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Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: Systematic Review to Update the 2004 U.S. Preventive Services Task Force Recommendation

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Structured Abstract

Background: In 2004, the U.S. Preventive Services Task Force (USPSTF) recommended against screening asymptomatic persons in the general population for hepatitis B virus (HBV).

Purpose: To systematically review the current evidence on the benefits and harms of screening for HBV infection in asymptomatic nonpregnant adolescents and adults.

Data Sources: We searched the Cochrane Central Register of Controlled Trials (through January 2014), the Cochrane Database of Systematic Reviews (2005 through January 2014), Ovid MEDLINE® (1946 through January 2014), and PsycINFO® (1806 through January 2014) and reviewed reference lists of relevant articles.

Study Selection: We included randomized trials of screening and treatment that reported intermediate or clinical outcomes. We also included observational studies of screening and on the association between improvement in intermediate outcomes after antiviral therapy and improvement in 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): We found no direct evidence on effects of screening for HBV infection versus no screening on clinical outcomes. HBV vaccination was associated with decreased risk of HBV acquisition in high-risk populations. Data from randomized trials suggest that antiviral therapy may be more effective than placebo for reducing risk of clinical outcomes associated with HBV infection, but differences were not statistically significant and pooled estimates were imprecise due to small numbers of events. Evidence consistently found antiviral therapy to be more effective than placebo or no treatment for various intermediate histological, virological, biochemical, and serological outcomes. Results were generally consistent when analyses were stratified by individual drug. Limited evidence from head-to-head trials found that entecavir and pegylated interferon alfa-2a had greater likelihood of achieving intermediate outcomes than lamivudine. Studies on the association between improvements in intermediate outcomes following antiviral therapy and clinical outcomes were heterogeneous and had methodological limitations, precluding strong conclusions. Antiviral therapy was associated with a higher risk of withdrawal due to adverse events than placebo, but there was no difference in risk of serious adverse events.

Limitations: We included only English-language publications. Studies conducted in countries where the prevalence and natural history of HBV infection differ from those in the United States were included due to limited evidence from settings more applicable to practice in the United States. Evidence from placebo-controlled trials on intermediate and clinical outcomes was limited or not available for some first-line antiviral therapies.

Conclusions: Although screening tests can accurately identify adolescents and adults with chronic HBV infection, more research is needed to understand the effects of screening and

subsequent interventions on clinical outcomes and to identify optimal screening strategies. The declining incidence and prevalence of HBV infection as a result of universal vaccination programs is likely to impact future assessments of the benefits and harms of HBV screening.

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Chapter 1. Introduction

Purpose and Previous U.S. Preventive Services Task Force Recommendation

This report was commissioned by the U.S. Preventive Services Task Force (USPSTF) in order to update its 2004 recommendation on screening for hepatitis B virus (HBV) infection in nonpregnant adolescents and adults.[1] The 2004 USPSTF recommendation was based on an evidence review with literature searches conducted through 2001.[2]

In 2004, the USPSTF recommended against screening asymptomatic persons in the general population for chronic HBV infection (D recommendation), based on a lack of evidence showing that screening improves morbidity or mortality associated with HBV infection; that the prevalence of HBV infection is low in the general population; and that the majority of infected individuals do not develop chronic infection, cirrhosis, or other HBV-related liver disease.[1] The USPSTF noted the poor predictive value of screening strategies for identifying persons at high risk for infection and limited evidence on the effectiveness of treatment interventions.[1] The USPSTF also pointed out that routine vaccination has reduced the number of new HBV infections, particularly for children and adolescents, decreasing the burden of chronic HBV infection.

In 2009, the USPSTF separately addressed prenatal screening for HBV infection, reaffirming its 2004 recommendation for screening at the first prenatal visit (A recommendation).[3,4] The current review focuses on screening nonpregnant persons; the USPSTF is not updating its recommendation on prenatal screening at this time.

Condition Definition

HBV is a double-stranded DNA virus enclosed in a nucleocapsid protein (core antigen) surrounded by an envelope protein (surface antigen, or sAg).[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. Acute HBV infection (within 6 months after infection) is typically characterized by the initial appearance of HBV surface antigen (HBsAg) without other serologic markers, followed by the appearance of immunoglobin M (IgM) antibody to the HBV core antigen (anti-HBc).[6,7] Chronic infection is characterized by the persistent presence of HBsAg for longer than 6 months; HBV DNA levels can fluctuate and are not a reliable marker of chronic infection.[6,7] The presence of HBV e antigen (HBeAg) is usually associated with high levels of HBV DNA in serum and high infectivity.[8,9] Resolution of HBV infection and immunity are typically characterized by disappearance of HBsAg and appearance of antibody to HBV surface antigen (anti-HBs) as well as anti-HBc. Although disappearance of HBeAg and appearance of antibody to HBeAg (anti-HBe) eventually occurs in most patients with chronic HBV infection, typically correlating with low levels of HBV DNA in serum and remission of liver disease,

patients (primarily from southern Europe or Asia) who are HBeAg negative due to mutations that prevent HBeAg expression can have persistent active disease.

Prevalence and Burden of Disease

The reported incidence of acute symptomatic HBV infections in the United States has fallen from over 20,000 cases annually in the mid-1980s to 2,890 cases in 2011.[10] Due to underreporting, the actual number of cases is estimated to be 6.5 times higher than the number of reported cases.[10] From 2000 to 2010, the incidence of acute HBV infection declined among all age groups.[11] In 2010, the highest rate of new HBV infections was among persons age 30 to 39 years (2.33 cases/100,000 population), with males and black persons at highest risk.[11]

As of 2008, an estimated 704,000 people in the United States were chronically infected with HBV.[12] In 2010, there were an estimated 0.5 deaths associated with HBV infection per 100,000 persons, with the highest death rates among persons age 55 to 64 years, persons of "non-white, non-black" race, and males.[13]

Etiology and Natural History

HBV is spread through percutaneous or mucous membrane exposure to blood or blood-containing body fluids (serum, semen, or saliva).[6,9,14] The liver is the primary site of viral replication. 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 can be seen on standard assays.

If symptoms of acute disease occur, they can take from 6 weeks to 6 months to appear.[15] 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. 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.[9,15] Chronic infection spontaneously resolves in 0.5 percent of individuals annually. 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.[15] Patients can also transition between different phases of chronic HBV infection. The phases include the immune tolerant phase, characterized by the presence of HBeAg and high levels of HBV viremia but absence of liver disease; the immune active or chronic hepatitis phase, characterized by high levels of HBV viremia and active liver inflammation, with presence or absence of HBeAg or presence of anti-HBe; and the inactive phase, characterized by the presence of anti-HBe, normal liver aminotransferase levels, and low or undetectable levels of HBV viremia. Although the course of chronic HBV infection varies widely, potential long-term sequelae include cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[16] 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.[17,18] Chronically infected persons are a reservoir for person-to-person transmission of HBV infection.

Risk Factors/Indicators

People born in countries with an HBV prevalence of ≥2 percent 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.[19-21] Regions of the world with very high HBV prevalence (≥8%) include most of Asia, most of Africa, Australasia with the exception of Australia and New Zealand, and parts of South America.[15] Persons at higher risk for acute HBV infection include men, black persons, and persons age 30 to 39 years.[11] Risk factors for HBV infection include having household contacts or sex partners with HBV infection (prevalence of chronic infection, 3 to 20%), 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%).[9,11,15,22,23] Settings with high proportions of persons at risk for HBV infection include sexually transmitted disease (STD) clinics, HIV testing and treatment centers, health care settings that target services toward injection drug users (IDUs) and men who have sex with men, correctional facilities, hemodialysis facilities, and institutions and nonresidential daycare centers for developmentally disabled persons.[6]

Rationale for Screening and 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. Data on the proportion of persons with chronic HBV infection in the United States who are not aware of their infection status are limited, although in studies of Asian-born persons living in the United States, the proportion is approximately one-third.[15] 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.

Interventions and 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 the United States, current policies are for universal vaccination of all infants at birth, catch-up vaccination of adolescents, and vaccination of high-risk groups, such as health care workers, IDUs, household contacts of patients with HBV infection, men who have sex with men, and persons with end-stage renal disease. HBV vaccines in the United States contain between 10 to 40 micrograms of HBsAg protein/mL for adolescents and adults, and generally involve at least three intramuscular doses administered at 0, 1, and 6 months.[6,9] Vaccination results in ≥90 percent protective antibody response after the third dose in adults and >95 percent in adolescents, although protective anti-HBs titers may be attained in some persons after one or two doses.[6, 9] As

of 2011, universal vaccination of children has been implemented in over 190 countries, with 81 countries targeting newborns.[24,25] The widespread implementation of universal vaccination strategies throughout the world has been credited with marked decreases in HBV incidence, particularly among younger persons.[26]

Treatment

Currently seven antiviral drugs are approved by the U.S. Food and Drug Administration (FDA) for treatment of chronic HBV infection: interferon alfa-2b, pegylated interferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. A number of combination therapies and drugs 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.[27,28] Drugs for HBV infection are broadly categorized as either interferons or nucleoside/nucleotide analogs.[21,28-30] The interferons affect viral replication as well as immune modulation.[8,27] Nucleoside/nucleotide analogues (lamivudine, adefovir, entecavir, and others) compete with binding sites on the HBV reverse transcriptase.

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; sustained remission is rare in the absence of treatment in patients with HBeAg-negative HBV infection.[27] Biopsy may be performed in some patients to establish the degree of liver inflammation and fibrosis.[27,28] In many cases, pegylated interferon alfa-2a, entecavir, or tenofovir are suggested as first-line drugs due to their tolerability, efficacy, and lower rates of inducing resistance.[27,28]

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.[21,29] The recommended duration of treatment varies depending on the HBeAg status, presence of cirrhosis, time required to achieve HBV DNA suppression, and choice of medication.[15,27,28] Interferon-based therapy is usually recommended for shorter duration of treatment than non–interferon-based therapy, in part due to limited tolerability and additional immunomodulatory effects of interferons.[27,28]

Other treatments in patients with chronic HBV infection could include counseling or education to reduce behaviors associated with accelerated progression of liver disease (such as alcohol use) or transmission, or surveillance with imaging tests to identify hepatocellular carcinoma.

Current Clinical Practice

Screening for HBV infection is usually performed by testing for HBsAg, anti-HBs, and anti-HBc.[27] The Centers for Disease Control and Prevention (CDC) recommends that FDA-approved tests be used to screen for HBsAg and a confirmatory test performed for initially reactive results.[15] In persons with serologic findings suggesting chronic infection, followup includes testing for viremia.

Current U.S. screening practices for HBV and rates of HBV testing are largely unreported. As described below, some groups recommend that screening be targeted to higher risk groups, including persons born in high-prevalence countries.[15,27]

Recommendations of Other Groups

The CDC[15] and the American Association for the Study of Liver Diseases (AASLD)[27] both recommend HBV screening for the following high-risk persons:

- All foreign-born persons from regions with HBsAg prevalence ≥2 percent, regardless of vaccination history
- U.S.-born persons not vaccinated as infants whose parents were born in regions with HBsAg ≥8 percent
- IDUs
- Men who have sex with men
- Immunosuppressed persons
- Persons with elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) of unknown etiology
- Hemodialysis patients
- Household contacts and sex partners of HBsAg-positive persons
- Persons with HIV
- Pregnant women and infants born to HBV-infected mothers

In addition, the CDC recommends screening of blood, organ, or tissue donors; persons with occupational or other exposures to infectious blood or body fluids; and persons who received HBV vaccination as adolescents or adults who have high-risk behaviors.[15] The AASLD recommends screening of persons with multiple sex partners or a history of STD, inmates of correctional facilities, and individuals with hepatitis C virus (HCV) infection.[27] The Institute of Medicine endorses screening in high-risk groups.[31]

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[32,33] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and Key Questions for this review. Evidence-based Practice Center (EPC) investigators created an analytic framework showing the Key Questions and the patient populations, interventions, and outcomes of the review (**Figure 1**).

The Key Questions are—

Key Question 1. What are the benefits of screening for HBV versus no screening in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?
Key Question 2. What are the harms of screening for HBV infection (e.g., labeling, anxiety, and harms of confirmatory tests, including biopsy)?
Key Question 3. How well do different screening strategies identify individuals with HBV infection (e.g., strategies that target persons from high-prevalence countries, men who have sex with men, injection drug users, immunization history, or other risk factors)?
Key Question 4. In nonpregnant adolescents and adults with no evidence of HBV immunity on screening, how effective is HBV vaccination for improving clinical outcomes?
Key Question 5. In nonpregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving intermediate outcomes (virological or histological improvement or clearance of HBeAg)?
Key Question 6. In nonpregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving health outcomes?
Key Question 7. In nonpregnant adolescents and adults with chronic HBV infection, how effective is education or behavior change counseling in reducing transmission and improving health outcomes?
Key Question 8. What are the harms associated with antiviral treatment for HBV infection?
Key Question 9. Do improvements in intermediate outcomes improve final health outcomes?

The overarching Key Questions (1 and 2) in the analytic framework focus on direct evidence on the effects of screening for HBV infection on health outcomes compared with not screening. When such direct evidence is sparse or unavailable, an indirect chain of evidence can be used to link screening with health outcomes, as shown in the rest of the analytic framework. Critical gaps in any of the links of the indirect chain of evidence can make it difficult or impossible to reliably estimate benefits and harms of screening. Links in the chain of indirect evidence include the performance of testing strategies for identifying individuals with HBV infection and the effectiveness of treatments in those with HBV infection, as well as any harms from the screening test and subsequent diagnostic tests and treatments. We did not re-review the diagnostic accuracy of HBV antibody testing and followup testing for viremia, which is considered accurate for diagnosing chronic infection.[3]

This review differs from the prior brief USPSTF evidence update[2] in that it included Key Questions on the benefits and harms of antiviral treatment, benefits of education or behavior change counseling, and the association between improvements in intermediate and clinical outcomes and excluded Key Questions related to prenatal screening and immunization of children.

Search Strategies

We searched the Cochrane Central Register of Controlled Trials (through January 2014), the Cochrane Database of Systematic Reviews (2005 through January 2014), Ovid MEDLINE® (1946 through January 2014), and PsycINFO® (1806 through January 2014) for relevant studies and systematic reviews. Search strategies are available in **Appendix A1.** We also reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on the basis of inclusion and exclusion criteria developed for each Key Question (**Appendix A2)**. For Key Questions related to screening, we included randomized trials, cohort studies, case-control studies, and cross-sectional studies that compared different screening strategies in asymptomatic adults without known liver enzyme abnormalities and reported clinical outcomes (including harms) or the sensitivity and number needed to screen to identify one HBV-infected person (or the data to calculate these parameters). For Key Questions related to treatment, we included placebo-controlled trials of vaccination in adults without known immunity to HBV infection and trials of counseling in HBV-infected people regarding high-risk behaviors. For antiviral therapy, we included trials of patients that compared monotherapy with an FDA-approved medication versus placebo or no treatment and reported clinical outcomes (mortality, cirrhosis, hepatic decompensation, hepatocellular carcinoma, need for transplantation, quality of life, or disease transmission) or intermediate outcomes (normalization of aminotransferase levels, decrease in HBV DNA level, improvement in liver histology, HBeAg clearance or development of anti-HBe in HBeAg-positive patients). We also included randomized trials of currently recommended first-line antiviral therapies (pegylated interferon, entecavir, and tenofovir)[27] versus older antiviral therapies (adefovir, nonpegylated interferon, lamivudine, or telbivudine).

Studies of treatment were excluded if they evaluated non–FDA-approved or discontinued drugs, with the exception of placebo-controlled trials of interferon alfa-2a. Although interferon alfa-2a has been supplanted by pegylated interferon and is no longer available in the United States, we included trials of interferon alfa-2a that reported clinical outcomes because evidence from placebo-controlled trials of nonpegylated interferon alfa-2b and pegylated interferon alfa-2a on clinical outcomes was sparse. For harms, we included randomized trials and controlled observational studies that reported withdrawals due to adverse events, serious adverse events, or overall adverse events. For harms, we also included head-to-head trials for currently recommended first-line antiviral therapies. For Key Question 9, we included cohort studies that

reported adjusted risk estimates for the association between clinical outcomes and either achieving or not achieving an intermediate outcome after antiviral treatment (e.g., clearance of HBeAg or HBV DNA from serum, normalization of serum transaminases, or histological improvement).

We excluded trials of antiviral therapy that focused on primary nonresponders to prior antiviral therapy or patients with virological relapse, and we did not evaluate development of drug resistance as an outcome. We excluded studies of patients with HIV or HCV coinfection, patients on hemodialysis, and transplant patients. We excluded systematic reviews of antiviral therapies unless we were unable to abstract the primary studies because they were in a foreign language. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

We abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results. Two investigators independently applied criteria developed by the USPSTF[32,33] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through a consensus process.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each Key Question (good, fair, poor) using methods developed by the USPSTF, based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence.[32,33]

We conducted meta-analyses to calculate relative risks for clinical outcomes (death, hepatocellular carcinoma, and incident cirrhosis), intermediate outcomes (HBeAg loss, HBV viral clearance, normalization of AST levels, and histological improvements), and harms (serious adverse events, withdrawals due to adverse events, and any adverse events) with antiviral drugs versus placebo/no treatment and for first-line antivirals versus other antivirals. We used the Mantel-Haenszel random-effects model with RevMan software (Review Manager Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Primary analyses for intermediate and clinical outcomes were based on total followup (including time following discontinuation of antiviral therapy), although we conducted sensitivity analysis restricted to events that occurred while patients were receiving antiviral therapy. For all analyses, we stratified results by antiviral drug. Statistical heterogeneity was assessed using the I^2 statistic.[34] We performed additional analyses in which trials were stratified by study quality, duration of followup (shorter or longer than 1 year), HBeAg status, and inclusion of patients with cirrhosis.

External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners (**Appendix A6**) and was posted for public comment. In response to public comments, we made minor revisions in the Introduction to more accurately describe the definition and natural history of chronic HBV infection.

Chapter 3. Results

Key Question 1. What Are the Benefits of Screening for HBV Versus No Screening in Asymptomatic, Nonpregnant Adolescents and Adults on Morbidity, Mortality, and Disease Transmission?

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 (e.g., Labeling, Anxiety, and Harms of Confirmatory Tests, Including Biopsy)?

No study compared harms between individuals screened and not screened for HBV infection.

Key Question 3. How Well Do Different Screening Strategies Identify Individuals With HBV Infection (e.g., Strategies That Target Persons From High-Prevalence Countries, Men Who Have Sex With Men, Injection Drug Users, Immunization History, or Other Risk Factors)?

Summary

One fair-quality (n=6,194) cross-sectional study found screening targeted at persons born in countries with higher (≥2%) chronic HBV prevalence, men, and unemployed persons identified 98 percent (48/49) of infections while testing about two-thirds of the population, for a number needed to screen to identify one case of HBV infection of 82. Screening strategies that targeted persons born in higher prevalence countries but focused on behavioral risk factors rather than male sex and employment status resulted in higher proportions of patients tested but lower sensitivities. Screening only patients born in higher prevalence countries would have resulted in testing of 12 percent of patients, a sensitivity of 31 percent, and a number needed to screen to identify one case of HBV infection of 16.

Evidence

One cross-sectional study provided data to calculate the diagnostic accuracy and yield of alternative HBV screening criteria (**Table 2 and Appendixes B1 and B2**).[35] It evaluated patients attending a French STD clinic and applied alternative screening criteria retrospectively. Of the

7,692 patients evaluated at the clinic during the study period, 6,194 (81%) were screened for HBV infection. Patients were primarily young adults (62% between age 20 and 29 years). Injection drug use was reported in 0.7 percent of patients, and 7.2 percent were born in a high-endemic area (defined as chronic HBV prevalence of ≥8%). Independent predictors of HBV infection in this cohort were medium (prevalence ≥2% to <8%) or high prevalence of HBV in birth country (adjusted odds ratio [OR], 15.8; 95% confidence interval [CI], 5.6 to 44, and OR, 44; 95% CI, 19 to 101, respectively, vs. low-prevalence country), male sex (adjusted OR, 2.4; 95% CI, 1.1 to 5.2), being unemployed (adjusted OR, 3.2; 95% CI, 1.6 to 6.1 vs. student), and unvaccinated status (adjusted OR, 2.9; 95% CI, 1.1 to 7.9 vs. vaccinated status). No cases of HBV infection were found in patients reporting injection drug use, although the sample was small.

The prevalence of HBV infection (based on presence of HBsAg) in the sample was 0.8 percent (49/6,194). Using a strategy of screening all patients, 126 persons would need to be screened to identify one case of HBV infection (**Table 3**). A strategy of screening only patients born in moderate- or high-prevalence countries (≥2% prevalence of chronic HBV infection) would have resulted in 13 percent (761/6,011) persons being screened, a sensitivity of 31 percent (15/48) for identifying patients with HBV infection, and a number needed to screen of 16. Also screening men and unemployed persons would have resulted in 64 percent (3,949/6,194) of the population being screened, a sensitivity of 98 percent (48/49), and a number needed to screen to identify one case of HBV infection of 82. The area under the receiver operating curve (AUROC) for this strategy was 0.92, indicating excellent discrimination. Strategies that included screening based on risk behaviors rather than employment history or being male were associated with higher proportions of patients screened, no increase in sensitivity, and numbers needed to screen similar to those for screening of the entire sample.

Key Question 4. In Nonpregnant Adolescents and Adults With No Evidence of HBV Immunity on Screening, How Effective Is HBV Vaccination for Improving Clinical Outcomes?

Summary

Vaccination is associated with decreased risk of HBV acquisition in health care workers (4 trials; relative risk [RR], 0.5; 95% CI, 0.4 to 0.7) and men who have sex with men (4 trials; RR, 0.2; 95% CI, 0.1 to 0.4) based on serologic markers. Studies were not designed to evaluate the effectiveness of HBV vaccination on long-term clinical outcomes.

Evidence

A recent systematic review found HBV vaccination in health care workers associated with decreased incidence of HBV acquisition based on serologic markers (appearance of HBsAg or anti-HBc) in four trials (RR, 0.5; 95% CI, 0.4 to 0.7; I^2=18%).[36] Pooled results from one other good-quality[37] and two fair-quality trials[38,39] of HBV vaccination in men who have sex with men

found vaccination strongly associated with decreased HBV acquisition versus placebo based on HBsAg seroconversion (RR, 0.2; 95% CI, 0.1 to 0.4; I^2=45%), development of elevated serum ALT (RR 0.2; 95% CI 0.2 to 0.3; I^2=2%), or either marker (RR, 0.4; 95% CI, 0.2 to 0.6; I^2=66%). The risk of serum anti-HBc conversion was also lower in vaccinated patients than in placebo, but the pooled result was not statistically significant (RR, 0.6; 95% CI, 0.3 to 1.4; I^2=74%).

Key Question 5. In Nonpregnant Adolescents and Adults With Chronic HBV Infection, How Effective Is Antiviral Treatment at Improving Intermediate Outcomes (Virological or Histological Improvement or Clearance of HBeAg)?

Summary

Twenty-two trials compared antiviral treatment to placebo or no treatment and reported intermediate outcomes. Antiviral treatment was 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 (9 trials; RR, 7.2; 95% CI, 3.2 to 16; I^2=58%), and histological improvement (7 trials; RR, 2.1; 95% CI, 1.8 to 2.6; I^2=0%). Results were generally consistent when stratified by individual drug, although some stratified estimates were imprecise and not statistically significant. Antiviral therapy was also more effective than placebo or no treatment for some composite intermediate outcomes, such as a reduction in HBV DNA level plus ALT normalization (6 trials; RR, 8.0; 95% CI, 2.0 to 32; I^2=79%). Results were generally consistent in sensitivity and subgroup analyses.

Although head-to-head comparisons of entecavir, pegylated interferon alfa-2a, and tenofovir versus older antiviral drugs were limited by small numbers of trials, entecavir and pegylated interferon alfa-2a were associated with greater likelihood of achieving some intermediate outcomes (virological improvement, histological improvement) than lamivudine.

Evidence

Antiviral Therapy Versus Placebo or No Treatment

Twenty-two trials of antiviral treatment versus placebo or no treatment reported intermediate health outcomes (**Table 4 and Appendix B5**). Four trials evaluated adefovir versus placebo,[40-43] eight trials interferon alfa-2b injection versus no treatment,[44-51] nine trials lamivudine versus placebo,[52-60] and one study tenofovir versus placebo.[61] No placebo-controlled trial of pegylated interferon alfa-2a or entecavir met inclusion criteria. One trial evaluated telbivudine versus placebo, but it evaluated only continuous outcomes and could not be included in pooled analyses.[62] Nine trials[40,41,45-47,49,55,58,61] were conducted primarily in the United States or Europe, and the remainder were conducted in other geographic areas, including countries with high HBV prevalence. Fifteen trials enrolled patients who were exclusively or primarily HBeAg-positive.[41-

[44,47-51,55-57,59-61] Two trials restricted inclusion to adolescents[41,61] and the rest focused on adults (mean age, 24 to 46 years). The trials predominantly enrolled men (proportion male, 60 to 94%). In 11 trials that reported the proportion of patients with baseline cirrhosis, rates ranged from 5 to 44 percent.[40,44-46,48,50,51,54,55,57,58] In trials that did not report the prevalence of baseline cirrhosis, patients with decompensated liver disease were generally excluded.[41-43,49,52,56,59-62] Study duration ranged from 8 weeks to 3 years. Twelve trials[40-44,47,48,53,57,58,60,61] reported outcomes on antiviral therapy, three trials[52,56,59] reported outcomes following discontinuation of antiviral therapy, and seven trials[45,46,49-51,54,55] reported both. Two trials were rated good quality,[49,61] four trials poor quality,[44,45,52,53] and the remainder fair quality (**Appendix B6**). Common methodological shortcomings were unclear or inadequate methods of randomization, allocation concealment, and blinding.

HBeAg loss or seroconversion. In patients with HBeAg-positive HBV infection, antiviral therapy was more effective than placebo or no treatment for achieving HBeAg loss or seroconversion (10 trials; RR, 2.1; 95% CI, 1.6 to 2.9; I^2=4%)[42-44,48,50,51,55,59-61] (**Figure 2**). One trial reported no HBeAg loss in either treated or control groups.[56] When analyses were stratified by specific antiviral drug, the risk estimate was larger for interferon alfa-2b (5 trials; RR, 3.6; 95% CI, 1.9 to 6.9; I^2=5%)[44,48,50,51] than for lamivudine (3 trials; RR, 1.7; 95% CI, 1.0 to 3.0; I^2=0%),[55,59,60] adefovir (2 trials; RR, 1.8; 95% CI, 0.8 to 4; I^2=58%),[42,43] or tenofovir (1 trial; RR, 1.4; 95% CI, 0.6 to 3.4),[61] although estimates were imprecise and based on only one or two trials for drugs other than interferon. The adefovir risk estimate had the most statistical heterogeneity. It was based on two trials: a longer duration trial[42] (72 weeks) found adefovir associated with an increased likelihood of HBeAg loss versus placebo (RR, 2.5; 95% CI, 1.5 to 4.2) and a shorter duration trial[43] (12 weeks) found no effect (RR, 1.1; 95% CI, 0.5 to 2.7).

The risk estimate was similar when restricted to outcomes assessed during antiviral treatment (10 trials; RR, 2.3; 95% CI, 1.6 to 3.1; I^2=5%).[42-44,48,50,51,55,59-61] Stratifying all antiviral trials according to duration resulted in similar estimates for studies 1 year or less in duration (6 trials; RR, 2.0; 95% CI, 1.3 to 3.2; I^2=27%)[42-44,48,59,60] and those of more than 1 year duration (4 trials; RR, 2.1; 95% CI, 1.4 to 3.1; I^2=0%).[50,51,55,61] Removing one poor-quality trial[44] also had no effect on the overall estimate (8 trials; RR, 2.1; 95% CI, 1.6 to 2.8; I^2=0%).[42,43,48,50,51,55,60,61]

HBsAg loss or seroconversion. Antiviral therapy was more effective than placebo for achieving HBsAg loss (11 trials; RR, 2.4; 95% CI, 1.2 to 4.9; I^2=0%)[44,46,48-52,54,55,58,61] (**Figure 3**). The pooled estimate was heavily influenced by studies of interferon alfa-2b, which accounted for 24 of the 30 events in patients on antiviral therapy (6 trials; RR, 2.7; 95% CI, 1.1 to 6.4; I^2=0%).[44,46,48-51] The pooled estimate favored lamivudine over placebo, but the difference was not statistically significant (4 trials; RR, 1.7; 95% CI, 0.4 to 7.1; I^2=0%).[52,54,55,58] The estimate for tenofovir was imprecise and based on one trial (RR, 3.1; 95% CI, 0.13 to 75).[61]

Estimates were similar for trials of HBeAg-positive patients (7 trials; RR, 2.6; 95% CI, 1.1 to 6.1; I^2=0%)[44,48-51,55,61] and HBeAg-negative patients (4 trials; RR, 1.9; 95% CI, 0.5 to 7.8; I^2=0%).[46,52,54,58] Results were also similar when the analysis was restricted to trials of greater than 1 year duration (7 trials; RR, 2.2; 95% CI, 0.9 to 5.1; I^2=0%)[46,50,51,54,55,58,61] or when excluding two poor-quality[44,52] trials (9 trials; RR, 2.2; 95% CI, 1.0 to 5.0; I^2=0%).[46,48-51,54,55,58,61]

Restricting the analysis to outcomes that occurred during antiviral therapy resulted in a somewhat attenuated risk estimate (RR, 1.6; 95% CI, 0.7 to 3.9; I^2=0).[44,48,50,51,55,58,61]

ALT normalization. Antiviral therapy was more effective than placebo for achieving normalization of ALT levels (12 trials; RR, 2.5; 95%, CI, 2.1 to 3.0; I^2=27%)[38-42,46,51-53,55,58,59] (**Figure 4**). Estimates were similar for adefovir (4 trials; RR, 2.9; 95% CI, 2.3 to 3.6; I^2=0%),[40-43] lamivudine (5 trials; RR, 2.4; 95% CI, 1.6 to 3.6; I^2=54%),[53-55,57,60] and tenofovir (1 trial; RR, 2.0; 95% CI, 1.4 to 2.9).[61] The estimate for interferon alfa-2b was imprecise (2 trials; RR, 5.0; 95% CI, 0.6 to 40; I^2=28%).[44,48] Although statistical heterogeneity was present in trials of lamivudine, all trials favored antiviral therapy (range of RR estimates, 1.6 to 5.6).

Results were similar for HBeAg-positive patients (9 trials; RR, 2.7; 95% CI, 2.2 to 3.3; I^2=11%)[41-44,48,55,57,60,61] and HBeAg-negative patients (3 trials; RR, 2.0; 95% CI, 1.4 to 2.9; I^2=26%),[40,53,54] for studies of more than 1 year duration (5 trials; RR, 2.4; 95% CI, 1.6 to 3.5; I^2=57%),[48,54,55,57,61] or after excluding two poor-quality[44,53] studies (10 trials; RR, 2.5; 95% CI, 2.0 to 3.0; I^2=31%).[40-43,48,54,55,57,60,61] The risk estimate was similar when the analysis was restricted to outcomes that occurred during antiviral treatment (12 trials; RR, 2.5; 95% CI, 2.2 to 3.0; I^2=0%).[38-42,46,51-53,55,58,59]

Virological improvement. Antiviral therapy was more effective than placebo or no treatment for achieving a reduction in HBV DNA level (9 trials; RR, 7.2; 95% CI, 3.2 to 16; I^2=58%)[40,43,48,50,54,55,59-61] (**Figure 5**). When results were stratified by individual antiviral drug, the estimate for lamivudine was the most precise (4 trials; RR, 4.4; 95% CI, 2.2 to 8.6; I^2=46%).[54,55,59,60] Although statistical heterogeneity was present, estimates from all trials favored lamivudine (range of RR estimates, 2.5 to 7.0). For adefovir (2 trials; RR, 29; 95% CI, 4.0 to 204; I^2=0%),[40,43] interferon alfa-2b (2 trials; RR, 7.5; 95% CI, 1.4 to 40; I^2=0%),[48,50] and tenofovir (1 trial; RR, 97; 95% CI, 6.1 to 1,526),[61] analyses were based on one or two trials with a total of no events or one event in the placebo or no-treatment groups, resulting in very imprecise estimates.

Limiting the analysis to outcomes that occurred during antiviral therapy (9 trials; RR, 8.6; 95% CI, 3.8 to 20; I^2=64%)[40,43,48,50,54,55,59-61] or to studies of more than 1 year duration (4 trials; RR, 8.4; 95% CI, 1.5 to 49; I^2=76%)[50,54,55,61] resulted in similar estimates, as did limiting the analysis to studies that enrolled HBeAg-positive patients (7 trials; RR, 6.2; 95% CI, 2.7 to 14; I^2=56%).[43,48,50,55,59-61] HBeAg-negative patients were enrolled in two trials, both of which reported statistically significant, but very imprecise, risk estimates favoring antiviral therapy (RR, 64; 95% CI, 4.0 to 1,009,[40] and RR, 4.8; 95% CI, 0.62 to 36[54]). None of the trials was rated poor quality.

