/L Prior interferon treatment: 14% vs. 16%	≥16 years, compensated chronic HBV, HBV DNA ≥3.0 MEq/ml, ALT 1.3–10x ULN	HCV, HDV, or HIV infection; > 12 weeks' therapy with a nucleoside or nucleotide analog active against HBV; therapy with any anti-HBV drug within 24 weeks	Screened: 962 Eligible: 525 Enrolled (randomized): 525 Analyzed: 519	Withdrawals: 3.1% (16/519) Loss to followup: 0.8% (4/519)	NR
Zheng, 2010[102] Fair From update	RCT	Single center China	24 weeks	A. Entecavir 0.5 mg daily (n=66) B. Telbivudine 600 mg daily (n=65)	A vs. B Age, mean: 33.5 vs. 31.6 years Male: 63.6% vs. 75.4% HBV DNA, mean: 7.51 vs. 7.45 log_{10} copies/mL ALT, mean: 160.3 vs. 167.3 U/L	18 to 65 years, HBeAg+ compensated chronic HBV, no prior treatment with nucleosides or nucleotides for HBV, HBV DNA ≥6 log_{10} copies/mL	HIV, HCV, or HDV; pregnancy, breastfeeding, alcohol abuse, impaired renal function, muscular disease, or serum creatinine phosphokinase >190 U/L	Screened: 286 Eligible: 131 Enrolled (randomized): 131 Analyzed: 131	Withdrawals (non-compliance): 0.8% (1/131) Loss to followup: 2.3% (3/131)	Scientific Research Foundation, Zhejiang Province

Abbreviations: AFP = alpha-fetoprotein; ALT = alanine aminotransferase; anti-HBs = antibody to hepatitis B surface antigen; anti-HBe = antibody to hepatitis B e-antigen; DNA = deoxyribonucleic acid; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; MEq = mega equivalents; NR = not reported; RCT = randomized controlled trial; ULN = upper limit of normal.

Appendix B Table 8. Trials of HBV Preferred vs. Non-Preferred Treatments – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Chang 2006[92]; Gish 2007[171]; Chang 2009[136] From prior report	A. Entecavir 0.5 mg daily (n=354) B. Lamivudine 100 mg daily (n=355)	Screened: 1,056 Eligible: NR Enrolled: 715 Analyzed: 709	N/A	A vs. B Blood tests (week 96, data from Chang 2009, Figure 2: HBV DNA loss: 80% (284/354) vs. 39% (137/355); RR 2.1 (95% CI, 1.8 to 2.4) HBsAg loss: 5% (18/354) vs. 3% (10/355); RR 1.8 (95% CI, 0.9 to 3.9) HBsAg seroconversion: 2% (6/354) vs. 2% (8/355); RR 0.75 (95% CI, 0.26 to 2.1) HBeAg seroconversion: 31% (110/354) vs. 25% (89/355); RR 1.2 (95% CI, 0.98 to 1.6) ALT normalization (≤1x ULN): 87% (307/354) vs. 79% (280/355); RR 1.1 (95% CI, 1.03 to 1.2) Histologic improvement (week 48): 72% (226/314) vs. 62% (195/314); RR 1.2 (95% CI, 1.03 to 1.3) HBV DNA by PCR, detection limit 300 copies/mL; seroconversion =antigen loss and antibody development; histologic improvement =Knodell necroinflammatory score improvement ≥2 points with no worsening of fibrosis score among patients with adequate biopsy specimen	A vs. B HCC: 0.3% (1/354) vs. 0% (0/355); RR 3.0 (95% CI, 0.12 to 74) Mortality: 0.6% (2/354) vs. 1% (4/355); RR 0.5 (95% CI, 0.09 to 2.72)	A vs. B Serious adverse events: 8% (27/354) vs. 8% (30/355); RR 0.9 (95% CI, 0.6 to 1.5) Withdrawals due to adverse events: 0.3% (1/354) vs. 3% (9/355); RR 0.1 (95% CI, 0.01 to 0.9) Any adverse event: 86% (306/354) vs. 84% (297/355); RR 1.0 (95% CI, 0.97 to 1.1)
Hou 2015[98] From update	A. Tenofovir disoproxil fumarate 300 mg daily (n=257) B. Adefovir dipivoxil 10 mg daily (n=255)	Screened: 969 Eligible: NR Enrolled (randomized): 512 Analyzed: 509	N/A	A vs. B HBV DNA <400 copies/mL: 88.7% vs. 50.4% Mean log reduction in HBV DNA: -5.5 vs. -4.3 ALT normalization: 80.9% vs. 79.0% Virologic breakthrough: 0% vs. 2.4% HBsAg loss: 0% vs. 0% HBeAg loss: 7.0% vs. 4.0% Histological Improvement: 75.9% of 83 vs. 73.7% of 99	A vs. B Mortality: 0.39 (1/257) vs. 0% (0/252)	A vs. B Withdrawals due to adverse events: 0.39% vs. 0% Serious adverse events: 0.8% vs. 2.4% Any adverse event: 32.2% (83/257) vs. 27.8% (70/252) Grade 3/4 abnormality: 16.0% vs. 9.5% ALT: 8.9% vs. 7.1% AST: 2.7% vs. 1.6% Bilirubin: 0.4% vs. 0% Platelets: 1.6% vs. 0.8% Prothrombin time: 1.2% vs. 1.2% Neutrophils: 1.2% vs. 0%

Appendix B Table 8. Trials of HBV Preferred vs. Non-Preferred Treatments – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Lai 2002[94] From prior report	A. Entecavir 0.5 mg daily (n=46) B. Lamivudine 100 mg daily (n=41) *Dose ranging study; results for 0.01 and 0.1 mg not abstracted*	Screened: 431 Eligible: NR Enrolled: 185 Analyzed: 169 (87 A vs. B)	N/A	A vs. B HBV DNA undetectable: 24% (11/46) vs. 17% (7/41); RR 1.4 (95% CI, 0.60 to 3.3) HBeAg loss (among HBeAg positive patients): 0% (0/36) vs. 6% (2/33); RR 0.2 (95% CI, 0.01 to 3.7) Anti-HBe seroconversion: 0% (0/36) vs. 3% (1/33); RR 0.3 (95% CI, 0.01 to 7.3) ALT normalization (among patients with elevated ALT at baseline): 69% (20/29) vs. 59% (13/22); RR 1.2 (95% CI, 0.8 to 1.8) HBV DNA loss + ALT normalization (and HBeAg loss if HBeAg positive at baseline): 16% (7/43) vs. 15% (6/40); RR 1.1 (95% CI, 0.4 to 3.3) HBV DNA by both PCR and hybridization, results reported for PCR, detection limit NR; seroconversion not defined ("seroconversion to anti-HBe")	None reported	A vs. B Serious adverse events: None reported Withdrawals due to adverse events (excluded lamivudine patient with baseline ALT elevation): 0% (0/46) vs. 0% (0/41); RR 0.89 (95% CI, 0.02 to 44) Any adverse event: 65% (30/46) vs. 73% (30/41); RR 0.9 (95% CI, 0.7 to 1.2)
Lai 2006[93] From prior report	A. Entecavir 0.5 mg daily (n=325) B. Lamivudine 100 mg daily (n=313)	Screened: 1,468 Eligible: 694 Enrolled: 648 Analyzed: 638	N/A	A vs. B (week 48 of minimum 52 weeks of treatment) HBV DNA loss: 90% (293/325) vs. 72% (225/313); RR 1.3 (95% CI, 1.2 to 1.4) ALT normalization (<1 x ULN): 78% (253/325) vs. 71% (222/313); RR 1.1 (95% CI, 1.0 to 1.2) Histologic improvement: 70% (208/296) vs. 61% (174/287); RR 1.2 (95% CI, 1.02 to 1.3) HBV DNA by PCR, detection limit 300 copies/mL; histologic improvement =≥2 point decrease in Knodell necroinflammatory score with no worsening of fibrosis score, among patients with adequate baseline biopsy specimen	A vs. B HCC: 0.3% (1/325) vs. 0% (0/313); RR 2.89 (95% CI, 0.12 to 71) Mortality: 0.6% (2/325) vs. 0% (0/313); RR 4.82 (95% CI, 0.23 to 100)	A vs. B Serious adverse events: 6% (21/325) vs. 8% (24/313); RR 0.8 (95% CI, 0.5 to 1.5) Withdrawals due to adverse events: 2% (6/325) vs. 3% (9/313); RR 0.6 (95% CI, 0.2 to 1.8) Any adverse event: 76% (246/325) vs. 79% (248/313); RR 1.0 (95% CI, 0.9 to 1.04)

