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 adults.

**Data Sources:** We searched the Cochrane Central Register of Controlled Trials (through August 2013), the Cochrane Database of Systematic Reviews (2005 through August 2013), Ovid MEDLINE (1946 through August 2013) and PsycINFO (1806 through August 2013) 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 entecavir and pegylated interferon alfa-2a with 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 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 persists for longer than 6 months and is characterized by persistent viremia and the presence of HBsAg and total anti-HBc (IgM antibody is generally only present during acute 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 is 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. Due to underreporting, the actual number of cases is estimated to be 6.5 times higher than the number of reported cases. From 2000 to 2010, the incidence of acute HBV infection declined among all age groups. In 2010, the highest rate of new HBV infections was among persons aged 30 to 39 years (2.33 cases/100,000 population) with males and black persons at highest risk.

As of 2008, an estimated 704,000 people in the United States were chronically infected with HBV. In 2010, there were an estimated 0.5 deaths associated with HBV infection per 100,000 persons, with the highest death rates among persons aged 55 to 64 years, persons of “nonwhite, nonblack” race, and males.

**Etiology and Natural History**

HBV is spread through percutaneous or mucous membrane exposure to blood or blood containing bodily fluids (serum, semen or saliva). The liver is the primary site of viral replication. Infected individuals may be asymptomatic or present with symptoms of acute infection like nausea, anorexia, fatigue, low grade fever and abdominal pain. 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. Acute infection generally self-resolves in 2 to 4 months, though 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 1 to 5 years of age, and less than 5 percent in those older than 5 years of age. The course of chronic HBV infection varies widely. Chronic infection spontaneously resolves in 0.5 percent of individuals annually. Many chronically infected individuals are asymptomatic, though others experience a range of symptoms including nonspecific symptoms of fatigue or other symptoms related to hepatitis, cirrhosis, or hepatocellular carcinoma. 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. 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. 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, though marked decreases in prevalence have been seen among younger persons born in these countries due to universal immunization programs. 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. Persons at higher risk for acute HBV infection include men, black persons, and those 30 to 39 years of age. 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%). 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 day care centers for developmentally disabled persons.

Rationale for Screening/Screening Strategies

Identification of asymptomatic persons with chronic HBV infection through screening may identify those who would benefit from earlier evaluation and management of their disease. Data on the proportion of persons with chronic HBV infection in the United States who are not aware of their infection status are limited, though in studies of Asian-born persons living in the United States, the proportion is approximately one-third. 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/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 mcg of HBsAg protein/mL for adolescents and adults, and generally involves at least 3 intramuscular doses administered at 0, 1, and 6 months. Vaccination results in ≥90 percent protective antibody response after the third dose in adults and >95 percent in adolescents, though protective anti-HBs titers may be attained in some persons after one or two doses. As of 2011, universal vaccination of children has been implemented in over 190 countries, with 81 countries
targeting newborns. The widespread implementation of universal vaccination strategies throughout the world has been credited with marked decreases in HBV incidence, particularly among younger persons.

**Treatment**

There are currently seven antiviral drugs 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. Drugs for HBV infection are broadly categorized as either interferons or nucleoside/nucleotide analogues. The interferons affect viral replication as well as immune modulation. 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). Biopsy may be performed in some patients to establish the degree of liver inflammation and fibrosis. 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.

The goals of treatment are to achieve sustained suppression of HBV replication and remission of liver disease in order to prevent cirrhosis, hepatic failure, and hepatocellular carcinoma. The recommended duration of treatment varies depending on the time required to achieve HBV DNA suppression, HBeAg status, presence of cirrhosis, and choice of medication. Interferon-based therapy is usually recommended for shorter duration of treatment than noninterferon-based therapy, in part due to limited tolerability and additional immunomodulatory effects of interferons.

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. 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. In persons with serological findings suggesting chronic infection, followup includes testing for viremia.

Current United States 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.\textsuperscript{15, 27}

## Recommendations of Other Groups

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

- All foreign-born persons from regions with HBsAg prevalence $\geq 2$ percent, regardless of vaccination history
- United States-born persons not vaccinated as infants whose parents were born in regions with HBsAg $\geq 8$ percent
- IDUs
- Men who have sex with men
- Immunosuppressed persons
- Persons with elevated 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 with high risk behaviors;\textsuperscript{15} and the AASLD recommends screening of persons with multiple sex partners or a history of STD, inmates of correctional facilities, and individuals with HCV infection.\textsuperscript{27} The Institute of Medicine (IOM) endorses screening in high risk groups.\textsuperscript{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).

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 adolescent 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 update2 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.
outcomes; and by excluding key questions related to prenatal screening and immunization of children.

**Search Strategies**

We searched the Cochrane Central Register of Controlled Trials (through August 2013), the Cochrane Database of Systematic Reviews (2005 through August 2013), Ovid MEDLINE (1946 through August 2013) and PsycINFO (1806 through August 2013) 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 persons 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) versus older antiviral therapies (adefovir, nonpegylated interferon, lamivudine, or telbivudine).

Studies of treatment were excluded if they evaluated nonFDA 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 achieving an intermediate outcome after antiviral treatment (e.g., clearance of HBeAg or HBV DNA from serum, normalization of serum transaminases, or histological improvement) versus not achieving the outcome and clinical outcomes.
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 hepatitis C virus (HCV) co-infection, 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, using the Mantel-Haenszel random effects model with RevMan software (Review Manager Version 5.2) (Copenhagen, Nordic Cochrane Centre, Cochrane Collaboration, 2012). Primary analyses for intermediate and clinical outcomes were based on were based on total followup (including time following discontinuation of antiviral therapy), though 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 and revised based on the comments received and will be posted for public comment for further comments.
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=6194) 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, Appendixes B1 and B2). It evaluated patients attending a French sexually transmitted disease clinic and applied alternative screening criteria
retrospectively. Of the 7692 patients evaluated at the clinic during the study period, 6194 (81%) were screened for HBV infection. Patients were primarily young adults (62% between the ages of 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 OR, 15.8 [95% CI, 5.6 to 44] and 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, though the sample was small.

The prevalence of HBV infection (based on presence of HBsAg) in the sample was 0.8 percent (49/6194). 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 only screening patients born in moderate or high prevalence countries (≥2% prevalence of chronic HBV infection) would have resulted in 13 percent (761/6011) 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 (3949/6194) 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 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 (four trials; RR, 0.5 [95% CI, 0.4 to 0.7]) and men who have sex with men (four 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 serological markers (appearance of HBsAg or anti-HBc) in four trials (RR, 0.5 [95% CI, 0.4 to 0.7]; $I^2=18\%$). Pooled results from one other good-quality and two fair-quality trials 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) 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 compared to 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 (nine trials; RR, 7.2 [95% CI, 3.2 to 16]; \(I^2=58\%\)) and histological improvement (seven trials; RR, 2.1 [95% CI, 1.8 to 2.6]; \(I^2=0\%\)). Results were generally consistent when stratified by individual drug, though 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 (six 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, 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 of 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 only evaluated 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 ranged from 60% to 94%). In 11 trials that reported the proportion of patients with baseline cirrhosis, rates ranged from 5 to 44 percent. In trials that did not report the prevalence of baseline cirrhosis, patients with decompensated liver disease were generally excluded. Study duration ranged from 8 weeks to 3 years. Twelve trials reported outcomes on antiviral therapy, three trials reported outcomes following discontinuation of antiviral therapy, and seven trials reported both. Two trials were rated good-quality, four trials poor-quality, 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]; \(I^2=4\%\)) (Figure 2). One trial reported no HBeAg loss in either treated or control groups. When analyses were stratified by specific antiviral drug, the risk estimate was larger for interferon alfa-2b (five trials; RR, 3.6 [95% CI, 1.9 to 6.9]; \(I^2=5\%\)) than for lamivudine (three trials: RR, 1.7 [95% CI, 1.0 to 3.0]; \(I^2=0\%\)), adeovir (two trials; RR, 1.8 [95% CI, 0.8 to 4]; \(I^2=58\%\)) or tenofovir (1 trial; RR, 1.4 [95% CI, 0.6 to 3.4]), though estimates were imprecise and based on only one or two trials for drugs other than interferon. The adeovir risk estimate had the most statistical heterogeneity. It was based on two trials: a longer duration trial (72 weeks) found adeovir 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 (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]; \(I^2=5\%\)). Stratifying all antiviral trials according to duration resulted in similar estimates for studies ≤1 year duration (six trials; RR, 2.0 [95% CI, 1.3 to 3.2]; \(I^2=27\%\)) and those of more than one year duration (four trials; RR, 2.1 [95% CI, 1.4 to 3.1]; \(I^2=0\%\)). Removing one poor-quality trial also had no effect on the overall estimate (eight trials; RR, 2.1 [95% CI, 1.6 to 2.8]; \(I^2=0\%\)).

**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]; \(I^2=0\%\)) (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 (six trials; RR, 2.7 [95% CI, 1.1 to 6.4]; \(I^2=0\%\)). The pooled estimate favored lamivudine over placebo, but the difference was not statistically significant (four trials; RR, 1.7 [95% CI, 0.4 to 7.1]; \(I^2=0\%\)). The estimate for tenofovir was imprecise and based on one trial (RR, 3.1 [95% CI, 0.13 to 75]).

Estimates were similar for trials of HBeAg-positive patients (seven trials; RR, 2.6 [95% CI, 1.1 to 6.1]; \(I^2=0\%\)) and HBeAg-negative patients (four trials; RR, 1.9 [95% CI, 0.5 to 7.8]; \(I^2=0\%\)). Results were also similar when the analysis was restricted to trials of greater than one year duration (seven trials; RR, 2.2 [95% CI, 0.9 to 5.1]; \(I^2=0\%\)) or when excluding two poor-quality trials (nine trials; RR, 2.2 [95% CI, 1.0 to 5.0]; \(I^2=0\%\)). 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]; $I^2=0$).

**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]; $I^2=27\%$) (Figure 4). Estimates were similar for adefovir (four trials; RR, 2.9 [95% CI, 2.3 to 3.6]; $I^2=0\%$), lamivudine (five trials; RR, 2.4 [95% CI, 1.6 to 3.6]; $I^2=54\%$), and tenofovir (one trial; RR, 2.0 [95% CI, 1.4 to 2.9]). The estimate for interferon alfa-2b was imprecise (two trials; RR, 5.0 [95% CI, 0.6 to 40]; $I^2=28\%$). 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 (nine trials; RR, 2.7 [95% CI, 2.2 to 3.3]; $I^2=11\%$) or negative patients (three trials; RR, 2.0 [95% CI, 1.4 to 2.9]; $I^2=26\%$), studies of more than 1 year duration (five trials; RR, 2.4 [95% CI, 1.6 to 3.5]; $I^2=57\%$), or after excluding two poor-quality studies (10 trials; RR, 2.5 [95% CI, 2.0 to 3.0]; $I^2=31\%$). 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]; $I^2=0\%$).

**Virological Improvement.** Antiviral therapy was more effective than placebo or no treatment for achieving a reduction in HBV DNA level (nine trials; RR, 7.2 [95% CI, 3.2 to 16]; $I^2=58\%$) (Figure 5). Stratified by individual antiviral drug, the estimate for lamivudine was the most precise (four trials; RR, 4.4 [95% CI, 2.2 to 8.6]; $I^2=46\%$). Although statistical heterogeneity was present, estimates from all trials favored lamivudine (range of RR estimates, 2.5 to 7.0). For adefovir (two trials; RR, 29 [95% CI, 4.0 to 204]; $I^2=0\%$), interferon alfa-2b (two trials; RR, 7.5 [95% CI, 1.4 to 40]; $I^2=0\%$), and tenofovir (one trial; RR, 97 [95% CI, 6.1 to 1526]), 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 (nine trials; RR, 8.6 [95% CI, 3.8 to 20]; $I^2=64\%$) or to studies of more than 1 year duration (four trials; RR, 8.4 [95% CI, 1.5 to 49]; $I^2=76\%$) resulted in similar estimates, as did limiting the analysis to studies that enrolled HBeAg-positive (seven trials; RR, 6.2 [95% CI, 2.7 to 14]; $I^2=56\%$) patients. 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 1009] and 4.8 [95% CI, 0.62 to 36]). None of the trials were rated poor-quality.

**Histological Improvement.** Antiviral therapy was more effective than placebo or no treatment at improving histological outcomes (seven trials; RR, 2.1 [95% CI, 1.8 to 2.6]; $I^2=0\%$) (Figure 6). The definition of histological improvement varied among the studies, though 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 (two trials; RR, 1.9 [95% CI, 1.3 to 2.8] and 2.1 [95% CI, 1.5 to 2.8]) and lamivudine (three trials; RR, 2.3 [95% CI, 1.7 to 3.2]; $I^2=0\%$). Estimates from trials of interferon alfa-2b were less precise but consistent with the other drugs (two trials; RR, 3.5 [95% CI, 0.8 to 15] and 4.0...
Estimates were similar when the analysis was restricted to studies of more than 1 year duration (five trials; RR, 2.4 [95% CI, 1.8 to 3.2]; $I^2=0\%$) or when results were stratified for HBeAg positive (four trials; RR, 2.2 [95% CI, 1.8 to 2.7]; $I^2=0\%$) and HBeAg negative (three trials; RR, 2.1 [95% CI, 1.4 to 3]; $I^2=0\%$) patients. No trial was rated poor-quality.

Composite Intermediate Outcomes. Composite intermediate outcomes were reported in 10 trials (Table 5). The most commonly reported composite outcome was loss of HBV DNA plus ALT normalization (six trials; RR, 8.0 [95% CI, 2.0 to 32]; $I^2=79\%$) (Figure 7). Estimates from all trials favored antiviral therapy (range of RR estimates, 4.0 to 78), though 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 (six trials; RR, 8.3 [95% CI, 4.1 to 17]; $I^2=21\%$). 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] and 78 [95% CI, 4.9 to 1236]). The risk estimate remained statistically significant when the analysis was restricted to HBeAg negative patients (four trials; RR, 4.8 [95% CI, 1.3 to 19]; $I^2=78\%$) or after excluding one poor-quality trial (RR, 9.3 [95% CI, 1.6 to 55]; $I^2=83\%$). Results were also similar, but imprecise, for trials with followup duration of more than 1 year (three trials; RR, 9.6 [95% CI, 0.3 to 331]; $I^2=88\%$).

The composite intermediate outcome of clearance of HBeAg plus suppression of HBV DNA was evaluated in four trials. 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] and 11 [95% CI, 1.5 to 75]) and lamivudine was more effective than placebo in one larger (n=358) trial (RR, 3.3 [95% CI, 1.1 to 10]) but not in another, smaller (n=42) trial (RR, 2.5 [95% CI, 0.17 to 38]). 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]).

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

Four trials (in six publications) compared entecavir versus lamivudine, two trials pegylated interferon alfa 2a versus lamivudine, and two trials (reported in one publication) tenofovir versus adefovir (Appendix B5). Duration of followup ranged from 48 to 96 weeks. Five trials predominantly enrolled HBeAg positive patients (78% to 100%), and the remaining three trials 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 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 (one to four) (Table 6). Compared to lamivudine, entecavir was associated with increased likelihood of virological (four trials; RR, 1.6 [95% CI, 1.1 to 2.5]; $I^2=94\%$) and histological (two trials; RR, 1.2 [95% CI,
improvement, and pegylated interferon alfa-2b with increased likelihood of HBeAg loss or seroconversion (one trial; RR, 1.6 [95% CI, 1.2 to 2.1]);  
ALT normalization (two trials; RR, 1.4 [95% CI, 1.2 to 1.6]; \( I^2 = 0 \)); virological improvement (two trials; RR, 2.8 [95% CI, 1.9 to 4.4]; \( I^2 = 0 \)) and histological improvement (two trials; RR, 1.2 [95% CI, 1.0 to 1.4]; \( I^2 = 0 \)). Results for entecavir versus lamivudine on virological response were characterized by marked heterogeneity (four trials; RR, 1.6 [95% CI, 1.1 to 2.5]; \( I^2 = 94\% \) (Figure 8). There were no clear differences between tenofovir versus adefovir on various intermediate outcomes, in part due to imprecise estimates. 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 (three trials; RR, 0.70 [95% CI, 0.33 to 1.46]; \( I^2 = 0\% \)), hepatocellular carcinoma (five trials; RR, 0.57 [95% CI, 0.32 to 1.04]; \( I^2 = 2\% \)), and mortality (five trials; RR, 0.55 [95% CI, 0.18 to 1.71]; \( I^2 = 43\% \)) all favored antiviral therapy over placebo. None of the differences were statistically significant, estimates were imprecise due to small numbers of events and some trials had relatively short duration of followup. One study found disease worsening more likely in placebo patients compared to lamivudine (adjusted 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, Appendix B5). Three trials evaluated interferon alfa-2b, interferon alfa-2a, and two trials adefovir and four trials lamivudine. One trial was rated good-quality and the remainder fair-quality (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 and adefovir. One of the lamivudine trials followed patients for 1 year and the other for a median of 32 months. The placebo-controlled phase of the adefovir trial was 12 weeks. The two longest duration trials followed patients for 7 years.
after completing 18 weeks or 6 months of interferon alfa-2a therapy. 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 and one trial of lamivudine 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 or cirrhosis. One study enrolled adolescents.