Histological improvement. Antiviral therapy was more effective than placebo or no treatment at improving histological outcomes (7 trials; RR, 2.1; 95% CI, 1.8 to 2.6; I^2=0%)[40,42,46,51,54,55,57] (**Figure 6**). The definition of histological improvement varied among the studies, although many used a reduction of two or more points in Histology Activity Index (HAI) scores (**Appendix B5**). When stratified by individual drug, estimates were similar for adefovir (2 trials; RR, 1.9; 95% CI, 1.3 to 2.8,[40] and RR, 2.1; 95% CI, 1.5 to 2.8[42]) and lamivudine (3 trials; RR, 2.3; 95% CI, 1.7 to 3.2; I^2=0%).[54,55,57] Estimates from trials of interferon alfa-2b were less precise but consistent

with those for the other drugs (2 trials; RR, 3.5; 95% CI, 0.8 to 15,[46] and RR, 4.0; 95% CI, 0.5 to 33[51]).

Estimates were similar when the analysis was restricted to studies of more than 1 year duration (5 trials; RR, 2.4; 95% CI, 1.8 to 3.2; I^2=0%)[46,51,54,55,57] or when results were stratified for HBeAg-positive patients (4 trials; RR, 2.2; 95% CI, 1.8 to 2.7; I^2=0%)[42,51,55,57] and HBeAg negative patients (3 trials; RR, 2.1; 95% CI, 1.4 to 3; I^2=0%).[40,46,54] No trial was rated poor quality.

Composite intermediate outcomes. Composite intermediate outcomes were reported in 10 trials (**Table 5)**.[45-47,49,50,54,57,58,61,63] The most commonly reported composite outcome was loss of HBV DNA plus ALT normalization (6 trials; RR, 8.0; 95% CI, 2.0 to 32; I^2=79%)[45,46,54,58,61,63] (**Figure 7**). Estimates from all trials favored antiviral therapy (range of RR estimates, 4.0 to 78), although some estimates were very imprecise and findings did not always reach statistical significance.

Results were similar when analyses were restricted to outcomes that occurred during antiviral therapy (6 trials; RR, 8.3; 95% CI, 4.1 to 17; I^2=21%).[45,46,54,58,61,63] Two trials of HBeAg-positive patients reported no events in the control groups, resulting in highly imprecise risk estimates (RR, 13; 95% CI, 0.8 to 215,[63] and RR, 78; 95% CI, 4.9 to 1,236[61]). The risk estimate remained statistically significant when the analysis was restricted to HBeAg-negative patients (4 trials; RR, 4.8; 95% CI, 1.3 to 19; I^2=78%)[45,46,54,58] or after excluding one poor-quality trial (RR, 9.3; 95% CI, 1.6 to 55; I^2=83%).[45] Results were also similar, but imprecise, for trials with followup duration of more than 1 year (3 trials; RR, 9.6; 95% CI, 0.3 to 331; I^2=88%).[46,54,61]

The composite intermediate outcome of clearance of HBeAg plus suppression of HBV DNA was evaluated in four trials.[49,50,57,59] Interferon alfa-2b was more effective than no treatment for achieving this outcome in two trials (RR, 4.6; 95% CI, 1.5 to 14,[49] and RR, 11; 95% CI, 1.5 to 75[50]), and lamivudine was more effective than placebo in one larger (n=358) trial (RR, 3.3; 95% CI, 1.1 to 10)[57] but not in another smaller (n=42) trial (RR, 2.5; 95% CI, 0.17 to 38).[59] One other trial found tenofovir more effective than placebo for achieving virological clearance, normalization of AST level, plus loss of HBeAg (RR, 24; 95% CI, 1.4 to 395).[61]

Entecavir, Pegylated Interferon, or Tenofovir Versus Adefovir, Nonpegylated Interferon, Lamivudine, Or Telbivudine

Four trials (in 6 publications) compared entecavir versus lamivudine,[64-69] two trials compared pegylated interferon alfa-2a versus lamivudine,[70,71] and two trials (reported in 1 publication)[72] compared tenofovir versus adefovir (**Appendix B5**). Duration of followup ranged from 48 to 96 weeks. Five trials predominantly enrolled HBeAg-positive patients (78 to 100%),[64-66,68-70,72] and the remaining three trials[67,71,72] enrolled almost exclusively HBeAg-negative patients (99 to 100%). All of the trials enrolled patients with compensated liver disease. Four studies were rated good quality[64,67,70,71] and the other four were rated fair quality, primarily due to inadequate or unclear blinding (**Appendix B6**).

All head-to-head comparisons were limited by small numbers of trials (1 to 4) (**Table 6**). Compared with lamivudine, entecavir was associated with increased likelihood of virological

improvement (4 trials; RR, 1.6; 95% CI, 1.1 to 2.5; I^2=94%)[64,67-69] and histological improvement (2 trials; RR, 1.2; 95% CI, 1.1 to 1.3; I^2=0%),[64,67] and pegylated interferon alfa-2b with increased likelihood of HBeAg loss or seroconversion (1 trial; RR, 1.6; 95% CI, 1.2 to 2.1),[70] HBsAg loss or seroconversion (2 trials; RR, 16; 95% CI, 2.2 to 121; I^2=0%),[70,71] ALT normalization (2 trials; RR, 1.4; 95% CI, 1.2 to 1.6; I^2=0),[70,71] virological improvement (2 trials; RR, 2.8; 95% CI, 1.9 to 4.4; I^2=0%),[70,71] and histological improvement (2 trials; RR, 1.2; 95% CI, 1.0 to 1.4; I^2=0%).[70,71] Results for entecavir versus lamivudine on virological response were characterized by marked heterogeneity (4 trials; RR, 1.6; 95% CI, 1.1 to 2.5; I^2=94%)[64,67-69] (**Figure 8**). There were no clear differences between tenofovir and adefovir on various intermediate outcomes, in part due to imprecise estimates.[72] There were too few studies to conduct meaningful sensitivity or stratified analyses.

Key Question 6. In Nonpregnant Adolescents and Adults With Chronic HBV Infection, How Effective Is Antiviral Treatment at Improving Health Outcomes?

Summary

Based on primarily fair-quality randomized trials of antiviral therapy versus placebo or no treatment, pooled estimates for incident cirrhosis (3 trials; RR, 0.70; 95% CI, 0.33 to 1.46; I^2=0%), hepatocellular carcinoma (5 trials; RR, 0.57; 95% CI, 0.32 to 1.04; I^2=2%), and mortality (5 trials; RR, 0.55; 95% CI, 0.18 to 1.71; I^2=43%) all favored antiviral therapy over placebo. None of the differences was statistically significant, estimates were imprecise due to small numbers of events, and some trials had relatively short duration of followup. One study found that disease worsening was more likely in placebo patients than those treated with lamivudine (adjusted hazard ratio [HR], 0.5; 95% CI, 0.6 to 0.7). There were too few clinical events in head-to-head trials of entecavir or pegylated interferon alfa-2a versus lamivudine and pegylated versus nonpegylated interferon to determine effects on clinical outcomes.

Evidence

Antiviral Therapy Versus Placebo or No Treatment

Eleven randomized, controlled trials (RCTs) of antiviral therapy versus placebo or no treatment for chronic HBV infection reported incident cirrhosis, hepatocellular carcinoma, or mortality (**Table 7 and Appendix B5**).[41,43,46,49,51,54,55,57,73,75,76] Three trials evaluated interferon alfa-2b,[46,49,51] two trials interferon alfa-2a,[73,75] two trials adefovir,[41,43] and four trials lamivudine.[54,55,57,76] One trial was rated good quality[49] and the remainder fair quality[41,43,46,51,54,55,57,73,75,76] (**Appendix B6**). Methodological shortcomings in the fair-quality trials included inadequate details about method of randomization and/or allocation concealment and blinding. Sample sizes ranged from 40 to 651 patients, and duration of followup ranged from 10 months to 7.5 years.

The largest trials evaluated lamivudine[57,76] and adefovir.[43] One of the lamivudine trials followed patients for 1 year[57] and the other for a median of 32 months.[76] The placebo-controlled phase of the adefovir trial was 12 weeks.[43] The two longest duration trials followed patients for 7 years after completing 18 weeks or 6 months of interferon alfa-2a therapy.[73,75] Five trials were conducted in the United States and/or European countries, and the remaining six trials were conducted in Asia or the Middle East. Most study participants were HBeAg-positive at baseline; one trial of interferon alfa-2b[46] and one trial of lamivudine[54] enrolled primarily HBeAg-negative patients. The proportion of patients with cirrhosis at baseline ranged from 5 to 40 percent in seven studies (median, 17%). Four studies excluded patients with decompensated liver disease[41,43,49] or cirrhosis.[75] One study enrolled adolescents.[41]

Analyses of clinical outcomes were limited by the small numbers of events. There were a total of 26 cases of incident cirrhosis, 47 cases of hepatocellular carcinoma, and 31 deaths. Among trials that reported mortality, two trials of adefovir[41,43] and two trials of lamivudine[55,57] recorded no deaths. Although pooled estimates for incident cirrhosis (3 trials; RR, 0.70; 95% CI, 0.33 to 1.46; I^2=0%)[51,73,75] (**Figure 9**), hepatocellular carcinoma (5 trials; RR, 0.57; 95% CI, 0.32 to 1.04; I^2=2%)[46,54,73,75,76] (**Figure 10**), and mortality (5 trials; RR, 0.55; 95% CI, 0.18 to 1.71; I^2=43%)[49,51,73,75,76] (**Figure 11**) all favored antiviral therapy over placebo, none of the differences was statistically significant. Excluding trials with less than 2 years of followup[46,54,73,75,76] resulted in similar trends, but with less precise estimates.

The pooled estimate for hepatocellular carcinoma nearly reached statistical significance and was heavily influenced by results from the largest trial (n=651), which enrolled Asian patients with more advanced liver disease and reported about 70 percent (33/47) of cases in the pooled analysis.[76] This trial was discontinued early (median followup, 2.7 years) after reaching a prespecified stopping threshold on a composite primary outcome (hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or liver-related mortality). For hepatocellular cancer, it reported an RR for lamivudine versus placebo of 0.52 (95% CI, 0.27 to 1.02), which was similar to the pooled estimate. When adjusted for country, sex, baseline ALT, Child-Pugh score, and Ishak fibrosis score, the estimate from this trial was statistically significant (adjusted HR, 0.49; 95% CI, 0.25 to 0.99).

Adjusted HRs in one fair-quality trial of lamivudine versus placebo found that worsening of liver disease, measured by an increase in Child-Pugh scores, was more likely in patients receiving placebo (adjusted HR, 0.5; 95% CI, 0.2 to 0.9); results for disease progression, which included Child-Pugh score increase and serious health outcomes (see footnote to **Table 7**), were similar (adjusted HR, 0.5; 95% CI, 0.6 to 0.7).[76]

No trial reported outcomes related to long-term quality of life.

Entecavir, Pegylated Interferon Alfa-2a, or Tenofovir Versus Adefovir, Interferon Alfa-2b, Lamivudine, or Telbivudine

Four large head-to-head trials of entecavir or pegylated interferon alfa-2a versus lamivudine reported rates of hepatocellular cancer or mortality (**Appendixes B5 and B6**).[64-67,70,71] All trials were rated good quality.

The two trials of entecavir versus lamivudine were of similar design, except that one enrolled HBeAg-positive patients[64-66] and the other HBeAg-negative patients.[67] Baseline rates of cirrhosis were 2 percent in both studies and duration of followup was up to 96 weeks. The incidence of clinical events was low, resulting in imprecise estimates for risk of hepatocellular cancer (2 events; RR 3.0; 95% CI, 0.31 to 28; I^2=0%) and mortality (4 events; RR, 1.1; 95% CI, 0.1 to 9.1; I^2=40%). The two trials[70,71] of pegylated interferon alfa-2a versus lamivudine reported no cases of hepatocellular cancer and only two deaths (RR, 1.0; 95% CI, 0.1 to 9.7; I^2=0%). Duration of followup was 72 weeks in both studies; one study[70] enrolled HBeAg-positive patients and the other[71] enrolled HBeAg-negative patients. Pooling results from all four trials for mortality also showed no statistically significant difference between entecavir or pegylated interferon alfa-2a and lamivudine, with a somewhat more precise estimate (RR, 0.9; 95% CI, 0.3 to 3.1; I^2=0%).

We identified no English-language trials of pegylated vs. nonpegylated interferon. One good-quality systematic review included nine Chinese-language trials of pegylated versus nonpegylated interferon, but no deaths were reported in the trials.[77]

Key Question 7. In Nonpregnant Adolescents and Adults With Chronic HBV Infection, How Effective Is Education or Behavior Change Counseling in Reducing Transmission and Improving Health Outcomes?

We 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.

Key Question 8. What Are the Harms Associated With Antiviral Treatment for HBV Infection?

Summary

There were no statistically significant differences between antiviral therapy and placebo or no treatment in risk for serious adverse effects (12 trials; RR, 0.8; 95% CI, 0.6 to 1.1; I^2=0%) or any adverse events (7 trials; RR, 0.96; 95% CI, 0.9 to 1.0; I^2=0%). Antiviral therapy was associated with more withdrawals due to adverse effects than placebo or no treatment (9 trials; RR, 3.97; 95% CI, 1.4 to 11; I^2=0%). Results were largely consistent across drugs.

In two head-to-head trials, 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%) than lamivudine. There were no differences between entecavir and lamivudine (3 trials) or between tenofovir and adefovir (2 trials).

Evidence

Antiviral Therapy Versus Placebo or No Treatment

Twenty-two trials of antiviral treatment for hepatitis B virus infection reported serious adverse events, withdrawals due to adverse events, or any adverse events during active treatment periods (**Table 8 and Appendix B5**).[40-42,44-52,54-62,76] Data were available for adefovir (3 trials),[40-42] interferon alfa-2b (8 trials),[44-51] lamivudine (9 trials),[52,54-60,76] telbivudine (1 trial),[62] and tenofovir (1 trial).[61] Sample sizes ranged from 35 to 651 patients, and active treatment periods (time on antiviral therapy) ranged from 1 month to 2.7 years. The proportion of patients with cirrhosis at baseline ranged from 5 to 44 percent in the 13 trials that reported this information.[40,44-48,50,51,54,55,57,58,76] The trials that did not report cirrhosis information excluded patients with decompensated liver disease.[41,42,49,52,56,59-62] One of the lamivudine trials[52] and two of the interferon alfa-2b trials[44,45] were rated poor quality, two trials were rated good quality,[49,61] and the remainder fair quality (**Appendix B6**).[40-42,46-48,50,51,54-60,62,76] Eight trials were conducted in the United States, Europe, Australia, or New Zealand;[41,45-47,49,55,58,61] 11 were conducted in regions with high HBV prevalence;[44,48,50-52,54,56,57,59,60,62] and 3 were conducted in both countries with low and countries with high HBV prevalence.[40,42,76]

Serious adverse events. There were no statistically significant differences between antiviral therapy and placebo in risk of serious adverse effects (12 trials; RR, 0.8; 95% CI, 0.6 to 1.1; I^2=0%)[40,42,54-62,76] (**Figure 12**). Rates of serious adverse events on antiviral therapy ranged from 0 to 15 percent in the trials. When analyses were stratified by individual drug, results were consistent for lamivudine (8 trials; RR, 0.8; 95% CI, 0.6 to 1.1; I^2=0%)[54-60,76] and adefovir (2 trials; RR, 1.0; 95% CI, 0.4 to 2.1; I^2=31%).[40,42] Results were also consistent for telbivudine (RR, 1.1; 95% CI, 0.9 to 1.3)[62] and tenofovir (RR, 0.5; 95% CI, 0.2 to 1.3)[61] but were based on only one trial each.

Four lamivudine studies[54-56,59] did not clearly report whether harms data were collected while patients were on antiviral therapy or included harms that occurred after discontinuing antiviral therapy. Excluding these trials did not affect the results for lamivudine (4 trials; RR, 0.7; 95% CI, 0.5 to 1.0; I^2=0%) or the overall estimate (8 trials; RR, 8; 95% CI, 0.6 to 1.03; I^2=0%). There were no poor-quality trials.

Three trials[45,50,51] reported no serious adverse events in patients randomized to interferon alfa-2b but did not report data for patients who did not receive treatment.

Withdrawals due to adverse events. Antiviral therapy was associated with more withdrawals due to adverse effects than placebo (9 trials; RR, 4.0; 95% CI, 1.4 to 11; I^2=0%)[40-42,46,48,49,52,58,60] (**Figure 13**). Rates of withdrawal due to adverse events on antiviral therapy ranged from 0 to 24 percent in the trials, with only one event reported in patients on placebo or no treatment. Results were consistent for lamivudine (3 trials; RR, 4.8; 95% CI, 0.6 to 41; I^2=0%),[52,58,60] adefovir (3 trials; RR, 2.9; 95% CI, 0.5 to 16; I^2=0%),[40-42] and interferon alfa-2b (3 trials; RR, 4.8; 95% CI, 0.9 to 26; I^2=0%),[46,48,49] although estimates for individual drugs were imprecise and did not reach statistical significance.

Removing one poor-quality trial[52] had no effect on the estimate (RR, 3.7; 95% CI, 1.2 to 11; I^2=0%). Three trials reported rates of withdrawal due to adverse events of 0 to 3.7 percent on interferon alfa-2b but were excluded from the analysis because they did not report this outcome with placebo or no treatment.[44,47,51]

Any adverse events. There was no statistically significant difference between antiviral therapy and placebo in risk for experiencing any adverse event (7 trials; RR, 0.96; 95% CI, 0.9 to 1.0; I^2=0%)[40,57,58,60-62,76] (**Figure 14**). Rates of experiencing any adverse event on antiviral therapy ranged from 36 to 85 percent in the trials. Results were consistent for lamivudine (4 trials; RR, 0.95; 95% CI, 0.9 to 1.0; I^2=14%),[57,58,60,76] adefovir (1 trial; RR, 1.0; 95% CI, 0.9 to 1.2),[40] and tenofovir (1 trial; RR, 0.95; 95% CI, 0.8 to 1.1),[61] although the latter two drugs were evaluated in only one trial each. The estimate for telbivudine favored placebo but was imprecise, did not reach statistical significance, and was based on a single trial (RR, 2.5; 95% CI, 0.4 to 16).[62] There were no poor-quality trials or trials that did not clearly report whether harms data were restricted to events that occurred while on antiviral therapy.

Entecavir, Pegylated Interferon Alfa-2a, or Tenofovir Versus Adefovir, Interferon Alfa-2b, Lamivudine, or Telbivudine

There were no differences between entecavir and lamivudine (3 trials)[64,67,68] or between tenofovir and adefovir (2 trials)[72] in risk of serious adverse events, withdrawal due to adverse events, or overall adverse events (**Table 9**). In two trials, 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%) than lamivudine.[70,71]

Key Question 9. Do Improvements in Intermediate Outcomes Improve Final Health Outcomes?

Summary

Ten observational studies (n=22 to 818 and duration of followup from 4 to 9.9 years) 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), but variability in patient populations (e.g., HBeAg status and prevalence of cirrhosis at baseline), intermediate and clinical outcomes evaluated, and methodological limitations make it difficult to draw strong conclusions. In some studies, results were not statistically significant. Three of the studies failed to address five key potential confounders (age, sex, fibrosis stages, HBV DNA level, and HBeAg status) through adjustment or restriction.

Evidence

We identified 10 studies on the association between improvement in intermediate outcomes following antiviral therapy for chronic HBV infection and clinical outcomes (**Tables 10 and 11 and Appendix B7**).[80-89] The studies varied in the intermediate outcomes that were evaluated. Four studies evaluated virological response (loss of HBV DNA and sustainability of HBV DNA loss),[80-82,88] two studies evaluated biochemical remission (normalization of serum transaminase levels),[83,87] one study evaluated HBeAg clearance,[86] one study evaluated histological response (improvement in biopsy findings),[84] and two studies evaluated composite intermediate outcomes (virological response plus HBeAg clearance[89] or virological plus biochemical response[85]). The clinical outcomes also varied. Three studies evaluated death,[82,83,89] two studies hepatocellular carcinoma,[80,88] and the remainder various composite clinical outcomes (2 or more of the following: death, liver transplantation, cirrhosis, or complications of cirrhosis). Four studies focused on HBeAg-positive patients[83,84,86,89] and the remainder on HBeAg-negative patients.[80-82,85,87,88] Sample sizes ranged from 22 to 818 patients, and duration of followup from 4 to 9.9 years. In three studies, the antiviral treatment was lamivudine;[80,82,88] in the remainder, patients received interferon. Two studies included only patients with cirrhosis,[80,83] one study excluded patients with cirrhosis,[81] and in the other studies, the proportion of patients with cirrhosis ranged from 12 to 60 percent. Seven studies were rated fair quality[80-82,85,86,88,89] and three studies poor quality (**Appendix B8**).[83,84,87] Important methodological shortcomings included unclear blinding status of outcome assessors and failure to report loss to followup. In addition, the poor-quality studies did not address at least four of five key confounders (age, sex, fibrosis stage, HBV viral load, HBeAg status) through adjustment or restriction (e.g., enrolling only HBeAg-negative or HBeAg-positive patients).

The variability in patient populations (e.g., HBeAg status and prevalence of cirrhosis at baseline), intermediate and clinical outcomes evaluated, and study quality makes it difficult to draw strong conclusions regarding the association between achieving intermediate outcomes after antiviral treatment and improvement in clinical outcomes (**Table 12**). In all studies of both HBeAg-positive and HBeAg-negative patients, estimates of risk favored achieving the intermediate outcomes, although results were not always statistically significant. For death, one study evaluated biochemical remission versus no biochemical remission (adjusted HR, 0.09; 95% CI, 0.01 to 0.71),[83] one study evaluated a composite intermediate outcome (virological response plus HBeAg clearance: adjusted HR, 0.59; 95% CI, 0.20 to 1.67)[89] in HBeAg-positive patients, and one study evaluated virological breakthrough in HBeAg-negative patients (adjusted HR, 0.34; 95% CI, 0.15 to 0.80).[82] For hepatocellular carcinoma, one study evaluated maintenance of virological remission (no virological breakthrough: adjusted HR, 0.10; 95% CI, 0.01 to 0.77)[80] and one study evaluated achieving virological remission during therapy (adjusted HR, 0.77; 95% CI, 0.35 to 1.69)[88] in HBeAg-negative patients. For composite clinical outcomes, one study evaluated HBeAg loss (adjusted HR, 0.06; 95% CI, 0.01 to 0.61)[86] and one study evaluated a 2-point improvement on the HAI score (adjusted HR, 0.62; 95% CI, 0.06 to 6.9)[84] in HBeAg-positive patients. One other study evaluated a composite intermediate outcome (virological clearance plus HBeAg loss) in HBeAg-positive patients (adjusted HR, 0.07; 95% CI, 0.02 to 3.3),[89] and three studies evaluated virological response (adjusted HR, 0.24; 95% CI, 0.06 to 0.96),[81] biochemical response (adjusted 0.48; 95% CI, 0.23 to 1.0),[88] or a composite intermediate outcome (virological plus biochemical response: adjusted HR, 0.53; 95% CI, 0.29

to 0.91)[85] in HBeAg-negative patients. Evidence was too limited and heterogeneous to draw strong conclusions regarding the effects on conclusions of methodological limitations, differences in intermediate or clinical outcomes evaluated, or variability in baseline cirrhosis.

Chapter 4. Discussion

Summary of Review Findings

As in the 2004 USPSTF evidence review, we found no direct evidence on effects of screening for HBV infection versus no screening on clinical outcomes.[2] The evidence reviewed in this update is summarized in **Table 13**. Additional areas addressed in this review that were not covered in the 2004 USPSTF review are benefits and harms of antiviral treatments, the association between improvement in intermediate outcomes following antiviral therapy and subsequent clinical outcomes, and effects of education and behavior change counseling.

Identification of chronic HBV infection is based on interpretation of serologic markers and has previously been assessed by the USPSTF as accurate (sensitivity and specificity greater than 98%).[4] Evidence on the usefulness of different screening strategies for identifying persons with HBV infection is limited to a single fair-quality cross-sectional study performed in France.[35] It found that an HBV screening strategy in an STD clinic that focused on testing only persons born in higher prevalence countries would have missed about two-thirds of patients. A broader strategy that also tested men and unemployed persons identified almost all patients with HBV infection in this population while screening about two-thirds of the population. Well-established risk factors, such as injection drug use and high-risk sexual behaviors, were not predictive in this study, underscoring the need for further validation, and the applicability of findings to screening in typical primary care settings in the United States may be limited.

Data from randomized trials suggest that antiviral therapy may be more effective than placebo for reducing risk of clinical outcomes associated with HBV infection, such as incident cirrhosis, hepatocellular carcinoma, and mortality.[41,43,46,49,51,54,55,57,73,75,76] However, results were based on small numbers of trials, differences were not statistically significant, trials were underpowered, and pooled estimates were imprecise due to small numbers of events. In addition, the patient populations evaluated in the trials differed on important characteristics (such as severity of baseline liver disease and presence of HBeAg), the trials evaluated different antiviral drugs, few trials evaluated currently recommended first-line antivirals (entecavir, pegylated interferon alfa-2a, and tenofovir), and duration of followup varied, making it difficult to draw strong conclusions. Although the pooled estimate for hepatocellular carcinoma nearly reached statistical significance (5 trials; RR, 0.57; 95% CI, 0.32 to 1.04; I^2=2%),[46,54,73,75,76] it was heavily influenced by results from one Asian trial that primarily enrolled patients with more advanced liver disease, potentially reducing its applicability to screen-detected U.S. populations.[76] Although some head-to-head trials of first-line versus older antivirals reported mortality or hepatocellular cancer, none was designed to evaluate clinical outcomes and all were severely underpowered. Our findings are similar to those from a recent systematic review that focused on results from randomized trials.[90] Although other reviews[91-96] reported an association between use of antiviral therapy and improvement in clinical outcomes, results were primarily based on observational studies, including studies that did not adjust well for confounders.

Evidence is stronger in showing that antiviral therapy is more effective than placebo or no treatment for various intermediate outcomes, such as HBeAg loss or seroconversion (10 trials;

RR, 2.1; 95% CI, 1.6 to 2.9; I^2=4%),[42-44,48,50,51,55,59-61] HBsAg loss or seroconversion (12 trials; RR, 2.4; 95% CI, 1.2 to 4.9; I^2=0%),[44,46,48-52,54,55,58,61] ALT normalization (12 trials; RR, 2.5; 95% CI, 2.1 to 3.0; I^2=27%),[38-42,46,51-53,55,58,59] reduction in HBV DNA (9 trials; RR, 7.2; 95% CI, 3.2 to 16; I^2=58%),[40,43,48,50,54,55,59-61] histological improvement (7 trials; RR, 2.1; 95% CI, 1.8 to 2.6; I^2=0%),[40,42,46,51,54,55,57] and various composite outcomes. Results were generally consistent when analyses were stratified by individual drug, although some estimates were imprecise and not statistically significant. Like other recently conducted systematic reviews, this review also found some evidence suggesting that the currently recommended first-line drugs tenofovir and entecavir are more effective than lamivudine for various intermediate outcomes.[90,97-100]

The degree to which improvements in intermediate outcomes are associated with improved clinical outcomes is less clear. Although observational studies generally found an association between experiencing an improved intermediate outcome following antiviral therapy and death, hepatocellular carcinoma, or a composite clinical outcome, results were not statistically significant in all studies, and there were important differences across studies in the intermediate and clinical outcomes evaluated, variability in patient populations, and methodological limitations (including failure to control for key confounders in some studies), precluding strong conclusions.[80-89]

Antiviral therapy was associated with greater risk of withdrawal due to adverse events than placebo (9 trials; RR, 4.0; 95% CI, 1.4 to 11; I^2=0%),[40-42,46,48,49,52,58,60] but trials found no difference in risk of serious adverse events (12 trials; RR, 0.8; 95% CI, 0.6 to 1.1; I^2=0%)[40,42,54-62,76] or experiencing any adverse event (7 trials; RR, 0.96; 95% CI, 0.9 to 1.0; I^2=0%).[40,57,58,60-62,76] Head-to-head trials found pegylated interferon alfa-2a associated with increased risk of serious adverse events and withdrawal due to adverse events versus lamivudine,[70,71] consistent with the known high prevalence of adverse events with interferon-based therapies.[101] In general, adverse events associated with antiviral therapy, including interferon, are self-limited and resolve following discontinuation of the drug.

Evidence on effects on clinical outcomes of interventions other than antiviral therapy as a result of screening was limited. Trials of health care workers and men who have sex with men found HBV vaccination of adults with no evidence of HBV immunity associated with decreased risk of HBV acquisition based on serologic and biochemical markers but did not evaluate long-term clinical outcomes. Observational studies in high-prevalence countries indicate that implementation of universal HBV vaccination of newborns and children is associated with reduced rates of hepatocellular carcinoma and other clinical outcomes related to chronic HBV infection, but they were outside the scope of this review.[26,102,103] We 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.

Limitations

We excluded non–English-language articles, which could result in language bias. However, some studies have found empirical evidence that restricting systematic reviews of noncomplementary medicine intervention to English-language studies has little effect on the

conclusions.[104,105] We also included a systematic review that included Chinese–language results from head-to-head trials of pegylated interferon versus nonpegylated interferon, which did not affect conclusions.[77] We did not search for studies published only as abstracts and could not formally assess for publication bias with graphical or statistical methods because of small numbers of studies for each Key Question and differences in study design, populations, and outcomes assessed. Evidence from placebo-controlled and head-to-head trials of first-line antiviral therapies (entecavir, tenofovir, and pegylated interferon alfa-2a) was limited, particularly for clinical outcomes, making it difficult to evaluate effectiveness of currently utilized treatments. We included observational studies to evaluate the association between improvement in intermediate outcomes following antiviral therapy and subsequent clinical outcomes, as it is not possible to randomize patients' response to therapy. We focused on results from studies that performed statistical adjustment 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 differ from those in the United States, since evidence from settings more applicable to U.S. practice was limited. Including such evidence potentially limits the applicability of the reviewed evidence to screening in the United States.

We also did not include evidence on the effectiveness of surveillance for hepatocellular carcinoma in patients with HBV infection. However, the only two randomized trials were conducted in Asia and reported somewhat mixed results, with one trial showing a 37-percent reduction in hepatocellular carcinoma–related mortality and the other showing no effect of surveillance on overall mortality.[106,107]

Emerging Issues

Symptomatic acute HBV infections in the United States have 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.[108,109] Substantial reductions in prevalence have been observed among U.S. adolescents and younger adults (up to 50 years of age).[109] In addition, universal HBV vaccination has been adopted in over 190 countries[24] and epidemiological data indicate declining HBV prevalence globally.[110] These trends have important potential implications for future assessments of benefits and harms of HBV screening.

Antiviral therapies for chronic HBV infection continue to evolve.[111] Among currently approved drugs for treatment of HBV infection, entecavir and tenofovir 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 are extremely limited.[112] Although a number of combination antiviral therapies have been evaluated for management of HBV infection, none has clearly been shown to be superior to monotherapy for achieving intermediate or clinical outcomes and avoiding drug resistance.[113] However, research on combination therapies and new investigational agents, including drugs with novel viral targets,[112,114] is ongoing.

Relevance for Priority Populations

HBV infection is more prevalent in the United States among persons originating from countries with high prevalence,[115] such as most of Asia and the western Pacific. Black persons are also at higher risk of HBV infection.[11] Although the prevalence of HBV infection has declined in adolescents and young adults, data from the 2006 National Health and Nutrition Examination Survey indicated little change in prevalence among adults age 50 years or older.[109]

Future Research

Important 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 prospective, as well-conducted retrospective studies could also be informative. In lieu of direct evidence on effects of screening on clinical outcomes, studies that prospectively evaluate the accuracy and efficiency of alternative screening strategies (such as strategies targeting persons originating from high-prevalence countries)[116] might help identify efficient screening strategies.

More research is also needed on the long-term clinical outcomes associated with use of currently recommended first-line antiviral therapies for chronic HBV infection. Studies evaluating whether antiviral therapy is associated with decreased risk of transmission (as has been shown in the case of HIV infection[117]) would be useful for identifying additional public health benefits of screening and subsequent treatment. Evidence from observational studies on the association between achieving intermediate outcomes (such as viral clearance or disappearance of HBeAg) and clinical outcomes would be greatly strengthened by improved standardization of the intermediate and clinical outcomes evaluated, and should be designed and analyzed to account for important confounders.[118]

Conclusions

Although screening tests can accurately identify adolescents and adults with chronic HBV infection, more research is needed to understand the effects of screening and subsequent interventions on clinical outcomes and to identify optimal screening strategies. The declining incidence and prevalence of HBV infection as a result of universal vaccination programs is likely to impact future assessments of the benefits and harms of HBV screening.