Appendix B Table 8. Trials of HBV Preferred vs. Non-Preferred Treatments – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Lau 2005[95] From prior report	A. Pegylated interferon alfa 2a 180 µg per week + placebo (n=271) B. Lamivudine (100 mg) (n=272) *n=543 (excluding 271 patients randomized to peg interferon + lamivudine combination therapy)*	Screened: NR Eligible: NR Enrolled: n=543 *(excluding 271 patients randomized to peg interferon + lamivudine combination therapy)* Analyzed: 543	N/A	A vs. B 48 weeks (end of treatment): HBV DNA loss: 25% (68/271) vs. 40% (108/272), RR 0.6 (95% CI, 0.5 to 0.8); HBeAg loss: 30% (81/271) vs. 22% (59/272), RR 1.4 (95% CI, 1.0 to 1.8) HBeAg seroconversion: 27% (72/271) vs. 20% (55/272), RR 1.3 (95% CI, 1.0 to 1.8) ALT normalization: 39% (105/271) vs. 62% (168/272), RR 0.6 (95% CI, 0.5 to 0.7) HBeAg seroconversion + ALT normalization + HBV DNA <100,000 copies/mL: 10% (27/271) vs. 18% (50/272), RR 0.5 (95% CI, 0.4 to 0.8) 72 weeks (end of followup): HBV DNA loss: 14% (39/271) vs. 5% (14/272); RR 2.8 (95% CI, 1.6 to 5.0) HBsAg seroconversion: 3% (8/271) vs. 0% (0/272); RR 17 (95% CI, 1.0 to 294) HBeAg loss: 34% (91/271) vs. 21% (57/272), RR 1.6 (95% CI, 1.2 to 2.1) HBeAg seroconversion: 32% (87/271) vs. 19% (52/272), RR 1.7 (95% CI, 1.2 to 2.3) ALT normalization: 41% (111/271) vs. 28% (76/272); RR 1.5 (95% CI, 1.2 to 1.9) HBeAg seroconversion + ALT normalization + HBV DNA <100,000 copies/mL: 23% (62/271) vs. 10% (28/272); RR 2.2 (95% CI, 1.5 to 3.4) Histologic improvement : 38% (102/271) vs. 34% (93/272); RR 1.1 (95% CI, 0.9 to 1.4) HBV DNA assay unclear, detection limit 400 copies/mL for DNA loss reported above; seroconversion =antigen loss and antibody development; histologic improvement =reduction of at least 2 points in the modified Histology Activity Index (Ishak score)	A vs. B (72 weeks) Mortality: 0% (0/271) vs. 0.4% (1/272)	A vs. B (through week 56) Serious adverse events: 4% (12/271) vs. 2% (5/272); RR 2.4 (95% CI, 0.9 to 6.7) Withdrawals due to adverse events: 3% (8/271) vs. 1% (2/272); RR 4.0 (95% CI, 0.9 to 19) Any adverse event: 89% (240/271) vs. 56% (152/272); RR 1.6 (95 % CI, 1.4 to 1.8)

Appendix B Table 8. Trials of HBV Preferred vs. Non-Preferred Treatments – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Lee 2017[99] From update	A. Entecavir 0.5 mg daily (n=57) B. Lamivudine 100 mg daily (n=65)	Screened: 200 Eligible: 122 Enrolled (randomized): 122 Analyzed: 106 (double-blind treatment period) Analyzed: 61 (open-label extension	N/A	A vs. B (Double-blind treatment period) HBV DNA <300 copies/mL: 94.6% vs. 48.4%, p<0.0001 Mean log reduction in HBV DNA: see figure 3 ALT normalization: 87.5% vs. 51.3%, p<0.0001 Virologic breakthrough: 1.8% vs. 42.6%, p<0.001	Mortality: 1.8% (1/56) vs. 0% (0/64)	A vs. B (through open-label extension) Withdrawals due to adverse events: 0% vs. 1.6% Serious adverse events: 12.5% vs. 26.6% A vs. B (though double-blind period) Grade 3/4 abnormalities: ALT: 0% vs. 9.7% AST: 0% vs. 4.8% Creatinine: 3.6% vs. 0% Bilirubin: 1.8% vs. 4.8% Glucose (fasting): 9.4% vs. 5.6% Lipase: 3.6% vs. 6.5% Platelets: 1.8% vs. 1.6% Prothrombin time: 1.8% vs. 0% Neutrophils: 0% vs. 1.6%

Appendix B Table 8. Trials of HBV Preferred vs. Non-Preferred Treatments – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Marcellin 2008[96] Study 102 (HBeAg negative at baseline) From prior report	A. Tenofovir disoproxil fumarate 300 mg daily (n=250) B. Adefovir dipivoxil 10 mg daily (n=125)	Screened: 846 Eligible: 382 Enrolled: 375 Analyzed: 375	Baseline ALT stratum	A vs. B HBV DNA loss (<400 copies/mL): 93.2% (233/250) vs. 63.2% (79/125); ARD 30.3 (95% CI, 21.3 to 39.2); RR 1.47 (95% CI, 1.28 to 1.69) HBsAg loss: 0% (0/250) vs. 0% (0/125); RR 0.50 (95% CI, 0.01 to 25.15) ALT normalization (among patients with elevated ALT as baseline): 76.3% (180/236) vs. 77.1% (91/118); ARD -0.8 (95% CI, -10.2 to 8.5); RR 0.99 (95% CI, 0.88 to 1.12) Histologic improvement: 72.4% (181/250) vs. 68.8% (86/125); ARD 5.2 (95% CI, -4.5 to 14.9); RR 1.05 (95% CI, 0.91 to 1.21) HBV DNA loss + histologic improvement: 70.8% (177/250) vs. 48.8% (61/125); RR 1.45 (95% CI, 1.19 to 1.77) HBV DNA by PCR, detection limit 169 copies/mL but 400 copies/mL used to define DNA loss; seroconversion not defined ("seroconversion to anti-HBe"); histologic improvement =≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis score	No deaths in either group; 3 cases of HCC but results NR according to study group	A (n=426) vs. B (n=215; results for studies 102 and 103 reported together) Any adverse event: 74.4% (317/426) vs. 73.5% (158/215); RR 1.01 (95% CI, 0.92 to 1.12) Serious adverse events overall: 6.3% (27/426) vs. 6.5% (14/215); RR 0.97 (95% CI, 0.52 to 1.82) *Assumes serious adverse events listed as drug-related (N=24) are included in overall serious adverse events (N=41)* Withdrawals due to adverse events: 1.2% (5/426) vs. 1.4% (3/215); RR 0.84 (95% CI, 0.20 to 3.49) Diarrhea: 6.6% (28/426) vs. 5.1% (11/215); RR 1.28 (95% CI, 0.65 to 2.53) Nausea: 9.4% (40/426) vs. 2.8% (6/215); RR 3.36 (95% CI, 1.45 to 7.81) Renal dysfunction (serum creatinine increase ≥0.5 mg/dL above baseline): 0% (0/426) vs. 0.5% (1/215); RR 0.17 (95% CI, 0.007 to 4.12) Renal dysfunction (creatinine clearance <50 mL/minute): 0% (0/426) vs. 0% (0/215); RR 0.51 (95% CI, 0.01 to 25.41) Vomiting, bone loss, fractures: NR

Appendix B Table 8. Trials of HBV Preferred vs. Non-Preferred Treatments – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Marcellin 2008[96] Study 103 (HBeAg positive at baseline) From prior report	A. Tenofovir disoproxil fumarate 300 mg daily (n=176) B. Adefovir dipivoxil 10 mg daily (n=90)	Screened: 603 Eligible: 272 Enrolled: 266 Analyzed: 266	Baseline ALT stratum	A vs. B HBV DNA loss: 76.1% (134/176) vs. 13.3% (12/90); ARD 63.1 (95% CI, 53.8 to 72.3); RR 5.71 (95% CI, 3.35 to 9.73) HBsAg loss: 3.2% (5/158) vs. 0% (0/82); ARD 10.9 (95% CI, 1.9 to 19.9); RR 5.74 (95% CI, 0.32 to 102.59) HBeAg seroconversion: 20.9% (32/153) vs. 17.5% (14/80); ARD 4.7 (95% CI, -5.5 to 14.9); RR 1.20 (95% CI, 0.68 to 2.11) ALT normalization: 68.0% (115/169) vs. 54.4% (49/90); ARD 13.6 (95% CI, 1.1 to 26.1); RR 1.25 (95% CI, 1.01 to 1.55) Histologic improvement: 74.4% (131/176) vs. 67.7% (61/90); ARD 5.8 (95% CI, -5.6 to 17.2); RR 1.10 (95% CI, 0.93 to 1.30) HBV DNA loss + histologic improvement: 66.5% (117/176) vs. 12.2% (11/90); ARD 54.1 (95% CI, 44.6 to 63.6); RR 5.44 (95% CI, 3.10 to 9.56) HBV DNA by PCR, detection limit 169 copies/mL but 400 copies/mL used to define DNA loss; seroconversion not defined ("seroconversion to anti-HBe"); histologic improvement =≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis score	No deaths in either group	As above; results for studies 102 and 103 reported together
Ren 2007[97] From prior report	A. Entecavir 0.5 mg daily (n=21) B. Lamivudine 100 mg daily (n=21) *n=42 (excluding 19 patients who previously failed lamivudine treatment and were switched to entecavir)*	Screened: NR Eligible: NR Enrolled: 61 Analyzed: unclear of efficacy, 61 for harms	N/A	A vs. B HBV DNA undetectable: 71.4% (15/21) vs. 38.1% (8/21); RR 1.9 (95% CI, 1.0 to 3.5) HBeAg seroconversion: 14.3% (3/21) vs. 19.0% (4/21); RR 0.8 (95% CI, 0.2 to 3.0) ALT normalization: 85.7% (18/21) vs. 76.2% (16/21); RR 1.1 (95% CI, 0.8 to 1.5) HBV DNA by PCR, detection limit NR; seroconversion =antigen loss and antibody development	A vs. B HCC: 0% (0/21) vs. 0% (0/21); RR not estimable Mortality: 0% (0/21) vs. 0% (0/21); RR not estimable	Serious adverse events: NR Withdrawals due to adverse events: NR Any adverse event: NR Diarrhea: 28.6% (6/21) vs. 33.3% (7/21); RR 0.86 (95% CI, 0.35 to 2.1)