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 and two trials of lamivudine recorded no deaths. Although pooled estimates for incident cirrhosis (three trials; RR, 0.70 [95% CI, 0.33 to 1.46]; I²=0%) hepatocellular carcinoma (five trials; RR, 0.57 [95% CI, 0.32 to 1.04]; I²=2%) and mortality (five trials; RR, 0.55 [95% CI, 0.18 to 1.71]; I²=43%) all favored antiviral therapy over placebo, none of the differences were statistically significant. Excluding trials with less than 2 years of followup 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. This trial was discontinued early (median followup, 2.7 years) after reaching a pre-specified stopping threshold on a composite primary outcome (hepatic decompensation, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or liver-related mortality). For hepatocellular cancer, it reported a relative risk for lamivudine versus placebo of 0.52 (95% CI, 0.27 to 1.02), 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 hazard ratios 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)—were similar (adjusted HR, 0.5 [95% CI, 0.6 to 0.7]).

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 (Appendix B5 and B6). All trials were rated good-quality.

The two trials of entecavir versus lamivudine were of similar design, except that one enrolled HBeAg-positive patients and the other HBeAg-negative patients. 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 to 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 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 enrolled HBeAg positive patients and the other enrolled HBeAg negative patients. Pooling results from all four trials for mortality also found 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.

**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 (seven 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 (nine 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]; $I^2=55\%$) versus lamivudine. There were no differences between entecavir versus lamivudine (three trials) or between tenofovir versus adefovir (two 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, Appendix B5). Data were available for adefovir (three trials), interferon alfa-2b (eight trials), lamivudine (nine trials), telbivudine (one trial), and tenofovir (one trial). 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. The trials that did not report cirrhosis information excluded patients with decompensated liver disease. One of the lamivudine trials and two of the interferon alfa-2b trials were rated poor-quality, two trials were rated good-quality, and the remainder fair-quality (Appendix B6). Eight trials were conducted in the United States, Europe, Australia, or New Zealand, and three were conducted in countries with both low and high HBV prevalence.

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]; $I^2=0\%$) (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 (eight trials; RR, 0.8 [95% CI, 0.6 to 1.1]; $I^2=0\%$) and adefovir (two trials; RR, 1.0 [95% CI, 0.4 to 2.1]; $I^2=31\%$). Results were also consistent for telbivudine (RR, 1.1 [95% CI, 0.9 to 1.3]) and tenofovir (RR, 0.5 [95% CI, 0.2 to 1.3]), but based on only one trial each.

Four lamivudine studies 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 (four trials; RR, 0.7 [95% CI, 0.5 to 1.0]; $I^2=0\%$) or the overall estimate (eight trials; RR, 8 [95% CI, 0.6 to 1.03]; $I^2=0\%$). There were no poor-quality trials.

Three trials 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 (nine trials; RR, 4.0 [95% CI, 1.4 to 11]; $I^2=0\%$) (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 (three trials; RR, 4.8 [95% CI, 0.6 to 41]; $I^2=0\%$), adefovir (three trials; RR, 2.9 [95% CI, 0.5 to 16]; $I^2=0\%$), and interferon alfa-2b (three trials; RR, 4.8 [95% CI, 0.9 to 26]; $I^2=0\%$) though estimates for individual drugs were imprecise and did not reach statistical significance.

Removing one poor-quality trial 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 versus placebo in risk for experiencing any adverse event (seven trials; RR, 0.96 [95% CI, 0.9 to 1.0]; $I^2=0\%$) (Figure 14).40, 57, 58, 60-62, 76 Rates of experiencing any adverse event on antiviral therapy ranged from 36 to 85 percent in the trials. Results were consistent for lamivudine (four trials; RR, 0.95 [95% CI, 0.9 to 1.0]; $I^2=14\%$)57, 58, 60, 76 adefovir (one trial; RR, 1.0 [95% CI, 0.9 to 1.2]),40 and tenofovir (one trial; RR, 0.95 [95% CI, 0.8 to 1.1]).61 though the latter two drugs were only evaluated in one trial each. The estimate for telbivudine favored placebo but was imprecise, did not reach statistical significance, and 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 versus lamivudine (three trials)64, 67, 68 or between tenofovir versus adefovir (two 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]; $I^2=55\%$) versus 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 outcomes) 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, 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), two studies evaluated biochemical remission (normalization of serum transaminase levels), one study evaluated HBeAg clearance, one study evaluated histological response (improvement in biopsy findings), and two studies evaluated composite intermediate outcomes (virological response plus HBeAg clearance, or virological plus biochemical response). The clinical outcomes also varied. Three studies evaluated death, two studies hepatocellular carcinoma, and the remainder various composite clinical outcomes (two or more of the following: death, liver transplantation, cirrhosis, or complications of cirrhosis). Four studies focused on HBeAg positive patients, and the remainder on HBeAg negative patients. 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; in the remainder patients received interferon. Two studies only included patients with cirrhosis, and in the other studies, the proportion of patients with cirrhosis ranged from 12 to 60 percent. Seven studies were rated fair-quality and three studies poor-quality. 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., only enrolling HBeAg negative or 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 make 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 negative patients, estimates of risk favored achieving the intermediate outcomes, though 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]). One study evaluated a composite intermediate outcome (virological response plus HBeAg clearance: adjusted HR, 0.59 [95% CI, 0.20 to 1.67]) 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]). For hepatocellular carcinoma, one study evaluated maintenance of virological remission (no virological breakthrough) (adjusted HR, 0.10 [95% CI, 0.01 to 0.77]), and one study evaluated achieving virological remission during therapy (adjusted HR, 0.77 [95% CI, 0.35 to 1.69]) in HBeAg negative patients. For composite clinical outcomes, one study evaluated HBeAg loss (adjusted HR, 0.06 [95% CI, 0.01 to 0.61]) and one study evaluated a 2-point improvement on the Histological Activity Index score (adjusted HR, 0.62 [95% CI, 0.06 to 6.9]) 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]) and three studies evaluated virological (adjusted HR, 0.24 [95% CI, 0.06 to 0.96]), biochemical (0.48 [95% CI, 0.23 to 1.0]), or a composite intermediate outcome (virological plus biochemical response: adjusted HR, 0.53 [95% CI, 0.29 to 0.91]) 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. 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 were 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%). 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. It found that an HBV screening strategy in a sexually transmitted disease clinic that only focused on testing of 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. 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 (five trials; RR, 0.57 [95% CI, 0.32 to 1.04]; $I^2=2\%$), 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 United States populations. Although some head-to-head trials of first-line versus older antivirals reported mortality or hepatocellular cancer, none were designed to evaluate clinical outcomes and all were severely underpowered. Our findings are similar to a recent systematic review that focused on results from randomized trials. Although other reviews 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]; $I^2=4\%$), 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]; $I^2=27\%$), ALT normalization (12 trials; RR, 2.5 [95% CI, 2.1 to 3.0]; $I^2=27\%$), reduction in HBV DNA (nine trials; RR, 7.2 [95% CI, 3.2 to 16]; $I^2=58\%$), reduction in HBV DNA (nine trials; RR, 7.2 [95% CI, 3.2 to 16]; $I^2=58\%$), histological improvement (seven trials; RR, 2.1 [95% CI, 1.8 to 2.6]; $I^2=0\%$), histological improvement (seven trials; RR, 2.1 [95% CI, 1.8 to 2.6]; $I^2=0\%$), and various composite outcomes. Results were generally consistent when analyses were stratified by individual drug, though some estimates were imprecise and not statistically significant. Like other recently conducted systematic reviews, we also found some evidence suggesting that the currently recommended first-line drugs tenofovir and entecavir are more effective than lamivudine at on various intermediate outcomes.

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.

Antiviral therapy was associated with greater risk of withdrawal due to adverse events versus placebo (nine trials; RR, 4.0 [95% CI, 1.4 to 11]; $I^2=0\%$), but trials found no difference in risk of serious adverse events (12 trials; RR, 0.8 [95% CI, 0.6 to 1.1]; $I^2=0\%$) or experiencing any adverse event (seven trials; RR, 0.96 [95% CI, 0.9 to 1.0]; $I^2=0\%$). 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, consistent with the known high prevalence of adverse events with interferon-based therapies. 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 serological and biochemical markers, but did not evaluate long-term clinical outcomes. Observational studies in high prevalence countries indicate that implementation of universal HBV vaccination is associated with reduced rates of hepatocellular carcinoma and other clinical outcomes related to chronic HBV infection, but were outside the scope of this review. 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 nonEnglish 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.\textsuperscript{104, 105} We also included a systematic review that included Chinese language, head-to-head trials of pegylated interferon versus nonpegylated interferon, which did not affect conclusions.\textsuperscript{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 the United States, since evidence from settings more applicable to United States practice was limited. Including such evidence potentially limits the applicability of the reviewed evidence to screening in the United States.

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.\textsuperscript{108, 109} Substantial reductions in prevalence have been observed among United States adolescents and younger adults (up to 50 years of age).\textsuperscript{109} In addition universal HBV vaccination has been adopted in over 190 countries\textsuperscript{24} and epidemiological data indicating declining HBV prevalence globally.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{113} However, research on combination therapies and new investigational agents, including drugs with novel viral targets,\textsuperscript{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, such as most of Asia and the western Pacific. Black persons are also at higher risk of HBV infection. 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 50 years of age 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) 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) 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.

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.
References

16. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: Special


hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. Gut. 2011;60(8):1109-16.


105. Pham B, Klassen TP, Lawson ML, et al. Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary. *J Clin Epidemiol*. 2005;58(8):769-76.


HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; KQ, key question.
Figure 2. HBeAg Loss, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>1.4.1 Adefovir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marcellin 2003 (1)</td>
<td>44</td>
<td>165</td>
<td>17</td>
</tr>
<tr>
<td>Zeng 2006</td>
<td>20</td>
<td>354</td>
<td>6</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td>3.9%</td>
</tr>
<tr>
<td>Total events</td>
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</tr>
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<td>Test for overall effect: Z = 1.52 (P = 0.13)</td>
<td></td>
</tr>
<tr>
<td>1.4.2 Interferon alfa 2b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayraktar 1993</td>
<td>15</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Perez 1990</td>
<td>10</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Sarin 1996</td>
<td>10</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Waked 1999</td>
<td>13</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>42</td>
<td>68</td>
<td>21.8%</td>
</tr>
<tr>
<td>Total events</td>
<td>48</td>
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<td></td>
</tr>
<tr>
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<td>Test for overall effect: Z = 3.89 (P = 0.0001)</td>
<td></td>
</tr>
<tr>
<td>1.4.3 Lamivudine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dienstag 1999 (2)</td>
<td>19</td>
<td>66</td>
<td>11</td>
</tr>
<tr>
<td>Lai 1997</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Yalco 2004</td>
<td>1</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Yao 1999</td>
<td>23</td>
<td>284</td>
<td>5</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>375</td>
<td>264</td>
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</tr>
<tr>
<td>Total events</td>
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<td>17</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.00; Chi² = 0.19, df = 2 (P = 0.94); I² = 0%</td>
<td>Test for overall effect: Z = 2.10 (P = 0.04)</td>
<td></td>
</tr>
<tr>
<td>1.4.4 Tenofovir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 2012</td>
<td>10</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>48</td>
<td>48</td>
<td>10.6%</td>
</tr>
<tr>
<td>Total events</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td>Test for overall effect: Z = 0.80 (P = 0.43)</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>1024</td>
<td>601</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>165</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.01; Chi² = 9.34, df = 9 (P = 0.41); I² = 4%</td>
<td>Test for overall effect: Z = 5.06 (P &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 3.96, df = 3 (P = 0.28), P = 24.7%</td>
<td>(1) 30 mg group vs placebo</td>
<td>(2) 6-week data</td>
<td></td>
</tr>
</tbody>
</table>

Screening for Hepatitis B Virus Infection 33 Pacific Northwest EPC
Figure 3. HBsAg Loss, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.5.2 Interferon alfa 2b</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayraktar 1993</td>
<td>1 25</td>
<td>0 10</td>
<td>5.4%</td>
<td>1.27 [0.06, 28.60]</td>
</tr>
<tr>
<td>Lamperotic 1997</td>
<td>2 21</td>
<td>0 21</td>
<td>5.9%</td>
<td>5.00 [0.25, 98.27]</td>
</tr>
<tr>
<td>Perez 1990</td>
<td>1 17</td>
<td>0 18</td>
<td>5.3%</td>
<td>3.17 [0.14, 72.90]</td>
</tr>
<tr>
<td>Pernillo 1990</td>
<td>11 126</td>
<td>0 43</td>
<td>6.6%</td>
<td>7.97 [0.48, 132.43]</td>
</tr>
<tr>
<td>Sarin 1986</td>
<td>3 20</td>
<td>1 21</td>
<td>11.1%</td>
<td>3.15 [0.36, 27.83]</td>
</tr>
<tr>
<td>Waked 1990</td>
<td>6 20</td>
<td>3 20</td>
<td>34.2%</td>
<td>2.00 [0.58, 6.91]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>229</td>
<td>133</td>
<td>68.5%</td>
<td>2.66 [1.11, 6.39]</td>
</tr>
<tr>
<td>Total events</td>
<td>24 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 5 (P = 0.93); I² = 0%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.19 (P = 0.03)</td>
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1.5.3 Lamivudine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Ali 2003</td>
<td>3 32</td>
<td>1 30</td>
<td>10.8%</td>
<td>2.81 [0.31, 25.58]</td>
</tr>
<tr>
<td>Chan 2007</td>
<td>1 89</td>
<td>0 47</td>
<td>5.2%</td>
<td>1.60 [0.07, 38.53]</td>
</tr>
<tr>
<td>Dienstag 1999</td>
<td>1 66</td>
<td>0 71</td>
<td>5.2%</td>
<td>3.22 [0.13, 77.78]</td>
</tr>
<tr>
<td>Tassopoulos 1999</td>
<td>0 60</td>
<td>1 64</td>
<td>5.2%</td>
<td>0.36 [0.01, 8.55]</td>
</tr>
<tr>
<td>Yalcin 2004</td>
<td>0 13</td>
<td>0 33</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>260</td>
<td>245</td>
<td>28.3%</td>
<td>1.72 [0.42, 7.06]</td>
</tr>
<tr>
<td>Total events</td>
<td>5 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.75 (P = 0.45)</td>
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1.5.4 Tenofovir

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Murray 2012</td>
<td>1 52</td>
<td>0 54</td>
<td>5.2%</td>
<td>3.11 [0.13, 74.74]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>52</td>
<td>54</td>
<td>5.2%</td>
<td>3.11 [0.13, 74.74]</td>
</tr>
<tr>
<td>Total events</td>
<td>1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.70 (P = 0.48)</td>
<td></td>
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</tr>
</tbody>
</table>

| Total (95% CI) | 541   | 432   | 100.0%   | 2.39 [1.16, 4.94] |
| Total events   | 30 6  |        |         |                      |                      |
| Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 10 (P = 0.98); I² = 0% |
| Test for overall effect: Z = 2.38 (P = 0.02) |
| Test for subgroup differences: Chi² = 0.29, df = 2 (P = 0.86), I² = 0% |
Figure 4. ALT Normalization, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>1.3.1 Adefovir</td>
<td>84</td>
<td>118</td>
<td>17 59 12.7%</td>
</tr>
<tr>
<td>Hadzhiyannis 2003</td>
<td>36</td>
<td>56</td>
<td>6 27 5.6%</td>
</tr>
<tr>
<td>Jonas 2008</td>
<td>81</td>
<td>168</td>
<td>26 164 14.0%</td>
</tr>
<tr>
<td>Marcellin 2003</td>
<td>140</td>
<td>330</td>
<td>15 106 10.4%</td>
</tr>
<tr>
<td>Zeng 2006</td>
<td>670</td>
<td>358</td>
<td>42.7%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>341</td>
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<tr>
<td>Total events</td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Chi² = 0.54, df = 3 (P = 0.91); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 8.86 (P &lt; 0.00001)</td>
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</tbody>
</table>

1.3.2 Interferon alfa 2b

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Bayraktar 1993</td>
<td>17</td>
<td>25</td>
<td>0 10 0.5%</td>
</tr>
<tr>
<td>Perez 1990</td>
<td>2</td>
<td>17</td>
<td>1 18 0.7%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>42</td>
<td>28</td>
<td>1.1%</td>
</tr>
<tr>
<td>Total events</td>
<td>19</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.64, Chi² = 1.39, df = 1 (P = 0.24); I² = 28%</td>
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<td>Test for overall effect: Z = 1.51 (P = 0.13)</td>
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</tbody>
</table>