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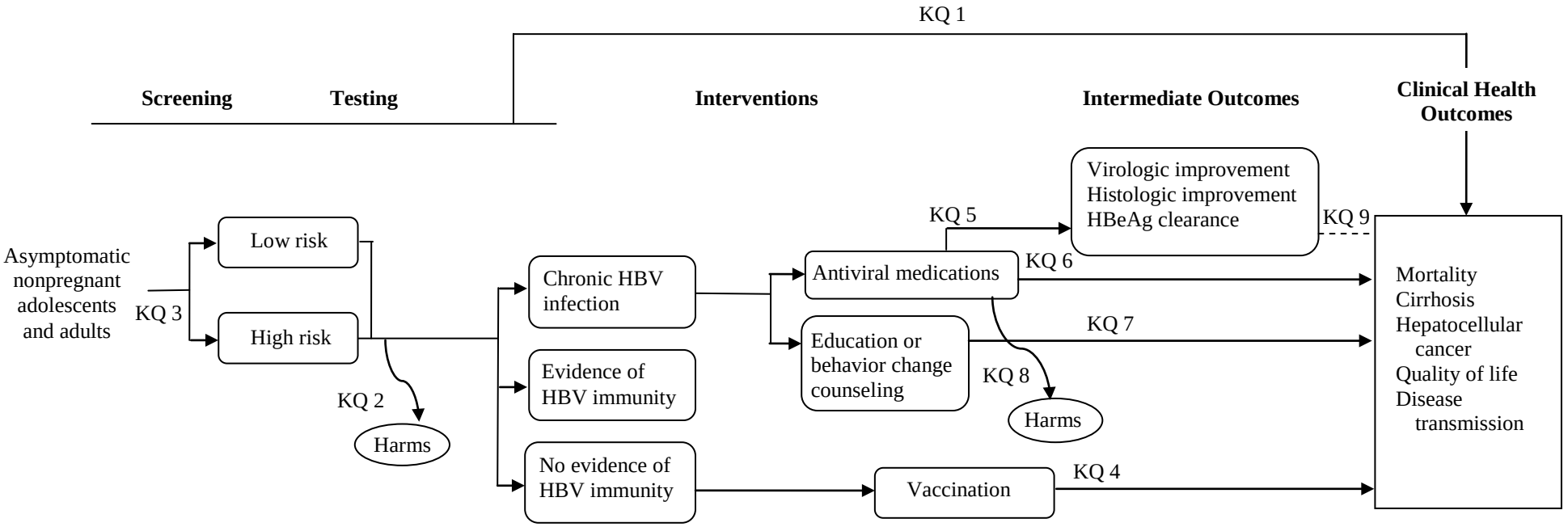
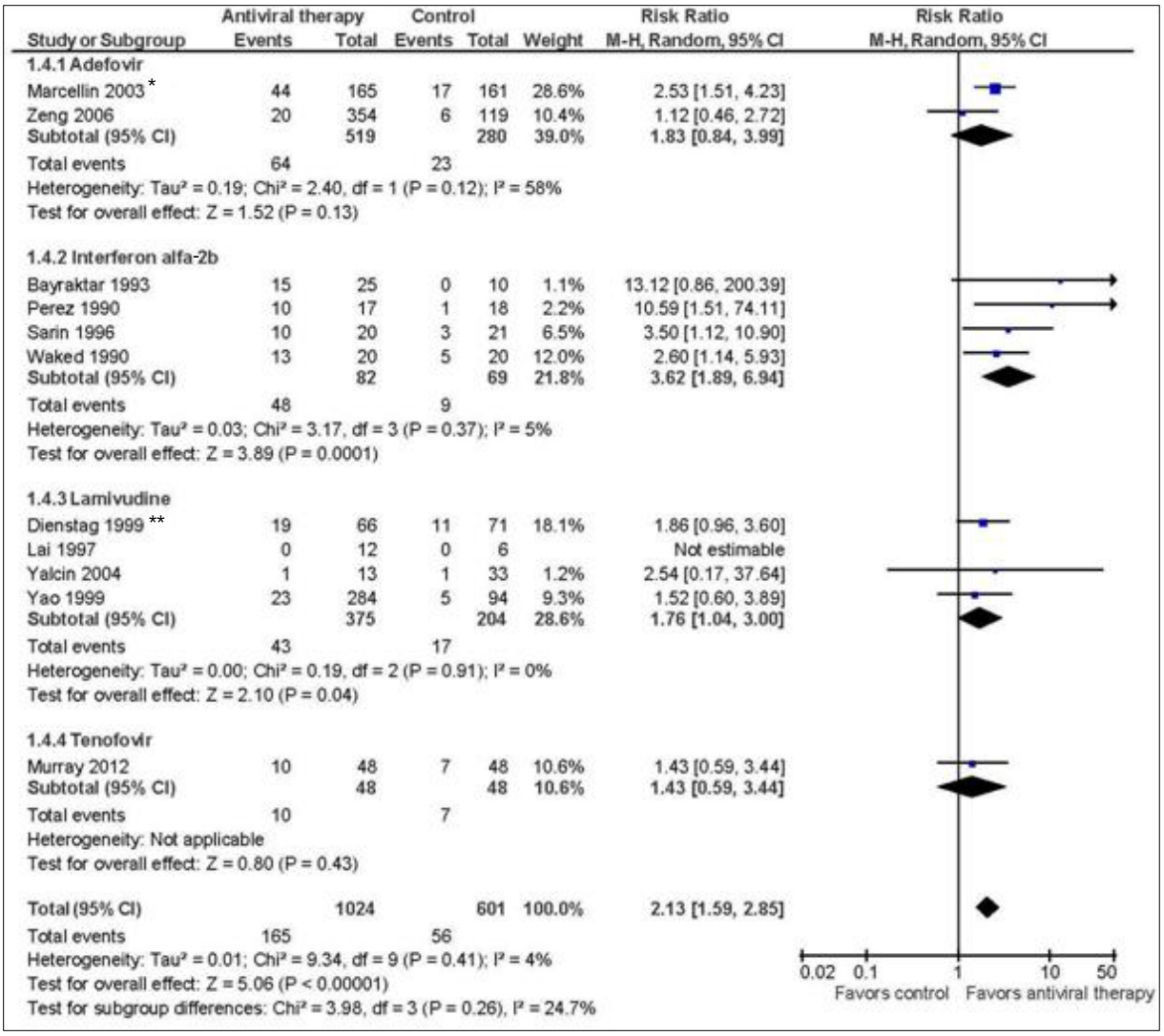
Figure 1. Analytic Framework



Abbreviations: HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; KQ = key question.

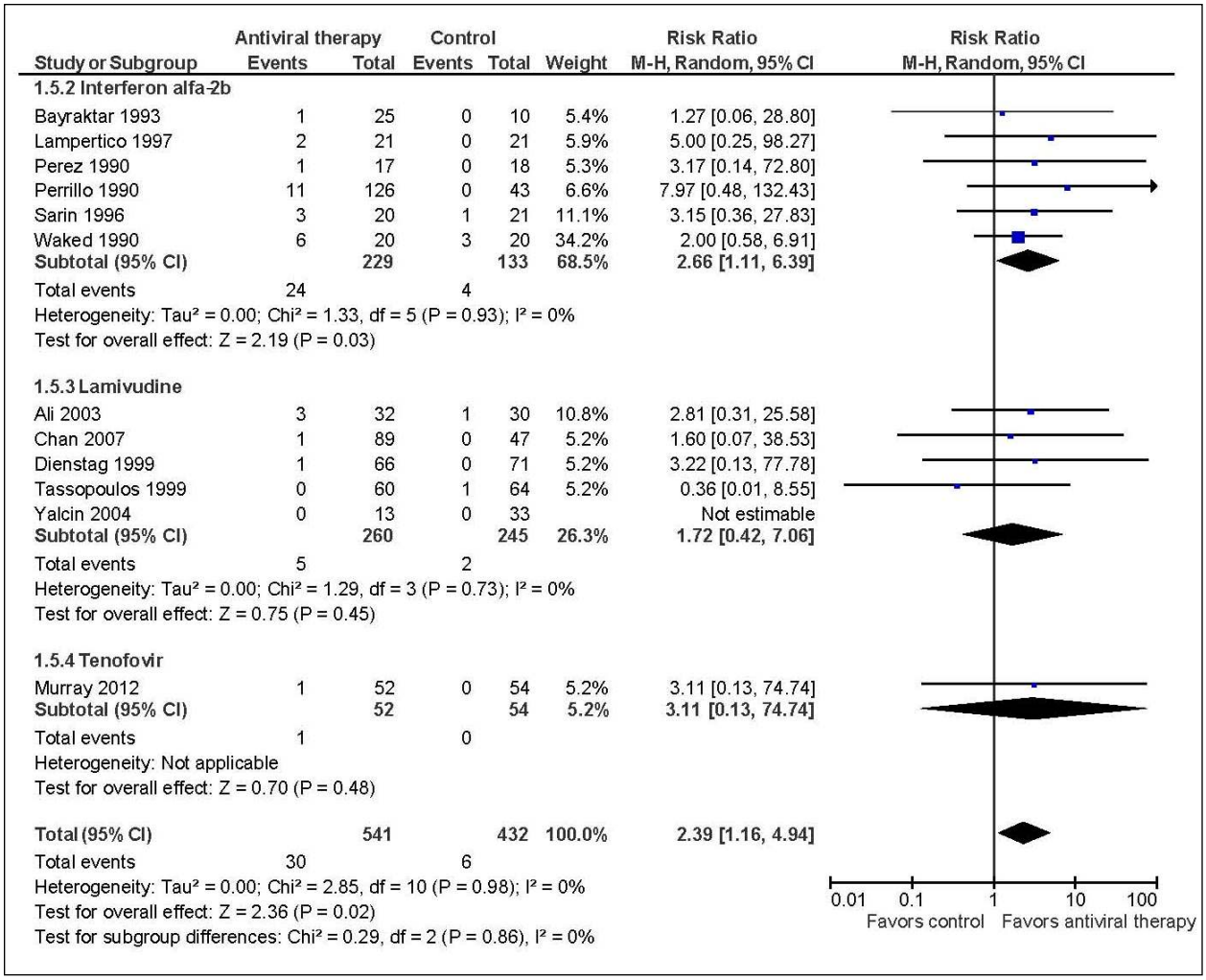
Figure 2. HBeAg Loss, Antiviral Therapy Versus Placebo or No Treatment



*30 mg–group versus placebo.
**68-week data.

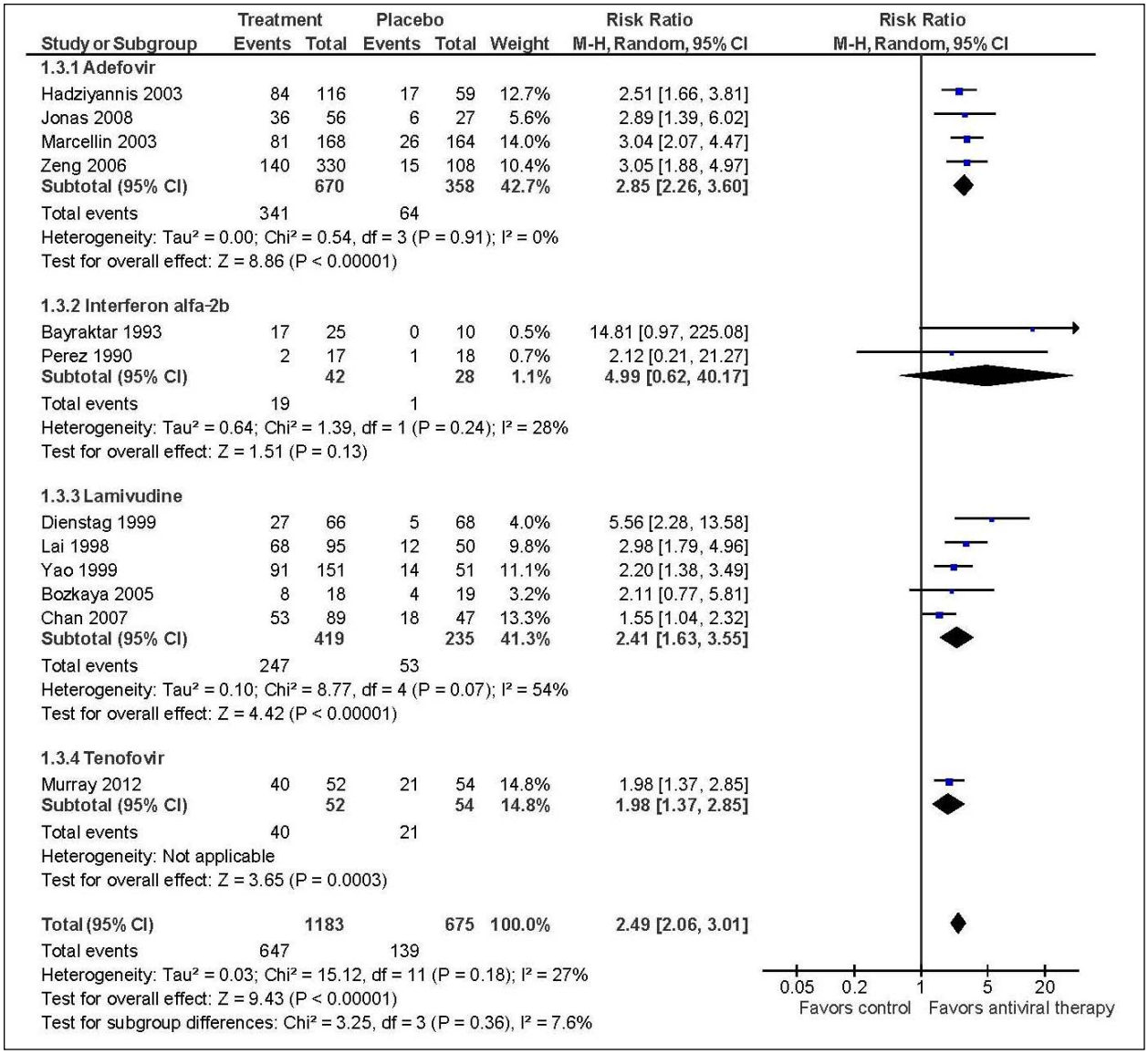
Abbreviations: df = degree of freedom; HBeAG = hepatitis B e antigen; M-H = Mantel-Haenszel.

Figure 3. HBsAg Loss, Antiviral Therapy Versus Placebo or No Treatment



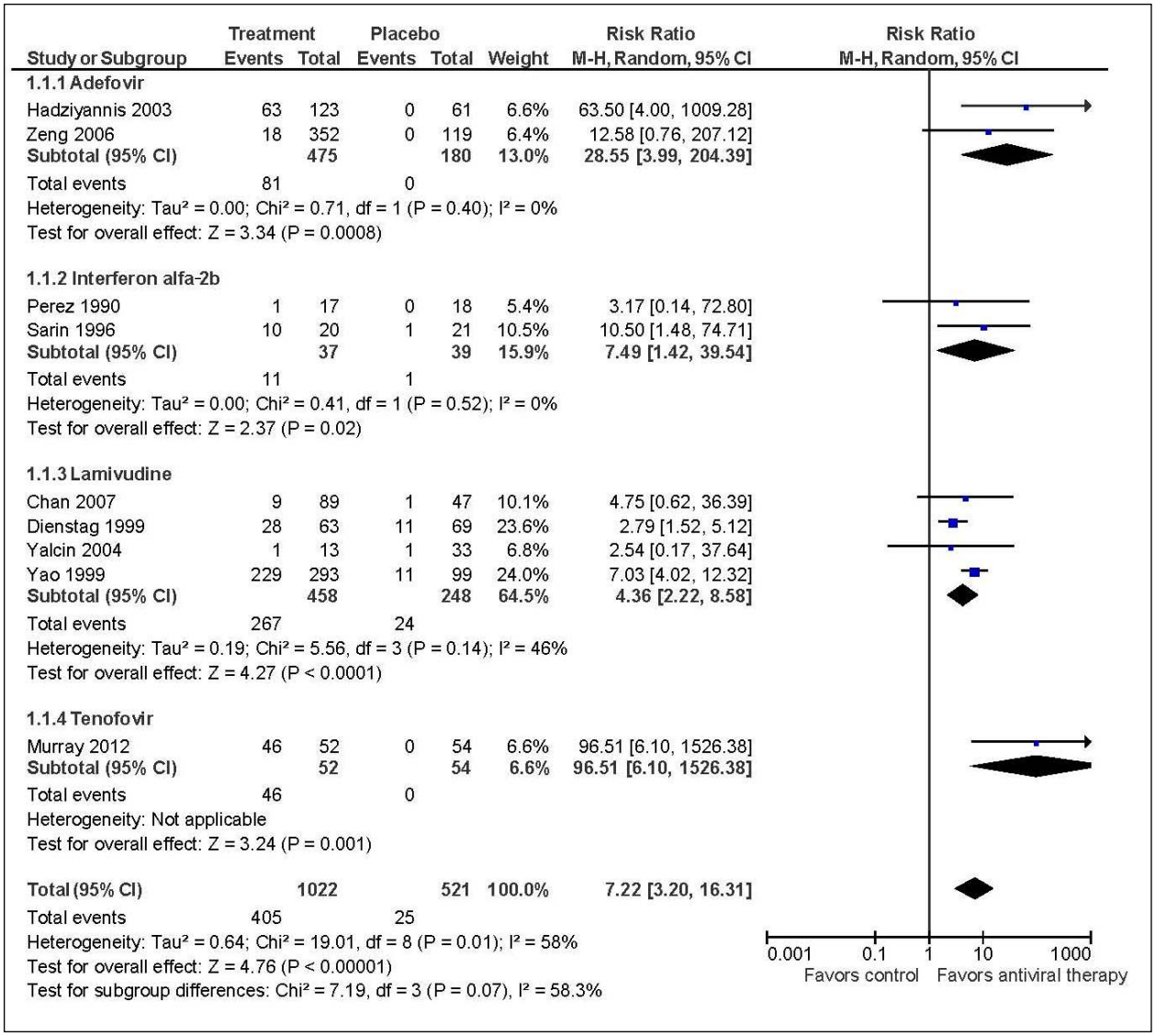
Abbreviations: df = degree of freedom; HBsAG = hepatitis B surface antigen; M-H = Mantel-Haenszel.

Figure 4. ALT Normalization, Antiviral Therapy Versus Placebo or No Treatment



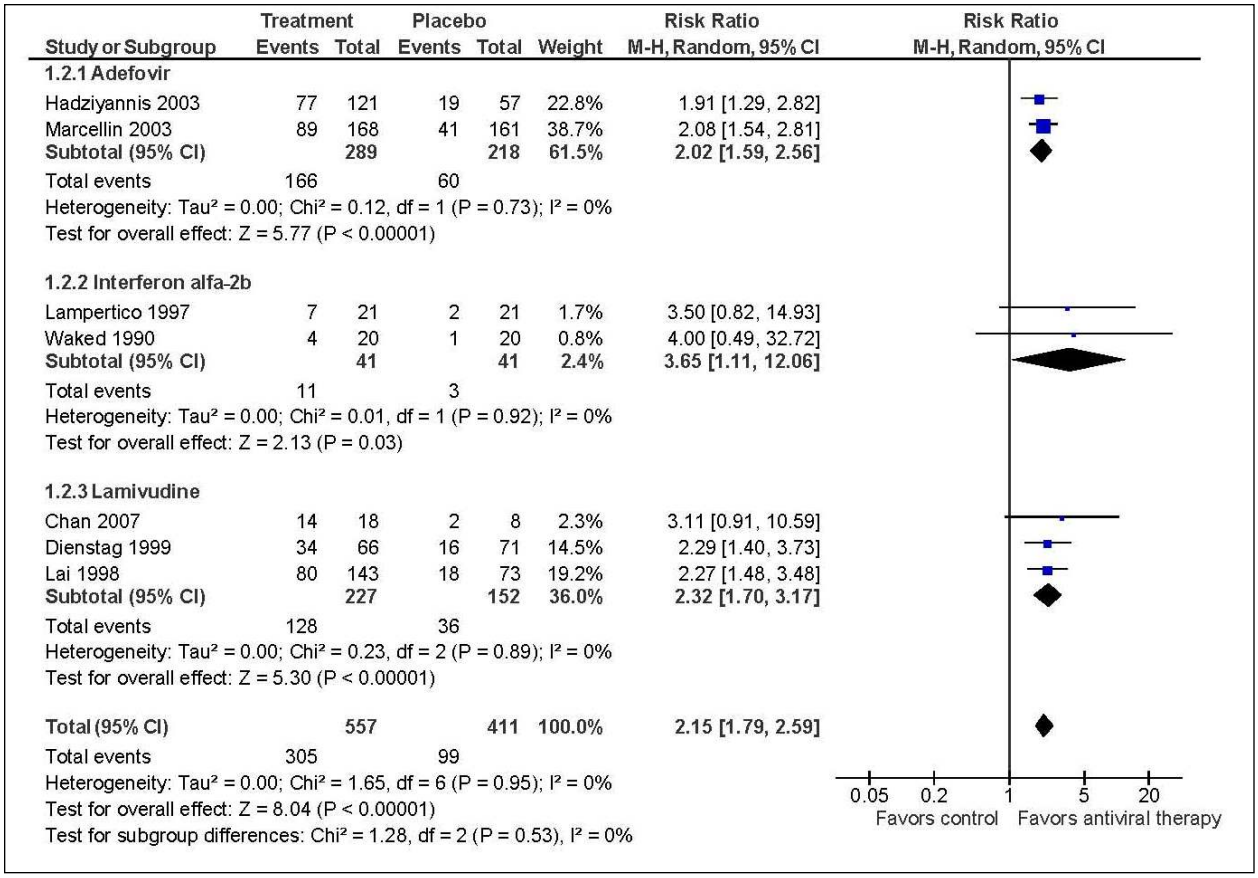
Abbreviations: ALT = alanine aminotransferase; df = degree of freedom; M-H = Mantel-Haenszel.

Figure 5. HBV DNA Loss, Antiviral Therapy Versus Placebo or No Treatment



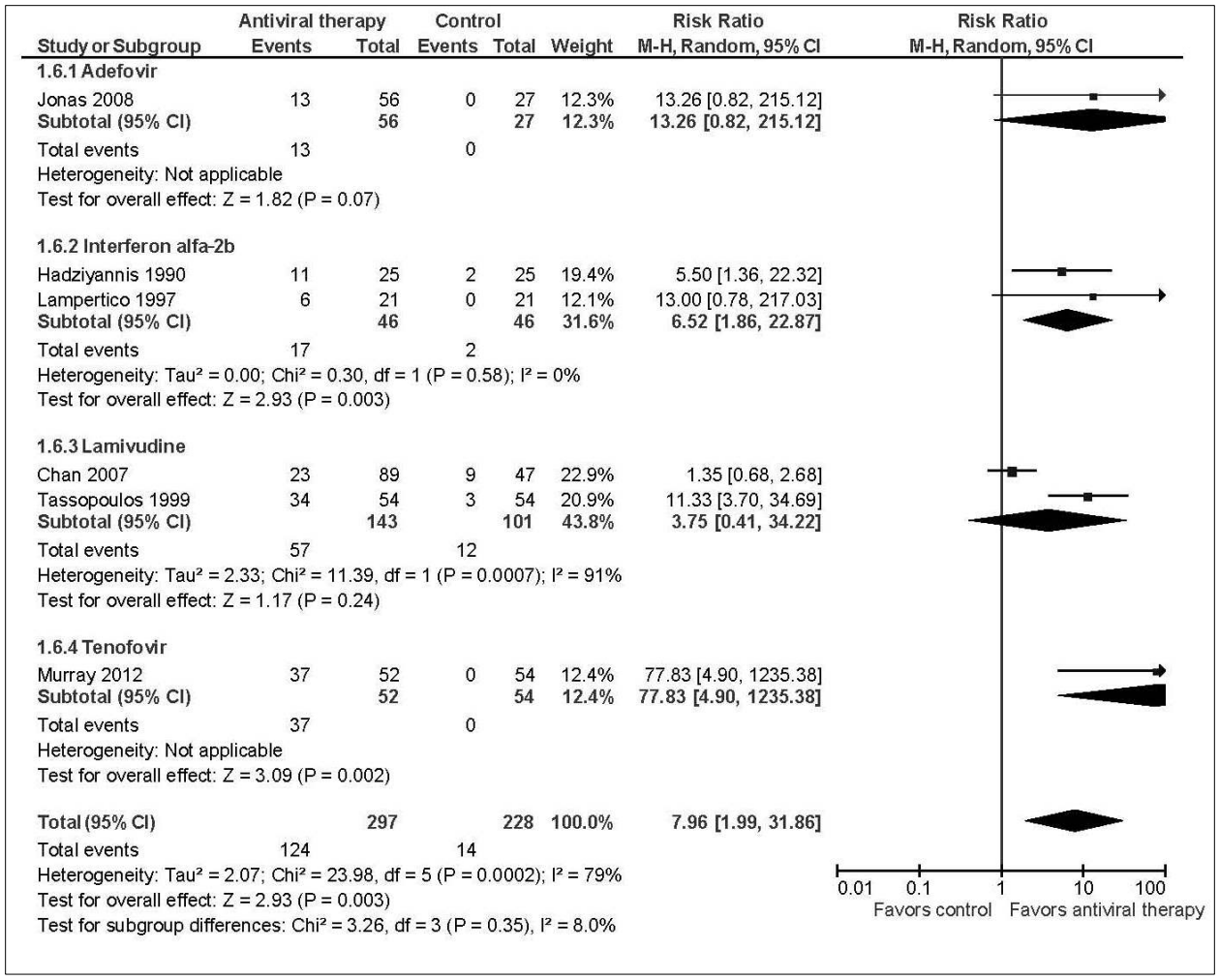
Abbreviations: df = degree of freedom; HBV = hepatitis B virus; M-H = Mantel-Haenszel.

Figure 6. Histologic Improvement, Antiviral Therapy Versus Placebo or No Treatment



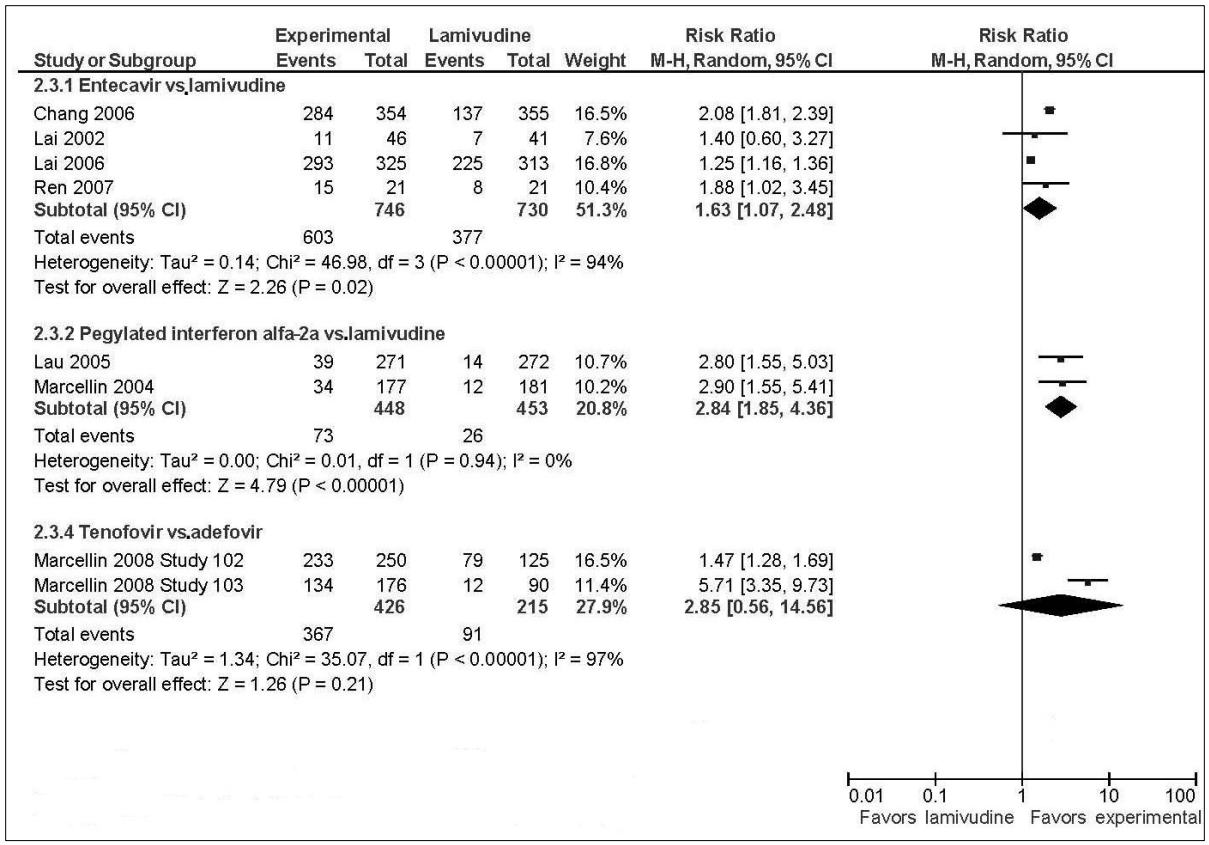
Abbreviations: df = degree of freedom; M-H = Mantel Haenszel.

Figure 7. HBV DNA Loss Plus ALT Normalization, Antiviral Therapy Versus Placebo or No Treatment



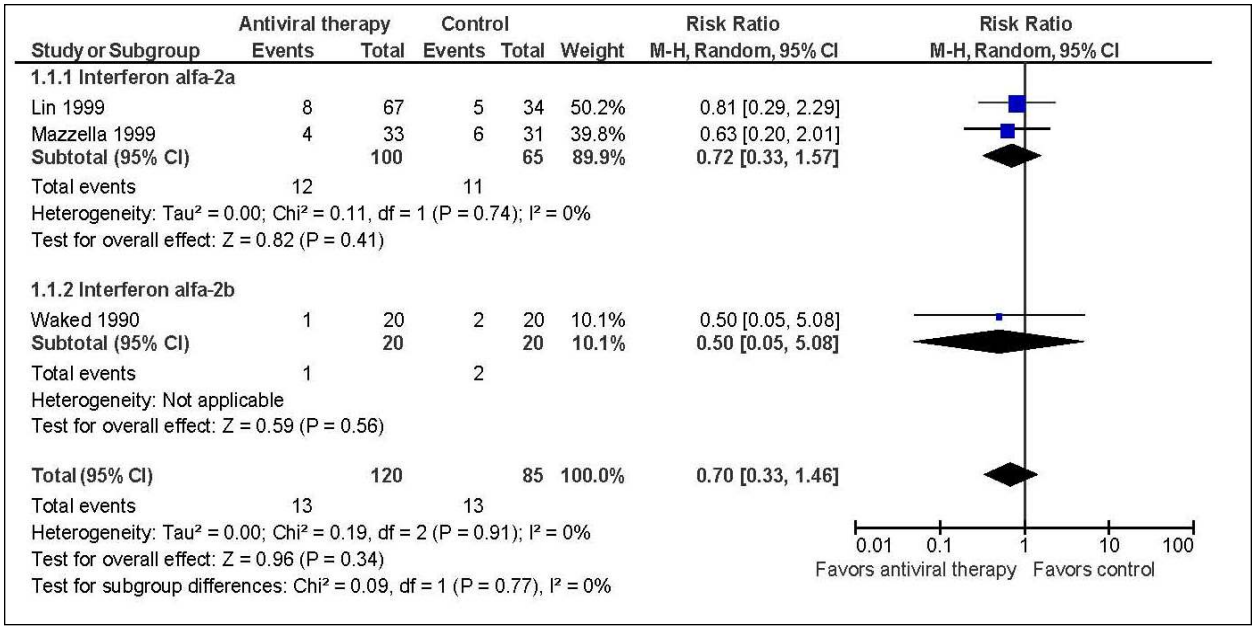
Abbreviations: ALT = alanine aminotransferase; df = degree of freedom; HBV = hepatitis B virus; M-H = Mantel-Haenszel.