Appendix B Table 8. Trials of HBV Preferred vs. Non-Preferred Treatments – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Suh, 2010[100] From update	A. Entecavir 0.5 mg daily (n=21) B. Telbivudine 600 mg daily (n=23)	Screened: NR Eligible: NR Enrolled (randomized): 44 Analyzed: 44	N/A	A vs. B HBV DNA undetectable by week 12: 28.6% (6/21) vs. 8.7% (2/23); RR 3.29 (95% CI 0.74 to 14.54) ALT, mean reduction baseline to week 12, IU/L (SD): 116.3 (162.81) vs. 108.0 (147.87) DNA limit of detection: 300 copies/mL	Not reported	Withdrawals due to adverse events: none Serious adverse events: NR Any adverse events: 61.9% (13/21) vs. 39.1% (9/23); RR 1.58 (95% CI 0.86 to 2.91) ALT increased: 4.8% (1/21) vs. 13.0% (3/23); RR 0.37 (95% CI 0.041 to 3.24) AST increased: 0% (0/21) vs. 4.3% (1/23); RR 0.37 (95% CI 0.016 to 8.47) Hypophosphatemia: 0% (0/21) vs. 4.3% (1/23); RR 0.37 (95% CI 0.016 to 8.47) Neutropenia: 0% (0/21) vs. 4.3% (1/23); RR 0.37 (95% CI 0.016 to 8.47) Thrombocytopenia: 0% (0/21) vs. 4.3% (1/23); RR 0.37 (95% CI 0.016 to 8.47)) Nausea: 9.5% (2/21) vs. 0% (0/23); RR 5.45 (95% CI 0.28 to 107.47)
Yao 2007[101] From update	A. Entecavir 0.5 mg daily (n=261) B. Lamivudine 100 mg daily (n=264)	Screened: 962 Eligible: 525 Enrolled (randomized): 525 Analyzed: 519	Baseline measurement, HBeAg status	A vs. B at 48 weeks HBV DNA <0.7 MEq/ml and ALT <1.25x ULN (composite primary endpoint): 90% (231/258) vs. 67% (174/261), p<0.0001 HBV DNA loss: 76% (197/258) vs. 43% (112/261), p<0.0001 HBeAg loss: 18% (41/225) vs. 20% (44/221), p=not significant HBeAg seroconversion: 15% (33/225) vs. 18% (39/221), p=not significant ALT normalization: 90% (231/258) vs. 78% (203/261), p=0.0003 HBV DNA limit of detection 300 copies/ml	Mortality: 0% (0/258) vs. 0% (0/261) HCC: 0% (0/258) vs. 0% (0/261)	Withdrawls due to adverse events: 0.4% (1/258) vs. 1% (3/261); RR 0.34 (95% CI 0.035 to 3.22) Serious adverse events: 3% (9/258) vs. 5% (12/261); RR 0.76 (95% CI 0.33 to 1.77) Any adverse event: 60% (154/258) vs. 56% (145/261); RR 1.07 (95% CI 0.93 to 1.25) ALT increased: 7% (17/258) vs. 9% (23/261); RR 0.75 (95% CI 0.41 to 1.37) Diarrhea: 5% (13/258) vs. 2% (4/261); RR 3.29 (1.09 to 9.95)

Appendix B Table 8. Trials of HBV Preferred vs. Non-Preferred Treatments – Results

Author, year From prior report or update	Interventions	Number screened, eligible, enrolled, analyzed	Adjusted variables for statistical analysis	Intermediate outcomes	Clinical health outcomes	Adverse events
Zheng, 2010[102] From update	A. Entecavir 0.5 mg daily (n=66) B. Telbivudine 600 mg daily (n=65)	Screened: 286 Eligible: 131 Enrolled (randomized): 131 Analyzed: 131	Baseline value of variable	A vs. B at 24 weeks HBV DNA loss: 57.6% (38/66) vs. 67.7% (44/65), p=0.232 HBeAg loss: 28.8% (19/66) vs. 36.9% (24/65), p=0.321 HBeAg seroconversion: 13.6% (9/66) vs. 24.6% (16/65), p=0.110 ALT normalization: 74.2% (49/66) vs. 78.5% (51/65), p=0.570 HBV DNA detection level 500 copies/mL HBeAg seroconversion = HBeAg loss with development of anti-HBe antibody	NR	Withdrawls due to adverse events: 0% (0/66) vs. 0% (0/65) Serious adverse events: 0% (0/66) vs. 0% (0/65) Any adverse event: NR Diarrhea: 3.0% (2/66) vs. 1.5% (1/65), p > 0.999 Creatinine phosphokinase increased: 0% (0/66) vs. 12.3% (8/65), p=0.003

Abbreviations: ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e-antigen; ARD = absolute risk difference between groups; AST = aspartate aminotransferase; CI = confidence interval; DNA = deoxyribonucleic acid; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; N/A = not applicable; NR = not reported; PCR = polymerase chain reaction; RR = relative risk; SD = standard deviation; ULN = upper limit of normal.

Appendix B Table 9. Cohort Studies of HBV Treatment – Study Characteristics

Author, year Quality	Study design	Number of sites Country	Treatment duration Followup Study period	Interventions (n)	Baseline characteristics	Eligibility criteria	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Funding source
Gordon 2014[103] *CHeCS* Fair	Cohort, retrospective and real time	4 sites United States	Median treatment duration: 45 months (interquartile range 22 to 81 months) Followup: Median 5.2 years Evaluated those diagnosed between the years of 1992 and 2011	A. HBV treatment, including interferon alpha-2b, pegylated interferon alpha-2a or alpha 2b, lamivudine, entecavir, tenofovir, telbivudine, or adefovir (n=820) 94% received nucleos(t)ide analog therapy, alone or before or after interferon-based therapy, whereas 6% received only interferon or pegylated interferon-based therapy B. No treatment (n=1,851)	A vs. B Age: 18% vs. 32% <40, 26% vs. 23% 40 to 50, 30% vs. 23% 50 to 60, 26% vs. 22% >60 years Male: 70% vs. 50% Race/ethnicity: 48% vs. 57% Asian or Pacific Islander, 45% vs. 30% white, black, or Native American, 6% vs. 13% unknown Serology: HBV DNA: NR HBeAg positive: NR Anti-HBe negative: NR ALT: 43% vs. 21% abnormal, 35% vs. 64% normal, 23% vs. 15% unknown AST: median APRI score (n=1,463) 0.42 Histopathology: Fibrosis stage: median FIB4 score (n=1,404) 1.25 Cirrhosis: NR Major comorbidity (Charlson/Deyo index score of 2 or 3): 9% HIV positive during followup: 6%	Patients had to fulfill at least 2 criteria, including: 2 positive laboratory tests consistent with current HBV infections (i.e., positive for HBV surface antigen, e-antigen, or DNA test, or a positive laboratory test and an ICD-9 code, or 2 ICD-9 codes) obtained at least 6 months apart Exclusion: Coinfection with HCV, diagnosis of HCC more than 60 days before the diagnosis of HBV	Screened: 4,158 Eligible: NR Enrolled: NR Analyzed: 2,671 after propensity score adjustment Withdrawals and loss to followup: NR	CDC Foundation, which receives grants from AbbVie, Genentech, Janssen Pharmaceutical Companies of Johnson & Johnson, and Vertex Pharmaceuticals.

Appendix B Table 9. Cohort Studies of HBV Treatment – Study Characteristics

Author, year Quality	Study design	Number of sites Country	Treatment duration Followup Study period	Interventions (n)	Baseline characteristics	Eligibility criteria	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Funding source
Hoang 2016[104] REVEAL-HBV Taiwanese Cohort + United States clinics Fair	Cohort, retrospective	Multisite United States (Northern California) and Taiwan	Treatment duration: NR Median followup: 8.9 years United States study period 1991 to 2014 Taiwanese study period 1991 to 1992	A. United States cohort, Treated. Any FDA-approved agent or combination: lamivudine, adefovir, entecavir telbivudine, tenofovir, or interferon (n=548) *82% received either entecavir or tenofovir monotherapy or in combination; remainder received adefovir, lamivudine, or pegylated interferon* B. United States cohort, Untreated (n= 754) C. Taiwan REVEAL cohort, Untreated (n=2,363)	A (treated) vs. B+C (untreated) Age, mean: 49.5 vs. 50.8 years Male: 66.4% vs. 59.3% Race/ethnicity: 98.2% Asian overall HBeAg positivity: 23.7% vs. 10.4% ALT, median (IU/mL), ALT <2x ULN: 32 vs. 14 ALT, median (IU/mL), ALT ≥2x ULN: 87 vs. 68 HBV DNA, median (log_{10} copies/mL), ALT <2x ULN: 4.7 vs. 3.5 HBV DNA, median (log_{10} copies/mL), ALT ≥2x ULN: 6.0 vs. 4.6	Patients ages 40 years and older with chronic HBV Exclusion: Coinfection with HCV, HDV, or HIV, HCC at presentation or within 6 months, cirrhosis at presentation or within 2 years	Screened: NR Eligible: NR Enrolled: NR Analyzed: 3,665 Withdrawals and loss to followup: NR	NR