1.3.3 Lamivudine

<table>
<thead>
<tr>
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<th>Treatment</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Dienstag 1999</td>
<td>27</td>
<td>66</td>
<td>5 68 4.0%</td>
</tr>
<tr>
<td>Lai 1998</td>
<td>65</td>
<td>95</td>
<td>12 50 9.8%</td>
</tr>
<tr>
<td>Yao 1999</td>
<td>91</td>
<td>151</td>
<td>14 51 11.1%</td>
</tr>
<tr>
<td>Bodilya 2005</td>
<td>8</td>
<td>18</td>
<td>4 19 3.2%</td>
</tr>
<tr>
<td>Chan 2007</td>
<td>53</td>
<td>89</td>
<td>18 47 13.3%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>419</td>
<td>235</td>
<td>41.3%</td>
</tr>
<tr>
<td>Total events</td>
<td>247</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.10, Chi² = 8.77, df = 4 (P = 0.07); I² = 54%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.42 (P &lt; 0.00001)</td>
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</tbody>
</table>

1.3.4 Tenofovir

<table>
<thead>
<tr>
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<th>Treatment</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Murray 2012</td>
<td>40</td>
<td>52</td>
<td>21 54 14.8%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>52</td>
<td>54</td>
<td>14.8%</td>
</tr>
<tr>
<td>Total events</td>
<td>40</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.65 (P = 0.0003)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| Total (95% CI)   | 1183      | 675     | 100.0%     | 2.49 [2.66, 3.01] |
| Total events     | 647       | 139     |            |                    |
| Heterogeneity: Tau² = 0.03, Chi² = 15.12, df = 11 (P = 0.18); I² = 27% |
| Test for overall effect: Z = 9.45 (P < 0.00001) |
| Test for subgroup differences: Chi² = 3.25, df = 3 (P = 0.36), I² = 7.8% |
Figure 5. HBV DNA Loss, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Adefovir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadziyannis 2003</td>
<td>63</td>
<td>123</td>
<td>0</td>
<td>61</td>
<td>6.6%</td>
<td>63.50 [4.00, 1009.28]</td>
<td></td>
</tr>
<tr>
<td>Zeng 2006</td>
<td>18</td>
<td>352</td>
<td>0</td>
<td>119</td>
<td>6.4%</td>
<td>12.56 [0.78, 207.12]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>81</td>
<td>475</td>
<td>189</td>
<td>13.0%</td>
<td></td>
<td>28.55 [3.99, 204.39]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>81</td>
<td></td>
<td>189</td>
<td></td>
<td>13.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.34 (P = 0.0008)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>1.1.2 Interferon alfa 2b</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez 1990</td>
<td>1</td>
<td>17</td>
<td>0</td>
<td>18</td>
<td>5.4%</td>
<td>3.17 [0.14, 72.80]</td>
<td></td>
</tr>
<tr>
<td>Sarrh 1996</td>
<td>10</td>
<td>20</td>
<td>1</td>
<td>21</td>
<td>10.5%</td>
<td>10.50 [1.48, 74.71]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>11</td>
<td>37</td>
<td>1</td>
<td>38</td>
<td>15.9%</td>
<td>7.49 [1.42, 39.54]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td></td>
<td>1</td>
<td></td>
<td>15.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.37 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>1.1.3 Lamivudine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan 2007</td>
<td>9</td>
<td>89</td>
<td>1</td>
<td>47</td>
<td>10.1%</td>
<td>4.75 [0.62, 36.39]</td>
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</tr>
<tr>
<td>Dienstag 1999</td>
<td>26</td>
<td>63</td>
<td>11</td>
<td>69</td>
<td>23.6%</td>
<td>2.79 [1.52, 5.12]</td>
<td></td>
</tr>
<tr>
<td>Yalcin 2004</td>
<td>1</td>
<td>13</td>
<td>1</td>
<td>33</td>
<td>6.6%</td>
<td>2.54 [0.17, 37.64]</td>
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</tr>
<tr>
<td>Yao 1999</td>
<td>228</td>
<td>263</td>
<td>11</td>
<td>99</td>
<td>24.0%</td>
<td>7.03 [4.02, 12.32]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>458</td>
<td>248</td>
<td></td>
<td>64.5%</td>
<td></td>
<td>4.36 [2.22, 8.58]</td>
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<tr>
<td>Total events</td>
<td>267</td>
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<td>24</td>
<td></td>
<td>64.5%</td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.19; Chi² = 5.56, df = 3 (P = 0.14); I² = 46%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 4.27 (P &lt; 0.0001)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.1.4 Tenofovir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 2012</td>
<td>46</td>
<td>52</td>
<td>0</td>
<td>54</td>
<td>6.6%</td>
<td>96.51 [6.10, 1526.38]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>46</td>
<td>52</td>
<td>0</td>
<td>54</td>
<td>6.6%</td>
<td>96.51 [6.10, 1526.38]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>46</td>
<td></td>
<td>0</td>
<td></td>
<td>6.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 3.24 (P = 0.001)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1022</td>
<td>521</td>
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<td></td>
<td>100.0%</td>
<td>7.22 [3.28, 16.31]</td>
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</tr>
<tr>
<td>Total events</td>
<td>405</td>
<td></td>
<td>25</td>
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<td></td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.64; Chi² = 19.01, df = 8 (P = 0.01); I² = 58%</td>
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<tr>
<td>Test for overall effect: Z = 4.76 (P &lt; 0.0001)</td>
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</tr>
<tr>
<td>Test for subgroup differences: Chi² = 7.19, df = 3 (P = 0.07), I² = 58.3%</td>
<td></td>
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</tbody>
</table>

Favors control Favors antiviral therapy
Figure 6. Histologic Improvement, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 Adefovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadziyannis 2003</td>
<td>77</td>
<td>121</td>
<td>197</td>
<td>22.8%</td>
<td>1.91 [1.29, 2.82]</td>
<td></td>
</tr>
<tr>
<td>Marcellin 2003</td>
<td>89</td>
<td>168</td>
<td>257</td>
<td>38.7%</td>
<td>2.08 [1.54, 2.61]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>255</td>
<td>329</td>
<td>664</td>
<td>61.5%</td>
<td>2.02 [1.53, 2.63]</td>
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</tr>
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<td>Total events</td>
<td>165</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Ch² = 1.12, df = 1 (P = 0.73); I² = 0%</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.77 (P &lt; 0.00001)</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1.2.2 Interferon alfa 2b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamertico 1997</td>
<td>7</td>
<td>21</td>
<td>70</td>
<td>1.7%</td>
<td>3.50 [0.82, 14.93]</td>
<td></td>
</tr>
<tr>
<td>Waked 1990</td>
<td>4</td>
<td>20</td>
<td>24</td>
<td>0.8%</td>
<td>4.00 [0.49, 32.72]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>11</td>
<td>41</td>
<td>52</td>
<td>2.4%</td>
<td>3.65 [1.11, 12.06]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>3</td>
<td></td>
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<td></td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Ch² = 0.01, df = 1 (P = 0.92); I² = 0%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.13 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1.2.3 Lamivudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan 2007</td>
<td>14</td>
<td>18</td>
<td>32</td>
<td>2.3%</td>
<td>3.11 [0.91, 10.59]</td>
<td></td>
</tr>
<tr>
<td>Dienstag 1999</td>
<td>34</td>
<td>66</td>
<td>100</td>
<td>14.5%</td>
<td>2.29 [1.40, 3.73]</td>
<td></td>
</tr>
<tr>
<td>Lai 1998</td>
<td>80</td>
<td>143</td>
<td>223</td>
<td>19.2%</td>
<td>2.27 [1.48, 3.48]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>128</td>
<td>36</td>
<td></td>
<td>36.0%</td>
<td>2.32 [1.70, 3.17]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>128</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Ch² = 0.23, df = 2 (P = 0.69); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.30 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>557</td>
<td>411</td>
<td>557</td>
<td>100.0%</td>
<td>2.15 [1.79, 2.59]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>305</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Ch² = 1.65, df = 6 (P = 0.95); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.04 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Ch² = 1.28, df = 2 (P = 0.53), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 7. HBV DNA Loss Plus ALT Normalization, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>13</td>
<td>56</td>
<td>27</td>
<td>12.3%</td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Not applicable</td>
<td>Test for overall effect: Z = 1.82 (P = 0.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.6.1 Adefovir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonas 2008</td>
<td>13</td>
<td>56</td>
<td>27</td>
<td>12.3%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>13</td>
<td>56</td>
<td>27</td>
<td>12.3%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>13</td>
<td>56</td>
<td>27</td>
<td>12.3%</td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Not applicable</td>
<td>Test for overall effect: Z = 1.82 (P = 0.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.6.2 Interferon alfa 2b</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadziyannis 1990</td>
<td>11</td>
<td>25</td>
<td>25</td>
<td>19.4%</td>
</tr>
<tr>
<td>Lamperdic 1997</td>
<td>6</td>
<td>20</td>
<td>20</td>
<td>19.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>17</td>
<td>45</td>
<td>45</td>
<td>31.6%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>17</td>
<td>45</td>
<td>45</td>
<td>31.6%</td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%</td>
<td>Test for overall effect: Z = 2.93 (P = 0.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.6.3 Lamivudine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan 2007</td>
<td>23</td>
<td>89</td>
<td>9</td>
<td>22.9%</td>
</tr>
<tr>
<td>Tassopoulous 1999</td>
<td>34</td>
<td>54</td>
<td>3</td>
<td>20.9%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>57</td>
<td>143</td>
<td>101</td>
<td>43.8%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>57</td>
<td>143</td>
<td>101</td>
<td>43.8%</td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tau² = 2.33; Chi² = 11.39, df = 1 (P = 0.0007); I² = 91%</td>
<td>Test for overall effect: Z = 1.17 (P = 0.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.6.4 Tenofovir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 2012</td>
<td>37</td>
<td>52</td>
<td>0</td>
<td>12.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>37</td>
<td>52</td>
<td>0</td>
<td>12.4%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>37</td>
<td>52</td>
<td>0</td>
<td>12.4%</td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Not applicable</td>
<td>Test for overall effect: Z = 3.02 (P = 0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>297</td>
<td>228</td>
<td>100.0%</td>
<td>7.96 [1.99, 31.86]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>124</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tau² = 2.07; Chi² = 23.98, df = 5 (P = 0.0002); I² = 79%</td>
<td>Test for overall effect: Z = 2.93 (P = 0.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for subgroup differences</strong></td>
<td>Chi² = 3.25, df = 3 (P = 0.35), I² = 8.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 2.3 HBV DNA undetectable

### 2.3.1 Entecavir vs lamivudine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Lamivudine Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2008</td>
<td>284</td>
<td>354</td>
<td>137</td>
<td>355</td>
<td>16.5%</td>
<td>2.08 [1.81, 2.39]</td>
<td></td>
</tr>
<tr>
<td>Lai 2002</td>
<td>11</td>
<td>45</td>
<td>7</td>
<td>41</td>
<td>7.5%</td>
<td>1.40 [0.60, 3.27]</td>
<td></td>
</tr>
<tr>
<td>Lai 2005</td>
<td>293</td>
<td>325</td>
<td>225</td>
<td>313</td>
<td>16.8%</td>
<td>1.25 [1.16, 1.36]</td>
<td></td>
</tr>
<tr>
<td>Ren 2007</td>
<td>15</td>
<td>21</td>
<td>8</td>
<td>21</td>
<td>10.4%</td>
<td>1.88 [1.02, 3.45]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>746</td>
<td>730</td>
<td>51.3%</td>
<td></td>
<td></td>
<td>1.63 [1.07, 2.48]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 603 vs 377

Heterogeneity: Tau² = 0.14; Chi² = 46.98; df = 3 (P < 0.00001); I² = 94%

Test for overall effect: Z = 2.26 (P = 0.02)

### 2.3.2 Pegylated interferon alfa 2a vs lamivudine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Lamivudine Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau 2005</td>
<td>39</td>
<td>271</td>
<td>14</td>
<td>272</td>
<td>10.7%</td>
<td>2.60 [1.55, 5.03]</td>
<td></td>
</tr>
<tr>
<td>Marcellin 2004</td>
<td>34</td>
<td>177</td>
<td>12</td>
<td>181</td>
<td>10.2%</td>
<td>2.90 [1.55, 5.41]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>448</td>
<td>453</td>
<td>20.8%</td>
<td></td>
<td></td>
<td>2.84 [1.85, 4.36]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 73 vs 26

Heterogeneity: Tau² = 0.00; Chi² = 0.01; df = 1 (P = 0.94); I² = 0%

Test for overall effect: Z = 4.79 (P < 0.00001)

### 2.3.4 Tenofovir vs adefovir

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Lamivudine Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcellin 2008 Study 102</td>
<td>233</td>
<td>250</td>
<td>79</td>
<td>125</td>
<td>16.5%</td>
<td>1.47 [1.28, 1.69]</td>
<td></td>
</tr>
<tr>
<td>Marcellin 2008 Study 103</td>
<td>134</td>
<td>176</td>
<td>12</td>
<td>90</td>
<td>11.4%</td>
<td>5.71 [3.35, 9.73]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>426</td>
<td>425</td>
<td>27.9%</td>
<td></td>
<td></td>
<td>2.85 [1.56, 5.30]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 367 vs 91

Heterogeneity: Tau² = 1.34; Chi² = 35.07; df = 1 (P < 0.00001); I² = 97%

Test for overall effect: Z = 1.28 (P = 0.21)
Figure 9. Incident Cirrhosis, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Interferon alfa 2a</td>
<td>Lin 1999</td>
<td>8</td>
<td>67</td>
<td>5</td>
<td>34</td>
<td>50.2%</td>
</tr>
<tr>
<td></td>
<td>Mazzella 1999</td>
<td>4</td>
<td>33</td>
<td>6</td>
<td>31</td>
<td>39.8%</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>100</td>
<td>65</td>
<td>65</td>
<td>89.9%</td>
<td>0.72 [0.33, 1.57]</td>
</tr>
<tr>
<td>Total events</td>
<td>12</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.82 (P = 0.41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.2 Interferon alfa 2b</td>
<td>Waked 1990</td>
<td>1</td>
<td>20</td>
<td>2</td>
<td>20</td>
<td>10.1%</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>10.1%</td>
<td>0.50 [0.05, 5.08]</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.59 (P = 0.56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>120</td>
<td>85</td>
<td>100.0%</td>
<td>0.70 [0.33, 1.46]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 2 (P = 0.91); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.96 (P = 0.34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors antiviral therapy Favors control
Figure 10. Hepatocellular Cancer, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.2.1 Interferon alfa 2a</td>
<td>Lin 1999</td>
<td>1</td>
<td>67</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mazzella 1999</td>
<td>2</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>100</td>
<td>65</td>
<td>17.4%</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 0.05; Chi² = 1.89; df = 1 (P = 0.17); I² = 47%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 0.99 (P = 0.32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.2 Interferon alfa 2b</td>
<td>Lampertico 1997</td>
<td>1</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>21</td>
<td>21</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 0.68 (P = 0.49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.3 Lamivudine</td>
<td>Chan 2007</td>
<td>3</td>
<td>89</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Law 2004</td>
<td>17</td>
<td>436</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>525</td>
<td>262</td>
<td>78.0%</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>20</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.87; df = 1 (P = 0.35); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 1.72 (P = 0.09)</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Total (95% CI)</td>
<td>646</td>
<td>348</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 0.01; Chi² = 4.07; df = 4 (P = 0.40); I² = 2%</td>
<td></td>
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<tr>
<td></td>
<td>Test for overall effect: Z = 1.83 (P = 0.07)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Test for subgroup differences: Chi² = 1.25, df = 2 (P = 0.53), I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Figure 11. Mortality, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.3.1 Adefovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonas 2008</td>
<td>0</td>
<td>56</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Zeng 2006</td>
<td>0</td>
<td>380</td>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>416</td>
<td>147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Not applicable</td>
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<td></td>
</tr>
</tbody>
</table>

1.3.2 Interferon alfa 2a

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Lin 1999</td>
<td>1</td>
<td>37</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>Mazzella 1999</td>
<td>0</td>
<td>33</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.16 (P = 0.03)</td>
<td></td>
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</tr>
</tbody>
</table>

1.3.3 Interferon alfa 2b

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Penttila 1990</td>
<td>1</td>
<td>126</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>Waked 1990</td>
<td>3</td>
<td>20</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>146</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 1.26; Chi² = 2.15, df = 1 (P = 0.14); P = 53%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.48 (P = 0.63)</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

1.3.4 Lamivudine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antiviral therapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Dienstag 1999</td>
<td>0</td>
<td>86</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>Lei 1998</td>
<td>0</td>
<td>285</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>Liaw 2004</td>
<td>12</td>
<td>436</td>
<td>4</td>
<td>215</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>787</td>
<td>359</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>12</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.69 (P = 0.49)</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Total (95% CI) 1449 634 100.0% 0.55 [0.18, 1.71]
Total events 17 14
Heterogeneity: Tau² = 0.89; Chi² = 7.03, df = 4 (P = 0.13); P = 43%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Chi² = 4.84, df = 2 (P = 0.09), P = 58.7%
### Figure 12. Serious Adverse Events, Antiviral Therapy Versus Placebo or No Treatment