Figure 8. HBV DNA Loss, Head-to-Head Studies of Antiviral Therapy



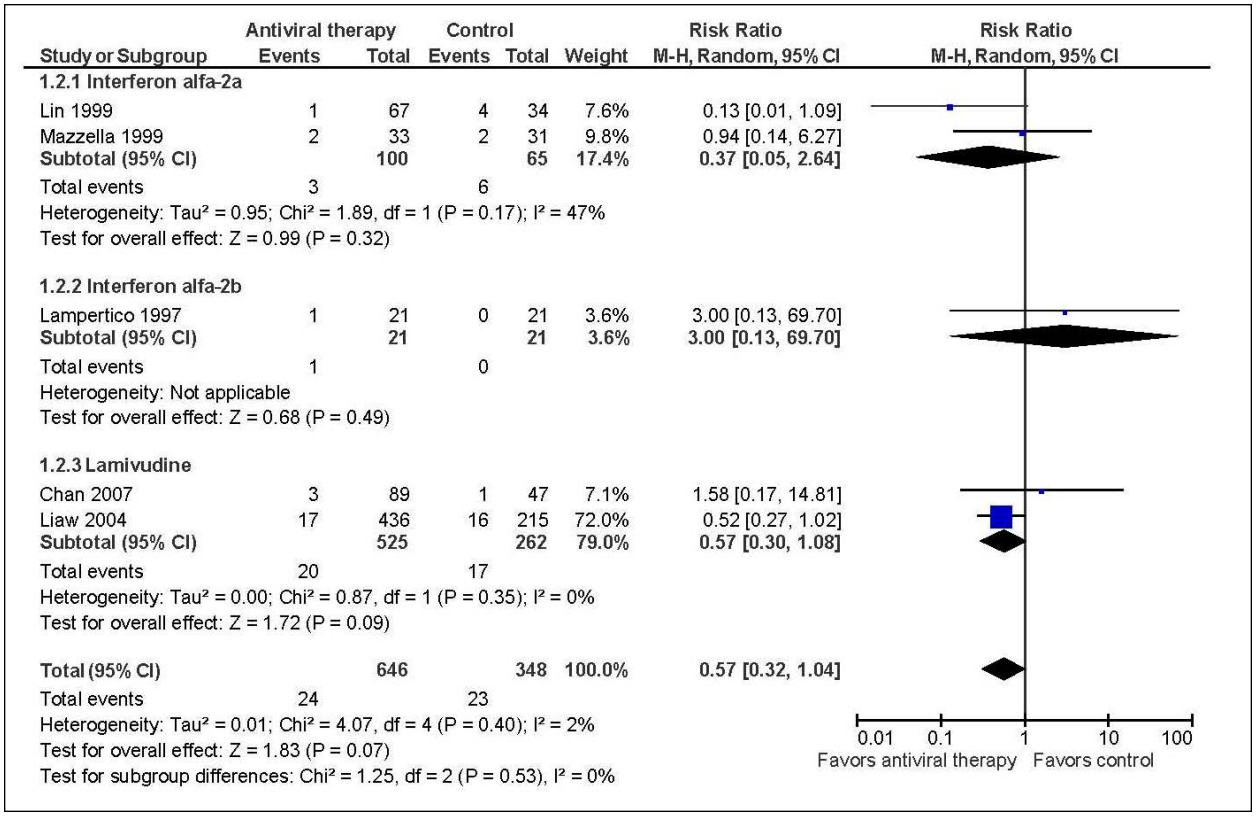
Abbreviations: df = degree of freedom; HBV = hepatitis B virus; M-H = Mantel-Haenszel.

Figure 9. Incident Cirrhosis, Antiviral Therapy Versus Placebo or No Treatment



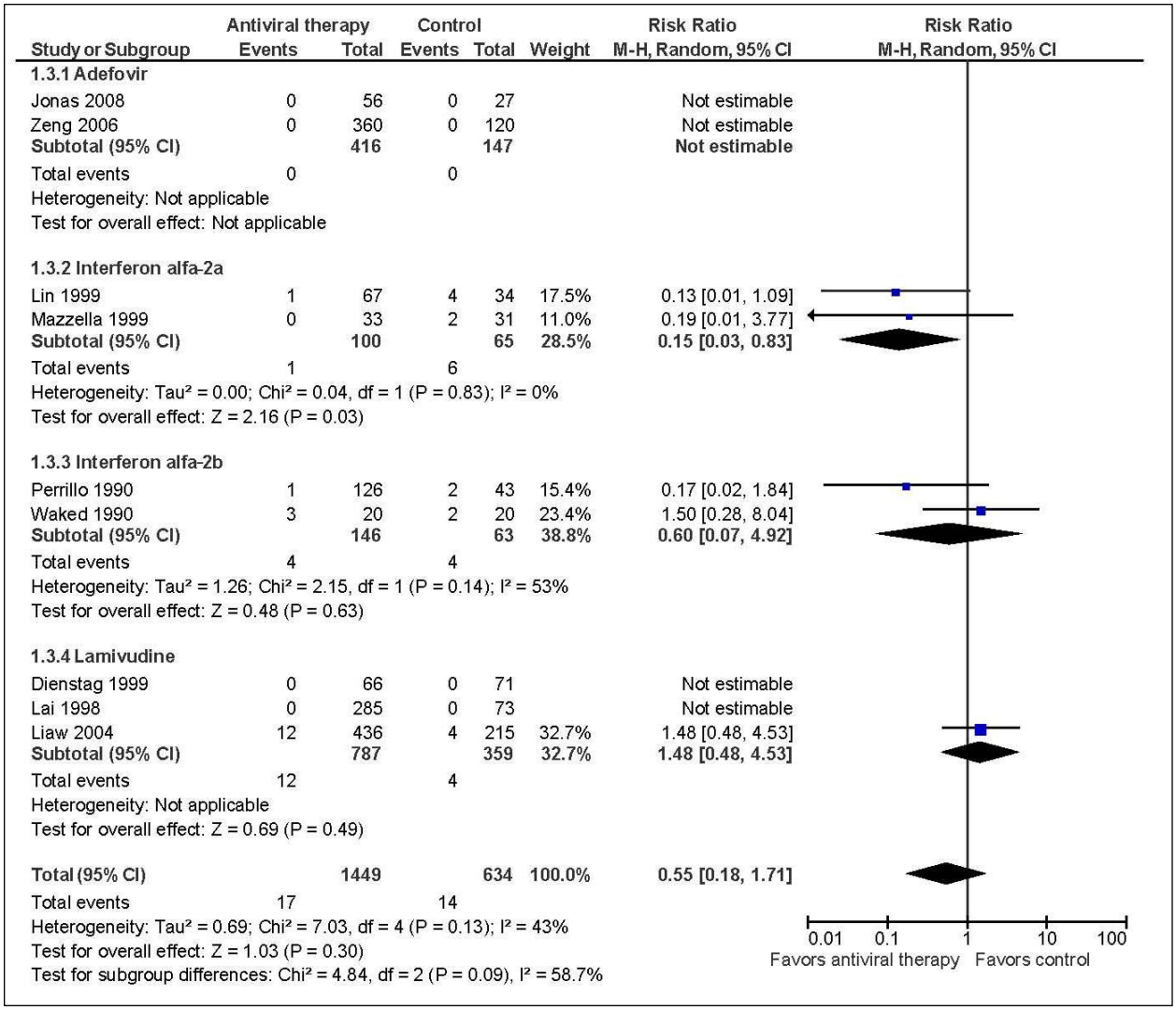
Abbreviations: df = degree of freedom; M-H = Mantel-Haenszel.

Figure 10. Hepatocellular Cancer, Antiviral Therapy Versus Placebo or No Treatment



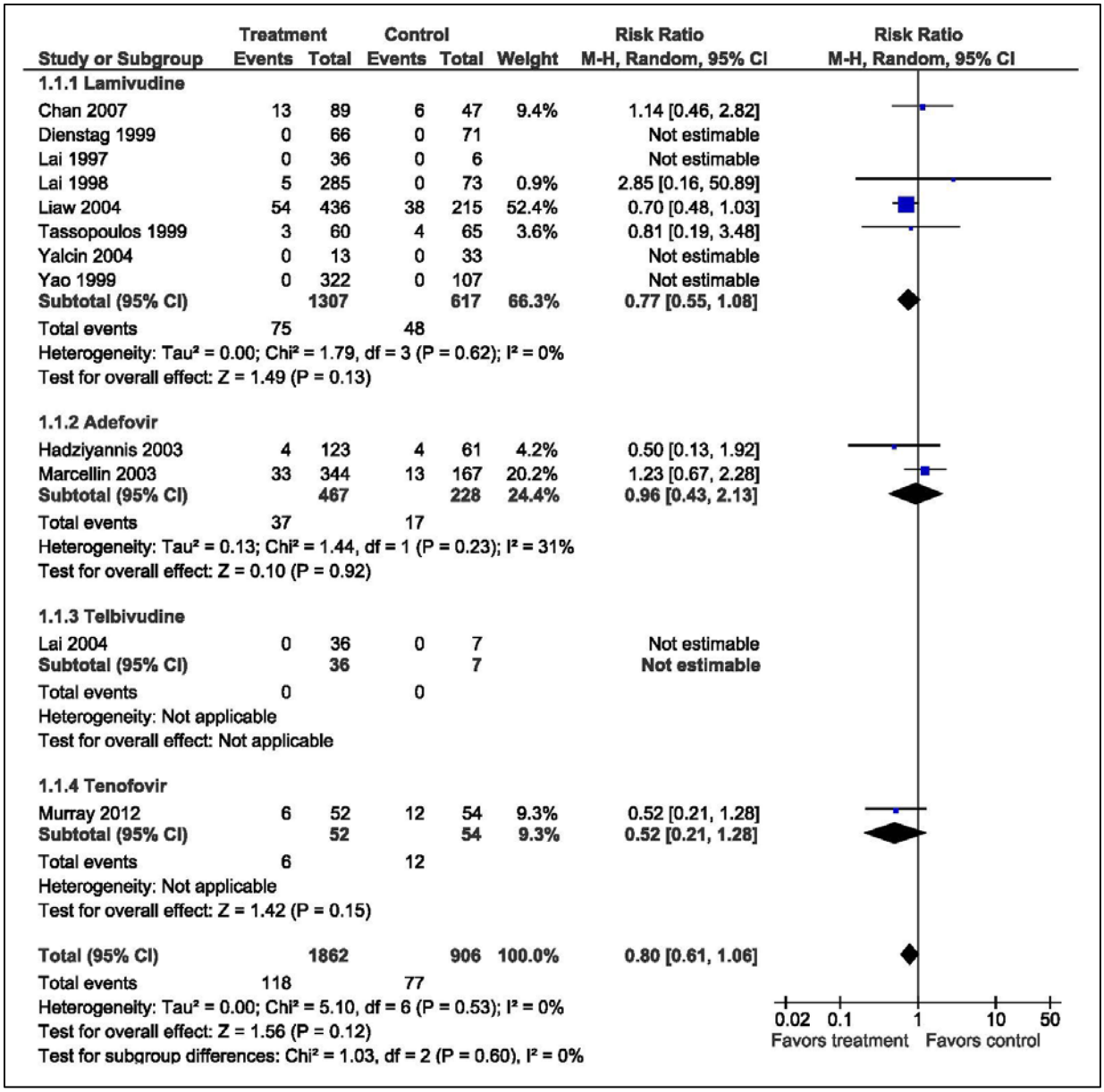
Abbreviations: df = degree of freedom; M-H = Mantel-Haenszel.

Figure 11. Mortality, Antiviral Therapy Versus Placebo or No Treatment



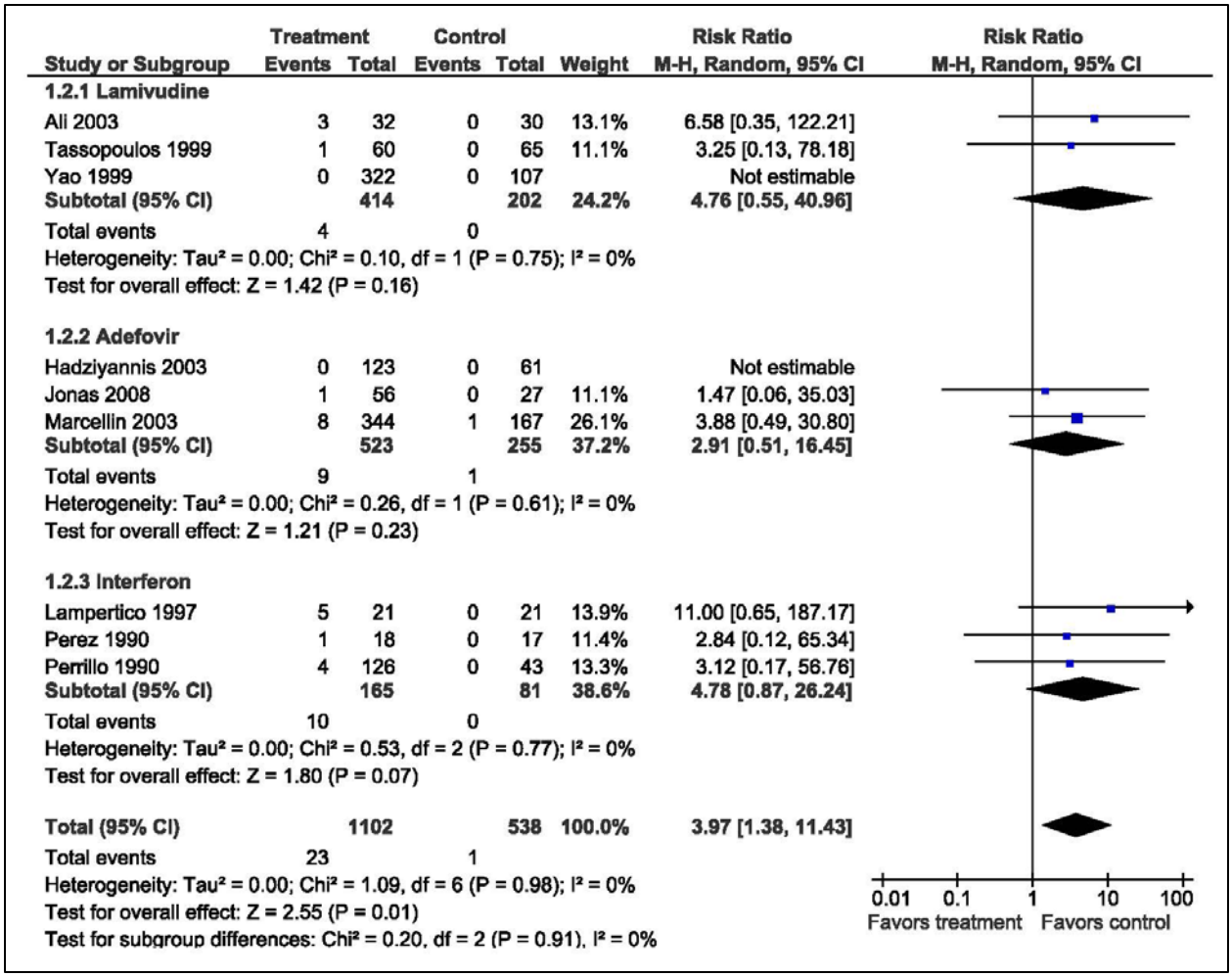
Abbreviations: df = degree of freedom; M-H = Mantel-Haenszel.

Figure 12. Serious Adverse Events, Antiviral Therapy Versus Placebo or No Treatment



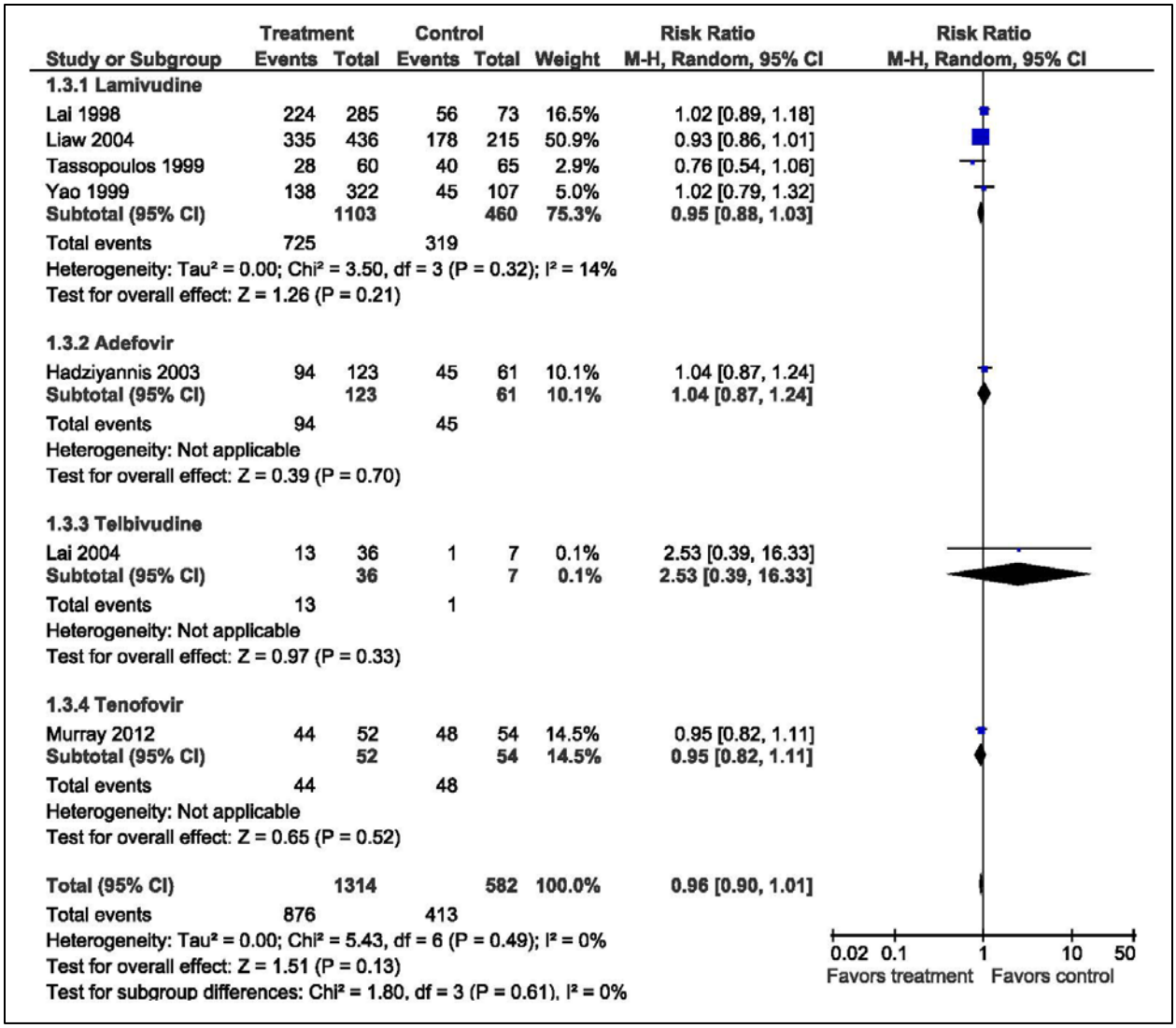
Abbreviations: df = degree of freedom; M-H = Mantel-Haenszel.

Figure 13. Withdrawals Due to Adverse Events, Antiviral Therapy Versus Placebo or No Treatment



Abbreviations: df = degree of freedom; M-H = Mantel-Haenszel.

Figure 14. Any Adverse Events, Antiviral Therapy Versus Placebo or No Treatment



Abbreviations: df = degree of freedom; M-H = Mantel-Haenszel.

Table 1. Typical Interpretation of Serologic Test Results for Hepatitis B Infection

Serologic Marker				Interpretation
HBsAg	**Total Anti-HBc**	**IgM Anti-HBc**	**Anti-HBs**	
-	-	-	-	Never infected
+*	-	-	-	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	-	Acute infection
-	+	+	+ or -	Acute resolving infection
-	+	-	+	Recovered from past infection and immune
+	+	-	-	Chronic infection
-	+	-	-	False-positive (i.e., susceptible), past infection, "low-level" chronic infection,** or passive transfer of anti-HBc to infant born to HBsAg-positive mother
-	**-**	**-**	+	Immune if concentration is $\geq$10 mIU/mL after vaccine series completion; passive transfer after hepatitis B immune globulin administration

*To ensure that an HBsAg-positive test result is not a false-positive, samples with reactive HBsAg results should be tested with a licensed neutralizing confirmatory test if recommended in the manufacturer's package insert.

**Persons positive only for anti-HBc are unlikely to be infectious except under unusual circumstances in which they are the source of direct percutaneous exposure of susceptible recipients to large quantities of virus (e.g., blood transfusion or organ transplant).

Note: Reproduced with permission from Mast et al, 2006.[6]

Abbreviations: - = negative test result; + = positive test result; anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to HBsAg; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M; mIU/mL = milli-International Units per milliliter.

Table 2. Alternative Screening Strategies: Study Characteristics

Author, Year Country	Study Design	Sample Size	Setting Population Characteristics	HBV Screening Strategies	Quality
Spenatto, 2013[35] France	Cross-sectional	N=6,194*	STD clinic Age 20-29 years: 62% Female: 56% Self-reported injection drug use: 0.7% High-endemic area (prevalence ≥8%) country of birth: 7.2%	A: Screen all B: Screen 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, or with transfusion history or blood contacts, tattoos, body piercing, more than 2 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	Fair

*183 patients (1 HBV case) did not have information on country of birth.

Abbreviations: HBV = hepatitis B virus; STD = sexually transmitted disease.

Table 3. Effects of Applying Alternative Screening Criteria on Sensitivity and Number Needed to Screen to Identify One Case of Hepatitis B Virus Infection

Author, Year Country	HBV Prevalence	Screening Strategy	Proportion Screened	Sensitivity	Specificity	Number Needed to Screen to Identify 1 Case of HBV Infection
Spenatto, 2013[35] France	0.8% (49/6,194)	A: Screen all B: Screen 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, or with transfusion history or blood contacts, tattoos, body piercing, more than 2 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	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: 31% (15/48) C: 98% (48/49) D: 84% (41/49) E: 94% (46/49)	A: 0% (0/6,145) B: 87% (5,217/5,963) C: 37% (2,244/6,145) D: 27% (1,682/6,145) E: 16% (986/6,145)	A: 126 B: 16 C: 82 D: 110 E: 113

Abbreviation: HBV = hepatitis B virus.

Table 4. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Intermediate Outcomes: Study Characteristics

Author, Year	Study Design, Duration	Country	Population	HBeAg Status	Cirrhosis	Intermediate Outcomes Reported	Quality
Adefovir Vs. Placebo							
Hadziyannis,2003[40]	RCT 48 weeks	Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore	n=185 Mean age, 46 years 83% male	Negative	11%	ALT normalization Virologic improvement Histologic improvement	Fair
Jonas, 2008[41]	RCT 48 weeks	Germany, Poland, Spain, United Kingdom, United States	n=83 Mean age, 14 years 75% male	Positive	NR	ALT normalization Composite outcomes	Fair
Marcellin, 2003[42]	RCT 48 weeks	Australia, Canada, France, Germany, Italy, Malaysia, The Philippines, Singapore, Spain, Taiwan, Thailand, United Kingdom, United States*	n=515 Mean age, 35 years 74% male	Positive	NR	HBeAg loss/seroconversion ALT normalization Histologic improvement	Fair
Zeng, 2006[43]	RCT 12 weeks	China	n=480 Mean age, 32 years 83% male	Positive	NR	HBeAg loss/seroconversion ALT normalization Virologic improvement	Fair
Interferon Alfa-2b Vs. No Treatment							
Bayraktar, 1993[44]	Controlled trial 6 months	Turkey	n=35 Mean age, 36 years 71% male	Positive	29%	HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization	Poor
Hadziyannis, 1990[45]	RCT 14-16 weeks treatment + 2 year followup	Greece	n=50 Mean age, 49 years 94% male	Negative	44%	Composite outcomes	Poor
Lampertico, 1997[46]	Open label RCT 3 years	Italy	n=42 Mean age, 46 years 86% male	Negative	17%	HBsAg loss/seroconversion Histologic improvement Composite outcomes	Fair

Table 4. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Intermediate Outcomes: Study Characteristics

Author, Year	Study Design, Duration	Country	Population	HBeAg Status	Cirrhosis	Intermediate Outcomes Reported	Quality
Muller, 1990[47]	RCT 10 months	Germany	n=58 Mean age NR; range, 18-65 years 79% male	Positive	5%	Composite outcomes	Fair
Perez, 1990[48]	RCT 24 weeks (control phase)	Argentina	n=35 Mean age, 39 years 77% male	Positive	14%	HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement	Fair
Perrillo, 1990[49]	RCT 10 months	United States	n=169 Mean age, 40 years 85% male	Positive	NR	HBsAg loss/seroconversion Composite outcomes	Good
Sarin, 1996[50]	RCT 16 months	India	n=41 Mean age, 35 years 94% male	Positive	44%	HBeAg loss/seroconversion HBsAg loss/seroconversion Virologic improvement Composite outcomes	Fair
Waked. 1990[51]	RCT 16 months	Egypt	n=40 Mean age, 36 years 78% male	Positive	40%	HBeAg loss/seroconversion HBsAg loss/seroconversion Histologic improvement	Fair
Lamivudine Vs. Placebo							
Ali, 2003[52]	RCT 12 months	Iraq	n=74 Mean age NR % male NR	Negative	NR	HBsAg loss/seroconversion	Poor
Bozkaya, 2005[53]	Controlled trial 12 months (control phase)	Turkey	n=55 Mean age, 36 years 60% male	Negative	NR**	ALT normalization	Poor
Chan, 2007*[,54]	RCT 30 months	China	n=139 Mean age, 39 years 84% male	Negative	27%	HBsAg loss/seroconversion ALT normalization Virologic improvement Histologic improvement Composite outcomes	Fair

Table 4. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Intermediate Outcomes: Study Characteristics

Author, Year	Study Design, Duration	Country	Population	HBeAg Status	Cirrhosis	Intermediate Outcomes Reported	Quality
Dienstag, 1999[55]	RCT 16 months	United States	n=137 Median age, 39 years 83% male	Positive	10%	HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement Histologic improvement	Fair
Lai, 1997[56]	RCT 8 weeks	Hong Kong	n=42 Mean age, 32 years 64% male	Positive	NR	HBeAg loss/seroconversion	Fair
Lai, 1998[57]	RCT 1 year	Hong Kong, Taiwan, Singapore	n=358 Median age, 31 years 73% male	Positive	5%	ALT normalization Histologic improvement Composite outcomes	Fair
Tassopoulos, 1999[58]	RCT 24 weeks	Greece	n=125 Median age, 43 years 80% male	Negative	15%	HBsAg loss/seroconversion Composite outcomes	Fair
Yalcin, 2004[59]	RCT 1 year	Turkey	n=46 Mean age, 24 years 54% male	Positive	NR	HBeAg loss/seroconversion HBsAg loss/seroconversion Virologic improvement Composite outcomes	Fair
Yao, 1999[60]	RCT 12 weeks	China	n=429 Mean age, 32 years 73% male	Positive	NR	HBeAg loss/seroconversion ALT normalization Virologic improvement	Fair
Tenofovir Vs. Placebo							
Murray, 2012[61]	RCT 72 weeks	United States, Bulgaria, France, Poland, Romania, Spain, Turkey	n=106 Mean age, 15 years 73% male	Positive	NR	HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement Composite outcomes	Good

*Patient population was 60% Asian.
**24% had fibrosis.

Table 4. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Intermediate Outcomes: Study Characteristics

Abbreviations: ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; NR = not reported; RCT = randomized, controlled trial.

Table 5. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Composite Outcomes

Author, Year	Results	Quality
Adefovir Vs. Placebo		
Jonas, 2008[63]	HBV DNA <1000 copies/mL + ALT normalization: 13/56 (23%) vs. 0/27 (0%); RR, 13; 95% CI, 0.8 to 215	Fair
Interferon Alfa-2b Vs. No Treatment		
Hadziyannis, 1990[45]	HBV DNA undetectable + ALT normalization: 11/25 (44%) vs. 2/25 (8%); **RR, 5.5; 95% CI, 1.4 to 22** HBV DNA + ALT reduced by >50% from baseline: 3/25 (12%) vs. 6/25 (24%); RR, 0.5; 95% CI, 0.1 to 1.8	Poor
Lampertico, 1997[46]	Loss of HBV DNA + ALT normalization: 6/21 (29%) vs. 0/21 (0%); RR, 13; 95% CI, 0.8 to 217 Loss of HBsAg +/or HBV DNA: 7/21 (33%) vs. 0/21 (0%); RR, 15; 95% CI, 0.9 to 247	Fair
Muller, 1990[47]	Loss of HBsAg, HBeAg, HBV DNA + ALT normalization: 1/30 (3%) vs. 0/28 (0%); RR, 2.8; 95% CI, 0.1 to 66 Loss of HBeAg, HBV DNA + ALT normalization : 8/30 (27%) vs. 0/28 (0%); RR, 15; 95% CI, 0.9 to 248	Fair
Perrillo, 1990[48]	Loss of HBeAg + HBV DNA: 38/126 (26%) vs. 3/43 (7%); **RR, 4.6; 95% CI, 1.5 to 14**	Good
Sarin, 1996[50]	Loss of HBeAg + HBV DNA: 10/20 (50%) vs. 1/21 (5%); **RR, 11; 95% CI, 1.5 to 75**	Fair
Lamivudine Vs. Placebo		
Lai, 1998[57]	HBeAg seroconversion + HBV DNA undetectable: 39/275 (14%) vs. 3/70 (4%); **RR, 3.31; 95% CI, 1.05 to 10.40**	Fair
Chan, 2007[54]	HBV DNA <10,000 copies/ml + ALT normalization at 24 months (time on treatment): 50/89 (56%) vs. 5/47 (11%); **reported adjusted OR,* 11; 95% CI, 3.8 to 30; RR, 5.3; 95% CI, 2.3 to 12** HBV DNA <10,000 copies/ml + ALT normalization at 30 months (6 months after treatment cessation): 23/89 (26%) vs. 9/47 (19%); RR, 1.3; 95% CI, 0.7 to 2.7	Fair
Tassopoulos, 1999[58]	HBV DNA <2.5 pg/mL + ALT normalization: 34/54 (63%) vs. 3/54 (6%); **RR, 11; 95% CI, 3.7 to 35**	Fair
Yalcin, 2004[59]	HBeAg seroconversion + HBV DNA loss: 1/13 (8%) vs. 1/33 (3%); RR, 2.5; 95% CI, 0.17 to 38	Fair
Tenofovir Vs. Placebo		
Murray, 2012[61]	HBV DNA <400 copies/mL + ALT normalization: 37/52 (71%) vs. 0/54 (0%); **RR, 77; 95% CI, 5 to 1,235** HBV DNA <400 copies/mL + ALT normalization + HBeAg loss: 11/52 (21%) vs. 0/54 (0%); **RR, 24; 95% CI, 1.4 to 395** HBV DNA <400 copies/mL + ALT normalization + HBsAg loss: 8/52 (15%) vs. 0/54 (0%); **RR, 18; 95% CI, 1.0 to 298**	Good

*OR adjusted for baseline ALT and HBV DNA.

Note: Statistically significant results appear in bold type.

Abbreviations: ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; OR = odds ratio; RR = relative risk.

Table 6. Head-to-Head Studies of Antiviral Therapy Reporting Intermediate Outcomes

Outcome	Entecavir Vs. Lamivudine	Pegylated Interferon Alfa-2a Vs. Lamivudine	Tenofovir Vs. Adefovir
HBeAg loss/seroconversion	RR, 1.2 (95% CI, 0.9 to 1.5; I^2=0%); 3 trials[64,68,69]	**RR, 1.6 (95% CI, 1.2 to 2.1);** 1 trial[70]	RR, 1.2 (95% CI, 0.7 to 2.1); 1 trial[72]
HBsAg loss/seroconversion	RR, 1.8 (95% CI, 0.9 to 3.9); 1 trial[64]	**RR, 16 (95% CI, 2.2 to 121; I^2=0%);** 2 trials[70,71]	RR, 5.7 (95% CI, 0.3 to 103); 1 trial[72]
ALT normalization	**RR, 1.1 (95% CI, 1.0 to 1.2; I^2=0%);** 4 trials[64,67-69]	**RR, 1.4 (95% CI, 1.2 to 1.6; I^2=0%);** 2 trials[70,71]	RR, 1.1 (95% CI, 0.9 to 1.4; I^2=73%); 2 trials[72]
Virological improvement	**RR, 1.6 (95% CI, 1.1 to 2.5; I^2=94%);** 4 trials[64,67-69]	**RR, 2.8 (95% CI, 1.9 to 4.4; I^2=0%);** 2 trials[70,71]	RR, 2.9 (95% CI, 0.6 to 15; I^2=97%); 2 trials[72]
Histologic improvement	**RR, 1.2 (95% CI, 1.1 to 1.3; I^2=0%);** 2 trials[64,67]	**RR, 1.2 (95% CI, 1.0 to 1.4; I^2=0%);** 2 trials[70,71]	**RR, 1.1 (95% CI, 1.0 to 1.2; I^2=0%);** 2 trials[72]

Note: Statistically significant results appear in bold type

Abbreviations: ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; RR = relative risk.