Appendix B Table 9. Cohort Studies of HBV Treatment – Study Characteristics

Author, year Quality	Study design	Number of sites Country	Treatment duration Followup Study period	Interventions (n)	Baseline characteristics	Eligibility criteria	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Funding source
Hosaka 2013[105] Fair	Cohort, prospective treatment and retrospective control	Unclear Japan	Treatment duration: NR Followup: 1 year or until the last visit before December 2011; entecavir 3.3 years vs. control 7.6 years (p<0.001), but adjusted to 5 years for each group with propensity matching Study periods: 2004 to 2019 for entecavir treated patients and 1973 to 1999 for untreated control group patients	A. Entecavir, 0.5 mg (n=472, reduced to 316) B. Non-treated control (n=1,143 reduced to 316)	A vs. B (propensity matched cohorts) Age, mean: 46 vs. 46 years Male: 50.5% vs. 50.5% Race/ethnicity: NR (Japan) HBeAg positive: 43% vs. 42% HBV DNA: 6.3 vs. 6.6 log_{10} copies/mL AST: 45 vs. 49 IU/L AST: 1.4 vs. 1.5 x ULN ALT: 61 vs. 60 IU/L ALT: 1.7 vs. 1.6 x ULN Preexisting cirrhosis: 25% vs. 29%	Chronically monoinfected with HBV and were confirmed as HBsAg positive for at least 6 months with followup at least 1 year; treatment naïve Exclusion: Incomplete data or serum samples. For those in control group, excluded if had corticosteroid withdrawal therapy, interferon treatment or nucleos(t)ide analog treatment was initiated during followup, or positive for anti-HCV antibodies	Screened: 2,842 Eligible: NR Enrolled: 1,615 Analyzed: 632 after propensity score matching Withdrawals and loss to followup: NR	NR

Appendix B Table 9. Cohort Studies of HBV Treatment – Study Characteristics

Author, year Quality	Study design	Number of sites Country	Treatment duration Followup Study period	Interventions (n)	Baseline characteristics	Eligibility criteria	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Funding source
Lee 2018[106] *Taiwan's National Health Insurance Research Database* Fair	Cohort, retrospective	Multisite (national database) Taiwan	Treatment duration: nucleos(t)ide therapy mean 3.1 years, median 2.2 years Followup: mean 5.6 years, median 5.8 years in each arm Study period: October 1, 2003 to December 31, 2012	A. Nucleos(t)ide analogue therapy (n=10,062) B. Untreated (n=10,062)	A vs. B (propensity matched cohorts) Age, mean: 45.5 vs. 45.5 years Male: 80.1% vs. 80.1% Race/ethnicity: NR (Taiwan) Hepatoprotectant: 0.8 vs. 1.0 years Alcoholic liver disease: 7.0% vs. 7.0% Cirrhosis: 26.0% vs. 26.0% Liver decompensation: 11.5% vs. 11.5%	Chronic HBV infection diagnosed at least 3 times in outpatient clinics or 1 time in a hospitalization; treatment for at least 90 days Exclusion: Patients with confounding disorders such as infection with HCV, HIV, or other hepatitis-associated viruses, liver flukes, biliary stone diseases, cholangitis, congenital biliary anomalies, biliary tract surgeries, or cancer Excluded patients treated for less than 90 days	Screened: 185,843 Eligible: 51,707 Enrolled: NR Analyzed: 20,124 after propensity score matching Withdrawals and loss to followup: NR 59% (5,934/10,062) vs. 59% (5,937/10,062) with data available for intrahepatic cholangiocarcinoma analysis at year 5	National Health Research Institutes, Taichung Veterans General Hospital

Appendix B Table 9. Cohort Studies of HBV Treatment – Study Characteristics

Author, year Quality	Study design	Number of sites Country	Treatment duration Followup Study period	Interventions (n)	Baseline characteristics	Eligibility criteria	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Funding source
Matsumoto 2005[107] Inuyama Hepatitis Study Group Fair	Cohort, retrospective	Multicenter (30 institutions) Japan	Treatment duration: median 18.9 months Followup: lamivudine arm 2.7 years vs. control arm 5.3 years Study period: 1980 to March 2002; analysis begins at time of liver biopsy	A. Lamivudine, 100 mg/day (n=657, reduced to 377) B. Untreated (n=2,138, reduced to 377)	A vs. B Age, mean: 41.5 vs. 41.4 years Male: 73.2% vs. 72.4% Race/ethnicity: NR (Japan) Previous interferon therapy: 34.2% vs. 37.9% Liver histology, grade of inflammation: A0 1.6% vs. 4.8%, A1 29.2% vs. 26.8%, A2 41.6% vs. 49.3%, A3 26.0% vs. 19.1%, unknown 1.6% vs. 0%, p=0.001 Stage of fibrosis: F0 1.9% vs. 1.6%, F1 27.3% vs. 31.0%, F2 25.2% vs. 25.7%, F3 28.4% vs. 23.9%, F4 17.2% vs. 17.8% HBeAg: positive 51.2% vs. 58.4%, negative 47.2% vs. 37.4%, unknown 1.6% vs. 4.2%, p=0.005 HBeAg: positive 33.4% vs. 32.1%, negative 65.0 vs. 62.9%, unknown 1.6% vs. 5.0%, p=0.030 Albumin: 4.00 vs. 4.00 g/dL AST: 118.5 vs. 95.5 IU/L, p=0.031 ALT: 191.7 vs. 151.5 IU/L, p=0.009 Platelet count: 161.7 vs. 164.3 x1000/mm^3	Histologically diagnosed chronic HBV patients; underwent liver biopsy; for those on treatment, started lamivudine within 2 years of liver biopsy; sufficient data available Exclusion: Excluded coinfection with HCV or HIV; liver biopsy >2 years after starting lamivudine therapy	Screened: 3,022 Eligible: NR Enrolled: NR Analyzed: 2,795 (reduced to 754 in propensity-score matching) Withdrawals and loss to followup: Details NR; 45% on lamivudine through end of followup period	Ministry of Health, Labor, and Welfare, Japan

Appendix B Table 9. Cohort Studies of HBV Treatment – Study Characteristics

Author, year Quality	Study design	Number of sites Country	Treatment duration Followup Study period	Interventions (n)	Baseline characteristics	Eligibility criteria	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Funding source
Wang 2015[108] *Taiwan's National Health Insurance Database* Fair	Cohort, retrospective	Multisite (national database) Taiwan	Treatment duration: mean 1.6 years, median 1.4 years Followup: 5.3 vs. 5.2 years Study period: October 1, 2003 to December 31, 2011	A. Nucleos(t)ide analogue therapy (lamivudine, telbivudine, entecavir, or tenofovir) (n=1,544) B. Untreated (n=1,544)	A vs. B (propensity match cohorts) Age, mean: 42.2 vs. 42.7 years Male: 72.7 vs. 74.7% Cirrhosis: 23.4% vs. 24.3% Ascites: 5.4% vs. 5.6% Charlson comorbidity index, mean: 0.77 vs. 0.75	Patients with a first-time diagnosis of HBV infection, who received nucleos(t)ide analogues for at least 90 days Exclusion: Patients diagnosed with HIV, HCV, other viral hepatitis, alcohol-related disease, or malignant tumors; or if they received interferon or nucleos(t)ide analogue therapy before October 1, 2003, or if they used nucleos(t)ide analogues for <90 days during or before the observational period	Screened: 1,001,932 Eligible: 19,936 Enrolled: NR Analyzed: 3,088 after propensity score matching Withdrawals and loss to followup: NR 30.2% (467/1,544) vs. 33.2% (513/1544) with data available for HCC analysis at year 7, after adjustments, etc.	Taipei Veterans General Hospital, National Science Council, the National Research Program for Biopharmaceutics of Taiwan

Appendix B Table 9. Cohort Studies of HBV Treatment – Study Characteristics

Author, year Quality	Study design	Number of sites Country	Treatment duration Followup Study period	Interventions (n)	Baseline characteristics	Eligibility criteria	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Funding source
Wei 2019[110] Fair	Cohort, retrospective	4 sites US	Treatment duration: NR Followup: median 4-5 years; 8 year cumulative Study period: 2008 to 2016	A. Tenofovir disoproxol fumarate (n=276) B. Entecavir (n=335) C. Untreated (n=613)	A vs. B vs. C Age, mean: 44.3 vs. 47.4 vs. 46.2, p=0.03 Male: 61.6% vs. 65.4% vs. 51.6%, p<0.001 Asian ethnicity: 100% Baseline cirrhosis: 16.3% vs. 17.6% vs. 2.6%, p<0.001 APRI interquartile range: 0.35 vs. 0.40 vs. 0.27, p<0.008 FIB-4, interquartile range: 1.06 vs. 1.13 vs. 0.94, p=0.042 Deyo-Charlson Comorbidity Index, mean: 3.76 vs. 3.39 vs. 2.61, p=0.0025 HBeAg positive: 26.3% vs. 24.3% vs. 8.8%, p<0.001 Log10 HBV DNA, IU/mL: 3.96 vs. 4.07 vs. 3.20, p<0.001 AST, U/L, interquartile range: 28 vs. 33 vs. 24, p<0.001 ALT, U/L, interquartile range: 42 vs. 46 vs. 31, p<0.001 Albumin, g/dL: 4.06 vs. 3.95 vs. 4.16, p<0.001 Total bilirubin, mg/dL, interquartile range: 0.7 vs. 0.7 vs. 0.7	Treatment-naïve, Asian, chronic HBV patients at least 18 years old without baseline osteopenia or osteoporosis Excluded patients taking medications with increased risk for osteopenia or osteoporosis, and those with HIV or HCV coinfection	Screened: 1,982 Eligible: 1,224 Enrolled: 1,224 Analyzed (baseline): 1,224 Analyzed (outcomes): 1,160 Withdrawals and loss to followup: 5.2% (64/1,224)	Unclear Five authors have served as either advisory members, speakers, or consultants, or received research support or has stock with from pharmaceutical companies