#### 1.1 Lamivudine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan 2007</td>
<td>13</td>
<td>89</td>
<td>102</td>
<td>1.14 [0.46, 2.82]</td>
</tr>
<tr>
<td>Dienstagger 1999</td>
<td>0</td>
<td>85</td>
<td>95</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Lai 1997</td>
<td>0</td>
<td>38</td>
<td>38</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Lai 1998</td>
<td>5</td>
<td>285</td>
<td>290</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Liaw 2004</td>
<td>54</td>
<td>438</td>
<td>492</td>
<td>0.70 [0.48, 1.03]</td>
</tr>
<tr>
<td>Tsachourous 1999</td>
<td>3</td>
<td>60</td>
<td>63</td>
<td>0.81 [0.19, 3.48]</td>
</tr>
<tr>
<td>Yalin 2004</td>
<td>0</td>
<td>13</td>
<td>13</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Yao 1999</td>
<td>0</td>
<td>322</td>
<td>322</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1387</strong></td>
<td><strong>817</strong></td>
<td><strong>2104</strong></td>
<td><strong>0.77 [0.55, 1.08]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>75</strong></td>
<td><strong>48</strong></td>
<td><strong>123</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 3 (P = 0.62); I² = 0%

Test for overall effect: Z = 1.49 (P = 0.13)

#### 1.1.2 Adefovir

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haddyaneas 2003</td>
<td>4</td>
<td>123</td>
<td>127</td>
<td>0.50 [0.13, 1.92]</td>
</tr>
<tr>
<td>Marcellin 2003</td>
<td>33</td>
<td>344</td>
<td>377</td>
<td>1.23 [0.67, 2.28]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>487</strong></td>
<td><strong>228</strong></td>
<td><strong>715</strong></td>
<td><strong>0.96 [0.43, 2.13]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>37</strong></td>
<td><strong>17</strong></td>
<td><strong>54</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.13; Chi² = 1.44, df = 1 (P = 0.23); I² = 31%

Test for overall effect: Z = 0.10 (P = 0.92)

#### 1.1.3 Telbivudine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lai 2004</td>
<td>0</td>
<td>36</td>
<td>36</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>36</strong></td>
<td><strong>7</strong></td>
<td><strong>43</strong></td>
<td><strong>Not estimable</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Not applicable

#### 1.1.4 Tenofovir

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray 2012</td>
<td>6</td>
<td>52</td>
<td>58</td>
<td>0.52 [0.21, 1.28]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>52</strong></td>
<td><strong>54</strong></td>
<td><strong>106</strong></td>
<td><strong>0.52 [0.21, 1.28]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>6</strong></td>
<td><strong>12</strong></td>
<td><strong>18</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 1.42 (P = 0.15)

Total (95% CI) 1862 / 906 = 100.0% 0.80 [0.61, 1.06]

Total events 118 / 77 = 150.0% 0.80 [0.61, 1.06]

Heterogeneity: Tau² = 0.00; Chi² = 5.10, df = 6 (P = 0.53); I² = 0%

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Chi² = 1.03, df = 2 (P = 0.60), I² = 0%
Figure 13. Withdrawals Due to Adverse Events, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All 2003</td>
<td>3</td>
<td>32</td>
<td>6.58 [0.35, 122.21]</td>
</tr>
<tr>
<td>Tassopoulos 1999</td>
<td>1</td>
<td>60</td>
<td>3.25 [0.13, 78.18]</td>
</tr>
<tr>
<td>Yao 1999</td>
<td>0</td>
<td>322</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>414</td>
<td>202</td>
<td>4.76 [0.55, 46.96]</td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.42 (P = 0.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Hadjizyannis 2003 | 0         | 123     | Not estimable |
| Jonas 2008        | 1         | 56      | 1.47 [0.06, 35.03] |
| Marcellin 2003    | 8         | 344     | 3.88 [0.49, 30.80] |
| Subtotal (95% CI) | 523       | 255     | 2.91 [0.51, 16.45] |
| Total events      | 9         | 1       |            |
| Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0% |
| Test for overall effect: Z = 1.21 (P = 0.23) |

| Lampanico 1997    | 5         | 21      | 11.00 [0.65, 187.17] |
| Perez 1990        | 1         | 18      | 2.84 [0.12, 65.34] |
| Pavlin 1990       | 4         | 126     | 3.12 [0.17, 56.78] |
| Subtotal (95% CI) | 165       | 81      | 4.76 [0.87, 26.24] |
| Total events      | 10        | 0       |            |
| Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0% |
| Test for overall effect: Z = 1.80 (P = 0.07) |
| Total (95% CI)    | 1102      | 538     | 3.97 [1.38, 11.43] |
| Total events      | 23        | 1       |            |
| Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 6 (P = 0.98); I² = 0% |
| Test for overall effect: Z = 2.55 (P = 0.01) |
| Test for subgroup differences: Chi² = 0.20, df = 2 (P = 0.91), I² = 0% |

Screening for Hepatitis B Virus Infection 44 Pacific Northwest EPC
Figure 14. Any Adverse Events, Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.3.1 Lamivudine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lai 1998</td>
<td>224</td>
<td>285</td>
<td>56</td>
<td>73</td>
<td>16.5%</td>
</tr>
<tr>
<td>Liew 2004</td>
<td>335</td>
<td>436</td>
<td>178</td>
<td>215</td>
<td>50.9%</td>
</tr>
<tr>
<td>Tassopoulos 1999</td>
<td>28</td>
<td>60</td>
<td>40</td>
<td>65</td>
<td>2.9%</td>
</tr>
<tr>
<td>Yao 1999</td>
<td>138</td>
<td>322</td>
<td>45</td>
<td>107</td>
<td>5.0%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1103</td>
<td>460</td>
<td></td>
<td>75.3%</td>
<td>0.95 [0.88, 1.03]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>725</td>
<td>319</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 3.50, df = 3 (P = 0.32); I² = 14%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.26 (P = 0.21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **1.3.2 Adefovir**  |                 |               |             |                               |                               |
| Hadziyannis 2003   | 94              | 123           | 45          | 61                            | 10.1%                         | 1.04 [0.87, 1.24]             |
| Subtotal (95% CI)  | 123             | 61            |             | 10.1%                         | 1.04 [0.87, 1.24]             |
| **Total events**   | 94              | 45            |             |                               |                               |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.39 (P = 0.70) |

| **1.3.3 Telbivudine** |                 |               |             |                               |                               |
| Lai 2004            | 13              | 36            | 1           | 7                             | 0.1%                          | 2.53 [0.39, 16.33]            |
| Subtotal (95% CI)   | 36              | 7             |             | 0.1%                          | 2.53 [0.39, 16.33]            |
| **Total events**    | 13              | 1             |             |                               |                               |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.97 (P = 0.33) |

| **1.3.4 Tenofovir**  |                 |               |             |                               |                               |
| Murray 2012         | 44              | 52            | 48          | 54                            | 14.5%                         | 0.96 [0.82, 1.11]             |
| Subtotal (95% CI)   | 52              | 54            |             | 14.5%                         | 0.96 [0.82, 1.11]             |
| **Total events**    | 44              | 46            |             |                               |                               |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.65 (P = 0.52) |

| Total (95% CI)      | 1314            | 582           | 100.0%      | 0.96 [0.90, 1.01]             |
| Total events        | 876             | 413           |             |                               |
| Heterogeneity: Tau² = 0.00; Chi² = 5.43, df = 6 (P = 0.49); I² = 0% |
| Test for overall effect: Z = 1.51 (P = 0.13) |
| Test for subgroup differences: Chi² = 1.80, df = 3 (P = 0.61), I² = 0% |
### Table 1. Typical Interpretation of Serologic Test Results for Hepatitis B Infection

<table>
<thead>
<tr>
<th>Serologic marker</th>
<th>HBsAg&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total anti-HBc&lt;sup&gt;b&lt;/sup&gt;</th>
<th>IgM&lt;sup&gt;c&lt;/sup&gt; anti-HBc</th>
<th>Anti-HBs&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Never infected</td>
</tr>
<tr>
<td>*&lt;sup&gt;f&lt;/sup&gt;&lt;sup&gt;,g&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Early acute infection; transient (up to 18 days) after vaccination</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ or -</td>
<td>-</td>
<td>Acute infection</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Recovered from past infection and immune</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>False-positive (i.e., susceptible); past infection; “low-level” chronic infection;&lt;sup&gt;h&lt;/sup&gt; or passive transfer of anti-HBc to infant born to HBsAg-positive mother</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Immune if concentration is ≥10 mIU/mL after vaccine series completion;&lt;sup&gt;i&lt;/sup&gt; passive transfer after hepatitis B immune globulin administration</td>
</tr>
</tbody>
</table>

Reproduced with Permission from Mast et al, 2006.<sup>6</sup><br>
<sup>a</sup>Hepatitis B surface antigen.<br>
<sup>b</sup>Antibody to hepatitis B core antigen.<br>
<sup>c</sup>Immunoglobulin M.<br>
<sup>d</sup>Antibody to HBsAg.<br>
<sup>e</sup>Negative test result.<br>
<sup>f</sup>Positive test result.<br>
<sup>g</sup>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.<br>
<sup>h</sup>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).<br>
<sup>i</sup>Milli-International units per milliliter.
Table 2. Alternative Screening Strategies: Study Characteristics

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Setting</th>
<th>Population characteristics</th>
<th>HBV Screening Strategies</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Spenatto, 2013 France | Cross-sectional | N=6,194<sup>a</sup> | 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: 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 | Fair |

<sup>a</sup>183 patients (1 HBV case) did not have information on country of birth.
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

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>HBV Prevalence</th>
<th>Screening Strategy</th>
<th>Proportion screened</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Number needed to screen to identify one case of HBV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spenatto, 2013&lt;sup&gt;36&lt;/sup&gt; France</td>
<td>0.8% (49/6194)</td>
<td>A: Screen all</td>
<td>A: 100% (6194/6194)</td>
<td>A: 100% (49/49)</td>
<td>A: 0% (0/6145)</td>
<td>A: 126</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: Screening those born in moderate or high prevalence (≥2%) country</td>
<td>B: 12% (761/6011)</td>
<td>B: 31% (15/48)</td>
<td>B: 87% (5217/5963)</td>
<td>B: 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: Same as B, plus men and unemployed</td>
<td>C: 64% (3949/6194)</td>
<td>C: 98% (48/49)</td>
<td>C: 37% (2244/6145)</td>
<td>C: 82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td>D: 73% (4504/6194)</td>
<td>D: 84% (41/49)</td>
<td>D: 110</td>
<td>D: 110</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E: Same as D, except prior vaccination history not considered</td>
<td>E: 84% (5205/6194)</td>
<td>E: 94% (46/49)</td>
<td>E: 16% (986/6145)</td>
<td>E: 113</td>
</tr>
</tbody>
</table>

HBV, hepatitis B virus.
Table 4. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Intermediate Outcomes: Study Characteristics

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design Duration</th>
<th>Country</th>
<th>Population</th>
<th>HBeAg status</th>
<th>Cirrhosis</th>
<th>Intermediate outcomes reported</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adefovir vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadziyannis 2003&lt;sup&gt;30&lt;/sup&gt;</td>
<td>RCT 48 weeks</td>
<td>Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore</td>
<td>n=185 Mean age 46 years 83% male</td>
<td>Negative</td>
<td>11%</td>
<td>ALT normalization Virologic improvement Histologic improvement</td>
<td>Fair</td>
</tr>
<tr>
<td>Jonas 2008&lt;sup&gt;31&lt;/sup&gt;</td>
<td>RCT 48 weeks</td>
<td>Germany, Poland, Spain, United Kingdom, United States</td>
<td>n=83 Mean age 14 years 75% male</td>
<td>Positive</td>
<td>NR</td>
<td>ALT normalization Composite outcomes</td>
<td>Fair</td>
</tr>
<tr>
<td>Marcellin 2003&lt;sup&gt;42&lt;/sup&gt;</td>
<td>RCT 48 weeks</td>
<td>Australia, Canada, France, Germany, Italy, Malaysia, The Philippines, Singapore, Spain, Taiwan, Thailand, United Kingdom, United States&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n=515 Mean age 35 years 74% male</td>
<td>Positive</td>
<td>NR</td>
<td>HBeAg loss/seroconversion ALT normalization Histologic improvement</td>
<td>Fair</td>
</tr>
<tr>
<td>Zeng 2006&lt;sup&gt;43&lt;/sup&gt;</td>
<td>RCT 12 weeks</td>
<td>China</td>
<td>n=480 Mean age 32 years 83% male</td>
<td>Positive</td>
<td>NR</td>
<td>HBeAg loss/seroconversion ALT normalization Virologic improvement</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Interferon Alfa 2b vs No Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayraktar 1993&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Controlled trial 6 months</td>
<td>Turkey</td>
<td>n=35 Mean age 36 years 71% male</td>
<td>Positive</td>
<td>29%</td>
<td>HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization</td>
<td>Poor</td>
</tr>
<tr>
<td>Hadziyannis 1990&lt;sup&gt;33&lt;/sup&gt;</td>
<td>RCT 14-16 weeks treatment + 2 year followup</td>
<td>Greece</td>
<td>n=50 Mean age 49 years 94% male</td>
<td>Negative</td>
<td>44%</td>
<td>Composite outcomes</td>
<td>Poor</td>
</tr>
<tr>
<td>Lampertico 1997&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Open label RCT 3 years</td>
<td>Italy</td>
<td>n=42 Mean age 46 years 86% male</td>
<td>Negative</td>
<td>17%</td>
<td>HBsAg loss/seroconversion Histologic improvement Composite outcomes</td>
<td>Fair</td>
</tr>
<tr>
<td>Muller 1990&lt;sup&gt;47&lt;/sup&gt;</td>
<td>RCT 10 months</td>
<td>Germany</td>
<td>n=58 Mean age NR; range 18-65 years 79% male</td>
<td>Positive</td>
<td>5%</td>
<td>Composite outcomes</td>
<td>Fair</td>
</tr>
<tr>
<td>Author, year</td>
<td>Study design Duration</td>
<td>Country</td>
<td>Population</td>
<td>HBeAg status</td>
<td>Cirrhosis</td>
<td>Intermediate outcomes reported</td>
<td>Quality</td>
</tr>
<tr>
<td>-------------</td>
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<td>---------</td>
</tr>
<tr>
<td>Perez 1990</td>
<td>RCT 24 weeks (control phase)</td>
<td>Argentina</td>
<td>n=35, Mean age 39 years 77% male</td>
<td>Positive</td>
<td>14%</td>
<td>HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement</td>
<td>Fair</td>
</tr>
<tr>
<td>Perrillo 1990</td>
<td>RCT 10 months</td>
<td>United States</td>
<td>n=169, Mean age 40 years 85% male</td>
<td>Positive</td>
<td>NR</td>
<td>HBsAg loss/seroconversion Composite outcomes</td>
<td>Good</td>
</tr>
<tr>
<td>Sarin 1996</td>
<td>RCT 16 months</td>
<td>India</td>
<td>n=41, Mean age 35 years 94% male</td>
<td>Positive</td>
<td>44%</td>
<td>HBeAg loss/seroconversion HBsAg loss/seroconversion Virologic improvement Composite outcomes</td>
<td>Fair</td>
</tr>
<tr>
<td>Waked 1990</td>
<td>RCT 16 months</td>
<td>Egypt</td>
<td>n=40, Mean age 36 years 78% male</td>
<td>Positive</td>
<td>40%</td>
<td>HBeAg loss/seroconversion HBsAg loss/seroconversion Histologic improvement</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Lamivudine vs Placebo**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design Duration</th>
<th>Country</th>
<th>Population</th>
<th>HBeAg status</th>
<th>Cirrhosis</th>
<th>Intermediate outcomes reported</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali 2003</td>
<td>RCT 12 months</td>
<td>Iraq</td>
<td>n=74, Mean age NR % male NR</td>
<td>Negative</td>
<td>NR</td>
<td>HBsAg loss/seroconversion</td>
<td>Poor</td>
</tr>
<tr>
<td>Bozkaya 2005</td>
<td>Controlled trial 12 months (control phase)</td>
<td>Turkey</td>
<td>n=55, Mean age 36 years 60% male</td>
<td>Negative</td>
<td>NR</td>
<td>ALT normalization</td>
<td>Poor</td>
</tr>
<tr>
<td>Chan 2007</td>
<td>RCT 30 months</td>
<td>China</td>
<td>n=139, Mean age 39 years 84% male</td>
<td>Negative</td>
<td>27%</td>
<td>HBsAg loss/seroconversion ALT normalization Virologic improvement Histologic improvement Composite outcomes</td>
<td>Fair</td>
</tr>
<tr>
<td>Dienstag 1999</td>
<td>RCT 16 months</td>
<td>United States</td>
<td>n=137, Median age39 years 83% male</td>
<td>Positive</td>
<td>10%</td>
<td>HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement Histologic improvement</td>
<td>Fair</td>
</tr>
<tr>
<td>Lai, 1997</td>
<td>RCT 8 weeks</td>
<td>Hong Kong</td>
<td>n=42, Mean age 32 years 64% male</td>
<td>Positive</td>
<td>NR</td>
<td>HBeAg loss/seroconversion</td>
<td>Fair</td>
</tr>
</tbody>
</table>
### Table 4. Studies of Antiviral Therapy Versus Placebo or No Treatment Reporting Intermediate Outcomes: Study Characteristics