Table 7. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Health Outcomes

Author, Year	Study Design Duration	Country	Population	HBeAg Status	Cirrhosis	Health Outcomes	Quality
Adefovir Vs. Placebo							
Jonas, 2008[41]	RCT 11 months	Germany, Poland, Spain, United Kingdom, United States	n=83 Mean age, 15 years 75% male	Positive	NR	Mortality	Fair
Zeng, 2006[43]	RCT 12 weeks	China	n=480 Mean age, 32 years 83% male	Positive	NR	Mortality	Fair
Interferon Alfa-2a Vs. Placebo							
Lin, 1999[73] Methods: Liaw, 1994[74]	RCT 4 months + mean 7 years followup	Taiwan	n=101 Mean age, 32 years 100% male	Positive	12%	Incident cirrhosis Hepatocellular cancer Mortality	Fair
Mazella, 1999[75]	RCT 6 months + 7 years followup	Italy	n=64 Mean age, 38 years 78% male	Positive	N/A*	Incident cirrhosis Hepatocellular cancer Mortality	Fair
Interferon Alfa-2b Vs. No Treatment							
Lampertico, 1997[46]	Open label RCT 2 years + 1 year followup	Italy	n=42 Mean age, 46 years 86% male	Negative	17%	Hepatocellular cancer	Fair
Perrillo, 1990[49]	RCT 16 weeks + 6 months followup	United States	n=169 Mean age, 40 years 85% male	Positive	NR	Mortality	Good
Waked, 1990[51]	RCT 16 weeks + 1 year followup	Egypt	n=40 Mean age, 36 years 78% male	Positive	40%	Incident cirrhosis Mortality	Fair
Lamivudine Vs. Placebo							
Chan, 2007[54]	RCT 2 years + 6 months followup	China	n=139 Mean age, 39 years 84% male	Negative	27%	Hepatocellular cancer	Fair
Dienstag, 1999[55]	RCT 1 year + 16 weeks followup	United States	n=137 Median age, 39 years 83% male	Positive	10%	Mortality	Fair
Lai, 1998[57]	RCT 1 year	Hong Kong, Taiwan, Singapore	n=358 Median age, 31 years 73% male	Positive	5%	Mortality	Fair
Liaw, 2004[76]	RCT Median 2.7 years	Australia, Hong Kong, New Zealand, Singapore, Taiwan, Thailand	n=651 Median age, 43 years 85% male	Positive	33%	Disease severity** Hepatocellular cancer Mortality	Fair

*People with cirrhosis excluded from study.

Table 7. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Health Outcomes

**Based on Child-Pugh score, separately and in combination with spontaneous bacterial peritonitis with sepsis, renal insufficiency, bleeding gastric or esophageal varices, development of hepatocellular carcinoma, or death related to liver disease.

Abbreviations: HBeAg = hepatitis B e antigen; N/A = not applicable; NR = not reported; RCT = randomized, controlled trial.

Table 8. Harms of Antiviral Therapy Versus Placebo or No Treatment

Author, Year	Duration, Followup	Time Period for Harms Data	Number, Country	Cirrhosis	Serious Adverse Events Treatment Vs. Control/No Treatment	Withdrawal Due to Adverse Events Treatment Vs. Control/No Treatment	Any Adverse Events Treatment Vs. Control/No Treatment	Quality	Notes
Adefovir Vs. Placebo									
Hadziyannis 2003[40]	11 months + 1 month followup	Both	n=185 Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore	11% cirrhosis	3% (4/123) vs. 7% (4/61); RR, 0.5 (95% CI, 0.1 to 1.9)	0% (0/123) vs. 0% (0/61); RR, 0.5 (95% CI, 0.0 to 25)	76% (94/123) vs. 74% (45/61); RR, 1.0 (95% CI, 0.9 to 1.2)	Fair	Any adverse event refers to those reported by at least 5% of patients
Jonas, 2008[41]	11 months	Time on treatment	n=83 United States and Europe	% cirrhosis NR*	NR separately for relevant age group	1.7% (1/56) vs. 0% (0/27); RR, 1.5 (95% CI, 0.1 to 35)	NR separately for relevant age group	Fair	
Marcellin, 2003[42]	11 months + 1 month followup	Both	n=515 North America, Europe, Australia, and Southeast Asia	% cirrhosis NR*	10% (33/344) vs. 8% (13/167); RR, 1.2 (95% CI, 0.7 to 2.3)	2.3% (8/344) vs. <1% (1/167); RR, 3.9 (95% CI, 0.5 to 31)	NR	Fair	N values calculated; combined treatment arms
Interferon Alfa-2b Vs. No Treatment									
Bayraktar, 1993[44]	6 months	Time on treatment	n=35 Turkey	29% cirrhosis	NR	0% (0/25)**	NR	Poor	Results reported for treated group only
Hadziyannis, 1990[45]	1 year + 1 year followup	Unclear	n=50 Greece	44% cirrhosis	0% (0/25)**	NR	NR	Poor	Results reported for treated group only
Lampertico, 1997[46]	2 years + 1 year followup	Time on treatment	n=42 Italy	17% cirrhosis	NR	24% (5/21) vs. 0% (0/21); RR, 11 (95% CI, 0.65 to 187)	NR	Fair	

Table 8. Harms of Antiviral Therapy Versus Placebo or No Treatment

Author, Year	Duration, Followup	Time Period for Harms Data	Number, Country	Cirrhosis	Serious Adverse Events Treatment Vs. Control/No Treatment	Withdrawal Due to Adverse Events Treatment Vs. Control/No Treatment	Any Adverse Events Treatment Vs. Control/No Treatment	Quality	Notes
Muller, 1990[47]	4 months + 6 months followup	Time on treatment	n=58 Germany	5% cirrhosis	NR	3.7% (1/27)**	NR	Fair	Results reported for treated group only
Perez, 1990[48]	6 months (2nd phase) + 6 months followup	Time on treatment	n=35 Argentina	14% cirrhosis	NR	6% (1/18) vs. 0% (0/17); RR, 2.7 (95% CI, 0.1 to 62)	NR	Fair	
Perrillo, 1990[49]	4 months + 6 months followup	Time on treatment	n=169 United States	% cirrhosis NR*	NR	3% (4/126) vs 0% (0/43); RR, 3.12 (95% CI, 0.17 to 57)	NR	Good	
Sarin, 1996[50]	4 months + 1 year followup	Unclear	n=41 India	44% cirrhosis	0% (0/20)**	NR	NR	Fair	Results reported for treated group only
Waked, 1990[51]	4 months + 1 year followup	Time on treatment	n=40 Egypt	40% cirrhosis	0% (0/20)**	0% (0/20)**	NR	Fair	Results reported for treated group only; serious adverse effects inferred
Lamivudine Vs. Placebo									
Ali, 2003[52]	6 months + 1 year followup	Unclear	n=74 Iraq	% cirrhosis NR*	NR	9.4% (3/32) vs. 0% (0/30); RR, 6.6 (95% CI, 0.4 to 122)	NR	Poor	
Chan, 2007[54]	2 years + 6 months followup	Unclear	n=139 China	27% cirrhosis	15% (13/89) vs. 13% (6/47); RR, 1.1 (95% CI, 0.5 to 2.8)	NR	NR	Fair	

Table 8. Harms of Antiviral Therapy Versus Placebo or No Treatment

Author, Year	Duration, Followup	Time Period for Harms Data	Number, Country	Cirrhosis	Serious Adverse Events Treatment Vs. Control/No Treatment	Withdrawal Due to Adverse Events Treatment Vs. Control/No Treatment	Any Adverse Events Treatment Vs. Control/No Treatment	Quality	Notes
Dienstag, 1999[55]	1 year + 4 months followup	Unclear	n=143 United States	10% cirrhosis	0% (0/66) vs 0% (0/71); RR, 1.1 (95% CI, 0.0 to 53)	NR	NR	Fair	Results inferred
Lai, 1997[56]	1 month + 1 month followup	Unclear	n=42 Hong Kong	% cirrhosis NR*	0% (0/36) vs. 0% (0/6); RR, 0.2 (95% CI, 0.0 to 8.8)	NR	NR	Fair	Combined treatment arms
Lai, 1998[57]	1 year	Time on treatment	n=358 Hong Kong, Taiwan, Singapore	5% cirrhosis	1.8% (5/285) vs. 0% (0/73); RR, 2.9 (95% CI, 0.2 to 51)	NR	78.6% (224/285) vs. 77% (56/73); RR, 1.0 (95% CI, 0.9 to 1.2)	Fair	Combined treatment arms
Liaw, 2004[76]	2.7 years median + ≤1 year followup	Time on treatment	n=651 Several countries in Asia, Australia, New Zealand	33% cirrhosis	12% (54/436) vs. 18% (38/215); RR, 0.7 (95% CI, 0.5 to 1.0)	NR	77% (335/436) vs. 83% (178/215); RR, 0.9 (95% CI, 0.9 to 1.0)	Fair	Any adverse event refers to those that occurred in greater than 10% of patients
Tassopoulo, 1999[58]	6 months	Time on treatment	n=125 Greece	15% cirrhosis	5% (3/60) vs. 6% (4/65); RR, 0.8 (95% CI, 0.2 to 3.5)	2% (1/60) vs. 0% (0/65); RR, 3.2 (95% CI, 0.1 to 78)	47% (28/60) vs. 62% (40/65); RR, 0.8 (95% CI, 0.5 to 1.1)	Fair	
Yalcin, 2004[59]	3 months + 1 year followup	Unclear	n=46 Turkey	% cirrhosis NR*	0% (0/13) vs. 0% (0/33); RR, 2.4 (95% CI, 0.1 to 116)	NR	NR	Fair	

Table 8. Harms of Antiviral Therapy Versus Placebo or No Treatment

Author, Year	Duration, Followup	Time Period for Harms Data	Number, Country	Cirrhosis	Serious Adverse Events Treatment Vs. Control/No Treatment	Withdrawal Due to Adverse Events Treatment Vs. Control/No Treatment	Any Adverse Events Treatment Vs. Control/No Treatment	Quality	Notes
Yao, 1999[60] *See also: Yao, 2000[78]; Yao, 2009[79]*	3 months + 9 months followup	Time on treatment	n=429 China	% cirrhosis NR*	0% (0/322) vs. 0% (0/107); RR, 0.3 (95% CI, 0.0 to 17)	0% (0/322) vs. 0% (0/107); RR, 0.3 (95% CI, 0.0 to 17)	43% (138/322) vs. 42% (45/107); RR, 1.0 (95% CI, 0.8 to 1.3)	Fair	
Tenofovir Vs. Placebo									
Murray, 2012[61]	1.4 years	Time on treatment	n=106 North America and Europe	% cirrhosis NR*	12% (6/52) vs 22% (12/54); RR, 0.5 (95% CI, 0.2 to 1.3)	NR	85% (44/52) vs 89% (48/54); RR, 0.95 (95% CI, 0.8 to 1.1)	Good	

*Decompensated liver disease as exclusion criterion.
**Excluded from meta-analyses.

Abbreviations: NR = not reported; RR = relative risk.

Table 9. Head-to-Head Studies of Antiviral Therapy Reporting Harms of Treatment

Outcomes	Entecavir Vs. Lamivudine	Pegylated Interferon Alfa-2a Vs. Lamivudine	Tenofovir Vs. Adefovir
Serious adverse events	RR, 0.9 (95% CI, 0.6 to 1.3, I^2=0%); 2 trials[64,67]	**RR, 2.1 (95% CI, 1.0 to 4.5, I^2=0%);** 2 trials[70,71]	RR, 1.0 (95% CI, 0.5 to 1.8); 2 trials (1 publication, results pooled)[72]
Withdrawals due to adverse events	RR, 0.5 (95% CI, 0.1 to 1.9, I^2=43%);3 trials[64,67,68]	**RR, 7.6 (95% CI, 1.1 to 52, I^2=38%);** 2 trials[70,71]	Not reported
Any adverse event	RR, 1.0 (95% CI, 0.9 to 1.1, I^2=34%); 3 trials[64,67,68]	**RR, 1.7 (95% CI, 1.5 to 2.0, I^2=55%);** 2 trials[70,71]	RR, 1.0 (95% CI, 0.9 to 1.1); 2 trials (1 publication, results pooled)[72]

Note: Statistically significant results appear in bold type

Abbreviations: RR = relative risk.

Table 10. Studies of Association Between Intermediate and Final Health Outcomes

Author, Year Country	Study Design	Intermediate Outcome Evaluated: Proportion of Patients With Intermediate Outcome	Treatment Duration of Followup	Characteristics of HBV Infection	Age, Sex, Race	Number Receiving Antiviral Treatment Lost to Followup	Quality
Andreone, 2004[80] Italy	Cohort (unclear if prospective or retrospective)	No virological breakthrough (HBV DNA became undetectable on treatment and remained undetectable): 41%	Lamivudine Median 42 months	HBeAg positive: None ALT (mean): 192 Serum HBV DNA (mean, pg/ml): 16 Cirrhosis: 100%	Mean age: 53 years Male: 82% Race: NR	n=22 Lost to followup: Unclear	Fair
Baltayiannis, 2006[81] Greece	Cohort (unclear if prospective or retrospective)	Virological response (HBV DNA <10,000 copies/ml at 6 months of treatment): 35%	Interferon alfa 6 years	HBeAg positive: None ALT (median): 177 Serum HBV DNA (median, copies/mL): 1.2×10^6 Cirrhosis: Excluded	Mean age: 51 years Male: 63% Race: NR	n=63 Lost to followup: 1 (1.6%)	Fair
Di Marco, 2004[82] Italy	Retrospective cohort	No virological breakthrough (HBV DNA $<10^5$ copies/ml throughout followup after achieving undetectability): 39%	Lamivudine 4 years	HBeAg positive: Excluded ALT >2 times ULN: 65% Serum HBV DNA: NR Cirrhosis on histology: 25%	Mean age: 49 years Male: 83% Race: NR	n=656 Lost to followup: NR; 40 patients had no virological response and were excluded from analysis	Fair
Fattovich, 1997[83] Italy	Cohort (unclear if prospective or retrospective)	Biochemical remission (normalization of ALT levels): 28%	Interferon alfa Mean 7 years	HBeAg positive: All ALT (mean): 5.3 times upper limit of normal Serum HBV DNA: NR Cirrhosis: 100%	Mean age: 47 years Male: 85% Race: 100% white	n=40 Lost to followup: NR for treated subgroup	Poor
Hui, 2008[84] China (Hong Kong)	Cohort (unclear if prospective or retrospective)	Histological response (improvement of 2 points or more on HAI score after end of treatment): 40%	Interferon alfa-2a or -2b Median 9.9 years	HBeAg positive: All ALT (mean): 113 Serum HBV DNA $>10^5$ copies/ml: 100% Cirrhosis: 12%	Mean age: 30 years Male: 78% Race: NR	n=89 Lost to followup: NR	Poor
Lampertico, 2003[85] Italy	Cohort (unclear if prospective or retrospective)	Sustained virological and biochemical response (normalization of serum ALT and clearance of HBV DNA): 30%	Interferon alfa-2b 68 months	HBeAg positive: None ALT (mean): 204 HBV DNA detectable: 61% Ishak F4-F6 fibrosis: 60%	Men age: 46 years Female: 13% Race: NR	n=101 Lost to followup: 4 (4.0%)	Fair

Table 10. Studies of Association Between Intermediate and Final Health Outcomes

Author, Year Country	Study Design	Intermediate Outcome Evaluated: Proportion of Patients With Intermediate Outcome	Treatment Duration of Followup	Characteristics of HBV Infection	Age, Sex, Race	Number Receiving Antiviral Treatment Lost to Followup	Quality
Lau, 1997[63] United States	Cohort (originally enrolled in RCTs)	Response (sustained loss of HBV DNA and clearance of HBeAg within 1 year of starting treatment): 30%	Interferon alfa Mean 6.2 years	HBeAg positive: All ALT (median): 154 Serum HBV DNA (mq/mL): 4,843 Cirrhosis: 17%	Mean age: 41 years Male: 83% Race: 94% white, 6% black	n=103 Lost to followup: 8 (7.8%); assumed to be alive and without liver-related complications	Fair
Niederau, 1996[86] Europe	Prospective cohort	Loss of HBeAg after therapy: 51%	Interferon alfa-2b Mean 50 months	HBeAg positive: All HBsAg clearance: 9.7% ALT: NR AST: NR HBV DNA: NR Fibrosis stage: NR Cirrhosis: NR (Child-Pugh class B or C excluded)	Mean age: NR Female: NR Race: NR	n=103 Lost to followup: None	Fair
Papatheodoridis, 2001[87] Greece	Cohort (unclear if prospective or retrospective)	Sustained biochemical response (normalization of ALT at the end of interferon therapy and persistently normal ALT levels throughout the post-treatment followup period): 27%	Interferon alfa Mean 6.0 years	HBeAg positive: Excluded ALT (median): 112 Serum HBV DNA (median, pg/ml): 4.4 Cirrhosis: 27%	Mean age: 47 years Male: 83% Race: NR	n=209 Lost to followup: 9 (4.3%)	Poor
Papatheodoridis, 2011[88] Greece	Retrospective cohort	Virological remission (HBV DNA <200 IU/ml throughout therapy): 28%	Lamivudine Median 4.7 years	HBeAg positive: Excluded ALT (median): 98 Serum HBV DNA (median, $x10^3$ IU/ml): 400 Cirrhosis: 26%	Mean age: 54 years Male: 72% Race: NR	n=818 Lost to followup: 180 (22%)	Fair

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HAI = histology activity index; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NR = not reported; RCT = randomized, controlled trial; ULN = upper limit of normal.

Table 11. Hazard Ratios for Associations Between Intermediate and Final Health Outcomes

HBeAg Status Author, Year Country	Confounders Adjusted for in Analysis	Death	Hepatocellular Carcinoma	Composite Outcomes	Quality
HBeAg-Positive Patients					
Fattovich, 1997[83] Italy	Age Sex Symptoms Hepatic stigmata Splenomegaly AST ALT AST/ALT ratio Bilirubin Albumin Gamma-globulins Platelets HBeAg clearance ALT normalization All patients HBeAg positive	Biochemical remission vs. no remission: adjusted HR, 0.09 (95% CI, 0.01 to 0.71)	NR	NR	Poor
Hui, 2008[84] China (Hong Kong)	Fibrosis HBV DNA level All patients HBeAg positive	NR	NR	Histological response on HAI score vs. no response: adjusted HR, 0.62 (95% CI, 0.06 to 6.9)	Poor
Lau, 1997[89] United States	Cirrhosis Age Sex ALT AST All patients HBeAg positive	Responder (virological response and HBeAg clearance) vs. nonresponder: adjusted HR, 0.59 (95% CI, 0.20 to 1.67)[a]	NR	Responder vs. nonresponder: adjusted HR, 0.07 (95% CI, 0.02 to 0.33)[b]	Fair
Niederau, 1996[86] Europe	Age Sex Baseline HBV DNA Duration of hepatitis Preexisting cirrhosis All patients HBeAg positive	NR	NR	HBeAg loss vs. no loss: adjusted HR, 0.06 (95% CI, 0.01 to 0.61)[c]	Fair

Table 11. Hazard Ratios for Associations Between Intermediate and Final Health Outcomes

HBeAg Status Author, Year Country	Confounders Adjusted for in Analysis	Death	Hepatocellular Carcinoma	Composite Outcomes	Quality
HBeAg-Negative Patients					
Andreone, 2004[80] Italy	Age Sex Child-Pugh class ALT HBV viral load Albumin Bilirubin Prothrombin activity Alpha-fetoprotein Previous interferon therapy Smoking status Months of treatment All patients HBeAg negative	NR	No virological breakthrough vs. breakthrough: adjusted HR, 0.10 (95% CI, 0.01 to 0.77)	NR	Fair
Baltayiannis, 2006[81] Greece	Age Sex Alcohol use ALT >200 IU/L at baseline HBV DNA >10,000 copies/ml at baseline Histologic grade >9 Histologic stage >2 All patients HBeAg negative	NR	NR	Virological response at 6 months vs. no virological response: adjusted HR, 0.24 (95% CI, 0.06 to 0.96)[d]	Fair

Table 11. Hazard Ratios for Associations Between Intermediate and Final Health Outcomes

HBeAg Status Author, Year Country	Confounders Adjusted for in Analysis	Death	Hepatocellular Carcinoma	Composite Outcomes	Quality
Di Marco, 2004[82] Italy	Age Sex HBV DNA level ALT Hepatic flare after virological breakthrough Previous interferon therapy Cirrhosis All patients HBeAg negative	No virological breakthrough vs. breakthrough: adjusted HR, 0.34 (95% CI, 0.15 to 0.80)	NR	NR	Fair
Lampertico, 2003[85] Italy	Age Sex ALT HBV viral load IgM anti-HBc level Necroinflammatory grade Fibrosis stage All patients HBeAg negative	NR	NR	Sustained virological and biochemical response vs. no sustained response: adjusted HR, 0.13 (95% CI, 0.03 to 0.55)[e]	Fair
Papatheodoridis, 2001[87] Greece	Cirrhosis Age All patients HBeAg negative	NR	NR	Death or liver transplantation Sustained biochemical response vs. no sustained biochemical response: adjusted HR, 0.48 (95% CI, 0.23 to 1.0) Severe clinical complications[f] Sustained biochemical response vs. no sustained biochemical response: adjusted HR, 0.53 (95% CI, 0.29 to 0.91)	Poor

Table 11. Hazard Ratios for Associations Between Intermediate and Final Health Outcomes

HBeAg Status Author, Year Country	Confounders Adjusted for in Analysis	Death	Hepatocellular Carcinoma	Composite Outcomes	Quality
Papatheodoridis, 2011[88] Greece	Age Sex Liver disease severity ALT AST Bilirubin Albumin Hemoglobin Platelet count HBV DNA Interferon alfa in the past All patients HBeAg negative	NR	Virological remission under therapy vs. no virological remission: adjusted HR, 0.77 (95% CI, 0.35 to 1.69)[g]	NR	Fair

[a]Only adjusted for age and sex.
[b]Outcome was death, variceal hemorrhage, ascites, or encephalopathy.
[c]Outcome was death; need for liver transplantation; development of ascites, jaundice, or hepatic encephalopathy; or occurrence of, or bleeding from, esophageal varices.
[d]Outcome was death or liver complications (not defined).
[e]Outcome was cirrhosis, ascites, jaundice, hepatic encephalopathy, gastroesophageal bleeding due to portal hypertension, or hepatocellular carcinoma.
[f]Outcome was death, liver transplantation, liver decompensation (ascites, variceal bleeding, hepatic encephalopathy), and hepatocellular carcinoma.
[g]Outcome was HBV-related decompensated liver cirrhosis or hepatocellular carcinoma.

Abbreviations: ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; AST = aspartate aminotransferase; HAI = histology activity index; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HR = hazard ratio; IgM = immunoglobulin M; NR = not reported.

Table 12. Associations Between Intermediate Outcomes and Final Health Outcomes

Intermediate Outcome	Death	Hepatocellular Carcinoma	Composite Outcome
ALT normalization	1 study;[83] HR, 0.09 (95% CI, 0.01 to 0.71)	No studies	1 study;[87] HR, 0.48 (95% CI, 0.23 to 1.0)*
Composite intermediate outcome	1 study;[89] HR, 0.59 (95% CI, 0.20 to 1.67)	No studies	2 studies;[85,89] HR, 0.07 (95% CI, 0.02 to 0.33); HR, 0.13 (95% CI, 0.03 to 0.55)*
HBeAg loss	No studies	No studies	1 study;[86] HR, 0.06 (95% CI, 0.01 to 0.61)
Histological response	No studies	No studies	1 study;[84] HR, 0.62 (95% CI, 0.06 to 6.9)
Virological response	1 study;[82] HR, 0.34 (95% CI, 0.15 to 0.80)*	2 studies;[80,88] HR, 0.10 (95% CI, 0.01 to 0.77);* HR, 0.77 (95% CI, 0.35 to 1.69)*	1 study;[81] HR, 0.24 (95% CI, 0.06 to 0.96)*

*Study performed in HBeAg-negative patients.

Abbreviations: ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HR = hazard ratio.

Table 13. Summary of Evidence

Key Question	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality
1. What are the benefits of screening for HBV versus no screening in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?	No studies	No studies	N/A	N/A	No evidence	No evidence
2. What are the harms of screening for HBV infection (e.g., labeling, anxiety, and harms of confirmatory tests, including biopsy)?	No studies	No studies	N/A	N/A	No evidence	No evidence
3. How well do different screening strategies identify individuals with HBV infection (e.g., strategies that target persons from high-prevalence countries, men who have sex with men, injection drug users, immunization history, or other risk factors)?	One cross-sectional study	Evidence available from only 1 study with methodological limitations	N/A	Study conducted in high-risk sexually transmitted disease clinic attendees	One study found screening targeted at persons born in countries with higher chronic HBV prevalence, men, and unemployed persons identified 98% (48/49) of infections; number needed to screen to identify 1 case of HBV infection of 82.	Poor
4. In nonpregnant adolescents and adults with no evidence of HBV immunity on screening, how effective is HBV vaccination for improving clinical outcomes?	No studies with evidence on long-term clinical outcomes	No evidence on long-term clinical outcomes	Moderate	Studies conducted in high-risk populations (health care workers or MSM) and/or children	Vaccination is associated with decreased risk of HBV acquisition in health care workers (4 trials; RR, 0.51; 95% CI, 0.35 to 0.73) and men who have sex with men (4 trials; RR, 0.21; 95% CI, 0.11 to 0.39) based on serologic markers. Studies did not evaluate the effectiveness of HBV vaccination on long-term clinical outcomes.	Fair
5. In nonpregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving intermediate outcomes (virological or histological improvement or clearance of HBeAg)?	30 RCTs	Study duration and patient characteristics varied widely Few good-quality studies	High	About half the studies conducted outside of the United States/Europe and about a third enrolled HBeAg-negative	Antiviral treatment was more effective than placebo or no treatment for HBeAg loss or seroconversion (10 trials; RR, 2.1; 95% CI, 1.6 to 2.9; I^2=4%), HBsAg loss/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%), loss of HBV DNA (9 trials; RR, 7.2; 95% CI, 3.2 to 16; I^2=58%) and	Fair

Table 13. Summary of Evidence

Key Question	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality
				patients	histologic improvement (7 trials; RR, 2.1; 95% CI, 1.8 to 2.6; I^2=0%). Results were generally consistent across specific antiviral drugs. Entecavir and pegylated interferon alfa-2a were each associated with greater likelihood of achieving some intermediate virological and other outcomes than lamivudine, based on few (1 to 4) trials.	
6. In nonpregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving health outcomes?	16 RCTs	Many studies were small, with few events Only 1 good-quality study	Moderate	About half the studies conducted outside of the United States/Europe and about a third enrolled HBeAg-negative patients	Estimates for incident cirrhosis (3 trials; RR, 0.70; 95% CI, 0.33 to 1.46; I^2=0%), hepatocellular carcinoma (5 trials; RR, 0.57; 95% CI, 0.32 to 1.04; I^2=2%), and mortality (5 trials; RR, 0.55; 95% CI, 0.18 to 1.71; I^2=43%) all favored antiviral therapy over placebo, although differences were not statistically significant. There were too few clinical events in head-to-head trials of entecavir or pegylated interferon alfa-2a vs. lamivudine or pegylated interferon vs. nonpegylated interferon to determine effects on clinical outcomes.	Fair
7. In nonpregnant adolescents and adults with chronic HBV infection, how effective is education or behavior change counseling in reducing transmission and improving health outcomes?	No studies	No evidence	N/A	N/A	No evidence	No evidence

Table 13. Summary of Evidence

Key Question	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality
8. What are the harms associated with antiviral treatment for HBV infection?	29 RCTs	Many studies were small, with few events	High	Many studies conducted outside of the United States/Europe	There were no differences between treatment and control groups for serious adverse effects (12 trials; RR 0.8; 95% CI, 0.6 to 1.1; I^2=0%) or any adverse events (7 trials; RR, 0.96; 95% CI, 0.9 to 1.0; I^2=0%). Antiviral therapy was associated with more withdrawals due to adverse effects, but estimates were imprecise due to small numbers of events (9 trials; RR, 3.97; 95% CI, 1.4 to 11; I^2=0%). Results were generally consistent across specific antiviral drugs. In 2 head-to-head trials, 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%) and withdrawal due to adverse events (RR, 7.6; 95% CI, 1.1 to 52; I^2=38%) vs. lamivudine.	Fair
KQ 9. Do improvements in intermediate outcomes improve final health outcomes?	10 observational studies	High variability in patient characteristics and outcomes evaluated No studies were good quality; 3 were poor quality and failed to address important confounders	Moderate	One study excluded patients with cirrhosis, 2 studies included only patients with cirrhosis, and in the remainder the proportion with cirrhosis ranged from 12% to 60%	Ten observational studies found an association between various intermediate outcomes and clinical outcomes (death, hepatocellular carcinoma, or a composite clinical outcome), but variability in patient populations, intermediate and clinical outcomes evaluated, and methodological limitations make it difficult to draw strong conclusions. In some studies, results were not statistically significant.	Poor

Table 13. Summary of Evidence

Abbreviations: ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; MSM = men who have sex with men; N/A = not applicable; RCT = randomized, controlled trial; RR = relative risk.

Appendix A1. Search Strategies

Screening - Key Questions 1, 2

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
1 exp Hepatitis B/
2 exp Hepatitis B virus/
3 hepatitis b.mp.
4 hbv.mp.
5 or/1-4
6 Mass Screening/
7 5 and 6
8 ((hepatitis b or hbv) adj1 screen$).mp.
9 7 or 8
10 Pregnancy/
11 9 not 10
12 limit 11 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
13 limit 12 to english language
14 limit 12 to abstracts
15 13 or 14

EBM Reviews - Cochrane Central Register of Controlled Trials
1 Hepatitis B/
2 Hepatitis B virus/
3 hepatitis b.mp.
4 hbv.mp.
5 or/1-4
6 Mass Screening/
7 5 and 6
8 ((hepatitis b or hbv) adj1 screen$).mp.
9 7 or 8
10 Pregnancy/
11 9 not 10

PsycINFO
1 hepatitis b.mp.
2 hbv.mp.
3 1 or 2
4 exp Screening Tests/ or exp Screening/ or screen$.mp.
5 3 and 4

Effectiveness of Screening Strategies - Key Question 3

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
1 exp Hepatitis B/ or exp Hepatitis B virus/ or hepatitis b.mp.
2 exp Mass Screening/
3 screen$.mp.
4 Risk Assessment/ or risk assessment.mp.
5 Program Evaluation/
6 Prognosis/
7 prognos$.mp.
8 "Sensitivity and Specificity"/
9 *"Community-Based Participatory Research"/
10 Community Health Services/ or Community Networks/
11 Statistics as Topic/ or Chi-Square Distribution/
12 (screen$ adj1 (strateg$ or method$ or algorithm$)).mp.
13 2 or 3 or 12

14 1 and 13
15 or/4-11
16 14 and 15
17 limit 16 to english language
18 limit 16 to abstracts
19 17 or 18
20 Pregnancy/
21 19 not 20

PsycINFO
1 hepatitis b.mp. (752)
2 hbv.mp. (270)
3 1 or 2 (795)
4 exp Screening Tests/ or exp Screening/ or screen$.mp. (63956)
5 3 and 4 (133)

Vaccination and Clinical Outcomes - Key Question 4

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
1 cirrhosis.mp. or Fibrosis/
2 morbidity.mp. or Morbidity/
3 Carcinoma, Hepatocellular/
4 Liver Cirrhosis/
5 "Quality of Life"/
6 mo.mp. or tm.fs.
7 or/1-6
8 hepatitis b vaccine.mp. or exp Hepatitis B Vaccines/
9 7 and 8
10 limit 9 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
11 Pregnancy/
12 10 not 11
13 limit 12 to english language
14 limit 12 to abstracts
15 13 or 14

EBM Reviews - Cochrane Central Register of Controlled Trials
1 cirrhosis.mp. or Fibrosis/
2 morbidity.mp. or Morbidity/
3 Carcinoma, Hepatocellular/
4 Liver Cirrhosis/
5 "Quality of Life"/
6 mo.mp. or tm.fs.
7 or/1-6
8 hepatitis b vaccine.mp. or exp Hepatitis B Vaccines/
9 7 and 8
10 Pregnancy/
11 9 not 10

Treatment – Key Questions 5, 6, 7

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
1 Hepatitis B/dt, th or Hepatitis B, Chronic/dt, th
2 Hepatitis B virus/de
3 (hepatitis b or hbv).mp.
4 th.fs.