Appendix B Table 9. Cohort Studies of HBV Treatment – Study Characteristics

Author, year Quality	Study design	Number of sites Country	Treatment duration Followup Study period	Interventions (n)	Baseline characteristics	Eligibility criteria	Number screened, eligible, enrolled, analyzed Withdrawals Loss to followup	Funding source
Wu 2014[109] *Taiwan's National Health Insurance Research Database* Fair	Cohort, retrospective	Multisite (national database) Taiwan	Treatment duration: mean 1.44 years, median 1.42 years Followup, mean: 3.46 vs. 5.24 years Study period: January 1, 1997 to December 31, 2010	A. Nucleos(t)ide analogue therapy (n=21,595) B. Untreated with nucleos(t)die therapy; used hepatoprotectants for at least 90 days (n=21,595)	A vs. B (propensity match cohorts) Age, mean: 43.5 vs. 43.5 years Male: 75.5% vs. 76.9% Hepatoprotective agents, mean: 0.78 vs. 1.24 years, p<0.001 Cirrhosis: 13.2% vs. 14.0%, p=0.018 Liver decompensation: 7.8% vs. 7.6% Charlson comorbidity index, mean: 0.79 vs. 0.80	Chronic HBV infection diagnosed at least 3 times in outpatient clinics or 1 time in a hospitalization; treatment for at least 90 days Exclusion: Patients with HCV, HIV, other viral hepatitis, and malignant tumors; excluded patients with HCC diagnosis within first 90 days of start of therapy	Screened: 199,451 Eligible: 72,458 Enrolled: NR Analyzed: 43,190 after propensity score matching Withdrawals and loss to followup: NR 18% (3,966/21,595) vs. 55% (11,780/21,595) with data available for HCC analysis at year 6, after adjustments, etc.	Taiwan's National Health Research Institutes, Taipei Veterans General Hospital and Department of Health, Center of Excellence for Cancer Research at Taipei Veterans General Hospital and National Yang-Ming University

Abbreviations: ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e-antigen; APRI = aspartate aminotransferase to platelet ratio index; AST = aspartate aminotransferase; CDC = Centers for Disease Control; CHeCS = Chronic Hepatitis Cohort Study; DNA = deoxyribonucleic acid; FDA = U.S. Food and Drug Administration; FIB4 = fibrosis-4 index; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; ICD = international classification of disease; NR = not reported; REVEAL = study name is not an acronym; ULN = upper limit of normal.

Appendix B Table 10. Cohort Studies of HBV Treatment – Results

Author, year	Followup	Interventions (n)	Adjusted variables for statistical analysis	Outcomes
Gordon 2014[103] *CHeCS*	Median 5.2 years	A. HBV treatment, including interferon alpha-2b, pegylated interferon alpha-2a or alpha 2b, lamivudine, entecavir, tenofovir, telbivudine, or adefovir (n=820) *94% received nucleos(t)ide analog therapy, alone or before or after interferon-based therapy, whereas 6% received only interferon or pegylated interferon-based therapy* B. No treatment (n=1,851)	ALT Serum markers of cirrhosis Study site Patient demographics Comorbidity Index	A vs. B HCC Unadjusted rates: 2.4% (20/820) vs.2.5% (47/1,851) cases, crude incidence rate 4.2 cases per 1,000 person-years Simple Cox regression, treatment vs. no treatment, aHR 0.50 (95% CI, 0.35 to 0.72), p<0.001 Propensity-adjusted Cox regression, after adjusting for abnormal ALT: lower risk for those who received treatment vs. no treatment, aHR 0.39 (95% CI, 0.27 to 0.56), p<0.001 Subgroup analysis (n=1,404), after adjusting for serum markers of cirrhosis: lower risk for those who received treatment vs. no treatment, aHR 0.24 (95% CI, 0.15 to 0.39), p<0.001 Subgroup analysis (n=1,986), of patients with data available on HBV DNA viral load: For viral loads >20,000 IU/mL, lower risk for those who received treatment vs. no treatment, aHR 0.17 (95% CI, 0.06 to 0.52), p=0.002 For viral loads 2,000 to 20,000 IU/mL, treatment vs. no treatment: 0.45 (95% CI, 0.14 to 1.47), p=0.185 For viral loads <2,000 IU/mL, treatment vs. no treatment: 0.72 (95% CI, 0.43 to 1.20), p=0.206
Hoang 2016[104] Taiwanese REVEAL-HBV Cohort + United States clinics	Median 8.9 years	A. United States cohort, Treated. Any FDA-approved agent or combination: lamivudine, adefovir, entecavir telbivudine, tenofovir, or interferon (n=548) *82% received either entecavir or tenofovir monotherapy or in combination; remainder received adefovir, lamivudine, or pegylated interferon* B. United States cohort, Untreated (n= 754) C. Taiwan REVEAL cohort, Untreated (n=2,363)	REACH-B predictive score (validated composite 17-point HCC risk-prediction score based on 5 clinical, laboratory, and virologic parameters, including gender, age, HBeAg status, ALT levels, and HBV DNA levels)	HCC Number of cases, A vs. B vs. C: 7/548 vs. 15/754 vs.180/2363 Incidence rates per 100,000 person years, A vs. B vs. C: 208.90 vs. 438.52 vs. 488.39 Incidence rates, adjusted for REACH-B score: A vs. B (United States groups only, treatment vs. no treatment): aHR 0.24 (95% CI, 0.10 to 0.58), p=0.0017 A vs. C (United States treatment vs. Taiwan no treatment): aHR 0.32 (95% CI, 0.15 to 0.70), p=0.0042 A vs. B+C (United States treatment vs. both United States and Taiwan untreated groups): aHR 0.31 (95% CI, 0.14 to 0.67), p=0.0027
Hosaka 2013[105]	Entecavir 3.3 years vs. control 7.6 years (p<0.001), but adjusted to 5 years for each group with propensity matching	A. Entecavir, 0.5 mg (n=472, reduced to 316) B. Non-treated control (n=1,143 reduced to 316 with propensity matching)	Age, sex, cirrhosis, HBeAg, HBV DNA, AST, ALT, gamma glutamyl transpeptidase, bilirubin, albumin, platelet counts	A vs. B HCC Cumulative incidence rate at 5 years: 3.7% vs. 13.7%, p<0.001 Cox proportional hazard regression analysis (adjusted for HCC risk factors): benefit to entecavir-treated group vs. no treatment, HR 0.37 (95% CI, 0.15 to 0.91), p=0.030

Appendix B Table 10. Cohort Studies of HBV Treatment – Results

Author, year	Followup	Interventions (n)	Adjusted variables for statistical analysis	Outcomes
Lee 2018[106] *Taiwan's National Health Insurance Research Database*	Mean 5.6 years, median 5.8 years in each arm	A. Nucleos(t)ide analogue therapy (n=10,062) B. Untreated (n=10,062)	Age, sex, cirrhosis, liver decompensation, diabetes mellitus, and hyperlidemia	A vs. B Intrahepatic cholangiocarcinoma Cumulative incidence, year 3: 1.28% (95% CI, 0.56% to 2.01%) vs. 3.14% (95% CI, 2.02% to 4.27%) Cumulative incidence, year 5: 1.53% (95% CI, 0.73% to 2.33%) vs. 4.32% (95% CI, 2.96% to 5.69%) Multivariable regression analysis, year 5: 0.17% (17/10,062) vs. 0.39% (39/10,062), HR 0.44 (95% CI, 0.25 to 0.78), p=0.005 HCC Cumulative incidence, year 5: 2.93% (95% CI, 2.57% to 3.28%) vs. 4.75% (95% CI, 4.31% to 5.20%), p<0.001
Matsumoto 2005[107] Inuyama Hepatitis Study Group	Lamivudine arm 2.7 years vs. control arm 5.3 years	A. Lamivudine, 100 mg/day (n=657, reduced to 377) B. Untreated (n=2,138, reduced to 377)	Age, gender, family clustering of HBV, stage of hepatic fibrosis, serum albumin level, platelet count	HCC Cox regression analysis: effect of lamivudine therapy vs. no treatment: HR 0.49 (95% CI, 0.31 to 0.77), p=0.002 Propensity-matched analysis Annual incidence rate: 0.4% patients/year vs. 2.5% patients/year, p<0.001 Number of events: 1.1% (4/377) vs. 13.3% (50/377)
Wang 2015[108] *Taiwan's National Health Insurance Database*	5.3 vs. 5.2 years	A. Nucleos(t)ide analogue therapy (lamivudine, telbivudine, entecavir, or tenofovir) (n=1,544) B. Untreated (n=1,544)	Sex, age, major coexisting comorbidities (such as diabetes, hypertension, etc.)	HCC Occurrence, after adjustments, 8.25 year cumulative incidence: 6.0% (95% CI, 4.4% to 7.9%) vs. 8.5% (95% CI, 6.6% to 10.6%), p=0.0025 aHR: 0.64 (95% CI, 0.45 to 0.93), p=0.017 Dose response between nucleos(t)ide analogue use and HCC: 90 to 365 daily dose: aHR 0.93 (95% CI, 0.58 to 1.48) 366 to 730 daily dose: aHR 0.67 (95% CI, 0.42 to 1.06) >730 daily dose: aHR 0.35 (95% CI, 0.17 to 0.70) Mortality Occurrence, 8.25 year cumulative incidence: 6.9% (95% CI, 5.3% to 8.7%) vs. 9.4% (95% CI, 7.7% to 11.3%), p=0.0003 aHR: 0.58 (95% CI, 0.43 to 0.79), p<0.001
Wei 2019[110]	Followup: median 4-5 years; 8 year cumulative	A. Tenofovir disoproxil fumarate (n=276) B. Entecavir (n=335) C. Untreated (n=613)	Age, sex, diabetes, vitamin D deficiency, treatment status, hepatitis B viral load, cirrhosis, PLT, ALT, Deyo Charlton Comorbodity Index	Harms Osteopenia/osteoporosis A vs. B vs. C 8 year cumulative incidence: 13.2% (95% CI 6.95% to 24.21%) vs. 15.1% (95% CI 10.95% to 20.60%) vs. 10.2% (95% CI 6.72% to 15.24%), p=0.22 Multivariable Cox regression Adjusted for various baseline demographic and clinical factors: Tenofovir disoproxol fumarate vs. untreated: aHR 0.74 (95% CI 0.34 to 1.59), p=0.44 Entecavir vs. untreated: aHR 0.98 (95% CI 0.51 to 1.90), p=0.96 Additionally adjusted for Deyo Charlton Comorbidity Index: Tenofovir disoproxol fumarate vs. untreated: aHR 0.69 (95% CI 0.32 to 1.50), p=0.35 Entecavir vs. untreated: aHR 0.89 (95% CI 0.45 to 1.75), p=0.73