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Duration</th>
<th>Country</th>
<th>Population</th>
<th>HBeAg status</th>
<th>Cirrhosis</th>
<th>Intermediate outcomes reported</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lai 1998⁷⁷</td>
<td>RCT</td>
<td>1 year</td>
<td>Hong Kong, Taiwan, Singapore</td>
<td>n=358 Median age 31 years 73% male</td>
<td>Positive</td>
<td>5%</td>
<td>ALT normalization Histologic improvement Composite outcomes</td>
<td>Fair</td>
</tr>
<tr>
<td>Tassopoulos 1999⁸⁸</td>
<td>RCT 24 weeks</td>
<td>Greece</td>
<td>n=125 Median age 43 years 80% male</td>
<td>Negative</td>
<td>15%</td>
<td>HBsAg loss/seroconversion Composite outcomes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Yalcin 2004⁹⁹</td>
<td>RCT 1 year</td>
<td>Turkey</td>
<td>n=46 Mean age 24 years 54% male</td>
<td>Positive NR</td>
<td></td>
<td>HBsAg loss/seroconversion Virologic improvement Composite outcomes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Yao, 1999⁹⁰</td>
<td>RCT 12 weeks</td>
<td>China</td>
<td>n=429 Mean age 32 years 73% male</td>
<td>Positive NR</td>
<td></td>
<td>HBeAg loss/seroconversion ALT normalization Virologic improvement</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Murray 2012²⁳</td>
<td>RCT 72 weeks</td>
<td>United States, Bulgaria, France, Poland, Romania, Spain, Turkey</td>
<td>n=106 Mean age 15 years 73% male</td>
<td>Positive NR</td>
<td></td>
<td>HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement Composite outcomes</td>
<td>Good</td>
<td></td>
</tr>
</tbody>
</table>

*Patient population was 60% Asian.
²4% had fibrosis.
ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NR, not reported; RCT, randomized controlled trial.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adefovir vs Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonas 2008&lt;sup&gt;33&lt;/sup&gt;</td>
<td>HBV DNA &lt;1000 copies/mL + ALT normalization: 13/56 (23%) vs. 0/27 (0%); RR 13, 95% CI 0.8 to 215</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Interferon Alfa 2b vs No Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadziyannis 1990&lt;sup&gt;45&lt;/sup&gt;</td>
<td>HBV DNA undetectable and ALT normalization: 11/25 (44%) vs 2/25 (8%); <strong>RR 5.5, 95% CI 1.4 to 22</strong></td>
<td>Poor</td>
</tr>
<tr>
<td>Lampertico 1997&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Loss of HBV DNA + ALT normalization: 6/21 (29%) vs 0/21 (0%); RR 13, 95% CI 0.8 to 217</td>
<td>Fair</td>
</tr>
<tr>
<td>Muller 1990&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Loss of HbsAg and/or HBV DNA: 7/21 (33%) vs 0/21 (0%); RR 15, 95% CI 0.9 to 247</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Lamivudine vs Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lai, 1998&lt;sup&gt;57&lt;/sup&gt;</td>
<td>HBeAg seroconversion + HBV DNA undetectable: 39/275 (14%) vs 3/70 (4%); <strong>RR 3.31, 95% CI 1.05 to 10.40</strong></td>
<td>Fair</td>
</tr>
<tr>
<td>Chan, 2007&lt;sup&gt;54&lt;/sup&gt;</td>
<td>HBV DNA &lt;10,000 copies/ml and ALT normalization at 24 months (time on treatment): 50/89 (56%) vs 5/47 (11%); <strong>reported adjusted OR&lt;sup&gt;a&lt;/sup&gt; 11, 95% CI 3.8 to 30; RR 5.3, 95% CI 2.3 to 12</strong></td>
<td>Fair</td>
</tr>
<tr>
<td>Tassopoulos 1999&lt;sup&gt;58&lt;/sup&gt;</td>
<td>HBV DNA &lt;2.5 pg/mL and ALT normalization: 34/54 (63%) vs 3/54 (6%); <strong>RR 11, 95% CI 3.7 to 35</strong></td>
<td>Fair</td>
</tr>
<tr>
<td>Yalcin 2004&lt;sup&gt;59&lt;/sup&gt;</td>
<td>HBeAg seroconversion + HBV DNA loss: 1/13 (8%) vs 1/33 (3%); RR 2.5, 95% CI 0.17 to 38</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Tenofovir vs Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 2012&lt;sup&gt;61&lt;/sup&gt;</td>
<td>HBV DNA &lt;400 copies/mL + ALT normalization: 37/52 (71%) vs 0/54 (0%); <strong>RR 77, 95% CI 5 to 1235</strong></td>
<td>Good</td>
</tr>
</tbody>
</table>

<sup>a</sup>OR adjusted for baseline ALT and HBV DNA.

ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NR, not reported; OR, odds ratio; RR, relative risk.
Table 6. Head-to-Head Studies of Antiviral Therapy Reporting Intermediate Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Entecavir vs lamivudine</th>
<th>Pegylated interferon alfa 2a vs lamivudine</th>
<th>Tenofovir vs adefovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg loss/seroconversion</td>
<td>RR 1.2 (95% CI 0.9 to 1.5, I²=0%); 3 trials</td>
<td>RR 1.6 (95% CI 1.2 to 2.1); 1 trial70</td>
<td>RR 1.2 (95% CI 0.7 to 2.1); 1 trial72</td>
</tr>
<tr>
<td>HBsAg loss/seroconversion</td>
<td>RR 1.8 (95% CI 0.9 to 3.9); 1 trial64</td>
<td>RR 16 (95% CI 2.2 to 121, I²=0%); 2 trials70,71</td>
<td>RR 5.7 (95% CI 0.3 to 103); 1 trial72</td>
</tr>
<tr>
<td>ALT normalization</td>
<td>RR 1.1 (95% CI 1.0 to 1.2, I²=0%); 4 trials64,67,69</td>
<td>RR 1.4 (95% CI 1.2 to 1.6, I²=0%); 2 trials70,71</td>
<td>RR 1.1 (95% CI 0.9 to 1.4, I²=73%); 2 trials72</td>
</tr>
<tr>
<td>Virological improvement</td>
<td>RR 1.6 (95% CI 1.1 to 2.5, I²=94%); 4 trials64,67,69</td>
<td>RR 2.8 (95% CI 1.9 to 4.4, I²=0%); 2 trials70,71</td>
<td>RR 2.9 (95% CI 0.6 to 15, I²=97%); 2 trials72</td>
</tr>
<tr>
<td>Histological improvement</td>
<td>RR 1.2 (95% CI 1.1 to 1.3, I²=0%); 2 trials64,67</td>
<td>RR 1.2 (95% CI 1.0 to 1.4, 0%); 2 trials70,71</td>
<td>RR 1.1 (95% CI 1.0 to 1.2, I²=0%); 2 trials72</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; CI, confidence interval; 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design Duration</th>
<th>Country</th>
<th>Population</th>
<th>HBcAg status</th>
<th>Cirrhosis</th>
<th>Health outcomes</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adefovir vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonas 2008*</td>
<td>RCT 11 months</td>
<td>Germany, Poland, Spain, United Kingdom, United States</td>
<td>n=83</td>
<td>Positive</td>
<td>NR</td>
<td>Mortality</td>
<td>Fair</td>
</tr>
<tr>
<td>Zeng 2006*</td>
<td>RCT 12 weeks</td>
<td>China</td>
<td>n=480</td>
<td>Positive</td>
<td>NR</td>
<td>Mortality</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Interferon Alfa 2a vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin 1999† Methods: Liaw 1994*</td>
<td>RCT 4 months + mean 7 years followup</td>
<td>Taiwan</td>
<td>n=101</td>
<td>Positive</td>
<td>12%</td>
<td>Incident cirrhosis Hepatocellular cancer Mortality</td>
<td>Fair</td>
</tr>
<tr>
<td>Mazella 1999*</td>
<td>RCT 6 months + 7 years followup</td>
<td>Italy</td>
<td>n=64</td>
<td>Positive</td>
<td>N/A†</td>
<td>Incident cirrhosis Hepatocellular cancer Mortality</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Interferon Alfa 2b vs No Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lampertico 1997**</td>
<td>Open label RCT 2 years + 1 year followup</td>
<td>Italy</td>
<td>n=42</td>
<td>Negative</td>
<td>17%</td>
<td>Hepatocellular cancer</td>
<td>Fair</td>
</tr>
<tr>
<td>Perrillo 1990*</td>
<td>RCT 16 weeks + 6 months followup</td>
<td>United States</td>
<td>n=169</td>
<td>Positive</td>
<td>NR</td>
<td>Mortality</td>
<td>Good</td>
</tr>
<tr>
<td>Waked 1990*</td>
<td>RCT 16 weeks + 1 year followup</td>
<td>Egypt</td>
<td>n=40</td>
<td>Positive</td>
<td>40%</td>
<td>Incident cirrhosis Mortality</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Lamivudine vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan 2007**</td>
<td>RCT 2 years + 6 months followup</td>
<td>China</td>
<td>n=139</td>
<td>Negative</td>
<td>27%</td>
<td>Hepatocellular cancer</td>
<td>Fair</td>
</tr>
<tr>
<td>Dienstag 1999**</td>
<td>RCT 1 year + 16 weeks followup</td>
<td>United States</td>
<td>n=137</td>
<td>Positive</td>
<td>10%</td>
<td>Mortality</td>
<td>Fair</td>
</tr>
<tr>
<td>Lai 1998**</td>
<td>RCT 1 year</td>
<td>Hong Kong, Taiwan, Singapore</td>
<td>n=358</td>
<td>Positive</td>
<td>5%</td>
<td>Mortality</td>
<td>Fair</td>
</tr>
<tr>
<td>Liaw 2004*</td>
<td>RCT Median 2.7 years</td>
<td>Australia, Hong Kong, New Zealand, Singapore, Taiwan, Thailand</td>
<td>n=651</td>
<td>Positive</td>
<td>33%</td>
<td>Disease severity Hepatocellular cancer Mortality</td>
<td>Fair</td>
</tr>
</tbody>
</table>

*Cirrhotics excluded from study.
†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.
HBcAg, hepatitis B c antigen; N/A, not applicable; NR, not reported; RCT, randomized controlled trial.
### Table 8. Harms of Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Drug Author, year</th>
<th>Duration Followup</th>
<th>Time period for harms data</th>
<th>N Country</th>
<th>Cirrhosis</th>
<th>Serious adverse events Treatment vs. control/no treatment</th>
<th>Withdrawal due to adverse events Treatment vs. control/no treatment</th>
<th>Any adverse events Treatment vs. control/no treatment</th>
<th>Quality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adefovir vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadziyannis 2003&lt;sup&gt;43&lt;/sup&gt;</td>
<td>11 months + 1 month followup</td>
<td>Both</td>
<td>n=185 Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore</td>
<td>11% cirrhosis</td>
<td>3% (4/123) vs. 7% (4/61) RR 0.5 (95% CI 0.1 to 1.9)</td>
<td>0% (0/123) vs. 0% (0/61) RR 0.5 (95% CI 0.0 to 25)</td>
<td>76% (94/123) vs. 74% (45/61) RR 1.0 (95% CI 0.9 to 1.2)</td>
<td>Fair</td>
<td>Any adverse event refers to those reported by at least 5% of patients</td>
</tr>
<tr>
<td>Jonas 2008&lt;sup&gt;41&lt;/sup&gt;</td>
<td>11 months</td>
<td>Time-on-treatment</td>
<td>n=83 United States and Europe</td>
<td>% cirrhosis NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR separately for relevant age group</td>
<td>1.7% (1/56) vs. 0% (0/27) RR 1.5 (95% CI 0.1 to 35)</td>
<td>NR separately for relevant age group</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Marcellin 2003&lt;sup&gt;42&lt;/sup&gt;</td>
<td>11 months + 1 month followup</td>
<td>Both</td>
<td>n=515 North America, Europe, Australia, and Southeast Asia</td>
<td>% cirrhosis NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10% (33/344) vs. 8% (13/167) RR 1.2 (95% CI 0.7 to 2.3)</td>
<td>2.3% (8/344) vs. &lt;1% (1/167) RR 3.9 (95% CI 0.5 to 31)</td>
<td>NR</td>
<td>Fair</td>
<td>N values calculated Combined treatment arms</td>
</tr>
<tr>
<td><strong>Interferon Alfa 2b vs No Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayraktar 1993&lt;sup&gt;44&lt;/sup&gt;</td>
<td>6 months</td>
<td>Time-on-treatment</td>
<td>n=35 Turkey</td>
<td>29% cirrhosis</td>
<td>NR</td>
<td>0% (0/25)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>Poor</td>
<td>Results reported for treated group only</td>
</tr>
<tr>
<td>Hadziyannis 1990&lt;sup&gt;45&lt;/sup&gt;</td>
<td>1 year + 1 year followup</td>
<td>Unclear&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n=50 Greece</td>
<td>44% cirrhosis</td>
<td>0% (0/25)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>Poor</td>
<td>Results reported for treated group only</td>
</tr>
<tr>
<td>Lampertico 1997&lt;sup&gt;46&lt;/sup&gt;</td>
<td>2 years + 1 year followup</td>
<td>Time-on-treatment</td>
<td>n=42 Italy</td>
<td>17% cirrhosis</td>
<td>NR</td>
<td>24% (5/21) vs 0% (0/21) RR 11 (95% CI 0.65 to 187)</td>
<td>NR</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Muller 1990&lt;sup&gt;47&lt;/sup&gt;</td>
<td>4 months + 6 months followup</td>
<td>Time-on-treatment</td>
<td>n=58 Germany</td>
<td>5% cirrhosis</td>
<td>NR</td>
<td>3.7% (1/27)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
<td>Fair</td>
<td>Results reported for treated group only</td>
</tr>
<tr>
<td>Perez 1990&lt;sup&gt;48&lt;/sup&gt;</td>
<td>6 months (2nd phase) + 6 month followup</td>
<td>Time-on-treatment</td>
<td>n=35 Argentina</td>
<td>14% cirrhosis</td>
<td>NR</td>
<td>6% (1/18) vs. 0% (0/17) RR 2.7 (95% CI 0.1 to 62)</td>
<td>NR</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Perrillo 1990&lt;sup&gt;49&lt;/sup&gt;</td>
<td>4 months + 6 month followup</td>
<td>Time-on-treatment</td>
<td>n=169 United States</td>
<td>% cirrhosis NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>3% (4/126) vs 0% (0/43) RR 3.12 (95% CI 0.17 to 57)</td>
<td>NR</td>
<td>Good</td>
<td></td>
</tr>
</tbody>
</table>