5 3 and 4
6 1 or 2
7 5 or 6
8 Pregnancy/
9 7 not 8
10 limit 9 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
11 randomized controlled trial.mp. or exp Randomized Controlled Trial/
12 randomized controlled trial.pt.
13 controlled clinical trial.mp. or exp Controlled Clinical Trial/
14 controlled clinical trial.pt.
15 clinical trial.mp. or exp Clinical Trial/
16 clinical trial.pt.
17 Comparative Study/
18 or/11-17
19 limit 18 to humans
20 10 and 19

EBM Reviews - Cochrane Central Register of Controlled Trials
1. Hepatitis B/dt, th or Hepatitis B, Chronic/dt, th
2. Hepatitis B virus/de
3. (hepatitis b or hbv).mp.
4. th.fs.
5. 3 and 4
6. 1 or 2
7. 5 or 6
8. Pregnancy/
9. 7 not 8
10. limit 9 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")

Education or Counseling Supplemental Search – Key Question 7

PsycINFO
1 ("hepatitis b" or "hbv").mp.
2 1 and (education or counsel$ or behavior$).mp.
3 limit 2 to all journals
4 limit 3 to (human and english language)

Harms of Treatment – Key Question 8

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
1 Hepatitis B/dt, th or Hepatitis B, Chronic/dt, th
2 Hepatitis B virus/de
3 (hepatitis b or hbv).mp.
4 th.fs.
5 3 and 4
6 1 or 2
7 5 or 6
8 Pregnancy/
9 7 not 8
10 limit 9 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
11 (ae or mo or po or to or ct).fs.
12 (adverse adj1 (effect$ or reaction$ or event$ or outcome$)).mp.
13 harm$.mp.
14 or/11-13
15 10 and 14

16 15 not (case series or case studies or editorial or comment).pt.
17 limit 16 to english language
18 limit 17 to abstracts
19 17 or 18

Improvement in Intermediate Outcome and Effect on Clinical Outcomes – Key Question 9

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)
1 Hepatitis B/ or Hepatitis B, Chronic/ or Hepatitis B virus/ or hepatitis b.mp.
2 hbv.mp.
3 1 or 2
4 Treatment Outcome/
5 3 and 4
6 limit 5 to english language
7 limit 6 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
8 Pregnancy/
9 7 not 8
10 9 not (case series or case reports or editorial or comment).pt.
11 cirrhosis.mp. or Fibrosis/
12 morbidity.mp. or Morbidity/
13 Carcinoma, Hepatocellular/
14 Liver Cirrhosis/
15 "Quality of Life"/
16 mo.mp. or tm.fs.
17 or/11-16
18 10 and 17

Systematic Reviews – All Key Questions

EBM Reviews - Cochrane Database of Systematic Reviews
1 (hepatitis b or hbv).ti.
2 limit 1 to full systematic reviews
3 limit 1 to recently updated reviews
4 limit 1 to new reviews
5 or/2-4

Ovid MEDLINE(R) without Revisions
1 Hepatitis B virus/ or Hepatitis B/ or Hepatitis B, Chronic/ or hepatitis b.mp.
2 limit 1 to yr="2008 -Current"
3 limit 2 to evidence based medicine reviews
4 meta-analysis.mp. or exp Meta-Analysis/
5 (cochrane or medline).tw.
6 search$.tw.
7 4 or 5 or 6
8 "Review Literature as Topic"/ or systematic review.mp.
9 7 or 8
10 2 and 9
11 3 or 10
12 limit 11 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
13 limit 12 to english language

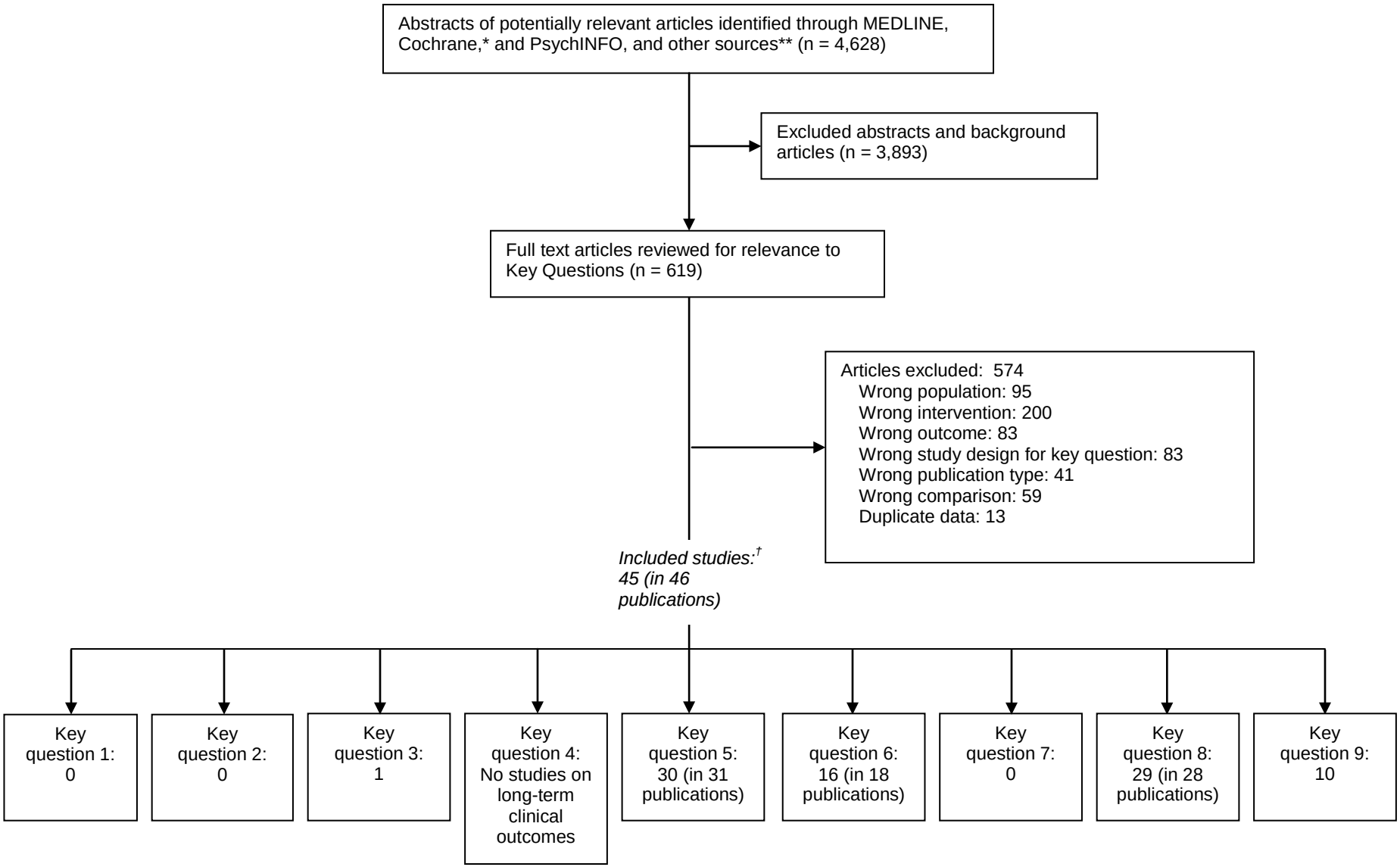
Appendix A2. Inclusion and Exclusion Criteria per Key Question

	Include	Exclude
Definition of Disease	Chronic HBV infection: detectable HBsAg in serum for >6 months	Acute HBV infection
Populations		
KQs 1-3	Nonpregnant adults (≥18 years of age) and adolescents (13 to <18 years of age) asymptomatic for HBV infection	Symptomatic patients, children and pregnant women, HIV(+) or HCV(+) persons or persons or other special populations, such as hemodialysis, transplant, and treatment failure populations
KQ 4	Persons without evidence of HBV immunity or disease on screening	
KQs 5-9	Nonpregnant adults and adolescents with chronic HBV infection	
Interventions		
KQs 1, 2	Screening	
KQ 3	Screening strategies	Lab test results
KQ 4	Vaccination	
KQs 5-9	Antiviral treatments for treatment naïve patients (Note: FDA-approved treatments include: Interferon alpha 2b, Pegylated interferon alpha 2a, Lamivudine, Adefovir, Entecavir, Telbivudine, Tenofovir) Education or behavior change counseling	Non-FDA approved antiviral treatments, combination therapy
Comparators		
KQs 1, 2	No screening	
KQ 4	No vaccination	
KQs 5-7	No treatment. Also, for currently recommended first-line antiviral therapies, the comparator was older antiviral therapies.	
KQ 3	Other screening strategies	
KQ 8	No treatment. Also, for currently recommended first-line antiviral therapies, the comparator was older antiviral therapies.	
Outcomes		
KQ 2	Labeling, anxiety, stigma Harms from liver biopsy Side effects	
KQ 3	Measures of predictive validity	
KQ 4	Disease prevention	
KQ 5	*Intermediate outcomes:* Virologic improvement Histologic improvement HBeAg clearance	Drug resistance Development of mutations or antibodies to drugs
KQs 1, 6, 7, 9	*Final outcomes:* Mortality Cirrhosis Hepatocellular cancer Quality of life Disease transmission	
KQ 8	Harms from antiviral medications Withdrawals due to adverse events	
Setting	Primary care and primary care referable settings, e.g., correctional settings and community care settings serving injection drug users/men who have sex with men/sexually transmitted disease populations United States and countries with similar HBV prevalence, except for antiviral therapies (all countries)	
Study Designs		
KQ 1	Randomized controlled trials and controlled observational studies	Uncontrolled studies
KQs 2, 8	Randomized controlled trials and controlled observational studies; or large, uncontrolled observational studies with long-term followup. Also for KQ 8, head-to-head trials for currently recommended first-line antiviral therapies.	Very small uncontrolled studies; case studies
KQ 3	Studies assessing predictive validity of screening strategies	
KQs 4-7	Randomized, placebo-controlled trials. Also, head-to-head trials for currently recommended first-line antiviral therapies.	
KQ 9	Cohort studies examining the association between intermediate and clinical outcomes after antiviral treatment	

Appendix A2. Inclusion and Exclusion Criteria per Key Question

Abbreviations: HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; FDA = U.S. Food and Drug Administration; HIV = human immunodeficiency virus; KQ = key question.

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
**Other sources include reference lists of relevant articles.
†Some studies are included for more than one key question.

Wrong Population

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Appendix A4. Excluded Studies

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Randomized, Controlled Trials 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 follow-up or overall high loss to follow-up.
- 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 (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be 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 follow-up; 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 done for RCTs.
Poor: Studies will be 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 at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Case-Control Studies

Criteria:

- Accurate ascertainment of cases.
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both.
- Response rate.
- Diagnostic testing procedures applied equally to each group.
- Measurement of exposure accurate and applied equally to each group.
- Appropriate attention to potential confounding variables.

Definition of ratings based on criteria above:
Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.
Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.
Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Source: *U.S. Preventive Services Task Force Procedure Manual.* AHRQ Publication No. 08-05118-EF, July 2008. Available at: http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm.

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Appendix B1. Screening Strategies Evidence Table

Author, Year Country	Eligibility	N	Baseline Characteristics	Screening Strategy	HBsAg Positive	Results	Funding Source	Quality	Comments
Spenatto 2013[35] France	STD clinic attendees in France	6,194	Age 20-29 years: 62% Female: 56% Self-reported injection drug use: 0.7% High endemic area (prevalence ≥8%) country of birth: 7.2%	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% (49/6194)	**A vs. B vs. C vs. D vs. E** Proportion screened: 100% (6194/6194) vs. 12% (761/6011) vs. 64% (3949/6194) vs. 73% (4504/6194) vs. 84% (5205/6194) Sensitivity: 100% (49/49) vs. 31% (15/48) vs. 98% (48/49) vs. 84% (41/49) vs. 94% (46/49) Specificity: 0% (0/6145) vs. 87% (5217/5963) vs. 37% (2244/6145) vs. 27% (1682/6145) vs. 16% (986/6145) Number needed to screen to identify one case of HBV infection: 126 vs. 16 vs. 82 vs. 110 vs. 113	Not stated	Fair	Proportion screened, and number needed to screen calculated from prevalence and sensitivity/specificity provided in the article. 183 patients did not have information on birth country (1 HBV case). No cases in patients with history of injection drug use. Prevalence in country of origin (adjusted OR 15.8 for medium prevalence, OR 44 for high prevalence), male sex (adjusted OR 2.4), unemployed (adjusted OR 3.2), and not vaccinated (adjusted OR 2.9) independent predictors. Blood transfusion, tattoos, body piercing, number of sex partners, men having sex with men, intranasal drug use not predictive. AUROC 0.92 for strategy C.

Abbreviations: AUROC = area under the receiver operating curve; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; N = number; OR = odds ratio; STD = sexually transmitted disease.

Appendix B2. Screening Strategies Quality Assessment

Study, Year	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
Spenatto 2013[35]	Yes	Yes	Yes	No (19%)	Yes	No	Fair

Appendix B3a. Vaccination Studies Evidence Table, Randomized, Controlled Trials

Author, Year	Study Design	Number of Centers, Country	Prevalence of Hepatitis B, if Reported	Study Duration, Mean Followup	Baseline Demographics	Eligibility Criteria
Coutinho 1983[38]	RCT	Netherlands Centers NR	Low prevalence country; among 2946 male homosexuals, 60% had evidence of past or present infection; among 316 at-risk men, annual attack rate of 28%	21.5 months	Vaccine vs. placebo Age, mean: 31 vs. 30 years 100% male ALT: see eligibility	Male homosexuals between 16 and 50 years of age, negative for HBsAg, anti-HBsAg, and anti-HBc, with ALT <50 IU/I, no serious illness, and >2 different male sexual partners in the preceding 6 months
Szmuness 1980[37]	RCT	United States Centers NR	In over 10,000 homosexual men tested, 68% had evidence of past or present infection	24 months	Vaccine vs. placebo Age, mean: 29 vs. 29 years 100% male 86% vs. 88% white ALT: see eligibility	HBV-negative persons who were exclusively or predominantly homosexual, with no recent symptoms of hepatitis, negative for HBsAg, anti-HBs, and anti-HBc, and with ALT<50 IU in a blood specimen from preceding 2 weeks
Francis 1982[39]	RCT	United States 5 centers	Not reported	18 months	Vaccine vs. placebo Age, mean: 30 vs. 29 years 100% male 88% vs. 91% white ALT: see eligibility	Men aged ≥18 years with homosexual preference who were negative for HBV serological markers (negative HBsAg, anti-HBc, anti-HBs) and had normal ALT (<53 IU)

Appendix B3a. Vaccination Studies Evidence Table, Randomized, Controlled Trials, *continued*

Author, Year	Exclusion Criteria	Number Screened, Number Eligible, Number Enrolled, Number Analyzed	Withdrawals, Loss to Followup	Adjusted Variables for Statistical Analysis (for Observational Studies)	Interventions	Results	Funding Source
Coutinho 1983[38]	See eligibility criteria	Number screened: NR Number eligible: 835 Number enrolled: 800 Number analyzed: 800	Withdrawals: NR Loss to followup: 4.4% (35/800)	NA (RCT)	A. HBV vaccine, 3 micrograms: 3 intramuscular injections at monthly intervals B. Placebo: as per vaccine	Vaccine (n=397) vs. placebo (n=403) Infection at 21.5 months Hepatitis B (ALT ≥50 IU/l): 5 vs. 23 All HBsAg-positive infections: 9 vs. 31 Anti-HBc-positive infections: 6 vs. 23 All definite infections: 15 vs. 54	Netherlands Foundation for Preventive Medicine
Szmuness 1980[37]	See eligibility criteria	Number screened: NR Number eligible: 2995 Number enrolled: 1083 Number analyzed: 1083	Withdrawals: 14% (78/549) vs. 17% (89/534) Loss to followup: 15% (167/1083)	NA (RCT)	A: HBV vaccine, 40 micrograms: 3 intramuscular injections at time 0, 1 month, and 6 months after first injection B: Placebo: as per vaccine	Vaccine (n=549) vs. placebo (n=534) Infection at 18 months Hepatitis B (ALT≥90 IU only): 7 vs. 45 HBV events with ALT≥45 IU: 13 vs. 56 All HBsAg-positive events: 11 vs. 70 All HBV events, excluding conversion to anti-HBc alone: 14 vs. 73 All HBV events, including anti-HBc conversion: 29 vs. 93 Anti-HBc: 15 vs 20	Department of Virus and Cell Biology of Merck Sharp and Dohme Research Laboratories; National Heart, Lung, Blood Institute, National Institutes of Health;
Francis 1982[39]	See eligibility criteria	Number screened: NR Number eligible: NR Number enrolled: 1402 Number analyzed: 1402	Withdrawals: NR Loss to followup: 16% (224/1402)	NA (RCT)	A: HBV vaccine, 20 micrograms: 3 intramuscular injections at time 0, 1 month, and 6 months after first injection	Vaccine (n=714) vs. placebo (n=688) Infection at 18 months HBsAg positive or anti-HBc positive with enzyme elevation: 23 vs. 72	None reported

					B: Placebo: as per vaccine	HBsAg positive without enzyme elevation: 5 vs. 12 Anti-HBc positive without enzyme elevation: 30 vs. 26 All groups: 58 vs. 110	

Abbreviations: ALT = alanine aminotransferase; Anti-HBc = hepatitis B core antigen antibody; Anti-HBs = hepatitis B surface antigen antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NR = not reported; RCT = randomized, controlled trial.

Appendix B3b. Vaccination Studies Evidence Table, Systematic Reviews

Author, Year	Purpose of Study	Databases Searched, Date of Last Search	Number of Studies	Types of Studies Included/ Limitations of Primary Studies	Methods for Rating Methodological Quality of Primary Studies	Methods for Synthesizing Results of Primary Studies	Number of Patients	Interventions	Results
Chen 2009[36]	Assess the harms/ benefits of HBV vaccine in health-care workers	Cochrane Hepato - Biliary Group Controlled Trials Registry, Cochrane Library, MEDLINE, EMBASE through February 2003	21 total; 4 placebo-controlled	4 PCTs; all included studies conducted in high-risk population and were rated low quality	Assessment of method of allocation and concealment, blinding and attrition	Random and fixed effects models applied	HBV vaccine: 1365 Placebo: 1332	A. Active HBV vaccine B. Placebo vaccine	A vs B HBV acquisition: 38/1365 (3%) vs 71/1332 (5%); RR 0.5, 95% CI 0.4 to 0.7, I^2=18%

Abbreviations: ALT = alanine aminotransferase; Anti-HBc = hepatitis B core antigen antibody; Anti-HBs = hepatitis B surface antigen antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NR = not reported; RCT = randomized, controlled trial; RR = relative risk.

Appendix B4a. Vaccination Studies Quality Assessment, Randomized, Controlled Trials

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup: Differential/ High?	Analyze People in the Groups in Which They Were Randomized?	Quality
Coutinho 1983[38]	Unclear; method not described	Unclear	Yes; only significant difference on history of jaundice	Yes	Yes	Unclear; described as double-blind	Unclear; described as double-blind	Unclear	No/No	Yes	Fair
Szmuness 1980[37]	Unclear; method not described	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Good
Francis 1982[39]	Unclear; method not described	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	No/No	Yes	Fair

Appendix B4b. Vaccination Studies Quality Assessment, Systematic Reviews

Author, Year	Study Design Pre-Determined	Dual Review Studies/ Data Abstraction	Comprehensive Search	Publication Status Used as Inclusion Criteria	List of Included and Excluded Studies Provided	Included Studies Described	Included Studies Quality Assessed	Quality of Studies Used in Formulating Conclusions	Appropriate Methods Used to Combine Studies?	Publication Bias Assessed?	Conflict of Interest Reported	Quality
Chen 2009[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Treatment Vs. Placebo or No Treatment							
Ali 2003[52]	RCT	1 site Iraq	24 months duration; 6-12 months of treatment and followup (variable based on efficacy measures) Mean followup: NR	A. Lamivudine 100 mg daily (n=32) B. Placebo (n=30)	Age range: 25-45 years Male: NR Race: NR Baseline liver function: NR HBV markers: see eligibility Prior HBV treatment: NR	HBsAg/anti-HBe positive with persistent anti-HBc IgM; asymptomatic	NR
Bayraktar 1993[44]	Controlled trial	Unclear (likely single site) Turkey	Study duration: 6 months Mean duration of followup: NR	A. Interferon alfa-2b 5 MU IM 3x/week (n=25) B. No treatment (n=10)	A vs. B Mean age 35 vs 36 years 72% vs 70% male Race NR 20% vs 30% cirrhosis	Serum transaminase elevation >2x ULN for >6 months; HCV, HIV negative; HBsAg and HBeAg positive; chronic active hepatitis (per liver histology)	Decompensated cirrhosis
Bozkaya 2005[53]	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 ALT, median (range): 64 (38-186) vs. 48 (35-168) vs. 17 (11-30) IU/l HBV-DNA, median (range): 1.2×10^3 (1×10^2 - 9.7×10^4) vs. 4.2×10^3 (1×10^2- 3.6×10^5) vs. 2.5×10^3 (1×10^2 - 5.2×10^5) copies/ml HAI, median (range): 4.5 (1.0-16.0) vs. 4.0 (1.0-8.0) vs. 2.0 (1.0-4.0) Presence of fibrosis: 33% vs. 24% vs. 0 Prior HBV treatment: No patients	ALT >1 x ULN; 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; BMI <30 kg/m^2	Presence of non-alcoholic steatohepatitis and significant liver steatosis; high BMI; high alcohol intake; drug-related toxicity

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Chan 2007[54]	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 Cirrhosis: 31% vs. 21% ALT, mean: 2.1 vs. 2.6 x ULN Necroinflammatory score, median: 5 vs. 5 Fibrosis score, median: 2 vs. 2 HBV DNA, mean: 5.7 vs. 5.6 log copies/ml HBeAg positive: 6% vs. 6% 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 to10 times ULN on >2 occasions in the previous 6 months or ALT above ULN with >1 flareup 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 titre >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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Dienstag 1999[55]	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 Median age: 40 vs. 38 years Sex: 86% vs. 80% male Race: 59% vs. 56% white, 24% vs. 17% Asian, 15% vs. 18% black Cirrhosis: 6% vs. 14% Median HAI score: 10 vs. 11 Median serum HBV DNA: 102.2 vs. 56.5 pg/ml Median serum ALT: 125 vs. 135 IU/l Median serum bilirubin: 0.7 vs. 07 mg/dl Median serum albumin: 3.9 vs. 3.8 g/dl	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 the upper limit of normal for at least 3 months; evidence of chronic hepatitis on liver biopsy; and detectable levels of HBV DNA	Previous antiviral therapy for hepatitis B; 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 3000 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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Hadziyannis 1990[45]	RCT	Unclear (likely single site) Greece	Study duration: 1 year (2 year followup for some patients) Mean duration of followup: NR	A. Interferon alfa-2b 3 MU 3x/week for 14-16 weeks (n=25) B. No treatment (n=25)	A vs. B Mean age 49 vs 48 years 92% vs 96% male Race NR 40% vs 48% cirrhosis 96% vs 100% anti-HBe positive Mean serum HBV DNA 26 vs 24 pg/mL Mean serum ALT 1203 vs 175 IU/L	Chronic, active hepatitis; HBsAg positive; HBeAg negative/serum HBV DNA positive for >1 year	Decompensated cirrhosis; use of corticosteroids, immunosuppressive drugs or antivirals with 6 months
Hadziyannis 2003[40]	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 ALT x ULN, mean: 3.5 vs. 3.6 HBV DNA, mean: 6.9 vs. 6.9 log copies/ml Knodell necroinflammatory activity score, mean: 7.7 vs 7.1 Knodell fibrosis score, mean: 1.9 vs 1.8 Cirrhosis: 11% vs. 10% 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 16-65 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 15 xULN. 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 alpha-fetoprotein 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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Jonas 2008[41]	RCT	12 sites in United States; 14 sites in Europe	48 weeks duration and followup	A. Adefovir 10mg daily (n=56) B. Placebo (n=27)	A vs. B Age group 12-17 years Age, mean: 14.5 vs. 14.1 Male: 75% vs. 74% Race: 73% vs. 78% white (includes Hispanics, Latinos), 23% vs. 19% Asian, 2% vs. 4% black, 2% vs. 0% American Indian or Alaska Native HBV DNA, mean: 8.60 vs. 8.63 log10 copies ALT (xULN), mean: 3.0 vs. 2.7 HBeAg positive: 96% vs. 100% Anti-HBeAg positive: 4% vs. 0% Prior treatment: 68% vs. 67%	HBsAg present for at least 6 months prior to randomization, positive HBeAg at screening, HBV DNA >1 x 10^5 copies/mL by PCR, ALT >1.5 xULN, compensated liver disease, adequate renal function, adequate hematologic function, negative serologic tests for HIV, HDV, HCV, and alpha-fetoprotein <50 ng/mL	Treatment for chronic HBV in previous 6 months, evidence of other liver diseases, received bone marrow transplant or organ transplants, received immunosuppressive, nephrotoxic, or hepatotoxic medications within 2 months of enrollment
Lai 1997[56]	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 Mean age: 33 vs. 33 vs. 34 vs. 26 years Male: 58% vs. 58% vs. 75% vs. 67% Mean HBV DNA: 91.3 vs. 94.5 vs. 103.0 vs. 67.1 pg/mL HBeAg positive: 100% vs. 100% vs. 100% vs. 100%	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 the upper limit of normal 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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Lai 1998[57]	RCT	Multiple sites (number NR) Hong Kong, Taiwan, Singapore	Study duration: 52 weeks Median followup: 365 days, range 2-409 days	A. Lamivudine 25 mg daily (n=142) B. Lamivudine 100 mg daily (n=143) C. Placebo (n=73)	A vs. B vs. C Median age: 33 vs. 31 vs. 29 years Male: 73% vs. 74% vs. 72% Race: 100% Asian Median serum HBV DNA: 70.7 vs. 74.2 vs. 99.4 pg/mL (A vs. C, p=0.04, B vs. C, p=0.08) HBeAg positive: 100% vs. 100% vs. 99% HBsAg positive: 100% vs. 100% vs. 100% Median ALT: 1.4 vs. 1.5 vs. 1.5 times upper limit of normal 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 upper limit of normal 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
Lampertico 1997[46]	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 IM 3x/week (n=21) B. No treatment (n=21)	A vs. B Mean age 44 vs 47 years 80% vs 90% male Race NR 19% vs 14% cirrhosis 67% vs 67% HBV DNA positive Mean ALT 140 vs 173 U/l Median Histology Activity Index 10 vs 10	Age 18-65 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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Liaw 2004[76]	RCT	41 sites Australia, China, Malaysia, New Zealand, the Philippines, Singapore, Taiwan, Thailand	Maximum 5 years (blinded phase terminated by data safety and monitoring board at second interim analysis because results showed efficacy) Treatment duration, median (range): 32.4 (0 -42) months Mean followup: NR	A. Lamivudine 100 mg daily (n=436) B. Placebo (n=215)	A vs. B Age, median: 43 vs. 44 years Male: 85% vs. 85% Race: Asian 98% vs. 98% Child-Pugh score 5: 78% vs. 73% 6: 17% vs. 19%; >7: 5% vs. 8% Ishak fibrosis score 4: 40% vs. 35% 5: 29% vs. 26% 6: 31% vs. 39% HBV DNA, median (range): 11.7 (<0.7-109,800) vs. 21.5 (<0.7-4234) mEq/ml HBV DNA >0.7 mEq/ml: 79% vs. 81% HBeAg positive: 58% vs. 58% ALT, median (range): 70 (14-959) vs. 68 (7-821) U/L ALT >1 x ULN: 78% vs. 80% Prior HBV treatment: NR, but allowed (see eligibility criteria)	Patients >16 years of age who were positive for HBsAg for at least 6 months, positive for HBeAg or negative for HBeAg with detectable HBV DNA at screening, and had liver biopsy showing Ishak fibrosis score at least 4 at screening or in previous 2 years	Evidence of hepatocellular carcinoma, serum ALT > 10 times ULM, hepatic decompensation, autoimmune hepatitis, coinfection with HCV, HDV, or HIV, serious concurrent illness, amylase or lipase >2 times ULN, elevated creatinine level, hemoglobin < 8 g per cubic deciliter, white cell count <15000 per cubic millimeter, platelet count <50,000 per cubic mm, treatment with immunomodulatory or chronic antiviral therapy within 6 months of screening, treatment with any investigational drug within 30 days of study start, or any previous treatment with lamivudine. Pregnant women excluded.
Lin 1999[73] *Additional publication: Liaw 1994*[74]	RCT	Single site China	18 weeks treatment + mean 7 years followup (range 1 to 11 years)	A. Interferon alfa-2a 4-5 MU/m^2 (n=67) B. Placebo (n=34)	A vs. B Mean age 32 vs 32 years 100% male (both groups) 100% Chinese (both groups) 10% vs 15% cirrhosis Mean ALT 227 vs 256 U/L Mean AFP 9 vs 11 mg/ml	Age 16-65 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; IV drug abuse; decompensated liver disease; other serious medical illness; AFP >100 ng/ml

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Marcellin 2003[42]	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. Adefovir 30 mg daily (n=173) C. Placebo (n=170)	A vs. B vs. C Age, mean: 34 vs. 34 vs. 37 years Male: 76% vs. 75% vs. 71% Race: 35% vs. 37% vs. 36% white, 5% vs. 3% vs. 2% black, 60% vs. 58 vs. 60% Asian, 1% vs. 2% vs. 2% other ALT (xULN), mean: 3.4 vs 3.0 vs. 3.4 HBV DNA, mean: 8.25 vs. 8.22 vs. 8.12 log copies/mL Total Knodell score, mean: 9.01 vs. 9.55 vs. 9.65 Knodell necroinflammatory score, mean: 7.37 vs. 7.84 vs. 7.83 Knodell fibrosis score, mean: 1.64 vs. 1.71 vs. 1.83 HBeAg positive: 100% Prior interferon alfa treatment: 24.9% (123/494)	Age 16-65 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 1.2-10 xULN. 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 alpha-fetoprotein level of at least 50ng/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.
Mazzella 1999[75]	RCT	Single site Italy	6 months treatment + 7 years followup	A. Interferon alfa-2a, mean dose 648 MU (n=33) B. No treatment (n=31)	A vs B Mean age 36 vs 41 years 76% vs 81% male Race NR 0% cirrhosis (both groups) Mean ALT 106 vs 144 U/L	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
Muller 1990[47]	RCT	Unclear (likely single site) Germany	Study duration: 4 months Mean duration of followup: NR	A. Interferon alfa-2b 3 MU SC 3x/week (n=30) B. No treatment (n=28)	A vs. B Mean age NR; range 18-65 years 79% male Race NR 5% cirrhosis 96% vs 96% HBeAg positive	Age 18-65 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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Murray 2012[61]	RCT	21 sites United States, Bulgaria, France, Poland, Romania, Spain, Turkey	72 weeks	A. Tenofovir 300 mg qd B. placebo	A vs. B Mean age 15 years both groups (SD 1; range 12-17 years) 73% vs 65% male 94% vs 91% white 1% vs 0% black 1% vs 1% Asian 1% vs 4% other 92% vs 89% HBeAg positive 83% vs 87% prior HBV treatment Mean HBV DNA 8.01 vs 8.24 $\log_{10}$ copies/mL Normal ALT 33% vs 22% Mean ALT 101 U/L	Age 12 to <18 years; chronic HBV defined as documented positive serum HBsAg for at least 6 months; positive or negative for HBeAg; HBV DNA ≥10^5 copies/mL and either ALT ≥2x upper limit of normal or any history of ALT≥2x the ULN within the past 24 months; weight at least 35 kg; able to swallow oral tablets; discontinuation of oral anti-HBV nucleoside/nucleotide therapy ≥16 weeks prior to screening and any interferon therapy ≥6 months prior to screening. Poland sites only required patients to have had a history of treatment for HBV or a contraindication for treatment with existing drugs	Previous tenofovir use; HCV, HDV or HIV coinfection; history of significant bone disease, decompensated liver disease, or renal disease; evidence of hepatocellular carcinoma
Perez 1990[48]	RCT	Unclear (likely single site) Argentina	Study duration: 24 weeks (control phase) Mean duration of followup: NR	A. Prednisone run-in + interferon alfa-2b 10 MU SC 3x/week (n=17) B. No treatment (n=18)	A vs. B Mean age 39 years 71% vs 83% male Race NR Mean HBV DNA 570 vs 480 U/L Mean ALT 160 vs 109 pg/mL	Age ≥18 years; HBsAg, HBeAg and HBV DNA for at least 6 months; ALT >1.3 ULN; compensated liver disease with prolonged prothrombin <3 seconds; normal serum albumin and bilirubin; no history of hepatic encephalopathy, bleeding esophageal varices or ascites	HDV or HIV positive; low hematocrit (<30%), platelets (<100,000/mm^3), white blood cells (<4,000/mm^3), granulocytes (<1,500/mm^3)