Appendix B Table 10. Cohort Studies of HBV Treatment – Results

Author, year	Followup	Interventions (n)	Adjusted variables for statistical analysis	Outcomes
Wu 2014[109] *Taiwan's National Health Insurance Research Database*	Mean: 3.46 vs. 5.24 years	A. Nucleos(t)ide analogue therapy (n=21,595) B. Untreated with nucleos(t)die therapy; used hepatoprotectants for at least 90 days (n=21,595)	Age, sex, cirrhosis, liver decompensation, comorbidities, use of statins, use of nonsteroidal anti-inflammatory drugs, use of metformin Conducted sensitivity analysis for differential followup periods between arms	HCC Incidence: 4.6% (992/21,595) vs. 20.6% (4,454/21,595), p<0.01 7 year cumulative incidence, adjusted for competing mortality: 7.32% (95% CI 6.77% to 7.7%) vs. 22.7% (95% CI, 22.1% vs. 23.3%), p<0.001 aHR 0.37 (95% CI, 0.34 to 0.39), p<0.001, favors treatment Death Death before HCC: 4.8% (1,036/21,595) vs. 11.8% (2,556/21,595), p<0.001 Overall death: 6.5% (1,406/21,595) vs. 22.1% (4,778/21,595), p<0.001

Abbreviations: aHR = adjusted hazard ratio; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CHeCS = Chronic Hepatitis Cohort Study; CI = confidence interval; DNA = deoxyribonucleic acid; FDA = U.S. Food and Drug Administration; HBeAg = hepatitis B e-antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HR = hazard ratio; REACH-B = risk estimation for hepatocellular carcinoma in chronic hepatitis B; REVEAL = study name is not an acronym.

Appendix B Table 11. Cohort Studies of HBV Treatment – Quality Assessment

Author, year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report the number of patients who met inclusion criteria excluded due to missing data or loss to followup?	Did the study perform appropriate statistical analyses on potential confounders, or appropriately account for them (should evaluate at least age, sex, fibrosis stage, HBV viral load, HBeAg status)?	Is there important (overall or differential) exclusion of patients due to missing data or loss to followup?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Gordon 2014[103]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Hoang 2016[104]	Yes, there were 2 distinct cohorts from different countries merged together, but also analyzed separately	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Hosaka 2013[105]	Yes, but separately; there were 2 separate cohorts for the treatment and control groups	Yes, by propensity matching	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Lee 2018[106]	Yes	Yes, by propensity matching	Yes	Unclear	No	Yes	Unclear, 59% remaining at year 5 after adjustments, etc.	Yes	Fair
Matsumoto 2005[107]	Yes	Mostly, by propensity matching; however still some significant differences	Yes	Yes	No	Yes	Unclear, 45% on remaining on treatment by end of followup period after adjustments, etc.	Yes	Fair
Wang 2015[108]	Yes	Yes, by propensity matching	Yes	Unclear	No	Yes	Unclear, 30% and 32% remaining at year 7 after adjustments, etc.	Yes	Fair
Wei 2019[110]	Yes	No, but adjustments were made in analysis	Yes	Unclear	Yes	Yes	No	Yes	Fair
Wu 2014[109]	Yes	Yes, by propensity matching	Yes	Unclear	No	Yes	Unclear, 18% and 55% remaining at year 6 after adjustments, etc.	Yes	Fair

Abbreviations: HBeAg = hepatitis B e-antigen; HBV = hepatitis B virus.

Appendix B Table 12. Association Studies of HBV Intermediate and Health Outcomes – Study Characteristics

Author, year Country From prior report or update	Study design	Comparison Definition	Treatment Duration of followup	Inclusion criteria	Number receiving antiviral treatment Lost to followup	Age Sex Race	Characteristics of HBV infection	Quality	Funding source
Arends 2015[117] European network of excellence for VIRGIL Surveillance Study Group 11 European referral centers From update	Cohort, retrospective Study period 2005 to May 2013	Virological response vs. no virological response Virological response=HBV DNA <80 IU/mL	Entecavir Followup, median 3.2 years	All chronic HBV monoinfected patients treated with entecavir for at least 3 months Excluded: HIV, HCV, or HDV, or if they had HCC at baseline	N=744 Lost to followup: NR	Age, mean: 44 years Male: 77% Race/ethnicity: 42% white, 29% Asian, 19% Asian, 10% unknown	HBeAg positive: 32% HBV DNA, mean: 5.3_{log} IU/mL Mean ALT: 1.4 xULN Cirrhosis: 22% Chinese University HCC risk score, mean: 8 Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis HCC risk score, mean: 62 REACH-B risk score, mean: 9	Fair	Foundation for Liver and Gastrointestinal Research Rotterdam, European Network of Excellence for Vigilance against Viral Resistance, Bristol Myers Squibb
Baltayiannis 2006[111] Greece From prior report	Cohort (unclear if prospective or retrospective)	Virological response at 6 months vs. no virological response Virological response=HBV DNA <10,000 copies/mL at 6 months of treatment	Interferon alfa 6 years	HBeAg-negative chronic HBV infection with elevated ALT and histologic evidence of chronic HBV Excluded: HCC, HCV, HDV, HIV	n=63 Lost to followup: 1.6% (1/63)	Age, mean: 51 years Male: 63% Race: NR	HBV DNA, median serum: 1.2×10^6 copies/mL HBsAg clearance: NR HBeAg positive: None ALT, median: 178 AST, median: 130 Fibrosis stage, mean Desmet: 2.2 Cirrhosis: Excluded	Fair	NR
Hui 2008[112] China (Hong Kong) From prior report	Cohort (unclear if prospective or retrospective)	Histological response in modified HAI score vs. no histological response Histological response=improvement of 2 points or more on modified HAI score after end of treatment	Interferon alfa 2a or 2b Median 9.9 years	HBeAg-positive chronic HBV infection Excluded: HDV, HCV, HIV	n=89 Lost to followup: NR	Age, mean: 30 years Male: 78% Race: NR	HBV DNA, serum $>10^5$ copies/mL: 100% HBsAg clearance: NR HBeAg positive: All ALT, mean: 113 AST: NR Fibrosis stage, mean Ishak: 2 Cirrhosis: 12%	Fair	Reports no funding received

Appendix B Table 12. Association Studies of HBV Intermediate and Health Outcomes – Study Characteristics

Author, year Country From prior report or update	Study design	Comparison Definition	Treatment Duration of followup	Inclusion criteria	Number receiving antiviral treatment Lost to followup	Age Sex Race	Characteristics of HBV infection	Quality	Funding source
Lau 1997[113] United States From prior report	Cohort (originally enrolled in RCTs)	Response vs. non-response Response=Sustained loss of HBV DNA and clearance of HBeAg within 1 year of starting treatment	Interferon alfa Mean 6.2 years	HBeAg-positive chronic HBV infection with elevated AST and/or ALT Excluded: HDV, HIV after 1988	n=103 Lost to followup: 7.8% (8/103); assumed to be alive and without liver-related complications	Age, mean: 41 years Male: 83% Race: 94% white, 6% black	Serum HBV DNA: 4843 MEq/mL HBsAg clearance: 86% (responder) vs. 11% (nonresponder) HBeAg positive: All ALT, median: 154 AST, median: 94 Fibrosis stage, mean HAI: 2.1 Cirrhosis: 17% HCV infection: 6.8% HIV infection: 14%	Fair	NR
Lin 2007[118] Taiwan From update	Cohort, matched with untreated controls Study period 1986 to 1995	HBeAg seroconversion vs. non-seroconversion (and treated vs. non-treated/control) Seroconverter=persistent loss of HBV–DNA with anti-HBe seropositivity ≥12 months until last followup	Interferon alpha Median followup 6.8 years (range up to 15 years)	HBeAg seropositive patients with active HBV demonstrated by a biopsy within 3 months before starting therapy Excluded those with HCV or HDV and alcohol-related etiology	N=466 total (233 received treatment vs. 233 control) Lost to followup: not applicable	Interferon vs. control: Age, mean: 32 vs. 31 years Male: 94% vs. 94% Race/ethnicity: NR (conducted in Taiwan)	Interferon vs. control: HBV DNA (pg/mL): 18% vs. 20% ≤200, 35% vs. 30% 201 to 500, 7% vs. 10% 501 to 1000, 40% vs. 40% >1000 ALT: 175 vs. 187 U/L AFP: 7 vs. 8 ng/mL Cirrhosis: 8.1% vs. 10.7% HBV genotype: 61% vs. 57% B, 32% vs. 35% C, 7% vs. 8% other	Fair	Grants from the Department of Health and the Prosperous Foundation Taipei, Taiwan