Screening for Hepatitis B Virus Infection 55 Pacific Northwest EPC
<table>
<thead>
<tr>
<th>Drug Author, year</th>
<th>Duration Followup</th>
<th>Time period for harms data</th>
<th>N Country</th>
<th>Cirrhosis</th>
<th>Serious adverse events Treatment vs. control/no treatment</th>
<th>Withdrawal due to adverse events Treatment vs. control/no treatment</th>
<th>Any adverse events Treatment vs. control/no treatment</th>
<th>Quality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarin 1996&lt;sup&gt;30&lt;/sup&gt;</td>
<td>4 months + 1 year followup</td>
<td>Unclear&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n=41 India</td>
<td>44% cirrhosis</td>
<td>0% (0/20)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>Fair</td>
<td>Results reported for treated group only</td>
</tr>
<tr>
<td>Waked 1990&lt;sup&gt;31&lt;/sup&gt;</td>
<td>4 months + 1 year followup</td>
<td>Time-on-treatment</td>
<td>n=40 Egypt</td>
<td>40% cirrhosis</td>
<td>0% (0/20)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0% (0/20)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>Fair</td>
<td>Results reported for treated group only Serious adverse effects inferred</td>
</tr>
<tr>
<td>Lamivudine vs Placebo</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ali 2003&lt;sup&gt;32&lt;/sup&gt;</td>
<td>6 months + 1 year followup</td>
<td>Unclear</td>
<td>n=74 Iraq</td>
<td>% cirrhosis NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>9.4% (3/32) vs. 0% (0/30) RR 6.6 (95% CI 0.4 to 122)</td>
<td>NR</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Chan 2007&lt;sup&gt;33&lt;/sup&gt;</td>
<td>2 years + 6 months followup</td>
<td>Unclear</td>
<td>n=139 China</td>
<td>27% cirrhosis</td>
<td>15% (13/89) vs. 13% (6/47) RR 1.1 (95% CI 0.5 to 2.8)</td>
<td>NR</td>
<td>NR</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Dienstag 1999&lt;sup&gt;34&lt;/sup&gt;</td>
<td>1 year + 4 months followup</td>
<td>Unclear</td>
<td>n=143 United States</td>
<td>10% cirrhosis</td>
<td>0% (0/66) vs 0% (0/71) RR 1.1 (95% CI 0.0 to 53)</td>
<td>NR</td>
<td>NR</td>
<td>Fair Results inferred</td>
<td></td>
</tr>
<tr>
<td>Lai 1997&lt;sup&gt;35&lt;/sup&gt;</td>
<td>1 month + 1 month followup</td>
<td>Unclear</td>
<td>n=42 Hong Kong</td>
<td>% cirrhosis NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0% (0/36) vs. 0% (0/6) RR 0.2 (95% CI 0.0 to 8.8)</td>
<td>NR</td>
<td>NR</td>
<td>Fair Combined treatment arms</td>
<td></td>
</tr>
<tr>
<td>Lai 1998&lt;sup&gt;36&lt;/sup&gt;</td>
<td>1 year</td>
<td>Time-on-treatment</td>
<td>n=358 Hong Kong, Taiwan, Singapore</td>
<td>5% cirrhosis</td>
<td>1.8% (5/285) vs. 0% (0/73) RR 2.9 (95% CI 0.2 to 51)</td>
<td>NR</td>
<td>78.6% (224/285) vs. 77% (56/73) RR 1.0 (95% CI 0.9 to 1.2)</td>
<td>Fair Combined treatment arms</td>
<td></td>
</tr>
<tr>
<td>Liaw 2004&lt;sup&gt;37&lt;/sup&gt;</td>
<td>2.7 years median + ≤1 year followup</td>
<td>Time-on-treatment</td>
<td>n=651 Several countries in Asia, Australia, New Zealand</td>
<td>33% cirrhosis</td>
<td>12% (54/436) vs. 18% (38/215) RR 0.7 (95% CI 0.5 to 1.0)</td>
<td>NR</td>
<td>77% (335/436) vs. 83% (178/215) RR 0.9 (95% CI 0.9 to 1.0)</td>
<td>Fair Any adverse event refers to those that occurred in greater than 10% of patients</td>
<td></td>
</tr>
<tr>
<td>Tassopoulos 1999&lt;sup&gt;38&lt;/sup&gt;</td>
<td>6 months</td>
<td>Time-on-treatment</td>
<td>n=125 Greece</td>
<td>15% cirrhosis</td>
<td>5% (3/60) vs. 6% (4/65) RR 0.8 (95% CI 0.2 to 3.5)</td>
<td>2% (1/60) vs. 0% (0/65) RR 3.2 (95% CI 0.1 to 78)</td>
<td>47% (28/60) vs. 62% (40/65) RR 0.8 (95% CI 0.5 to 1.1)</td>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Harms of Antiviral Therapy Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Drug Author, year</th>
<th>Duration Followup</th>
<th>Time period for harms data</th>
<th>N</th>
<th>Country</th>
<th>Cirrhosis</th>
<th>Serious adverse events Treatment vs. control/no treatment</th>
<th>Withdrawal due to adverse events Treatment vs. control/no treatment</th>
<th>Any adverse events Treatment vs. control/no treatment</th>
<th>Quality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yalcin 2004&lt;sup&gt;59&lt;/sup&gt;</td>
<td>3 months + 1 year followup</td>
<td>Unclear</td>
<td>n=46</td>
<td>Turkey</td>
<td>% cirrhosis NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0% (0/13) vs. 0% (0/33) RR 2.4 (95% CI 0.1 to 116)</td>
<td>NR</td>
<td>NR</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Yao 1999&lt;sup&gt;60&lt;/sup&gt; See also: Yao 2000&lt;sup&gt;78&lt;/sup&gt;; Yao 2009&lt;sup&gt;79&lt;/sup&gt;</td>
<td>3 months + 9 month followup</td>
<td>Time-on-treatment</td>
<td>n=429</td>
<td>China</td>
<td>% cirrhosis NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0% (0/322) vs. 0% (0/107) RR 0.3 (95% CI 0.0 to 17)</td>
<td>0% (0/322) vs. 0% (0/107) RR 0.3 (95% CI 0.0 to 17)</td>
<td>43% (138/322) vs. 42% (45/107) RR 1.0 (95% CI 0.8 to 1.3)</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td><strong>Tenofovir vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 2012&lt;sup&gt;61&lt;/sup&gt;</td>
<td>1.4 years</td>
<td>Time-on-treatment</td>
<td>n=106</td>
<td>North America and Europe</td>
<td>% cirrhosis NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12% (6/52) vs 22% (12/54) RR 0.5 (95% CI 0.2 to 1.3)</td>
<td>NR</td>
<td>85% (44/52) vs 89% (48/54) RR 0.95 (95% CI 0.8 to 1.1)</td>
<td>Good</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Decompensated liver disease as exclusion criterion.
<sup>b</sup> Excluded from meta-analyses.
CI, confidence interval; NR, not reported; RR, relative risk.
### Table 9. Head-to-Head Studies of Antiviral Therapy Reporting Harms of Treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Entecavir vs lamivudine</th>
<th>Pegylated interferon alfa 2a vs lamivudine</th>
<th>Tenofovir vs adefovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>RR 0.9 (95% CI 0.6 to 1.3, I²=0%); 2 trials⁶⁴, ⁶⁷</td>
<td>RR 2.1 (95% CI 1.0 to 4.5, I²=0%); 2 trials⁷⁰, ⁷¹</td>
<td>RR 1.0 (95% CI 0.5 to 1.8); 2 trials (one publication, results pooled)⁷²</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>RR 0.5 (95% CI 0.1 to 1.9, I²=43%); 3 trials⁶⁴, ⁶⁷, ⁶⁸</td>
<td>RR 7.6 (95% CI 1.1 to 52, I²=38%); 2 trials⁷⁰, ⁷¹</td>
<td>Not reported</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>RR 1.0 (95% CI 0.9 to 1.1, I²=34%); 3 trials⁶⁴, ⁶⁷</td>
<td>RR 1.7 (95% CI 1.5 to 2.0, I²=55%); 2 trials⁷⁰, ⁷¹</td>
<td>RR 1.0 (95% CI 0.9 to 1.1); 2 trials (one publication, results pooled)⁷²</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Intermediate outcome evaluated</th>
<th>Treatment</th>
<th>Duration of followup</th>
<th>Characteristics of HBV infection</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Number receiving antiviral treatment</th>
<th>Lost to followup</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreone 2004&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Italy</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>No virological breakthrough (HBV DNA became undetectable on treatment and remained undetectable): 41%</td>
<td>Lamivudine</td>
<td>Median 42 months</td>
<td>HBeAg positive: None ALT (mean): 192 Serum HBV-DNA (mean, pg/ml): 16 Cirrhosis: 100%</td>
<td>Mean age: 53 years Male: 82% Race: NR</td>
<td>n=22</td>
<td>Lost to followup: Unclear</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baltayiannis 2006&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Greece</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Virological response (HBV DNA &lt;10,000 copies/ml at 6 months of treatment): 35%</td>
<td>Interferon alfa</td>
<td>6 years</td>
<td>HBeAg positive: None ALT (median): 177 Serum HBV-DNA (median, copies/mL): 1.2 x 10&lt;sup&gt;6&lt;/sup&gt; Cirrhosis: Excluded</td>
<td>Mean age: 51 years Male: 63% Race: NR</td>
<td>n=63</td>
<td>Lost to followup: 1 (1.6%)</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Marco 2004&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Italy</td>
<td>Retrospective cohort</td>
<td>No virological breakthrough (HBV DNA &lt;10&lt;sup&gt;5&lt;/sup&gt; copies/ml throughout followup after achieving undetectability): 39%</td>
<td>Lamivudine</td>
<td>4 years</td>
<td>HBeAg positive: Excluded ALT &gt;2 times ULN: 65% Serum HBV-DNA: NR Cirrhosis on histology: 25%</td>
<td>Mean age: 49 years Male: 83% Race: NR</td>
<td>n=656</td>
<td>Lost to followup: NR; 40 patients had no virological response and excluded from analysis</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fattovich 1997&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Italy</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Biochemical remission (normalization of ALT levels): 28%</td>
<td>Interferon alfa</td>
<td>Mean 7 years</td>
<td>HBeAg positive: All ALT (mean): 5.3 times upper limit of normal Serum HBV-DNA: NR Cirrhosis: 100%</td>
<td>Mean age: 47 years Male: 85% Race: 100% white</td>
<td>n=40</td>
<td>Lost to followup: NR for treated subgroup</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hui 2008&lt;sup&gt;24&lt;/sup&gt;</td>
<td>China (Hong Kong)</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Histological response (improvement of 2 points or more on HAI score after end of treatment): 40%</td>
<td>Interferon alfa</td>
<td>2 or 2b Median 9.9 years</td>
<td>HBeAg positive: All ALT (mean): 113 Serum HBV-DNA &gt;10&lt;sup&gt;5&lt;/sup&gt; copies/ml: 100% Cirrhosis: 12%</td>
<td>Mean age: 30 years Male: 78% Race: NR</td>
<td>n=89</td>
<td>Lost to followup: NR</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lampertico 2003&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Italy</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Sustained virological and biochemical response (normalization of serum ALT and clearance of HBV DNA): 30%</td>
<td>Interferon alfa</td>
<td>2b 68 months</td>
<td>HBeAg positive: None ALT (mean): 204 HBV DNA detectable: 61% Ishak F4-F6 fibrosis: 60%</td>
<td>Men age: 46 years Female: 13% Race: NR</td>
<td>n=101</td>
<td>Lost to followup: 4 (4.0%)</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Table 10. Studies of Association Between Intermediate and Final Health Outcomes

<table>
<thead>
<tr>
<th>Author, year Country</th>
<th>Study design</th>
<th>Intermediate outcome evaluated</th>
<th>Treatment Duration of followup</th>
<th>Characteristics of HBV infection</th>
<th>Age Sex Race</th>
<th>Number receiving antiviral treatment Lost to followup</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau 1997&lt;sup&gt;33&lt;/sup&gt; USA</td>
<td>Cohort (originally enrolled in RCTs)</td>
<td>Response (sustained loss of HBV DNA and clearance of HBeAg within 1 year of starting treatment): 30%</td>
<td>Interferon alfa Mean 6.2 years</td>
<td>HBeAg positive: All ALT (median): 154 Serum HBV DNA (mg/mL): 4843 Cirrhosis: 17%</td>
<td>Mean age: 41 years Male: 83% Race: 94% white, 6% black</td>
<td>n=103 Lost to followup: 8 (7.8%); assumed to be alive and without liver-related complications</td>
<td>Fair</td>
</tr>
<tr>
<td>Niederau 1996&lt;sup&gt;66&lt;/sup&gt; Europe</td>
<td>Prospective cohort</td>
<td>Loss of HBeAg after therapy: 51%</td>
<td>Interferon alfa 2b Mean 50 months</td>
<td>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)</td>
<td>Mean age: NR Female: NR Race: NR</td>
<td>n=103 Lost to followup: None</td>
<td>Fair</td>
</tr>
<tr>
<td>Papatheodoridis 2001&lt;sup&gt;87&lt;/sup&gt; Greece</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Sustained biochemical response (normalization of ALT at the end of interferon therapy and persistently normal ALT levels throughout the post-treatment followup period): 27%</td>
<td>Interferon alfa Mean 6.0 years</td>
<td>HBeAg positive: Excluded ALT (median): 112 Serum HBV DNA (median, pg/mL): 4.4 Cirrhosis: 27%</td>
<td>Mean age: 47 years Male: 83% Race: NR</td>
<td>n=209 Lost to followup: 9 (4.3%)</td>
<td>Poor</td>
</tr>
<tr>
<td>Papatheodoridis 2011&lt;sup&gt;88&lt;/sup&gt; Greece</td>
<td>Retrospective cohort</td>
<td>Virological remission (HBV DNA &lt;200 IU/ml throughout therapy): 28%</td>
<td>Lamivudine Median 4.7 years</td>
<td>HBeAg positive: Excluded ALT (median): 98 Serum HBV DNA (median, x10&lt;sup&gt;3&lt;/sup&gt; IU/ml): 400 Cirrhosis: 26%</td>
<td>Mean age: 54 years Male: 72% Race: NR</td>
<td>n=818 Lost to followup: 180 (22%)</td>
<td>Fair</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author, year Country</th>
<th>Confounders adjusted for in analysis</th>
<th>Death</th>
<th>Hepatocellular carcinoma</th>
<th>Composite outcomes</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg Positive Patients</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fattovich 1997&lt;sup&gt;it&lt;/sup&gt; Italy</td>
<td>Age, Sex, Symptoms, Hepatic stigmata, Splenomegaly, AST, ALT, AST/ALT ratio, Bilirubin, Albumin, Gamma-globulins, Platelets, HBeAg clearance, ALT normalization, All patients HBeAg positive</td>
<td>Biochemical remission vs. no remission: adjusted HR 0.09 (95% CI 0.01 to 0.71)</td>
<td>NR</td>
<td>NR</td>
<td>Poor</td>
</tr>
<tr>
<td>Hui 2008&lt;sup&gt;st&lt;/sup&gt; China (Hong Kong)</td>
<td>Fibrosis, HBV DNA level, All patients HBeAg positive</td>
<td>NR</td>
<td>NR</td>
<td>Histological response on HAI score vs. no response: adjusted HR 0.62 (95% CI 0.06 to 6.9)</td>
<td>Poor</td>
</tr>
<tr>
<td>Lau 1997&lt;sup&gt;nt&lt;/sup&gt; USA</td>
<td>Cirrhosis, Age, Sex, ALT, AST, All patients HBeAg positive</td>
<td>Responder (virological response and HBeAg clearance) vs. non-responder: adjusted HR 0.59 (95% CI 0.20 to 1.67)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>Responder vs. non-responder: adjusted HR 0.07 (95% CI 0.02 to 0.33)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Fair</td>
</tr>
<tr>
<td>Niederau 1996&lt;sup&gt;nt&lt;/sup&gt; Europe</td>
<td>Age, Sex, Baseline HBV DNA, Duration of hepatitis, Preexisting cirrhosis, All patients HBeAg positive</td>
<td>NR</td>
<td>NR</td>
<td>HBeAg loss vs. no loss: adjusted HR 0.06 (95% CI 0.01 to 0.61)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Screening for Hepatitis B Virus Infection 61 Pacific Northwest EPC
<table>
<thead>
<tr>
<th>Author, year Country</th>
<th>Confounders adjusted for in analysis</th>
<th>Death</th>
<th>Hepatocellular carcinoma</th>
<th>Composite outcomes</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg Negative Patients</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Andreone 2004 Italy</td>
<td>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</td>
<td>NR</td>
<td>No virological breakthrough vs. breakthrough: adjusted HR 0.10 (95% CI 0.01 to 0.77)</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Baltayiannis 2006 Greece</td>
<td>Age Gender Alcohol use ALT &gt;200 IU/L at baseline HBV-DNA &gt;10,000 copies/ml at baseline Histologic grade &gt;9 Histologic stage &gt;2 All patients HBeAg negative</td>
<td>NR</td>
<td>NR</td>
<td>Virological response at 6 months vs. no virological response: adjusted HR 0.24 (95% CI 0.06 to 0.96)</td>
<td>Fair</td>
</tr>
<tr>
<td>Di Marco 2004 Italy</td>
<td>Age Sex HBV DNA level ALT Hepatic flare after virological breakthrough Previous interferon therapy Cirrhosis All patients HBeAg negative</td>
<td>No virological breakthrough vs. breakthrough: adjusted HR 0.34 (95% CI 0.15 to 0.80)</td>
<td>NR</td>
<td>NR</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Table 11. Hazard Ratios for Associations Between Intermediate and Final Health Outcomes

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Confounders adjusted for in analysis</th>
<th>Death</th>
<th>Hepatocellular carcinoma</th>
<th>Composite outcomes</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lampertico 2003&lt;sup&gt;36&lt;/sup&gt; Italy</td>
<td></td>
<td>Age, Sex, ALT, HBV viral load, IgM anti-HBc level, Neco-inflammatory grade, Fibrosis stage, All patients HBeAg negative</td>
<td>NR</td>
<td>NR</td>
<td>Sustained virological and biochemical response vs. no sustained response: adjusted HR 0.13 (95% CI 0.03 to 0.55)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fair</td>
</tr>
<tr>
<td>Papatheodoridis 2001&lt;sup&gt;87&lt;/sup&gt; Greece</td>
<td></td>
<td>Cirrhosis, Age, All patients HBeAg negative</td>
<td>NR</td>
<td>NR</td>
<td>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&lt;sup&gt;f&lt;/sup&gt; Sustained biochemical response vs. no sustained biochemical response: adjusted HR 0.53 (95% CI 0.29 to 0.91)</td>
<td>Poor</td>
</tr>
<tr>
<td>Papatheodoridis 2011&lt;sup&gt;88&lt;/sup&gt; Greece</td>
<td></td>
<td>Age, Sex, Liver disease severity, ALT, AST, Bilirubin, Albumin, Hemoglobin, Platelet count, HBV DNA, Interferon alfa in the past, All patients HBeAg negative</td>
<td>NR</td>
<td>Virological remission under therapy vs. no virological remission: adjusted HR 0.77 (95% CI 0.35 to 1.69)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>NR</td>
<td>Fair</td>
</tr>
</tbody>
</table>

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

ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; AST, aspartate aminotransferase; CI, confidence interval; HAI, histology activity index; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HR, hazard ratio; IgM, immunoglobulin M; NR, not reported.
<table>
<thead>
<tr>
<th>Intermediate outcome</th>
<th>Death</th>
<th>Hepatocellular carcinoma</th>
<th>Composite outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT normalization</td>
<td>1 study(^a); HR 0.09 (95% CI 0.01-0.71)</td>
<td>No studies</td>
<td>1 study(^a); HR 0.48 (95% CI 0.23-1.0)(^a)</td>
</tr>
<tr>
<td>Composite intermediate outcome</td>
<td>1 study(^a); HR 0.59 (95% CI 0.20-1.67)</td>
<td>No studies</td>
<td>2 studies(^a); HR 0.07 (95% CI 0.02-0.33); HR 0.13 (95% CI 0.03-0.55)(^a)</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>No studies</td>
<td>No studies</td>
<td>1 study(^a); HR 0.06 (95% CI 0.01-0.61)</td>
</tr>
<tr>
<td>Histological response</td>
<td>No studies</td>
<td>No studies</td>
<td>1 study(^a); HR 0.62 (95% CI 0.06-6.9)</td>
</tr>
<tr>
<td>Virological response</td>
<td>1 study(^a); HR 0.34 (95% CI 0.15-0.80)(^a)</td>
<td>2 studies(^a); HR 0.10 (95% CI 0.01-0.77);(^a) HR 0.77 (95% CI 0.35-1.69)(^a)</td>
<td>1 study(^a); HR 0.24 (95% CI 0.06-0.96)(^a)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HR, hazard ratio.