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Perrillo 1990[49]	RCT	Multicenter (number of sites NR) United States	Study duration: 16 weeks (+ 6 months post-treatment observation) Mean duration of followup: NR	A. Prednisone run-in + interferon alfa-2b 5 MU qd (n=44) B. Placebo run-in + interferon alfa-2b, 1 MU qd (n=41) C. Placebo run-in + interferon alfa-2b 5 MU qd (n=41) D. No treatment (n=43)	A vs. B vs. C vs. D Mean age 40 vs 41 vs 41 vs 43 years 86% vs 80% vs 88% vs 84% male Race NR Mean HBV DNA 117 vs 127 vs 176 vs 146 pg/mL Mean serum ALT 152 vs 183 vs 182 vs 168 U/L	Age ≥18 years; HBsAg positive for at least 6 months; HBeAg and HBV DNA positive in 6 months prior to study entry; serum ALT ≥1.3 ULN; compensated liver disease; chronic hepatitis B (per liver biopsy)	Corticosteroid or antiviral therapy during previous 12 months; pregnancy; serious medical illness; low hematocrit (<30%), platelet (<70x10^9), white-cell (<3x10^9) and granulocyte (<1.5x10^9) counts; elevated serum creatinine; alcoholism; drug abuse; other potential causes of liver disease; HDV or HIV positive
Sarin 1996[50]	RCT	Unclear (likely single site) India	Study duration: 4 months + 12 months post-treatment followup Mean duration of followup: NR	A. Interferon alfa 2b 3 MU SC 3x/week (n=20) B. No treatment (n=21)	A vs. B Mean age 32 vs 37 years 80% vs 81% male Race NR 45% vs 43% cirrhosis	Age <70 years; HBsAg positive for at least 6 months; HBeAg and HBV DNA positive on at least 2 occasions 1 month apart; compensated liver disease; chronic hepatitis with or without cirrhosis	Antiviral therapy within 12 months; pregnancy; platelet count <70,000/cmm; white cell count <3,000/cmm; elevated serum creatinine

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Tassopoulos 1999[58]	RCT	1 site Greece	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 (55-425) vs.189 (11-257) 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% vs. 77% Race: NR Cirrhosis: 14% vs. 16% (table 1 states 18% (10/64) of persons in placebo group had cirrhosis) Knodell score, median (range): 5 (1-9) vs. 7 (2-10) Abnormal ALT: 97% vs. 95% ALT x ULN, median (range): 3.2 (0.6-16.4) vs. 3.3 (0.7-12.5) HBV DNA positive: 92% vs. 86% HBV DNA, median (range): 255.0 (1.3-18,000) vs. 95.5 (1.3-3900) pg/mL HBeAg negative: 98% vs. 98% Anti-HBeAg positive: 98% vs. 100% HBsAg positive: 100% vs. 100% Prior HBV treatment: NR, but allowed (see eligibility criteria)	Men and women 16 to 70 years of age with detectable HBsAg, detectable HBeAg antibody, 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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Waked 1990[51]	RCT	Unclear (likely single site) Egypt	Study duration: 16 weeks (+ 12 months post-treatment observation) Mean duration of followup: NR	A. Interferon alfa-2b 5 MU SC 2x/week (n=12) or daily (n=8) B. No treatment (n=20)	Mean age 36 years 78% male Race NR 40% cirrhosis	HBsAg positive for >6 months; elevated aminotransferase; histologically active liver disease; normal blood count; normal renal function; compensated liver disease	Normal aminotransferase; chronic persistent hepatitis; inactive cirrhosis or normal histology; serum albumin <3 gm/dL; serum bilirubin >4 mg/dL; serum creatinine >1/5 mg/dL; history of encephalopathy, ascites or bleeding esophageal varices; HDV infection; male homosexuality; pregnancy; corticosteroid or antiviral therapy within preceding 12 months; inadequate blood counts; asymptomatic heart disease or ECG evidence of ischemic heart disease
Yalcin 2004[59]	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 vs. 25 years Male: 54% vs. 56% Race: NR HBV DNA, median: 4116 vs. 4094 pg/ml ALT, median: 27 vs. 30 IU/L HBeAg positive: 100% in both groups Inflammation score, median: 1 vs. 2 Fibrosis score, median: 0 in both groups	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	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 one year of study entry

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
						completion	
Yao 1999[60] *Additional publications: Yao 2000[78] and Yao 2009[79]*	RCT	Multiple sites (number NR) China	Blinded treatment duration: 12 weeks Open-label treatment: 9 months	A. Lamivudine 100 mg daily (n=322) B. Placebo (n=107)	A vs. B Age: 32 vs. 31 years (unclear if this is mean or median) Male: 74% vs. 69% Race: NR, conducted in China HBV DNA: 96.9 vs. 91.9 pg/mL (unclear if this is mean or median) ALT: 1.7 vs. 1.5 times upper limit of normal (unclear if this is mean or median)	Aged 16 to 65 years; HBeAg and HBsAg positive in the 6 months prior to screening; detectable HBV DNA at screening; ALT levels <10 times the upper limit of normal 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 times the upper limit of normal; 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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Zeng, 2006[43]	RCT	Seven cities China	52 weeks; only first 12 weeks met inclusion criteria	A. Adefovir 10 mg daily for first 12 weeks, open label adefovir 10 mg daily for next 28 weeks, adefovir 10 mg daily for remaining 12 weeks (n=240) B. Adefovir 10 mg daily for first 12 weeks, open label adefovir 10 mg daily for next 28 weeks, placebo for remaining 12 weeks (n=120) C. Placebo for first 12 weeks, open label adefovir 10 mg daily for next 28 weeks, adefovir 10 mg daily for remaining 12 weeks (n=120) Note: only data from first 12 weeks included; during this time, there were two treatment groups adefovir (A+B above) vs. placebo (C above)	A vs. B vs. C Age, mean: 31 vs. 32 vs. 32 years Male: 84% vs. 82% vs. 82% Race: 100% Chinese Cirrhosis: None ALT (xULN), mean: 3.9 vs. 3.3 vs. 3.8 HBV DNA, mean: 8.6 vs. 8.5 vs. 8.6 log10copies/mL HBeAg positive: 99% vs. 96% vs. 99% Prior lamivudine treatment: 35% vs. 32% vs. 27%	At least 18 years old with detectable HBsAg for previous 6 months, detectable HBeAg, HBV DNA $>10^6$ copies/mL, ALT level more than 1 xULN, and ALT more than 2 xULN sometime in previous 6 months	Evidence of hepatocellular carcinoma, clinical signs of liver decompensation, creatinine greater than 1.5 mg/dL, ALT more than 10 xULN, seropositivity for HCV or HDV or HIV; lamivudine therapy in previous 3 months, ADV therapy or other anti-HBV therapy in previous 6 months Note: systemic antiviral therapy, immunomodulators, immunosuppressive therapies, Chinese traditional medicines, or agents known to lower ALT not permitted during study

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Head-to-Head							
Chang 2006;[64] Gish 2007;[65] Chang 2009[66]	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 qd B. Lamivudine 100 mg qd	A vs B n=354 vs 355 Mean age 35 vs 35 years 77% vs 74% male 58% vs 57% Asian 40% vs 40% white 2% vs 2% black <1% vs 1% other 98% vs 99% HBeAg positive 2% vs 2% cirrhosis	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 1.3-10x 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 >100mg/ml, history of ascites requiring diuretics or paracentesis, previous entecavir treatment
Lai 2002[68]	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 qd B. Lamivudine 100 mg qd *Dose ranging study; results for 0.01 and 0.1 mg not abstracted*	A vs B n=46 vs 41 Mean age 31 vs 29 years 65% vs 85% male 50% vs 56% Asian/Pacific Islander 35% vs 39% white 15% vs 5% other 78% vs 80% HBeAg positive	Age ≥16 years, HBsAg positive, HBeAg positive or HBeAg negative and anti-HBeAg 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
Lai 2006[67]	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 follow-up 56 weeks	A. Entecavir 0.5 mg qd B. Lamivudine 100 mg qd	n=638 Mean age 44 years 76% male 58% white 39% Asian 2% black <1% other 1% HBeAg positive 2% cirrhosis	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 1.3-10x 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 >100ng/ml, history of ascites requiring diuretics or paracentesis, previous entecavir treatment

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Lau 2005[70]	RCT	67 centers 16 countries in Asia, Australasia, Europe, North America, South America	72 weeks (48 weeks treatment + 24 weeks follow-up)	A. Pegylated interferon alfa-2a 180 µg per week + placebo B. Lamivudine (100 mg)	n=543 (excluding 271 patients randomized to peg interferon + lamivudine combination therapy) Mean age 32 years 79% male 86% Asian 10% white 2% other 1% black 100% HBeAg positive 18% bridging fibrosis or cirrhosis	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
Marcellin 2004[71]	RCT	54 centers 13 countries, primarily Asia and Europe	72 weeks (48 weeks treatment + 24 weeks follow-up)	A. Pegylated interferon alfa-2a 180 µg per week + placebo B. Lamivudine (100 mg)	n=358 (excluding 179 patients randomized to peg interferon + lamivudine combination therapy) Mean age 40 years 61% Asian 38% White >1% Black >1% other 100% HBeAg negative 30% bridging fibrosis or cirrhosis	Adults, HBeAg negative, anti-HBe antibody and HBsAg positive, HBV DNA >100,000 copies/mL, serum ALT >1 and <10x ULN, HBV positive confirmed by liver biopsy within previous 24 months, evidence of prominent necroinflammatory activity	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 s

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Marcellin 2008[72] Study 102 (HBeAg negative at baseline)	RCT	106 centers 15 countries in Europe, North America, Australia and New Zealand	48 weeks (time on treatment)	A. Tenofovir 300 mg qd B. Adefovir 10 mg qd	n=375 Mean age 44 years 77% male 65% white 25% Asian 3% black 7% other 0% HBeAg positive 20% cirrhosis	Age 18-69 years, compensated liver disease, Knodell necroinflammatory score ≥3 (scale 0-18, 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
Study 103 (HBeAg positive at baseline)					n=266 Mean age 34 years 69% male 52% white 36% Asian 7% black 5% other 100% HBeAg negative 20% cirrhosis	Age 18-69 years, compensated liver disease, Knodell necroinflammatory score ≥3 (scale 0-18, 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	
Ren 2007[69]	RCT	Single center (?) China	48 weeks (time on treatment)	A. Entecavir 0.5 mg qd B. Lamivudine 100 mg qd	n=42 (excluding 19 patients who previously failed lamivudine treatment and were switched to entecavir) Mean age 32 years 55% male 100% Asian (?) 100% HBeAg positive (?) Cirrhosis not reported	Age 19-68 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,	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

Appendix B5. Treatment Trials Evidence Table

Author, Year	Study Design	Number of Sites, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
						detectable HBsAg, HBV DNA positive, serum ALT 1.3-10 X ULN	adefovir

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Treatment Vs. Placebo or No Treatment								
Ali 2003[52]	Screened: NR Eligible: NR Enrolled: 74 Analyzed: 62	Withdrawals: 8.1% (6/74) Loss to followup: 8.1% (6/74)	N/A	A vs. B HBsAg seroclearance: 9.4% (3/32) vs. 3.3% (1/30); RR 2.8 (95% CI 0.3 to 25.6) Anti-HBsAg development : 9.4% (3/32) vs. 6.7% (2/30); RR 2.8 (95% CI 0.3 to 25.6) HBeAg reversion: 0 vs. 0 Note: text states that 2 patients in the placebo group experienced seroconversion, but this does not match other text and table about antibody development and HBsAg loss	NR	A vs. B Withdrawal due to adverse events 9.4% (3/32) vs. 0% (0/30) RR 6.6 (95% CI 0.4 to 122)	Poor	NR
Bayraktar 1993[44]	Screened: NR Eligible: NR Enrolled: unclear Analyzed: 35	Withdrawals: none reported Loss to followup: none reported (unclear if results for all enrolled patients reported)	N/A	A vs. B ALT normalization: 17/25 (68%) vs 0/10 (0%); RR 15 (95% CI 0.97 to 225) HBeAg loss: 15/25 (60%) vs 0/10 (0%); RR 13 (95% CI 0.86 to 200) HBsAg loss: 1/25 (4%) vs 0/10 (0%); RR 1.27 (95% CI 0.06 to 29)	NR	Interferon alfa-2b (no results presented for untreated group) Withdrawals due to adverse events 0% (0/25)	Poor	NR
Bozkaya 2005[53]	Screened: 390 Eligible: 55 Enrolled: 55 Analyzed: 55	NR	N/A	A vs. B vs. C Month 12 ALT normalization (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	Poor	NR

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Chan 2007[54]	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)	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 3.8-30.2) 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: 78% (14/18) vs. 25% (2/8); RR 3.1 (95% CI 0.9 to 10.6) Fibrosis improvement: 33% (6/18) vs. 0% (0/8); RR 6.2 (95% CI 0.4 to 97.7)	A vs. B Mortality: NR Hepatocellular cancer: 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 hepatocellular carcinoma	A vs. B Serious adverse events 15% (13/89) vs. 13% (6/47) RR 1.1 (95% CI 0.5 to 2.8)	Fair	Glaxo-SmithKline

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Dienstag 1999[55]	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)	Adjustments for odds ratios: ALT, HBV DNA, HAI score, race, age, sex, weight, and the presence of cirrhosis	A vs. B 1-year results (on treatment) Histologic improvement: 52% (34/66) vs. 23% (16/71); RR 2.29 (95% CI 1.40-3.73) ALT normalization: 41% (27/66) vs. 7% (5/68); RR 5.56 (95% CI 2.28-13.58) HBV DNA loss: 44% (28/63) vs. 16% (11/69); RR 2.79 (95% CI 1.52-5.12) HBeAg loss: 17% (11/63) vs. 6% (4/69); RR 3.01 (95% CI 1.01-8.98) 16 month results (post-treatment) HBeAg seroconversion: 17% (11/63) vs. 9% (6/69); RR 2.01 (95% CI 0.79-5.11) HBeAg loss: 29% (19/66) vs. 15% (11/71); RR 1.86 (95% CI 0.96-3.60) HBsAg loss: 2% (1/66) vs. 0% (0/71); RR 3.22 (95% CI 0.13-77.78) HBV DNA undetectable at least once during treatment: 98% (62/63) vs. 33% (23/69); RR 2.95 (95% CI 2.11-4.13) Likelihood of histologic response: OR 7.5, 95% CI 2.7-20.9 Likelihood of HBeAg seroconversion: OR 9.7, 95% CI 1.7-56.1	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)	Fair	Glaxo Wellcome; Hepatitis Research Fund of Massachusetts General Hospital; National Institutes of Health Clinical Research Center

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Hadziyannis 1990[45]	Screened: NR Eligible: NR Enrolled: 50 Analyzed: 35 (at 12 months)	Withdrawals: NR Loss to followup: unclear; results presented for 35/50 enrolled patients	N/A	A vs. B 4-month outcomes (time on treatment) Complete treatment response: 10/25 (40%) vs 0/25 (0%); RR 21 (95% CI 1.30 to 340) Partial treatment response: 7/25 (28%) vs 4/25 (16%); RR 1.75 (95% CI 0.59 to 5.24) 12-month outcomes (post-treatment) Complete treatment response: 11/25 (44%) vs 2/25 (8%); RR 5.5 (95% CI 1.36 to 22) Partial treatment response: 3/25 (12%) vs 6/25 (24%); RR 0.5 (95% CI 0.14 to 1.78)	NR	Interferon alfa-2b (no results presented for untreated group) Serious adverse events 0/25 (0%)	Poor	NR
Hadziyannis 2003[40]	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)	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 1009) ALT normalization: 72% (84/116) vs. 29% (17/59); RR 2.5 (95% CI 1.7 to 3.8)	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	Fair	Gilead Sciences

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Jonas 2008[41]	Screened: 293 Eligible: 173 Enrolled: 173 Analyzed: 170 Note: only 12-17 year old age group included, n=83	A vs. B Withdrawals: 5% (3/56) vs. 0% (0/27) Loss to followup: none	N/A	A vs. B HBV DNA <1000 copies/mL and ALT normalization: 23% (13/56) vs. 0% (0/27); RR 13 (95% CI 0.8 to 215.1) Note: p-value in text is significant for above association ALT normalization: 64% (36/56) vs. 22% (6/27); RR 2.9 (95% CI 1.4 to 6.0) Note: n values calculated from proportions provided by study, based on the number of participants at baseline in target age group	Mortality: None	A vs. B Withdrawal due to adverse event 1.7% (1/56) vs. 0% (0/27) RR 1.5 (95% CI 0.1 to 35)	Fair	Gilead Sciences
Lai 1997[56]	Screened: NR Eligible: NR Enrolled: 42 Analyzed: 42	None	N/A	A vs. B HBeAg loss: 0/36 vs 0/6	NR	A vs. B Serious adverse events 0% (0/36) vs. 0% (0/6) RR 0.2 (95% CI 0.0 to 8.8)	Fair	NR

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Lai 1998[57]	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)	N/A	A vs. B vs. C Histological improvement: 49% (70/142) vs. 56% (80/143) vs. 25% (18/73); RR of A vs. C: 2.00 (95% CI, 1.29-3.09); RR of B vs. C: 2.27 (95% CI 1.48-3.48) 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 0.89-9.69); RR of B vs. C: 3.67 (95% CI 1.14-11.83) Sustained ALT response: 65% (64/98) vs. 72% (68/95) vs. 24% (12/50); RR of A vs. C: 2.72 (95% CI 1.63-4.55); RR of B vs. C: 2.98 (95% CI 1.79-4.96) Treated vs. untreated Histological improvement: 52.6% (150/285) vs. 25% (18/73); RR 2.13 (95% CI 1.41-3.24) HBeAg seroconversion and HBV DNA undetectable: 14.2% (39/275) vs. 4% (3/70); RR 3.31 (95% CI 1.05-10.40) Sustained ALT response: 68.4% (132/193) vs. 24% (12/50); RR 2.85 (95% CI 1.72-4.71)	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)	Fair	Glaxo Wellcome Research and Development

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Lampertico 1997[46]	Screened: NR Eligible: NR Enrolled: 42 Analyzed: unclear	Withdrawals: 6/42 (14%) Loss to followup: 3/42 (7%)	N/A	A vs. B 2-year outcomes (on treatment) HBsAg loss: 0/21 vs 0/21 Loss of HBV DNA + ALT normalization: 8/21 (38%) vs 2/21 (10%); RR 4.0 (95% CI 0.96 to 17) Histology Activity Index improvement: 7/21 (33%) vs 2/21 (10%); RR 3.5 (95% CI 0.82 to 15) 3-year outcomes (post treatment) Loss of HBsAg: 2/21 (10%) vs 0/21 (0%); RR 5 (95% CI 0.25 to 98) Loss of HBV DNA + ALT normalization: 6/21 (29%) vs 0/21 (0%); RR 13 (95% CI 0.78 to 217) Loss of HBsAg and/or HBV DNA: 7/21 (33%) vs 0/21 (0%); RR 15 (95% CI 0.91 to 247)	A vs. B Hepatocellular cancer 1/21 (5%) vs 0/21 (0%); RR 3 (95% CI 0.13 to 70)	A vs. B Withdrawals due to adverse events 24% (5/21) vs 0% (0/21) RR 11 (95% 0.65 to 187)	Fair	Istituto Superiore di Sanità (Italian National Health Service)
Liaw 2004[76]	Screened: NR Eligible: NR Enrolled: 651 Analyzed: 651	Per-protocol withdrawals: 21% (135/651) Withdrawals for other reasons: 8% (52/651)	HR adjusted for country, sex, baseline alanine amino-transferase level, Child-Pugh score, and Ishak fibrosis score; CI unadjusted for interim analyses	NR	A vs. B Mortality: 2.8% (12/436) vs. 1.9% (4/215); RR 1.5 (95% CI 0.5 to 4.5); 9 died while on lamivudine (2 during blind phase: 1 death from pre-existing lymphoma, 1 death from drowning after acute myocardial infarction); 7 died during followup; 14 died after clinical end point reached	A vs. B Serious adverse event 12% (54/436) vs. 18% (38/215) RR 0.7 (95% CI 0.5 to 1.0) Any adverse event 77% (335/436) vs. 83% (178/215) RR 0.9 (95% CI 0.9 to 1.0) Note: Any adverse event refers to those that occurred in >10% of patients in a treatment group	Fair	Glaxo-SmithKline; some authors received funding by industry

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
					Mortality during double-blind phase: <1% (2/436) vs. 0 Hepatocellular carcinoma: 3.9% (17/436) vs. 7.4% (16/215); adjusted HR 0.49 (95% CI 0.25 to 0.99); excluding 5 cases diagnosed in first year; HR 0.47 (95% CI 0.22 to 1.00) Increase in Child-Pugh score: 3.4% (15/436) vs. 8.8% (19/215); adjusted HR 0.45 (95% CI 0.22 to 0.90) Disease progression: 7.8% (34/436) vs. 18% (38/215); adjusted HR 0.45 (95% CI 0.58 to 0.73)			
Lin 1999[73] *Additional publication: Liaw 1994*[74]	Screened: NR Eligible: NR Enrolled: 120 Analyzed: 101	NR	Age, baseline ALT, baseline HBV-DNA, preexisting cirrhosis, AFP level, duration of hepatitis, treatment regimen	Not relevant[a]	A vs. B Mortality: 1/67 (1%) vs 4/34 (12%); RR 0.13 (95% CI 0.01 to 1.09) Hepatocellular cancer: 1/67 (1%) vs 4/34 (12%); RR 0.13 (95% CI 0.01 to 1.09) Incident cirrhosis:	Not relevant[a]	Fair	The Prosperous Foundation (Taipei, Taiwan)

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
					8/67 (12%) vs 5/34 (15%); RR 0.81 (95% CI 0.29 to 2.29)			
Marcellin 2003[42]	Screened: NR Eligible: NR Enrolled: 515 Analyzed: 494 for histologic outcomes Note: 4 patients (1 in group A, 3 in group C) took no study medications and were excluded after randomization, baseline n=171 in group A, 173 in group B, 167 in group C	A vs. B vs. C Withdrawals: 7% (12/171) vs. 8% (14/173) vs. 8% (13/167) Loss to followup for baseline biopsies: 1.8% (3/171) vs. 4.6% (8/173) vs. 3.6% (6/167) Loss to followup for total group: Unclear	Adjustments made for 7 geographic regions	A vs. B vs. C Histologic improvement (unassessable data: 1-2%, missing data: 9-10%): 53 (89/168) vs. 59% (98/165) vs. 25% (41/161); A vs. C adjusted RR 2.1 (95% CI 1.6 to 2.8); B vs. C adjusted RR 2.3 (95% CI 1.7 to 3.1) HBeAg loss: 24% (41/171) vs. 27% (44/165) vs. 11% (17/161); A vs. C RR 2.3 (95% CI 1.3 to 3.8); B vs. C RR 2.5 (95% CI 1.5 to 4.2) HBeAg seroconversion: 12% (20/171) vs. 14% (23/165) vs. 6% (9/161); A vs. C RR 2.1 (95% CI 1.0 to 4.5); B vs. C RR 2.5 (95% CI 1.2 to 5.2) ALT normalization: 48% (81/168) vs. 55% (93/169) vs. 16% (26/164); A vs. C RR 3.0 (95% CI 2.1 to 4.5); B vs. C RR 3.5 (95% CI 2.4 to 5.1)	NR	A + B vs. C Serious adverse events 10% (33/344) vs. 8% (13/167) RR 1.2 (95% CI 0.7 to 2.3) Withdrawal due to adverse events 2.3% (8/344) vs. <1% (1/167) RR 3.9 (95% CI 0.5 to 31) Note: n values calculated from proportions provided by study, based on the number of participants at baseline Combined treatment arms	Fair	Gilead Sciences
Mazzella 1999[75]	Screened: NR Eligible: NR Enrolled: 64 Analyzed: 64	NR	N/A	Not relevant[a]	A vs. B Mortality: 0/33 (0%) vs 2/31 (6%); RR 0.19 (95% CI 0.01 to 3.77) Hepatocellular cancer: 2/33 (3%) vs 2/31 (6%); RR 0.94 (95% CI 0.14 to 6.27) Incident cirrhosis:	Not relevant[a]	Fair	NR

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
					4/33 (12%) vs 6/31 (19%); RR 0.63 (95% CI 0.2 to 2.01)			
Muller 1990[47]	Screened: NR Eligible: NR Enrolled: 58 Analyzed: 55	Withdrawals: 3/58 (5%) Loss to followup: none reported	N/A	A vs. B Complete response: 1/30 (3%) vs 0/28 (0%); RR 2.81 (95% CI 0.12 to 66) Partial response: 8/30 (27%) vs 3/28 (0%); RR 2.49 (95% CI 0.73 to 8.45)	NR	Interferon alfa-2b (no results presented for untreated group) Withdrawals due to adverse events 3.7% (1/27)	Fair	NR
Murray 2012[61]	Screened: 149 Eligible: NR Enrolled: 106 Analyzed: 101	Withdrawals: 5/106 (5%) Loss to followup: none reported	N/A	A vs. B Viral load achieved: 46/52 (89%) vs 0/54 (0%); RR 97 (95% CI 6 to 1526) Viral load undetectable: 44/52 (85%) vs 0/54 (0%); RR 92 (95% CI 6 to 1462) ALT normalization, patients >ULN at baseline (n=35 tenofovir, 42 placebo): 26/35 (74%) vs 13/42 (31%); RR 2.4 (95% CI 1.47 to 3.93) ALT normalization, all patients: 40/52 (77%) vs 21/54 (39%); RR 1.98 (95% CI 1.37 to 2.85) HBeAg loss, patients HBeAg positive at baseline (n=48 tenofovir, 48 placebo): 10/48 (21%) vs 7/48 (15%); RR 1.43 (95% CI 0.59 to 3.44) HBsAg loss: 1/52 (2%) vs 0/54 (0%); RR 3.11 (95% CI 0.13 to 75) Composite outcomes - Viral load achieved + ALT normalization: 37/52 (71%) vs 0/54 (0%); RR 77 (95% CI 5 to 1235) Viral load achieved + ALT	NR	A vs. B Serious adverse events 12% (6/52) vs 22% (12/54) RR 0.5 (95% CI 0.2 to 1.3) Any adverse event 85% (44/52) vs 89% (48/54) RR 0.95 (95% CI 0.8 to 1.1)	Good	Gilead Sciences

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
				normalization + HBeAg loss: 11/52 (21%) vs 0/54 (0%); RR 24 (95% CI 1.44 to 395) Viral load achieved + ALT normalization + HBsAg loss: 8/52 (15%) vs 0/54 (0%); RR 18 (95% CI 1.04 to 298)				
Perez 1990[48]	Screened: NR Eligible: NR Enrolled: 35 Analyzed: 35	Withdrawals: none reported Loss to followup: none reported	N/A	A vs. B HBeAg loss: 10/17 (59%) vs 1/18 (6%); RR 11 (95% CI 1.59 to 78) HBsAg loss: 1/17 (6%) vs 0/18 (0%); RR 3.17 (95% CI 0.14 to 73) HBV DNA loss: 1/17 (6%) vs 0/18 (0%); RR 3.17 (95% CI 0.14 to 73) ALT normalization: 2/17 (12%) vs 1/18 (6%); RR 2.12 (95% CI 0.21 to 21)	NR	A vs. B Withdrawals due to adverse events 6% (1/18) vs. 0% (0/17) RR 2.7 (95% CI 0.1 to 62)	Fair	NR
Perrillo 1990[49]	Screened: 545 Eligible: 169 Enrolled: 169 Analyzed: 169	Withdrawals: 4/169 (2%) Loss to followup 2/169 (1%)	N/A	A vs B vs C vs D vs no treatment Loss of HBV DNA + HBcAg: 16/44 (36%) vs 15/41 (37%) vs 7/41 (17%) vs 3/43 (7%); treatment (33/126) vs no treatment (3/43) RR 3.75 (95% CI 1.21 to 12) Loss of HBsAg: 5/44 (11%) vs 5/41 (12%) vs 1/41 (2%) vs 0/43 (0%); treatment (11/125) vs no treatment (0/43) RR 8.03 (95% CI 0.48 to 133) ALT and AST normalization: 19/44 (43%) vs 18/41 (44%) vs 11/41 (27%) vs 8/43 (19%); treatment (48/126) vs no treatment (8/43) RR 2.05 (95% CI 1.05 to 3.98)	A + B + C (all arms) vs C (no treatment) Mortality: 1/126 (0.8%) vs 2/43 (5%); RR 0.17 (95% CI 0.02 to 1.84)	A vs. B Withdrawals due to adverse events 3% (4/126) vs 0% (0/43) RR 3.12 (95% CI 0.17 to 57)	Good	University of California Public Health Service; National Institutes of Health

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Sarin 1996[50]	Screened: NR Eligible: NR Enrolled: 41 Analyzed: 41	Withdrawals: none reported Loss to followup: none reported	N/A	A vs. B 4-month outcomes Complete response: 10/20 (50%) vs 1/21 (5%); RR 11 (95% CI 1.48 to 75) HBeAg loss: 10/20 (50%) vs 3/21 (14%); RR 3.5 (95% CI 1.12 to 11) HBV DNA loss: 10/20 (50%) vs 1/21 (5%); RR 11 (95% CI 1.48 to 75) HBsAg loss: 1/20 (5%) vs 1/21 (5%); RR 1.05 (95% CI 0.07 to 16) 16-month outcomes HBsAg loss: 3/20 (15%) vs 1/21 (5%); RR 3.15 (95% CI 0.36 to 28)	NR	Interferon alfa-2b (no results presented for untreated group) Serious adverse events 0% (0/20)	Fair	Schering-Plough
Tassopoulos 1999[58]	Screened: 260 Eligible: 125 Enrolled: 125 Analyzed: 124	A vs. B. Withdrawals: 12% (7/60) vs. 6.3% (4/64) Per-protocol withdrawals at week 26 (HBV DNA >2.5 pg/mL): 8.3% (5/60) vs. 43/64 (67%) Withdrawals for other reasons (protocol violation/adverse event): 3.3% (2/60) in treated group	N/A	A vs. B Week 24 Complete response: 63% (34/54) vs. 6% (3/54); RR 11 (95% CI 3.7 to 34.7) Partial response: 28% (15/54) vs. 20% (11/54); RR 1.4 (95% CI 0.7 to 2.7) HBsAg loss: 0% (0/60) vs. 2% (1/64); RR 0.4 (95% CI 0.02 to 8.55) HBsAg seroconversion: 0 vs. 0	NR	A vs. B Serious adverse events 5% (3/60) vs. 6% (4/65) RR 0.8 (95% CI 0.2 to 3.5) Withdrawal due to adverse events 2% (1/60) vs. 0% (0/65) RR 3.2 (95% CI 0.1 to 78) Any adverse events 47% (28/60) vs. 62% (40/65) RR 0.8 (95% CI 0.5 to 1.1)	Fair	Glaxo Wellcome Research and Development

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Waked 1990[51]	Screened: NR Eligible: NR Enrolled: 40 Analyzed: 35	Withdrawals: 5/40 (13%) Loss to followup: 1/40 (3%)	N/A	A (both dosing strategies) vs. B 16-week outcomes (on treatment) HBeAg loss: 16/20 (80%) vs 5/20 (25%); RR 3.2 (95% CI 1.45 to 7.05) HBeAg seroconversion: 11/20 (55%) vs 4/20 (20%); RR 2.75 (95% CI 1.05 to 7.2) HBsAg loss: 5/20 (25%) vs 3/20 (15%); RR 1.67 (95% CI 0.46 to 6.06) Development of anti HBsAg: 4/20 (20%) vs 1/20 (5%); RR 4 (95% CI 0.49 to 33) End of followup outcomes (post-treatment) HBeAg loss: 13/20 (65%) vs 5/20 (25%); RR 2.6 (95% CI 1.14 to 5.93) HBeAg seroconversion: 10/20 (50%) vs 5/20 (25%); RR 2 (95% CI 0.83 to 4.81) Loss of HBsAg: 6/20 (30%) vs 3/20 (15%); RR 2 (95% CI 0.58 to 6.91) HBsAg seroconversion: 4/20 (20%) vs 1/20 (5%); RR 4 (95% CI 0.49 to 33) Histologic improvement: 4/20 (20%) vs 1/20 (5%); RR 4 (95% CI 0.49 to 33)	A vs. B 16-week outcomes - Mortality: 3/20 (15%) vs 1/20 (5%); RR 3 (95% CI 0.34 to 26) End of followup outcomes - Mortality: 0/20 (0%) vs 1/20 (5%); RR 0.33 (95% CI 0.01 to 7.72) Cirrhosis: 1/20 (5%) vs 2/20 (10%); RR 0.5 (95% CI 0.05 to 5.08)	Interferon alfa-2b (no results presented for untreated group) Withdrawals due to adverse events 0% (0/20)	Fair	NR