Appendix B Table 12. Association Studies of HBV Intermediate and Health Outcomes – Study Characteristics

Author, year Country From prior report or update	Study design	Comparison Definition	Treatment Duration of followup	Inclusion criteria	Number receiving antiviral treatment Lost to followup	Age Sex Race	Characteristics of HBV infection	Quality	Funding source
Niederau 1996[114] Europe From prior report	Prospective cohort	Loss of HBeAg after therapy vs. no loss	Interferon alfa 2b Mean 4.2 years	HBeAg-positive chronic HBV infection, ALT >2 times ULN and histologic evidence of active hepatitis Excluded: HDV, HIV, advanced cirrhosis	n=103 Lost to followup: None	Age, mean: NR Male: NR Race: NR	HBV DNA: NR HBsAg clearance: 9.7% HBeAg positive: All ALT: NR AST: NR Fibrosis stage: NR Cirrhosis: NR (Child-Pugh class B or C excluded)	Fair	Van Meeteren Foundation
Papatheodoridis 2001[115] Greece From prior report	Cohort (unclear if prospective or retrospective)	Sustained biochemical response vs. no sustained biochemical response Sustained biochemical response=normalization of ALT at the end of interferon therapy and persistently normal ALT levels throughout the post-treatment followup period	Interferon alfa Mean 6 years	HBeAg-negative chronic HBV infection with elevated ALT and histologic evidence of chronic HBV Excluded: decompensated liver disease, HCC, HCV, HDV, HIV	n=209 Lost to followup: 9 (4.3%)	Age, mean: 47 years Male: 83% Race: NR	HBV DNA, median serum: 4.4 pg/mL HBsAg clearance: 13% (27/209, mean 2.9 years after end of treatment) HBeAg positive: Excluded ALT, median: 112 AST, median: 67 Fibrosis stage, mean Ishak: 3.3 Cirrhosis: 27%	Fair	NR
Papatheodoridis 2011[116] Greece From prior report	Retrospective cohort	Virological remission vs. no virological remission Virological remission=HBV DNA <200 IU/mL throughout therapy	Lamivudine Median 4.7 years	HBeAg-negative chronic HBV infection with at least 2 of the following: elevated ALT, HBV DNA >2000 IU/mL, or histologic evidence of chronic HBV Excluded: HDV, HCV, HIV, HCC diagnosed before or within first 6 months of treatment	n=818 Lost to followup: 180 (22%)	Age, mean: 54 years Male: 72% Race: NR	HBV DNA, median serum: 400 $x10^3$ IU/mL HBsAg clearance: NR HBeAg positive: Excluded ALT (median): 98 AST (median): 68 Fibrosis stage: NR Cirrhosis: 26%	Fair	Hellenic Center for Disease Control and Prevention

Appendix B Table 12. Association Studies of HBV Intermediate and Health Outcomes – Study Characteristics

Author, year Country From prior report or update	Study design	Comparison Definition	Treatment Duration of followup	Inclusion criteria	Number receiving antiviral treatment Lost to followup	Age Sex Race	Characteristics of HBV infection	Quality	Funding source
Wong 2013[119] Hong Kong From update	Cohort, retrospective and prospective December 2005 to August 2012 (Patients treated prior to October 2009 were retrospectively identified)	Duration of virological remission ≥24 months vs. shorter duration Virological remission=undetectable serum HBV DNA	Entecavir Duration of followup: 3.5 years	Chronic HBV patients treated with entecavir 0.5 mg daily for at least 12 months, positive HBsAg for ≥6 months, life expectancy of >1 year at recruitment Excluded: preexisting HCC or HCC diagnosed within the first year on entecavir, other chronic liver diseases, Child class C cirrhosis, autoimmune hepatitis, HCV or another concurrent illness (e.g. alcoholism, uncontrolled diabetes, or cancer)	1531 Lost to followup: NR	Age: 51 years Male: 72% Race/ethnicity: NR (Hong Kong)	HBeAg positive: 30% HBV DNA: 5.0 log_{10} IU/mL HBV DNA ≥2000 IU/mL: 77% HBsAg: 3.0 log_{10} IU/mL HBsAg >1000 IU/mL: 61% Cirrhosis: 22%	Fair	Direct Grant of the Chinese University of Hong Kong

Abbreviations: ALT = alanine aminotransferase; APRI = AST/platelet ratio index; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; FIB4 = fibrosis-4 index; HAI = histology activity index; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; MEq = mega equivalents; NR = not reported; RCT = randomized controlled trial; REACH-B = Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; ULN = upper limit of normal; VIRGIL = Vigilance Against Viral Resistance.

Appendix B Table 13. Association Studies of HBV Intermediate and Health Outcomes – Results

Author, year Country From prior report or update	Comparison	Treatment Duration of followup	Number receiving antiviral treatment	Proportion of patients with intermediate outcome	Confounders adjusted for in analysis	Results (by clinical outcome)
Arends 2015[117] European network of excellence for VIRGIL Surveillance Study Group 11 European referral centers From update	Virological response vs. no virological response	Entecavir Followup, median 3.2 years	744	Virological response: 88% (655/744); cumulative probability at 5 years, 99%	Unclear for this analysis, but age, sex, cirrhosis, albumin, bilirubin, HBV DNA, ALT, HBeAg status were examined for risk scores	HCC and virologic response (HBV DNA <80 IU/mL) as a time dependent factor: HR 0.87 (95% CI, 0.17 to 4.58), p=0.87 Clinical event (composite endpoint of development of HCC, liver decompensation, or death) and virologic response (HBV DNA <80 IU/mL) as a time dependent factor: HR 0.70 (95% CI, 0.28 to 1.77), p=0.46 Univariate analysis, association of HCC and HBV DNA: HR 0.82 (95% CI, 0.64 to 1.05), p=0.12 Overall clinical events and HBV DNA: HR 1.09 (95% CI, 0.94 to 1.27), p=0.26 HCC and HBeAg negative: HR 0.81 (95% CI, 0.25 to 2.57), p=0.72 Overall clinical events and HBeAg negative: HR 1.11 (95% CI, 0.55 to 2.34), p=0.78
Baltayiannis 2006[111] Greece From prior report	Virological response at 6 months vs. no virological response	Interferon alfa 6 years	63	Virological response at 6 months: 35% (22/63)	Age Gender Alcohol use HBV DNA >10,000 copies/mL at baseline HBeAg: all patients negative ALT >200 IU/L at baseline Histologic grade >9 Histologic stage >2	Death or disease complication (hepatic encephalopathy, ascites, variceal bleeding, HCC) Virological response at 6 months vs. no virological response: aHR 0.24 (95% CI, 0.06 to 0.96)
Hui 2008[112] China (Hong Kong) From prior report	Histological response in HAI score vs. no histological response	Interferon alfa 2a or 2b Median 9.9 years	89	Histological response in HAI score: 40% (36/89) Histological response in fibrosis stage: 18% (16/89)	HBV DNA level HBeAg: all patients positive Fibrosis	Liver complications (HBV-related decompensated liver cirrhosis or HCC) Histological response on HAI score vs. no response: aHR 0.62 (95% CI, 0.06 to 6.9)
Lau 1997[113] United States From prior report	Response vs. non-response	Interferon alfa Mean 6.2 years	103	Response: 30% (31/103) (Response=Sustained loss of HBV DNA and clearance of HBeAg within 1 year of starting treatment)	Age Sex HBeAg: all patients positive ALT AST Cirrhosis	Death (results only adjusted for age and sex) Responder vs. non-responder: aHR 0.59 (95% CI, 0.20 to 1.67) Death or liver-related complication (variceal hemorrhage, ascites, encephalopathy) Responder vs. non-responder: aHR 0.07 (95% CI, 0.02 to 0.33)

Appendix B Table 13. Association Studies of HBV Intermediate and Health Outcomes – Results

Author, year Country From prior report or update	Comparison	Treatment Duration of followup	Number receiving antiviral treatment	Proportion of patients with intermediate outcome	Confounders adjusted for in analysis	Results (by clinical outcome)
Lin 2007[118] Taiwan From update	HBeAg seroconversion vs. non-seroconversion (and treated vs. non-treated/control)	Interferon alpha Median followup 6.8 years (range up to 15 years)	233 (466 in total sample)	At the end of 15 years of followup: HBeAg seroconversion rates of 74.6% in interferon vs. 51.7% in control group, p=0.031 HBsAg seroclearance 3% vs. 0.4%, p=0.03	Age ALT HBV-DNA Platelet count Preexisting cirrhosis AFP Known duration of hepatitis HBV genotype and regimen Corticosteroid priming Duration of interferon treatment HBeAg seroconversion	Multivariate analysis: HBeAg seroconversion and cirrhosis: HR 0.41 (95% CI, 0.32 to 0.88), p=0.027 HBeAg seroconversion and HCC: HR 0.13 (95% CI, 0.08 to 0.57), p=0.022
Niederau 1996[114] Europe From prior report	Loss of HBeAg after therapy vs. no loss	Interferon alfa 2b Mean 4.2 years	103	HBeAg loss: 51% (53/103)	Age Sex HBV DNA at baseline HBeAg: all patients positive ALT at baseline Duration of hepatitis Cirrhosis at baseline	Liver complications (death; need for liver transplantation; development of ascites, jaundice, or hepatic encephalopathy; occurrence of, or bleeding from, esophageal varices) HBeAg loss vs. no loss: aHR 0.06 (95% CI, 0.01 to 0.61)
Papatheodoridis 2001[115] Greece From prior report	Sustained biochemical response vs. no sustained biochemical response	Interferon alfa Mean 6 years	209	Sustained biochemical response: 27% (57/209) (Sustained biochemical response=normalization of ALT at the end of interferon therapy and persistently normal ALT levels throughout the post-treatment followup period)	Age HBeAg: all patients negative Cirrhosis	Death or liver transplantation Sustained biochemical response vs. no sustained biochemical response: aHR 0.48 (95% CI, 0.23 to 1.0) Severe clinical complications (death, liver transplantation, liver decompensation [ascites, variceal bleeding, hepatic encephalopathy], and HCC) Sustained biochemical response vs. no sustained biochemical response: aHR 0.53 (95% CI, 0.29 to 0.91)