\(^a\) Study performed in HBeAg-negative patients.
Table 13. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Number and type of studies identified for update</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of findings</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What are the benefits of screening for HBV versus no screening in asymptomatic, non-pregnant adolescents and adults on morbidity, mortality, and disease transmission?</td>
<td>No studies</td>
<td>No studies</td>
<td>N/A</td>
<td>N/A</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>2. What are the harms of screening for HBV infection (e.g., labeling, anxiety, and harms of confirmatory tests, including biopsy)?</td>
<td>No studies</td>
<td>No studies</td>
<td>N/A</td>
<td>N/A</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>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)?</td>
<td>One cross-sectional study</td>
<td>Evidence only available from one study with methodologic limitations</td>
<td>N/A</td>
<td>Study conducted in high-risk sexually transmitted disease clinic attendees</td>
<td>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 one case of HBV infection of 82.</td>
<td>Poor</td>
</tr>
<tr>
<td>4. In non-pregnant adolescents and adults with no evidence of HBV immunity on screening, how effective is HBV vaccination for improving clinical outcomes?</td>
<td>No studies with evidence on long-term clinical outcomes</td>
<td>No evidence on long-term clinical outcomes</td>
<td>Moderate</td>
<td>Studies conducted in high-risk populations (health-care workers or MSM) and/or children</td>
<td>Vaccination is associated with decreased risk of HBV acquisition in healthcare workers (four trials, RR 0.51, 95% CI 0.35 to 0.73) and men who have sex with men (four 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.</td>
<td>Fair</td>
</tr>
<tr>
<td>5. In non-pregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving intermediate outcomes (virologic or histologic improvement or clearance of HBeAg)?</td>
<td>30 RCTs</td>
<td>Study duration and patient characteristic varied widely Few good-quality studies</td>
<td>High</td>
<td>About half the studies conducted outside of the United States/Europe and about 1/3 enrolled HBeAg negative patients</td>
<td>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, I²=44%), HBsAg loss/seroconversion (12 trials, RR 2.4, 95% CI 1.2 to 4.9, I²=0%), ALT normalization (12 trials, RR 2.5, 95% CI 2.1 to 3.0, I²=27%), loss of HBV DNA (9 trials, RR 7.2, 95% CI 3.2 to 16; I²=58%) and histologic improvement (7 trials, RR 2.1, 95% CI 1.8 to 2.6; I²=0%). Results were generally consistent across specific antiviral drugs.</td>
<td>Fair</td>
</tr>
<tr>
<td>Key Question</td>
<td>Number and type of studies identified for update</td>
<td>Limitations</td>
<td>Consistency</td>
<td>Applicability</td>
<td>Summary of findings</td>
<td>Overall quality</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>6. In non-pregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving health outcomes?</td>
<td>16 RCTs</td>
<td>Many studies were small, with few events</td>
<td>Moderate</td>
<td>About half of the studies conducted outside of the United States/Europe and about 1/3 enrolled HBeAg negative patients</td>
<td>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 (one to four) of trials.</td>
<td>Fair</td>
</tr>
<tr>
<td>7. In non-pregnant adolescent and adults with chronic HBV infection, how effective is education or behavior change counseling in reducing transmission and improving health outcomes?</td>
<td>No studies</td>
<td>No evidence</td>
<td>N/A</td>
<td>N/A</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
</tbody>
</table>

*Table 13. Summary of Evidence*
### Table 13. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Number and type of studies identified for update</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of findings</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. What are the harms associated with antiviral treatment for HBV infection?</td>
<td>29 RCTs</td>
<td>Many studies were small, with few events</td>
<td>High</td>
<td>Many studies conducted outside of the United States/Europe</td>
<td>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, I²=0%) or any adverse events (7 trials, RR 0.96, 95% CI 0.9 to 1.0, I²=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, I²=0%). Results were generally consistent across specific antiviral 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, I²=0%) and withdrawal due to adverse events (RR 7.6, 95% CI 1.1 to 52, I²=38%) versus lamivudine.</td>
<td>Fair</td>
</tr>
<tr>
<td>KQ 9. Do improvements in intermediate outcomes improve final health outcomes?</td>
<td>10 observational studies</td>
<td>High variability in patient characteristic s and outcomes evaluated</td>
<td>Moderate</td>
<td>One study excluded patients with cirrhosis, two studies only included patients with cirrhosis, and in the remainder the proportion with cirrhosis ranged from 12 to 60 percent.</td>
<td>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.</td>
<td>Poor</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; 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
Appendix A1. Search Strategies

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.
Appendix A1. Search Strategies

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)"
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

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
Appendix A1. Search Strategies

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

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition of Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic HBV infection: detectable HBsAg in serum for &gt;6 months</td>
<td>Acute HBV infection</td>
</tr>
<tr>
<td><strong>Populations</strong></td>
<td></td>
</tr>
<tr>
<td>KQs 1-3 Nonpregnant adults (&gt;18 years of age) and adolescents (13 to</td>
<td>Symptomatic patients, children and pregnant women, HIV(+) or HCV(+)</td>
</tr>
<tr>
<td>&lt;18 years of age) asymptomatic for HBV infection</td>
<td>persons or persons or other special populations, such as hemodialysis,</td>
</tr>
<tr>
<td>KQ 4 Persons without evidence of HBV immunity or disease on screening</td>
<td>transplant, and treatment failure populations</td>
</tr>
<tr>
<td>KQs 5-9 Nonpregnant adults and adolescents with chronic HBV infection</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>KQs 1, 2 Screening</td>
<td></td>
</tr>
<tr>
<td>KQ 3 Screening strategies</td>
<td>Lab test results</td>
</tr>
<tr>
<td>KQ 4 Vaccination</td>
<td></td>
</tr>
<tr>
<td>KQs 5-9 Antiviral treatments for treatment naïve patients (Note: FDA-</td>
<td>Non-FDA approved antiviral treatments, combination therapy</td>
</tr>
<tr>
<td>approved treatments include: Interferon alpha 2b, Pegylated interferon</td>
<td></td>
</tr>
<tr>
<td>alpha 2a, Lamivudine, Adefovir, Entecavir, Telbivudine, Tenofovir)</td>
<td></td>
</tr>
<tr>
<td>Education or behavior change counseling</td>
<td></td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td></td>
</tr>
<tr>
<td>KQs 1, 2 No screening</td>
<td></td>
</tr>
<tr>
<td>KQ 4 No vaccination</td>
<td></td>
</tr>
<tr>
<td>KQs 5-7 No treatment. Also, for currently recommended first-line</td>
<td></td>
</tr>
<tr>
<td>antiviral therapies, the comparator was older antiviral therapies.</td>
<td></td>
</tr>
<tr>
<td>KQ 3 Other screening strategies</td>
<td></td>
</tr>
<tr>
<td>KQ 8 No treatment. Also, for currently recommended first-line antiviral</td>
<td></td>
</tr>
<tr>
<td>therapies, the comparator was older antiviral therapies.</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>KQ 2 Labeling, anxiety, stigma</td>
<td></td>
</tr>
<tr>
<td>Harms from liver biopsy</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
</tr>
<tr>
<td>KQ 3 Measures of predictive validity</td>
<td></td>
</tr>
<tr>
<td>KQ 4 Disease prevention</td>
<td></td>
</tr>
<tr>
<td>KQ 5 Intermediate outcomes:</td>
<td></td>
</tr>
<tr>
<td>Virologic improvement</td>
<td>Drug resistance</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>Development of mutations or antibodies to drugs</td>
</tr>
<tr>
<td>HBsAg clearance</td>
<td></td>
</tr>
<tr>
<td>KQs 1, 6, 7, 9 Final outcomes:</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular cancer</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td>Disease transmission</td>
<td></td>
</tr>
<tr>
<td>KQ 8 Harms from antiviral medications</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td></td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
</tr>
<tr>
<td>Primary care and primary care referable settings, e.g., correctional</td>
<td></td>
</tr>
<tr>
<td>settings and community care settings serving injection drug users/men</td>
<td></td>
</tr>
<tr>
<td>who have sex with men/sexually transmitted disease populations</td>
<td></td>
</tr>
<tr>
<td>United States and countries with similar HBV prevalence, except</td>
<td></td>
</tr>
<tr>
<td>for antiviral therapies (all countries)</td>
<td></td>
</tr>
<tr>
<td><strong>Study Designs</strong></td>
<td></td>
</tr>
<tr>
<td>KQ 1 Randomized controlled trials and controlled observational studies</td>
<td>Uncontrolled studies</td>
</tr>
<tr>
<td>KQs 2, 8 Randomized controlled trials and controlled observational</td>
<td>Very small uncontrolled studies; case studies</td>
</tr>
<tr>
<td>studies; or large, uncontrolled observational studies with long-term</td>
<td></td>
</tr>
<tr>
<td>followup. Also for KQ 8, head-to-head trials for currently recommended</td>
<td></td>
</tr>
<tr>
<td>first-line antiviral therapies.</td>
<td></td>
</tr>
<tr>
<td>KQ 3 Studies assessing predictive validity of screening strategies</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix A2. Inclusion and Exclusion Criteria per Key Question

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQs 4-7</strong> Randomized, placebo-controlled trials. Also, head-to-head trials for currently recommended first-line antiviral therapies.</td>
<td></td>
</tr>
<tr>
<td><strong>KQ 9</strong> Cohort studies examining the association between intermediate and clinical outcomes after antiviral treatment</td>
<td></td>
</tr>
</tbody>
</table>

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; KQ, key question.
Abstracts of potentially relevant articles identified through MEDLINE, Cochrane\textsuperscript{a}, and PsychINFO, and other sources\textsuperscript{b} (N = 4,506)

Excluded abstracts and background articles (n = 3,893)

Full text articles reviewed for relevance to Key Questions (n = 613)

Articles excluded: 567
- Wrong population: 94
- Wrong intervention: 196
- Wrong outcome: 83
- Wrong study design for Key Question: 81
- Wrong publication type: 41
- Wrong comparison: 59
- Duplicate data: 13

Included studies\textsuperscript{c}: 45
(in 46 publications)

Key Question 1: 0
Key Question 2: 0
Key Question 3: 1
Key Question 4: No studies on long-term clinical outcomes
Key Question 6: 16 (in 18 publications)
Key Question 7: 0
Key Question 8: 29 (in 28 publications)
Key Question 9: 10

\textsuperscript{a} Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

\textsuperscript{b} Other sources include reference lists of relevant articles.

\textsuperscript{c} Some studies are included for more than one Key Question.
Appendix A4. Excluded Studies

Wrong Population


Appendix A4. Excluded Studies


McDonald EM, Mann AH, Thomas HC. Interferons as mediators of psychiatric morbidity. An
Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Summers PR, Biswas MK, Pastorek JG, 2nd, Pernoll ML, Smith LG, Bean BE. The pregnant hepatitis B


**Wrong Intervention**


Appendix A4. Excluded Studies

no better than lamivudine alone in anti-HBe-positive chronic hepatitis B. *Antivir Ther*. 2004; 9(3):325-34.


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Hoofnagle JH, Peters M, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, et al. Randomized, controlled trial of recombinant human alpha-


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Perrillo RP. The use of corticosteroids in conjunction with antiviral therapy in chronic hepatitis B with
Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


**Wrong Outcome**


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Wai CT, Chu CJ, Hussain M, Lok AS. HBV genotype B is associated with better response to interferon therapy in HBeAg(+) chronic hepatitis than genotype C. *Hepatology.* 2002; 36(6):1425-30.


**Wrong Study Design for Key Question**


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Van Thiel DH, Friedlander L, Fagiuloi S, Wright HI, Irish W, Gavaler JS. Response to interferon alpha therapy is influenced by the iron content of the liver. *J Hepatol.* 1994; 20(3):410-5.

Wong GLH, Yiu KKL, Wong VWS, Tsoi KKF, Chan HLY. Meta-analysis: reduction in hepatic
Appendix A4. Excluded Studies


Wrong Publication Type


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


**Wrong Comparison**


Appendix A4. Excluded Studies


Ma H, Yang R-F, Wei L. Quantitative serum HBsAg and HBeAg are strong predictors of sustained HBeAg serocconversion to pegylated interferon alfa-2b in HBeAg-positive patients. *J Gastroenterol Hepatol*. 2010; 25(9):1498-506.


Appendix A4. Excluded Studies


Appendix A4. Excluded Studies


Duplicate Data


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.
Appendix A5. U.S. Preventive Services Task Force Quality Criteria

- 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.

## Appendix B1. Screening Strategies Evidence Table

<table>
<thead>
<tr>
<th>Author, year Country</th>
<th>Eligibility</th>
<th>N</th>
<th>Baseline characteristics</th>
<th>Screening strategy</th>
<th>HBsAg positive</th>
<th>Results</th>
<th>Funding source</th>
<th>Quality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spenatto 2013&lt;sup&gt;35&lt;/sup&gt; France</td>
<td>STD clinic attendees in France</td>
<td>6,194</td>
<td>Age 20-29 years: 62% Female: 56% Self-reported injection drug use: 0.7% High endemic area (prevalence &gt;8%) country of birth: 7.2%</td>
<td>A: Screen all B: Screening those born in moderate or high prevalence (&gt;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</td>
<td>0.8% (49/6194)</td>
<td>A vs. B vs. C vs. D vs. E</td>
<td>Not stated</td>
<td>Fair</td>
<td>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.</td>
</tr>
</tbody>
</table>

AUROC, area under the receiver operating curve; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; OR, odds ratio; STD, sexually transmitted disease.
### Appendix B2. Screening Strategies Quality Assessment

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>Did the study evaluate a representative spectrum?</th>
<th>Did the study report the proportion of eligible patients who met inclusion criteria who underwent screening?</th>
<th>Was there a high rate of non-screening among eligible patients?</th>
<th>Did the study describe methods for ascertaining risk factors?</th>
<th>Did the study prospectively compare different pre-defined screening strategies?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spengtto 2013&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No (19%)</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Appendix B3. Vaccination Studies Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>No. of centers</th>
<th>Country</th>
<th>Prevalence of Hepatitis B, if reported</th>
<th>Study duration</th>
<th>Baseline demographics</th>
<th>Eligibility criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coutinho 1983&lt;sup&gt;34&lt;/sup&gt;</td>
<td>RCT</td>
<td>Netherlands</td>
<td>Centers NR</td>
<td>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%</td>
<td>21.5 months</td>
<td>Vaccine vs. placebo Age, mean: 31 vs. 30 years 100% male ALT: see eligibility</td>
<td>Male homosexuals between 16 and 50 years of age, negative for HBsAg, anti-HBsAg, and anti-HBc, with ALT &lt;50 IU/I, no serious illness, and &gt;2 different male sexual partners in the preceding 6 months</td>
<td>See eligibility criteria</td>
</tr>
<tr>
<td>Szmuness 1980&lt;sup&gt;37&lt;/sup&gt;</td>
<td>RCT</td>
<td>United States</td>
<td>Centers NR</td>
<td>In over 10,000 homosexual men tested, 68% had evidence of past or present infection</td>
<td>24 months</td>
<td>Vaccine vs. placebo Age, mean: 29 vs. 29 years 100% male 86% vs. 88% White ALT: see eligibility</td>
<td>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&lt;50 IU in a blood specimen from preceding 2 weeks</td>
<td>See eligibility criteria</td>
</tr>
<tr>
<td>Francis 1982&lt;sup&gt;33&lt;/sup&gt;</td>
<td>RCT</td>
<td>United States</td>
<td>5 centers</td>
<td>Not reported</td>
<td>18 months</td>
<td>Vaccine vs. placebo Age, mean: 30 vs. 29 years 100% male 88% vs. 91% White ALT: see eligibility</td>
<td>Men aged &gt;18 years with homosexual preference who were negative for HBV serological markers (negative HBsAg, anti-HBc, anti-HBs) and had normal ALT (&lt;53 IU)</td>
<td>See eligibility criteria</td>
</tr>
</tbody>
</table>