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Yalcin 2004[59]	Screened: 53 Eligible: 46 Enrolled: 46 Analyzed: 46	Withdrawals: 0 vs. 3% (1/33) Loss to followup: None	N/A	A vs. B Month 1 (on treatment) Loss of HBV DNA: 100% (13/13) vs. 0% (0/33); RR 66 (95% CI 4.2 to 1029) Month 12 (treatment plus post-treatment followup) HBeAg seroconversion: 8% (1/13) vs. 3% (1/33); RR 2.5 (95% CI 0.2 to 37.6) Loss of HBV DNA: 8% (1/13) vs. 3% (1/33); RR 2.5 (95% CI 0.2 to 37.6) Loss of HBsAg: 0/13 vs. 0/33 HBeAg seroconversion + HBV DNA loss: 1/13 (8%) vs 1/33 (3%); RR 2.5 (95% CI 0.2 to 37.6)	NR	A vs. B Serious adverse events 0% (0/13) vs. 0% (0/33) RR 2.4 (95% CI 0.1 to 116)	Fair	NR
Yao 1999[60] *Additional publications: Yao 2000[78] and Yao 2009[79]*	Screened: 440 Eligible: 429 Enrolled: 429 Analyzed: 429	A vs. B Withdrawals: 2.8% (9/322) vs. 1.8% (2/110)	N/A	A vs. B Cumulative undetectable HBV DNA at week 12: 92% (270/293) vs. 14% (14/99); RR 6.52 (95% CI 4.01-10.56) Sustained undetectable HBV DNA at week 12: 78% (229/293) vs. 11% (11/99); RR 7.03 (95% CI 4.02-12.32) HBeAg loss: 8.1% (23/284) vs. 5.3% (5/94); RR 1.52 (95% CI 0.60-3.89) Development of anti-HBeAg: 10.2% (29/284) vs. 6.4% (6/94); RR 1.60 (95% CI 0.69-3.73) HBeAg seroconversion: 5.3% (15/284) vs. 4.3% (4/94); RR 1.24 (95% CI 0.42-3.65) Sustained ALT response at or below ULN with no subsequent increases above upper limit of normal: 60.3% (91/151) vs. 27.5%	NR	A vs. B Serious adverse events 0% (0/322) vs. 0% (0/107) RR 0.3 (95% CI 0.0 to 17) Withdrawal due to adverse events 0% (0/322) vs. 0% (0/107) RR 0.3 (95% CI 0.0 to 17) Any adverse events 43% (138/322) vs. 42% (45/107) RR 1.0 (95% CI 0.8 to 1.3)	Fair	NR

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
				(14/51); RR 2.20 (95% CI 1.38-3.49)				
Zeng, 2006[43]	Screened: NR Eligible: NR Enrolled: 480 Analyzed: 480	A vs. B vs. C Withdrawals: NR for first 12 weeks, 1.2% (6/480) after 52 weeks Loss to followup: NR for first 52 weeks, 6% (14/240) vs. 5% (6/120) vs. 11% (13/120) after 5 years	N/A	A + B vs. C Week 12 HBV DNA undetectable: 5% (18/352) vs. 0% (0/119); RR 12.6 (95% CI 0.8 to 207.1) ALT normalization: 42% (140/330) vs. 14% (15/108); RR 3.1 (95% CI 1.9 to 5.0) HBeAg loss: 6% (20/354) vs. 5% (6/119); RR 1.1 (95% CI 0.5 to 2.7) HBeAg seroconversion: 6% (20/344) vs. 5% (6/119); 1.1 (95% CI 0.5 to 2.8) Note: no adjustment for missing data	Mortality: None	A vs. B vs. C Serious adverse event during 52 weeks (off treatment since week 12): 2% (4/240) vs. 7% (8/120) vs. 0.9% (1/120); A vs. C RR 2.0 (95% CI 0.2 to 17.7); B vs. C RR 8.0 (95% CI 1.0 to 63.0) Withdrawal due to adverse events during 52 weeks (off treatment since week 12): 0.6% (3/480); 0.8% (2/240) vs. 0.8% (1/120) vs. 0% (0/120); A vs. C: RR 2.5 (95% CI 0.1 to 51.9); B vs. C RR 3.0 (95% CI 0.1 to 72.9)	Fair	Glaxo-SmithKline

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Head-to-Head								
Chang 2006;[64] Gish 2007;[65] Chang 2009[66]	Screened: 1,056 Eligible: NR Enrolled: 715 Analyzed: 709	Withdrawals: unclear; 10/715 (1%) withdrew due to AEs Loss to follow up: 54/715 (8%)	N/A	A vs B HBeAg loss: 110/354 (31%) vs 92/355 (26%); RR 1.2 (95% CI 0.95 to 1.5) HBsAg loss: 18/354 (5%) vs 10/355 (3%); RR 1.8 (95% CI 0.9 to 3.9) HBV DNA < 300 copies/ml: 284/354 (80%) vs 137/355 (39%); RR 2.1 (95% CI 1.8 to 2.4) ALT normalization (≤1x ULN): 307/354 (87%) vs 280/355 (79%); RR 1.1 (95% CI 1.03 to 1.2) Histologic improvement (Knodell necroinflammatory score improvement ≥2 points with no worsening of fibrosis score among patients with adequate biopsy specimen): 226/314 (72%) vs 195/314 (62%); RR 1.2 (95% CI 1.03 to 1.3)	A vs B Hepatocellular cancer: 1/354 (0.3%) vs 0/355 (0%); RR 3.0, 95% CI 0.12 to 74 Mortality: 2/354 (0.6%) vs 4/355 (1%); RR 0.5, 95% CI 0.09 to 2.72	A vs B Serious adverse events: 27/354 (8%) vs 30/355 (8%); RR 0.9 (95% CI 0.6 to 1.5) Withdrawals due to adverse events: 1/354 (0.3%) vs 9/355 (3%); RR 0.1 (95% CI 0.01 to 0.9) Any adverse event: 306/354 (86%) vs 297/355 (84%); RR 1.0 (95% CI 0.97 to 1.1)	Good	Bristol Myers Squibb
Lai 2002[68]	Screened: 431 Eligible: NR Enrolled: 185 Analyzed: 169 (87 A vs B)	Withdrawals: 8/185 (4%) Loss to followup: None reported	N/A	A vs B HBV DNA undetectable: 11/46 (24%) vs 7/41 (17%) ALT normalization (among patients with elevated ALT at baseline): 20/29 (69%) vs 13/22 (59%); RR 1.2 (95% CI 0.8 to 1.8) HBeAg loss (among HBeAg positive patients): 0/36 (0%) vs 2/36 (6%); RR 0.2 (95% CI 0.01 to 4.0) HBV DNA loss + ALT normalization (and HBeAg loss if HBeAg positive at baseline): 7/43 (16%) vs 6/40 (15%); RR 1.1 (95% CI 0.4 to 3.3)	None reported	A vs B Serious adverse events: None reported Withdrawals due to adverse events: 2/46 (4%) vs 1/41 (2%); RR 1.8 (95% CI 0.2 to 19) Any adverse event: 30/46 (65%) vs 30/41 (73%); RR 0.9 (95% CI 0.7 to 1.2)	Fair	Not reported

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Lai 2006[67]	Screened: 1,468 Eligible: 694 Enrolled: 648 Analyzed: 638	Withdrawals: 31/638 (5%) Loss to follow-up: None reported	N/A	A vs B (time on treatment) Histologic improvement (among patients with adequate baseline biopsy specimen and Knodell necroinflammatory score ≥2; improvement=at least 2 pt decrease in necroinflammatory score with no worsening of fibrosis score): 208/296 (70%) vs 174/287 (61%); RR 1.2 (95% CI 1.02 to 1.3) HBV DNA loss (<300 copies/mL): 293/325 (90%) vs 225/313 (72%); RR 1.3 (95% CI 1.2 to 1.4) ALT normalization (<1 x ULN): 253/325 (78%) vs 222/313 (71%); RR 1.1 (95% CI 1.0 to 1.2)	A vs B Hepatocellular cancer: 1/325 (0.3%) vs 0/313 (0%); RR 2.89, 95% CI 0.12 to 71 Mortality: 2/325 (0.6%) vs 0/313 (0%); RR 4.82, 95% CI 0.23 to 100	A vs B Serious adverse events: 21/325 (6%) vs 24/313 (8%); RR 0.8 (95% CI 0.5 to 1.5) Withdrawals due to adverse events: 6/325 (2%) vs 9/313 (3%); RR 0.6 (95% CI 0.2 to 1.8) Any adverse event: 246/325 (76%) vs 248/313 (79%); RR 1.0 (95% CI 0.9 to 1.04)	Good	Bristol Myers Squibb
Lau 2005[70]	Screened: Not reported Eligible: Not reported Enrolled: n=543 (excluding 271 patients randomized to peg interferon + lamivudine combination therapy) Analyzed: 543	Withdrawals: 70/543 (13%) Loss to followup: not reported	N/A	A vs B HBeAg loss/seroconversion: Time on treatment, loss: 81/271 (30%) vs 59/272 (22%), RR 1.4 (95% 1.0 to 1.8); Time on treatment, seroconversion: 72/271 (27%) vs 55/272 (20%), RR 1.3 (95% CI 1.0 to 1.8); Time on treatment + follow-up, loss: 91/271 (34%) vs 57/272 (21%), RR 1.6 (95% CI 1.2 to 2.1); Time on treatment + follow-up, seroconversion: 87/271 (32%) vs 52/272 (19%), RR 1.7 (95% CI 1.2 to 2.3) HBsAg loss/seroconversion: Time on treatment + follow-up, seroconversion: 8/271 (3%) vs 0/272 (0%); RR 17 (95% CI 1.0 to 294) HBV DNA loss: Time on treatment: 68/271 (25%) vs 108/272 (40%), RR 0.6 (95% CI 0.5 to 0.8); Time	A vs B Mortality: 0/271 (0%) vs 1/272 (0.4%)	A vs B (through week 56) Serious adverse events: 12/271 (12%) vs 5/272 (2%); RR 2.4 (95% CI 0.9 to 6.7) Withdrawals due to adverse events: 8/271 (3%) vs 2/272 (1%); RR 4.0 (95% CI 0.9 to 19) Any adverse event: 240/271 (89%) vs 152/272 (56%); RR 1.6 (95 % CI 1.4 to 1.8)	Good	Roche Pharmaceuticals

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
				on treatment + follow-up: 39/271 (14%) vs 14/272 (5%); RR 2.8 (95% CI 1.6 to 5.0) ALT normalization: Time on treatment: 105/271 (39%) vs 168/272 (62%), RR 0.6 (95% CI 0.5 to 0.7); Time on treatment + follow-up: 111/271 (41%) vs 76/272 (28%); RR 1.5 (95% CI 1.2 to 1.9) Histologic improvement (reduction of at least 2 points in the modified Histology Activity Index): Time on treatment: + follow-up: 102/271 (38%) vs 93/272 (34%); RR 1.1 (95% CI 0.9 to 1.4) HBeAg seroconversion + ALT normalization + HBV DNA <100,000 copies/ml: Time on treatment: 27/271 (10%) vs 50/272 (18%), RR 0.5 (95% CI 0.4 to 0.8); Time on treatment + follow-up: 62/271 (23%) vs 28/272 (10%), RR 2.2 (95% CI 1.5 to 3.4)				

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Marcellin 2004[71]	Screened: Not reported Eligible: Not reported Enrolled: 552 Analyzed: 537	Withdrawals: 38/358 (11%) Loss to followup: not reported	N/A	A vs B HBsAg loss/seroconversion: Time on treatment + follow-up, loss: 7/177 (4%) vs 0/181 (0%); RR 15 (95% CI 0.9 to 267) HBV DNA loss: Time on treatment: 112/177 (63%) vs 133/181 (73%), RR 0.9 (95% CI 0.7 to 1.0); Time on treatment + follow-up: 34/177 (19%) vs 12/181 (7%), RR 2.9 (95% CI 1.6 to 5.4) ALT normalization: Time on treatment: 67/177 (38%) vs 132/181 (73%), RR 0.5 (95% CI 0.4 to 0.6); Time on treatment + follow-up: 105/177 (59%) vs 80/181 (44%), RR 1.3 (95% CI 1.1 to 1.7) Histologic improvement: Time on treatment + follow-up: 85/177 (48%) vs 72/181 (40%); RR 1.2 (95% CI 1.0 to 1.5) ALT normalization + HBV DNA <400 copies/ml Time on treatment: 47/177 (27%) vs 109/181 (60%), RR 0.4 (95% CI 0.3 to 0.6); Time on treatment + follow-up: 26/177 (15%) vs 11/181 (6%), RR 2.4 (95% CI 1.2 to 4.7)	A vs B Mortality: 1/177 (1%) vs 0/181 (0%); RR 3.1 (95% CI 0.1 to 75)	A vs B Serious adverse events: 9/177 (5%) vs 5/181 (3%); RR 1.8 (95% CI 0.6 to 5.4) Withdrawals due to adverse events: 13/177 (7%) vs 0/181 (0%); RR 28 (95% CI 0.7 to 461) Any adverse event: 155/177 (88%) vs 86/181 (48%); RR 1.8 (95% CI 1.6 to 2.2)	Good	Roche Pharmaceuticals

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Marcellin 2008[72] Study 102 (HBeAg negative at baseline)	Screened: 846 Eligible: 382 Enrolled: 375 Analyzed: 375	Withdrawals: 10/375 (3%) Loss to followup: 1/375 (0.3%)		A vs B HBsAg loss: 0/250 (0%) vs 0/125 (0%); RR not estimable HBV DNA loss (<400 copies/mL): 233/250 (93%) vs 79/125 (63%); ARD* 30 (95% CI 21 to 39); RR 1.5 (95% CI 1.3 to 1.7) Histologic improvement:** 181/250 (72%) vs 86/125 (69%); ARD 5.2 (95% CI -4.5 to 15); RR 1.1 (95% CI 0.9 to 1.2) ALT normalization (among patients with elevated ALT as baseline): 180/236 (76%) vs 91/118 (77%); ARD -0.8 (95% CI -10 to 8.5); RR 1.0 (95% CI 0.9 to 1.1) HBV DNA loss + histologic improvement: 177/250 (71%) vs 61/125 (49%); RR 1.5 (95% CI 1.2 to 1.8) **ARD=adjusted relative difference between groups* ***Histologic improvement defined as ≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis score*	No deaths in either group; 3 cases of HCC but results not reported according to study group	A (n=426) vs B (n=215; results for studies 102 and 103 reported together) Serious adverse events: 27/426 (6%) vs 14/215 (7%); RR 1.0 (95% CI 0.5 to 1.8) Withdrawals due to adverse events: unclear; 5 withdrawals due to AEs in tenofovir group, results for adefovir not reported Any adverse event: 317/426 (74%) vs 158/215 (73%); RR 1.0 (95% CI 0.9 to 1.1)	Fair	Gilead Sciences

Appendix B5. Treatment Trials Evidence Table, *continued*

Author, Year	Number Screened, Eligible, Enrolled, Analyzed	Withdrawals (Number, %) Loss to Followup (Number, %)	Adjusted Variables for Statistical Analysis	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality	Funding Source
Study 103 (HBeAg positive at baseline)	Screened: 603 Eligible: 272 Enrolled: 266 Analyzed: 266	Withdrawals: 15/266 (6%) Loss to followup: none reported		A vs B HBeAg seroconversion: 32/153 (21%) vs 14/80 (18%); ARD* 4.7 (95% CI -5.5 to 15); RR 1.2 (95% CI 0.7 to 2.1) HBsAg loss: 5/158 (3%) vs 0/82 (0%); ARD 11 (95% CI 1.9 to 20); RR 5.7 (95% CI 0.3 to 103) HBV DNA loss: 134/176 (76%) vs 12/90 (13%); ARD 63 (95% CI 54 to 72); RR 5.7 (95% CI 3.4 to 9.7) Histologic improvement: 131/176 (74%) vs 61/90 (68%); ARD 5.8 (95% CI -5.6 vs 17); RR 1.1 (95% CI 0.9 to 1.3) ALT normalization: 115/169 (68%) vs 49/90 (54%); ARD 14 (95% CI 1.1 to 26); RR 1.3 (95% CI 1.0 to 1.6) HBV DNA loss + histologic improvement: 117/176 (66%) vs 11/90 (12%); ARD 54 (95% CI 45 to 64); RR 5.4 (95% CI 3.1 to 9.6) *Histologic improvement defined as ≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis score*	No deaths in either group			
Ren 2007[69]	Screened: Not reported Eligible: Not reported Enrolled: 61 Analyzed: unclear of efficacy, 61 for harms	Withdrawals: 1/61 (2%) Loss to followup: None reported	N/A	A vs B HBV DNA undetectable: 15/21 (71%) vs 8/21 (38%); RR 1.9 (95% CI 1.0 to 3.5) HBeAg loss/seroconversion: 3/21 (14%) vs 4/21 (19%); RR 0.8 (95% CI 0.2 to 3.0) ALT normalization: 18/21 (86%) vs 16/21 (76%); RR 1.1 (95% CI 0.8 to 1.5)	A vs B Hepatocellular cancer: 0/21 (0%) vs 0/21 (0%); RR not estimable Mortality: 0/21 (0%) vs 0/21 (0%); RR not estimable	Serious adverse events: Not reported Withdrawals due to adverse events: Not reported Any adverse event: Not reported	Fair	Not reported

[a]Not approved by the U.S. Food and Drug Administration; included for clinical outcomes (key question 6) only.

Abbreviations: AFP = alpha -fetoprotein; ALT = alanine aminotransferase; ARD = adjusted relative difference between groups; BMI = body mass index; ECG = electrocardiogram; HAI = histology activity index; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV = human immunodeficiency virus; HBsAg = hepatitis B surface antigen; IgM = immunoglobin M; IM = intramuscular; MU = million units; N/A = not applicable; NR = not reported; PCR = polymerase chain reaction; RCT= randomized, controlled trial; RR = relative risk; SC = subcutaneous; SD = standard deviation; qd = once per day; ULN = upper limit of normal.

Appendix B6. Treatment Trials Quality Assessment

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup: Differential/ High?	Analyze People in the Groups in Which They Were Randomized?	Quality
Ali 2003[52]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Yes	Poor
Bayraktar 1993[44]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	No	Unclear	Yes	Poor
Bozkaya 2005[53]	No	No	Yes	Yes	No	No	No	No	Unclear	Unclear	Poor
Chan 2007[52]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/No	Yes	Fair
Chang 2006;[64] Gish 2007;[65] Chang 2009[66]	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Dienstag 1999[55]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Fair
Hadziyannis 1990[45]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	No	Unclear	Yes	Poor
Hadziyannis 2003[40]	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Jonas 2008[41]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Lai 1997[55]	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Fair
Lai 1998[57]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Fair
Lai 2002[68]	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Lai 2006[67]	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Lampertico 1997[46]	Yes	Yes	Yes	Yes	No	No	No	Yes	Unclear	Yes	Fair
Lau 2005[70]	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Liaw 2004[76]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Fair
Lin 1999[73]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair

Appendix B6. Treatment Trials Quality Assessment

Marcellin 2003[42]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Unclear	Fair
Marcellin 2004[71]	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Marcellin 2008[72]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No/No	Yes	Fair
Mazzella 1999[75]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Muller 1990[47]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Murray 2012[61]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Perez 1990[48]	Unclear	Unclear	No	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Perrillo 1990[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Ren 2007[69]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Sarin 1996[50]	Yes	Unclear	Yes	Yes	Unclear	Unclear	No	Yes	No	Yes	Fair
Tassopoulos 1999[58]	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Waked 1990[51]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Yalcin 2004[59]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Yao 1999[60]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Fair
Zeng 2006[43]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	Fair

Appendix B7. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table

Author, Year Country	Study Design	Comparison	Treatment Duration of Followup	Inclusion Criteria	Number Receiving Antiviral Treatment, Lost to Followup	Age, Sex, Race
Andreone 2004[80] Italy	Cohort (unclear if prospective or retrospective)	No virological breakthrough vs. breakthrough (all cases of breakthrough had lamivudine resistance) No virological breakthrough=HBV DNA became undetectable on treatment and remained undetectable	Lamivudine Median 3.5 years	HBeAg negative chronic HBV infection with elevated ALT and compensated cirrhosis Excluded: HCC, HDV, HCV, HIV	n=22 Lost to followup: Unclear	Mean age: 53 years Male: 82% Race: NR
Baltayiannis 2006[81] Greece	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 hepatitis Excluded: HCC, HCV, HDV, HIV	n=63 Lost to followup: 1 (1.6%)	Mean age: 51 years Male: 63% Race: NR
Di Marco 2004[82] Italy	Retrospective cohort	No virological breakthrough vs. breakthrough No virological breakthrough=HBV DNA <105 copies/ml throughout followup after achieving undetectability	Lamivudine 4 years	HBeAg-negative chronic HBV infection with histologic evidence of chronic hepatitis Excluded: HCC, HDV, HCV, HIV	n=656 Lost to followup: NR; 40 patients had no virological response and excluded from analysis	Mean age: 49 years Male: 83% Race: NR
Fattovich 1997[83] Italy	Cohort (unclear if prospective or retrospective)	Biochemical remission vs. no remission Biochemical remission=Normalization of ALT levels	Interferon alfa Mean 7 years	HBeAg-positive, HBsAg-positive chronic HBV infection with compensated cirrhosis and AST or ALT >1.5 times ULN Excluded: HCC, HDV	n=40 Lost to followup: NR for treated subgroup	Mean age: 47 years Male: 85% Race: 100% white
Hui 2008[84] China (Hong Kong)	Cohort (unclear if prospective or retrospective)	Histological response in HAI score vs. no histological response Histological response=improvement of 2 points or more on 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	Mean age: 30 years Male: 78% Race: NR

Appendix B7. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table

Author, Year Country	Study Design	Comparison	Treatment Duration of Followup	Inclusion Criteria	Number Receiving Antiviral Treatment, Lost to Followup	Age, Sex, Race
Lampertico 2003[85] Italy	Cohort (unclear if prospective or retrospective)	Sustained virological and biochemical response vs. no sustained response Sustained virological and biochemical response=Normalization of serum ALT and clearance of HBV DNA	Interferon alfa-2b 5.7 years	HBeAg-negative chronic HBV infection with Ishak >3 fibrosis or Ishak ≤3 fibrosis with at least one ALT >200 IU/L during the past 12 months Excluded: HCV, HDV, HIV	n=101 Lost to followup: 4 (4.0%)	Mean age: 46 years Male: 87% Race: NR
Lau 1997[89] United States	Cohort (originally enrolled in RCT's)	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: 8 (7.8%); assumed to be alive and without liver-related complications	Mean age: 41 years Male: 83% Race: 94% white, 6% black
Niederau 1996[86] Europe	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 upper limit of normal and histologic evidence of active hepatitis Excluded: HDV, HIV, advanced cirrhosis	n=103 Lost to followup: None	Mean age: NR Female: NR Race: NR
Papatheodoridis 2001[87] Greece	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 hepatitis Excluded: decompensated liver disease, HCC, HCV, HDV, HIV	n=209 Lost to followup: 9 (4.3%)	Mean age: 47 years Male: 83% Race: NR

Appendix B7. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table

Author, Year Country	Study Design	Comparison	Treatment Duration of Followup	Inclusion Criteria	Number Receiving Antiviral Treatment, Lost to Followup	Age, Sex, Race
Papatheodoridis 2011[88] Greece	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 two of the following: elevated ALT, HBV DNA >2000 IU/ml, or histologic evidence of chronic hepatitis Excluded: HDV, HCV, HIV, HCC diagnosed before or within first 6 months of treatment	n=818 Lost to followup: 180 (22%)	Mean age: 54 years Male: 72% Race: NR

Appendix B7. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table, *continued*

Author, Year Country	Characteristics of HBV Infection	Proportion of Patients With Intermediate Outcome	Confounders Adjusted for in Analysis	Results (by Clinical Outcome)	Quality	Funding Source
Andreone 2004[80] Italy	HBeAg positive: None HBsAg clearance: NR ALT (mean): 192 AST: NR Serum HBV-DNA (mean, pg/ml): 16 Fibrosis stage: All with cirrhosis	No virological breakthrough: 41% (9/22)	Age Sex Child-Pugh class ALT HBV viral load Albumin Bilirubin Prothrombin activity Alpha-fetoprotein Previous interferon therapy Smoking status Months of treatment All patients HBeAg negative	Hepatocellular carcinoma No virological breakthrough vs. breakthrough: adjusted HR 0.10 (95% CI 0.01 to 0.77)	Fair	Assocaizaione per la Ricerca sulle Malattie Epatiche
Baltayiannis 2006[81] Greece	HBeAg positive: None HBsAg clearance: NR ALT (median): 177 AST (median): 130 Serum HBV-DNA (median, copies/mL): 1.2 x 106 Fibrosis stage (mean, Desmet): 2.2 Cirrhosis: Excluded	Virological response at 6 months: 35% (22/63)	Age Gender Alcohol use ALT >200 IU/L at baseline HBV-DNA >10,000 copies/ml at baseline Histologic grade >9 Histologic stage >2 All patients HBeAg negative	Death or disease complication (not defined) Virological response at 6 months vs. no virological response: adjusted HR 0.24 (95% CI 0.06 to 0.96)	Fair	NR
Di Marco 2004[82] Italy	HBeAg positive: Excluded HBsAg clearance: NR ALT >2 times ULN: 65% AST: NR Serum HBV-DNA: NR Fibrosis stage: NR Cirrhosis on histology: 25%	No virological breakthrough: 39% (240/616)	Age Sex HBV DNA level ALT Hepatic flare after virological breakthrough Previous interferon therapy Cirrhosis All patients HBeAg negative	Death No virological breakthrough vs. breakthrough: adjusted HR 0.34 (95% CI 0.15 to 0.80)	Fair	NR

Appendix B7. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table, *continued*

Author, Year Country	Characteristics of HBV Infection	Proportion of Patients With Intermediate Outcome	Confounders Adjusted for in Analysis	Results (by Clinical Outcome)	Quality	Funding Source
Fattovich 1997[83] Italy	HBeAg positive: All HBsAg clearance: ~40% ALT (mean): 5.3 times upper limit of normal AST (mean): 3.7 times upper limit of normal Serum HBV-DNA: NR Fibrosis stage: All cirrhosis Cirrhosis: 100%	Biochemical remission: 28% (11/40)	Age Sex Symptoms Hepatic stigmata Splenomegaly AST ALT AST/ALT ratio Bilirubin Albumin Gamma-globulins Platelets HBeAg clearance ALT normalization All patients HBeAg positive	Death Biochemical remission vs. no remission: adjusted HR 0.09 (95% CI 0.01 to 0.71)	Poor	NR
Hui 2008[84] China (Hong Kong)	HBeAg positive: All HBsAg clearance: NR ALT (mean): 113 AST: NR Serum HBV-DNA >105 copies/ml: 100% Fibrosis stage (mean, Ishak): 2 Cirrhosis: 12%	Histological response in HAI score: 40% (36/89) Histological response in fibrosis stage: 18% (16/89)	Fibrosis HBV DNA level All patients HBeAg positive	Liver complications (HBV-related decompensated liver cirrhosis or HCC) Histological response on HAI score vs. no response: adjusted HR 0.62 (95% CI 0.06 to 6.9)	Poor	Reports no funding received
Lampertico 2003[85] Italy	HBeAg positive: None HBsAg clearance: 15% ALT (mean): 204 AST: NR HBV DNA detectable: 61% Fibrosis stage (median, Ishak): 4 Ishak F4-F6 fibrosis: 60%	Sustained virological and biochemical response: 30% (30/101)	Age Sex ALT HBV viral load IgM anti-HBc level Necroinflammatory grade Fibrosis stage All patients HBeAg negative	Liver complications (cirrhosis, ascites, jaundice, hepatic encephalopathy, gastroesophageal bleeding due to portal hypertension, or HCC) Sustained virological and biochemical response vs. no sustained response: adjusted HR 0.13 (95% CI 0.03 to 0.55)	Fair	Fondazione Italiana Ricerca Cancro and the consorzio Interuniversitario Trapianti d'Organo (Rome)

Appendix B7. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table, *continued*

Author, Year Country	Characteristics of HBV Infection	Proportion of Patients With Intermediate Outcome	Confounders Adjusted for in Analysis	Results (by Clinical Outcome)	Quality	Funding Source
Lau 1997[89] United States	HBeAg positive: All HBsAg clearance: 86% (responder) vs. 11% (nonresponder) ALT (median): 154 AST (median): 94 Serum HBV-DNA (meq/mL): 4843 Fibrosis stage (mean, HAI): 2.1 Cirrhosis: 17% HCV infection: 6.8% HIV infection: 14%	Response: 30% (31/103)	Cirrhosis Age Sex ALT AST All patients HBeAg positive	Death (results only adjusted for age and sex) Responder vs. non-responder: adjusted HR 0.59 (95% CI 0.20 to 1.67) Death or liver-related complication (variceal hemorrhage, ascites, encephalopathy) Responder vs. non-responder: adjusted HR 0.07 (95% CI 0.02 to 0.33)	Fair	NR
Niederau 1996[86] Europe	HBeAg positive: All HBsAg clearance: 9.7% ALT: NR AST: NR HBV DNA: NR Fibrosis stage: NR Cirrhosis: NR (Child-Pugh class B or C excluded)	HBeAg loss: 51% (53/103)	Age Sex Baseline HBV DNA Baseline ALT Duration of hepatitis Preexisting cirrhosis All patients HBeAg positive	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: adjusted HR 0.06 (95% CI 0.01 to 0.61)	Fair	Van Meeteren Foundation
Papatheodoridis 2001[87] Greece	HBeAg positive: Excluded HBsAg clearance: 13% mean 2.9 years after end of treatment) ALT (median): 112 AST (median): 67 Serum HBV DNA (median, pg/ml): 4.4 Fibrosis stage (mean, Ishak): 3.3 Cirrhosis: 27%	Sustained biochemical response: 27% (57/209)	Cirrhosis Age All patients HBeAg negative	Death or liver transplantation Sustained biochemical response vs. no sustained biochemical response: adjusted HR 0.48 (95% CI 0.23 to 1.0) Severe clinical complications (death, liver transplantation, liver decompensation [ascites, variceal bleeding, hepatic encephalopathy], and hepatocellular carcinoma) Sustained biochemical response vs. no sustained biochemical response: adjusted HR 0.53 (95% CI 0.29 to 0.91)	Poor	NR

Appendix B7. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table, *continued*

Author, Year Country	Characteristics of HBV Infection	Proportion of Patients With Intermediate Outcome	Confounders Adjusted for in Analysis	Results (by Clinical Outcome)	Quality	Funding Source
Papatheodoridis 2011[88] Greece	HBeAg positive: Excluded HBsAg clearance: NR ALT (median): 98 AST (median): 68 Serum HBV DNA (median, x103 IU/ml): 400 Fibrosis stage: NR Cirrhosis: 26%	Virological remission: 28% (228/818)	Age Sex Liver disease severity ALT AST Bilirubin Albumin Hemoglobin Platelet count HBV DNA Interferon alfa in the past All patients HBeAg negative	Hepatocellular carcinoma Virological remission under therapy vs. no virological remission: adjusted HR 0.77 (95% CI 0.35 to 1.69)	Fair	Hellenic Center for Disease Control and Prevention

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HAI = histology activity index; HR = hazard ratio; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV = human immunodeficiency virus; HBsAg = hepatitis B surface antigen; IgM = immunoglobin M; NR = not reported; ULN = upper limit of normal.

Appendix B8. Studies of Association Between Intermediate and Final Health Outcomes 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 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, and HBeAg Status)?	Is There Important (Overall or Differential) Exclusion of Patients Due to Missing Data or Loss to Followup?	Were Outcomes Prespecified and Defined, and Ascertained Using Accurate Methods?	Quality
Andreone 2004[80]	Yes	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Baltayiannis 2006[81]	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair
Di Marco 2004[82]	Yes	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Fattovich 1997[83]	Yes	Unclear	Yes	Unclear	Yes	No	No	Yes	Poor
Hui 2008[84]	Yes	Unclear	Yes	Unclear	No	No	Unclear	Yes	Poor
Lampertico 2003[85]	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Lau 1997[89]	Yes	No	Yes	Unclear	Yes	No	No	Yes	Fair
Niederau 1996[86]	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair
Papatheodoridis 2001[87]	Yes	Yes	Yes	Unclear	Yes	No	No	Yes	Poor
Papatheodoridis 2011[88]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Fair

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