Appendix B Table 13. Association Studies of HBV Intermediate and Health Outcomes – Results

Author, year Country From prior report or update	Comparison	Treatment Duration of followup	Number receiving antiviral treatment	Proportion of patients with intermediate outcome	Confounders adjusted for in analysis	Results (by clinical outcome)
Papatheodoridis 2011[116] Greece From prior report	Virological remission vs. no virological remission	Lamivudine Median 4.7 years	818	Virological remission: 28% (228/818) (Virological remission=HBV DNA <200 IU/mL throughout therapy)	Age Sex HBV DNA HBeAg: all patients negative ALT AST Bilirubin Albumin Hemoglobin Platelet count Liver disease severity Interferon alfa in the past	HCC Virological remission under therapy vs. no virological remission: aHR 0.77 (95% CI, 0.35 to 1.69)
Wong 2013[119] Hong Kong From update	Duration of virological remission ≥24 months vs. shorter duration	Entecavir Duration of followup: 3.5 years	1,531	Maintained virologic response: 77% (1,174/1,531) Duration of virologic remission: 34 months	Unclear for this analysis, but adjustments reported	Duration of virologic remission ≥24 months and subsequent development of HCC: Entire cohort: aHR 0.3 (95% CI, 0.1 to 0.6), p=0.007 Previously treatment-naïve patients: aHR 0.4 (95% CI, 0.2 to 0.7), p=0.009 Incidence of HCC: 3.1% (47/1,531) Association between HCC and achieving a maintained virologic response (response rates among those developing HCC vs. not): 64% (30/47) vs. 77% (1,144/1,484), p=0.03; with a shorter duration of virologic remission: 31 (HCC) vs. 35 months (no HCC), p<0.009

Abbreviations: AFP = alpha-fetoprotein; aHR = adjusted hazard ratio; ALT = alanine aminotransferase; APRI = AST/platelet ratio index; AST = aspartate aminotransferase; CI = confidence interval; DNA = deoxyribonucleic acid; FIB4 = fibrosis-4 index; HAI = histology activity index; HBV = hepatitis B virus; HBeAg = hepatitis B e-antigen; HCC = hepatocellular carcinoma; HR = hazard ratio; NR = not reported; VIRGIL = Vigilance Against Viral Resistance.

Appendix B Table 14. Association Studies of HBV Intermediate and Health Outcomes – Quality Assessment

Author, year From prior report or update	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining intermediate outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report the number of patients who met inclusion criteria excluded due to missing data or loss to followup?	Did the study perform appropriate statistical analyses on potential confounders, or appropriately account for them (should evaluate at least age, sex, fibrosis stage, HBV viral load, HBeAg status)?	Is there important (overall or differential) exclusion of patients due to missing data or loss to followup?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Arends, 2015[117] From update	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Yes	Fair
Baltayiannis 2006[111] From prior report	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair
Hui 2008[112] From prior report	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	Fair
Lau 1997[113] From prior report	Yes	No	Yes	Unclear	Yes	No	No	Yes	Fair
Lin 2007[118] From update	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Niederau 1996[114] From prior report	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair
Papatheodoridis 2001[115] From prior report	Yes	No	Unclear	Unclear	Yes	Unclear	No	Yes	Fair
Papatheodoridis 2011[116] From prior report	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Wong 2013[119] From update	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Yes	Fair

Abbreviations: HBeAg = hepatitis B e-antigen; HBV = hepatitis B virus.

Appendix C Table 1. CDC Hepatitis Risk Assessment Tool

Questions	Recommendations and Explanation
1. Have you ever been diagnosed with a clotting factor disorder?	If yes, talk to your doctor about getting vaccinated for Hepatitis A.
2. Have you ever been diagnosed with a chronic liver disease?	If yes, talk to your doctor about getting vaccinated for Hepatitis A and B.
3. Were you or at least one parent born outside of the United States?	If yes, talk to a doctor about getting a blood test for Hepatitis B. Many parts of the world have high rates of Hepatitis B, including the Amazon Basin, parts of Asia, Sub-Saharan Africa and the Pacific Islands.
4. Do you currently live with someone who is diagnosed with Hepatitis B?	If yes, talk to a doctor about getting a blood test for Hepatitis B.
5. Have you previously lived with someone who has been diagnosed with hepatitis B?	If yes, talk to a doctor about getting a blood test for Hepatitis B.
6. Have you recently been diagnosed with a STD?	If yes, talk to a doctor about getting vaccinated for Hepatitis B.
7. Have you been diagnosed with diabetes?	If yes, talk to a doctor about getting vaccinated for Hepatitis B.
8. Have you been diagnosed with HIV/AIDS?	If yes, talk to a doctor about getting vaccinated for Hepatitis B and getting a blood test for Hepatitis B and Hepatitis C.
9. If you are a man, do you have sexual encounters with other men?	If yes, talk to a doctor about getting vaccinated for Hepatitis A and B, and getting a blood test for Hepatitis B.
10. Do you currently inject drugs?	If yes, talk to a doctor about getting vaccinated for Hepatitis A and B, and getting a blood test for Hepatitis B and C.
11. Were you born from 1945 to 1965?	If yes, talk to a doctor about getting a blood test for Hepatitis C.
12. Have you ever received a blood transfusion or organ transplant before July 1992?	If yes, talk to a doctor about getting a blood test for Hepatitis C.
13. Have you ever received a clotting factor concentrate before 1987?	If yes, talk to a doctor about getting a blood test for Hepatitis C.
14. Have you ever injected drugs, even if just once?	If yes, talk to a doctor about getting a blood test for Hepatitis C.
15. Do you plan on traveling outside of the United States within the next year?	If yes, talk to a doctor about what vaccines may be needed for travel outside the United States.

Source: Centers for Disease Control and Prevention, available at: https://www.cdc.gov/hepatitis/riskassessment/pdfs/HepatitisRiskAssessment.pdf
Abbreviations: CDC = Centers for Disease Control and Prevention, STD = sexually transmitted disease.

Appendix C Table 2. AGA Risk Groups for HBV Reactivation

Risk group	HBVr drug risk estimates (HBsAg positive or anti-HBc positive)
High-risk group (>10%)	B cell–depleting agents such as rituximab and ofatumumab • HBsAg positive/anti-HBc positive: 30% to 60% (A) • HBsAg negative/anti-HBc positive: >10% (A) Anthracycline derivatives such as doxorubicin and epirubicin • HBsAg positive/anti-HBc positive: 15% to 30% (A) Corticosteroid therapy for ≥4 weeks • HBsAg positive/anti-HBc positive: >10% (B) (moderate/high dose[a])
Moderate-risk group (1%–10%)	TNF-a inhibitors: etanercept, adalimumab, certolizumab, infliximab • HBsAg positive/anti-HBc positive: 1% to 10% (B) • HBsAg negative/anti-HBc positive: 1% (C) Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab • HBsAg positive/anti-HBc positive: 1% to 10% (C) • HBsAg negative/anti-HBc positive: 1% (C) Tyrosine kinase inhibitors: imatinib, nilotinib • HBsAg positive/anti-HBc positive: 1% to 10% (B) • HBsAg negative/anti-HBc positive: 1% (C) Corticosteroid therapy for ≥4 weeks • HBsAg positive/anti-HBc positive: 1 to 10% (C) (low dose[a]) • HBsAg negative/anti-HBc positive: 1 to 10% (C) (moderate/high dose[a]) Anthracycline derivatives: doxorubicin and epirubicin • HBsAg negative/anti-HBc positive: 1% to 10% (C)
Low-risk group (<1%)	Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate • HBsAg positive/anti-HBc positive: <1% (A) • HBsAg negative/anti-HBc positive: <1% (A) Intra-articular corticosteroids • HBsAg positive/anti-HBc positive: <1% (A) • HBsAg negative/anti-HBc positive: <1% (A) Corticosteroid therapy for ≤1 week • HBsAg positive/anti-HBc positive: <1% (B) • HBsAg negative/anti-HBc positive: <1% (A) Corticosteroid therapy for ≥4 weeks • HBsAg negative/anti-HBc positive: <1% (B) (low dose[a])

Source: Perillo 2015 for the American Gastroenterological Association[149]
NOTE. Confidence in evidence was graded as follows:
(A), high confidence that the estimate lies within group risk boundaries;
(B), moderate confidence that the estimate lies within group risk boundaries;
(C), little or no confidence that the estimate lies within group risk boundaries.
[a]Glucocorticoids: prednisone (or equivalent): low dose, <10 mg; moderate dose, 10 to 20 mg; high dose, >20 mg.

Abbreviations: AGA = American Gastroenterological Association; anti-HBc = antibody to hepatitis B core antigen; HBV = hepatitis B virus; HBVr = hepatitis B virus reactivation; HBsAg = hepatitis B surface antigen; anti-HBc = antibody to hepatitis B core antigen; TNF = tumor necrosis factor.