### Systematic Review

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Purpose of study</th>
<th>Databases searched, date of last search</th>
<th>Number of studies</th>
<th>Types of studies included/ limitations of primary studies</th>
<th>Methods for rating methodological quality of primary studies</th>
<th>Methods for synthesizing results of primary studies</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2009&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Assess the harms/ benefits of HBV vaccine in health-care workers</td>
<td>Cochrane Hepato-Biliary Group Controlled Trials Registry, Cochrane Library, MEDLINE, EMBASE through February 2003</td>
<td>21 total; 4 placebo-controlled</td>
<td>4 PCTs; all included studies conducted in high-risk population and were rated low quality</td>
<td>Assessment of method of allocation and concealment, blinding and attrition</td>
<td>Random and fixed effects models applied</td>
<td>HBV vaccine: 1365 Placebo: 1332</td>
</tr>
</tbody>
</table>
## Appendix B3. Vaccination Studies Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number screened</th>
<th>Number eligible</th>
<th>Number enrolled</th>
<th>Number analyzed</th>
<th>Withdrawals</th>
<th>Loss to followup</th>
<th>Adjusted variables for statistical analysis (for observational studies)</th>
<th>Interventions</th>
<th>Results</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Coutinho 1983<sup>3</sup> | 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<sup>3</sup> | 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 six 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<sup>3</sup> | 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 of at time 0, 1 month, and six months after first injection  
B: Placebo: as per vaccine | Vaccine (n=714) vs. placebo (n=688)  
Infection at 18 months  
HBsAg positive or anti-HBc positive with enzyme elevation: 23 vs. 72  
HBsAg positive without enzyme elevation: 5 vs. 12  
Anti-HBc positive without enzyme elevation: 30 vs. 26  
All groups: 58 vs. 110 | None reported |

### Systematic Review

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Interventions</th>
<th>Results</th>
</tr>
</thead>
</table>
| Chen 2009<sup>3</sup> | 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, I²=18% | |

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 B4. Vaccination Studies Quality Assessment

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
<th>Attrition and withdrawals reported?</th>
<th>Loss to follow-up: differential/high?</th>
<th>Analyze people in the groups in which they were randomized?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coutinho 1983</td>
<td>Unclear; method not described</td>
<td>Unclear</td>
<td>Yes; only significant difference on history of jaundice</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear; described as double-blind</td>
<td>Unclear; described as double-blind</td>
<td>Unclear</td>
<td>No/No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Szmuness 1980</td>
<td>Unclear; method not described</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No/No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Francis 1982</td>
<td>Unclear; method not described</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No/No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>

| Author, year | Study design predetermined | 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    | Yes                         | Yes                                  | Yes                   | Yes                                          | Yes                             | Yes                           | Yes                                           | Yes                                      | Yes                           | Yes                         | Good    |
### Appendix B5. Treatment Trials Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Number of sites</th>
<th>Study duration</th>
<th>Interventions</th>
<th>Baseline demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo-controlled</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ali 2003</td>
<td>RCT</td>
<td>1 site</td>
<td>Iraq</td>
<td>24 months duration; 6-12 months of treatment and followup (variable based on efficacy measures) Mean followup: NR</td>
<td>A. Lamivudine 100 mg daily (n=32) B. Placebo (n=30)</td>
</tr>
<tr>
<td>Bayraktar 1993</td>
<td>Controlled trial</td>
<td>Unclear (likely single site) Turkey</td>
<td>Study duration: 6 months Mean duration of followup: NR</td>
<td>A. Interferon alfa 2b 5 MU IM 3x/week (n=25) B. No treatment (n=10)</td>
<td>A. vs. B Age range 35 vs. 36 years 72% vs. 70% male Race: NR 20% vs. 30% cirrhosis</td>
</tr>
<tr>
<td>Bozkaya 2005</td>
<td>Non-randomized controlled trial</td>
<td>1 site</td>
<td>Turkey</td>
<td>1 year treatment; 6 months post-treatment followup (for those in treatment group) Mean followup: NR</td>
<td>A. Lamivudine 100 mg daily (n=18) B: Untreated group with raised ALT (n=19) C: Untreated group with normal ALT (n=18)</td>
</tr>
<tr>
<td>Chan 2007</td>
<td>RCT</td>
<td>8 sites</td>
<td>China</td>
<td>24 months of treatment; 6 months followup Mean followup: NR</td>
<td>A. Lamivudine 100 mg daily (n=89) B. Placebo (n=47)</td>
</tr>
</tbody>
</table>
### Appendix B5. Treatment Trials Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Number of sites</th>
<th>Study duration</th>
<th>Interventions</th>
<th>Baseline demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dienstag 1999&lt;sup&gt;25&lt;/sup&gt;</td>
<td>RCT</td>
<td>34 sites United States</td>
<td>Study duration: 68 weeks Treatment duration: 52 weeks Post-treatment followup: 16 weeks</td>
<td>A. Lamivudine 100 mg daily (n=66) B. Placebo (n=71)</td>
<td>A vs. B&lt;br&gt;Median age: 40 vs. 38 years&lt;br&gt;Sex: 86% vs. 80% male&lt;br&gt;Race: 59% vs. 56% White, 24% vs. 17% Asian, 15% vs. 18% Black&lt;br&gt;Cirrhosis: 6% vs. 14%&lt;br&gt;Median HAI score: 10 vs. 11&lt;br&gt;Median serum HBV DNA: 102.2 vs. 56.5 pg/ml&lt;br&gt;Median serum ALT: 125 vs. 135 IU/l&lt;br&gt;Median serum bilirubin: 0.7 vs. 07 mg/dl&lt;br&gt;Median serum albumin: 3.9 vs. 3.8 g/dl</td>
</tr>
<tr>
<td>Hadziyannis 1990&lt;sup&gt;25&lt;/sup&gt;</td>
<td>RCT</td>
<td>Unclear (likely single site) Greece</td>
<td>Study duration: 1 year (2 year followup for some patients) Mean duration of followup: NR</td>
<td>A. Interferon alfa 2b 3 MU 3x/week for 14-16 weeks (n=25) B. No treatment (n=25)</td>
<td>A vs. B&lt;br&gt;Mean age 49 vs 48 years&lt;br&gt;92% vs 96% male&lt;br&gt;Race NR&lt;br&gt;40% vs 48% cirrhosis&lt;br&gt;96% vs 100% anti-HBe positive&lt;br&gt;Mean serum HBV DNA 26 vs 24 pg/mL&lt;br&gt;Mean serum ALT 123 vs 175 IU/L</td>
</tr>
<tr>
<td>Hadziyannis 2003&lt;sup&gt;25&lt;/sup&gt;</td>
<td>RCT</td>
<td>32 sites; Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore</td>
<td>48 weeks duration and followup; Safety analysis included all events that occurred within 30 days of drug discontinuation</td>
<td>A. Adefovir 10 mg daily (n=123) B. Placebo (n=62)</td>
<td>A vs. B&lt;br&gt;Age, mean: 46 vs. 45 years&lt;br&gt;Male: 83% vs. 82%&lt;br&gt;Race: 67% vs. 66% white; 4% vs. 2% black; 29% vs. 33% Asian&lt;br&gt;ALT x ULN, mean: 3.5 vs. 3.6&lt;br&gt;HBV DNA, mean: 6.9 vs. 6.9 log copies/ml&lt;br&gt;Knodell necroinflammatory activity score, mean: 7.7 vs. 7.1&lt;br&gt;Knodell fibrosis score, mean: 1.9 vs. 1.8&lt;br&gt;Cirrhosis: 11% vs. 10%&lt;br&gt;Prior interferon alfa treatment: 39% vs. 46%&lt;br&gt;Prior lamivudine treatment: 8% vs. 7%&lt;br&gt;Prior fámiclovir treatment: 6% vs. 11%&lt;br&gt;Note: some patients had received more than one medication</td>
</tr>
</tbody>
</table>
### Appendix B5. Treatment Trials Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Number of sites</th>
<th>Study duration</th>
<th>Interventions</th>
<th>Baseline demographics</th>
</tr>
</thead>
</table>
| Jonas 2008<sup>42</sup> | 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% |
| Lai 1997<sup>26</sup> | 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%  |
| Lai 1998<sup>27</sup> | 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) |
| Lampertico 1997<sup>46</sup> | 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 |
### Appendix B5. Treatment Trials Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Number of sites Country</th>
<th>Study duration Mean followup</th>
<th>Interventions</th>
<th>Baseline demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liaw 2004</td>
<td>RCT</td>
<td>41 sites Australia, China, Malaysia, New Zealand, the Philippines, Singapore, Taiwan, Thailand</td>
<td>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</td>
<td>A. Lamivudine 100 mg daily (n=436) B. Placebo (n=215)</td>
<td>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% &gt;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 (&lt;0.7-109,800) vs. 21.5 (&lt;0.7-4234) mEq/ml HBV DNA &gt;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 &gt;1 x ULN: 78% vs. 80% Prior HBV treatment: NR, but allowed (see eligibility criteria)</td>
</tr>
<tr>
<td>Lin 1999</td>
<td>RCT</td>
<td>Single site China</td>
<td>18 weeks treatment + mean 7 years followup (range 1 to 11 years)</td>
<td>A. Interferon alfa 2a 4-5 MU/m² (n=67) B. Placebo (n=34)</td>
<td>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</td>
</tr>
<tr>
<td>Marcellin 2003</td>
<td>RCT</td>
<td>78 sites North America, Europe, Australia, and Southeast Asia</td>
<td>48 weeks duration and followup; Safety analysis included all events that occurred within 30 days of drug discontinuation</td>
<td>A. Adefovir 10 mg daily (n=172) B. Adefovir 30 mg daily (n=173) C. Placebo (n=170)</td>
<td>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</td>
</tr>
<tr>
<td>Author, year</td>
<td>Study design</td>
<td>Number of sites Country</td>
<td>Study duration Mean followup</td>
<td>Interventions</td>
<td>Baseline demographics</td>
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<tr>
<td>Mazzella 1999</td>
<td>RCT</td>
<td>Single site Italy</td>
<td>6 months treatment + 7 years followup</td>
<td>A. Interferon alfa 2a, mean dose 648 MU (n=33) B. No treatment (n=31)</td>
<td>HBeAg positive: 100% Prior interferon alfa treatment: 24.9% (123/494)</td>
</tr>
<tr>
<td>Muller 1990</td>
<td>RCT</td>
<td>Unclear (likely single site) Germany</td>
<td>Study duration: 4 months Mean duration of followup: NR</td>
<td>A. Interferon alfa 2b 3 MU SC 3x/week (n=30) B. No treatment (n=28)</td>
<td>Age, gender, race, cirrhosis, HBeAg positivity</td>
</tr>
<tr>
<td>Murray 2012</td>
<td>RCT</td>
<td>21 sites United States, Bulgaria, France, Poland, Romania, Spain, Turkey</td>
<td>72 weeks</td>
<td>A. Tenofovir 300 mg qd B. placebo</td>
<td>Mean age 15 years both groups (SD 1; range 12-17 years) 73% vs 65% male 94% vs 91% White1% vs 0% Black1% vs 1% Asian1% vs 4% other 92% vs 89% HBeAg positive 83% vs 87% prior HBV treatment Mean HBV DNA 8.01 vs 8.24 log10 copies/mL Normal ALT 33% vs 22% Mean ALT 101 U/L</td>
</tr>
<tr>
<td>Perez 1990</td>
<td>RCT</td>
<td>Unclear (likely single site) Argentina</td>
<td>Study duration: 24 weeks (control phase) Mean duration of followup: NR</td>
<td>A. Prednisone run-in + interferon alfa 2b 10 MU SC 3x/week (n=17) B. No treatment (n=18)</td>
<td>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</td>
</tr>
<tr>
<td>Perrillo 1990</td>
<td>RCT</td>
<td>Multicenter (number of sites NR) United States</td>
<td>Study duration: 16 weeks (+ 6 months post-treatment observation) Mean duration of followup: NR</td>
<td>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)</td>
<td>Mean age 40 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</td>
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</tbody>
</table>
### Appendix B5. Treatment Trials Evidence Table

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<tr>
<td>Sarin 1996&lt;sup&gt;54&lt;/sup&gt;</td>
<td>RCT</td>
<td>Unclear (likely single site)</td>
<td>Study duration: 4 months + 12 months post-treatment followup Mean duration of followup: NR</td>
<td>A. Interferon alfa 2b 3 MU SC 3x/week (n=20) B. No treatment (n=21)</td>
<td>A vs. B Mean age 32 vs 37 years 80% vs 81% male Race NR 45% vs 43% cirrhosis</td>
</tr>
<tr>
<td>Tassopoulos 1999&lt;sup&gt;56&lt;/sup&gt;</td>
<td>RCT</td>
<td>1 site</td>
<td>Greece</td>
<td>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</td>
<td>A. Lamivudine 100 mg daily (n=60) B. Placebo (n=64) Note: Comparison data only available up to week 26</td>
</tr>
<tr>
<td>Waked 1990&lt;sup&gt;51&lt;/sup&gt;</td>
<td>RCT</td>
<td>Unclear (likely single site)</td>
<td>Egypt</td>
<td>Study duration: 16 weeks (+ 12 months post-treatment observation) Mean duration of followup: NR</td>
<td>A. Interferon alfa 2b5 MU SC 2x/week (n=12) or daily (n=8)</td>
</tr>
<tr>
<td>Yalc in 2004&lt;sup&gt;57&lt;/sup&gt;</td>
<td>RCT</td>
<td>One site</td>
<td>Turkey</td>
<td>Duration: 12 months Active treatment: 12 weeks</td>
<td>A. Lamivudine 100 mg daily (n=13) B. Control (n=33)</td>
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<tr>
<td>Yao 1999&lt;sup&gt;57&lt;/sup&gt;</td>
<td>RCT</td>
<td>Multiple sites (number NR) China</td>
<td>Blinded treatment duration: 12 weeks Open-label treatment: 9 months</td>
<td>A. Lamivudine 100 mg daily (n=322) B. Placebo (n=107)</td>
<td>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)</td>
</tr>
<tr>
<td>Zeng, 2006&lt;sup&gt;63&lt;/sup&gt;</td>
<td>RCT</td>
<td>Seven cities China</td>
<td>52 weeks; Only first 12 weeks met inclusion criteria</td>
<td>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)</td>
<td>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 log10 copies/mL HBeAg positive: 99% vs. 96% vs. 99% Prior lamivudine treatment: 35% vs. 32% vs. 27%</td>
</tr>
<tr>
<td>Chang, 2006&lt;sup&gt;64&lt;/sup&gt;; Gish 2007&lt;sup&gt;65&lt;/sup&gt;; Chang 2009&lt;sup&gt;66&lt;/sup&gt;</td>
<td>RCT</td>
<td>137 centers North America, Asia, Australia, South America</td>
<td>96 weeks (52 weeks treatment + additional 44 weeks for partial responders; results for responders, partial responders and non-responders included in results)</td>
<td>A. Entecavir 0.5 mg qd B. Lamivudine 100 mg qd</td>
<td>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 &lt;1% vs 1% other 98% vs 99% HBeAg positive 2% vs 2% cirrhosis</td>
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</table>
| Lai 2002<sup>22</sup> | 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 |
| Lai 2006<sup>32</sup> | 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 |
| Lau 2005<sup>10</sup> | 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 |
| Marcellin 2004<sup>71</sup> | 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 |
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<tbody>
<tr>
<td>Marcellin 2008&lt;sup&gt;72&lt;/sup&gt; Study 102 (HBeAg negative at baseline)</td>
<td>RCT</td>
<td>106 centers from 15 countries in Europe, North America, Australia, and New Zealand</td>
<td>48 weeks (time on treatment)</td>
<td>A. Tenofovir 300 mg qd B. Adefovir 10 mg qd</td>
<td>n=375 Mean age 44 years 77% male 65% White 25% Asian 3% Black 7% other 0% HBeAg positive 20% cirrhosis</td>
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<tr>
<td>Study 103 (HBeAg positive at baseline)</td>
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<td></td>
<td></td>
<td>n=266 Mean age 34 years 69% male 52% White 36% Asian 7% Black 5% other 100% HBeAg negative 20% cirrhosis</td>
<td></td>
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<tr>
<td>Ren 2007&lt;sup&gt;73&lt;/sup&gt;</td>
<td>RCT</td>
<td>Single center (?) in China</td>
<td>48 weeks (time on treatment)</td>
<td>A. Entecavir 0.5 mg qd B. Lamivudine 100 mg qd</td>
<td>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</td>
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<tr>
<td>Placebo-controlled</td>
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<tr>
<td>Ali 2003&lt;sup&gt;72&lt;/sup&gt;</td>
<td>HBsAg/anti-HBe positive with persistent anti-HBc IgM; asymptomatic</td>
<td>NR</td>
<td>Screened: NR Eligible: NR Enrolled: 74 Analyzed: 62</td>
<td>Withdrawals: 8.1% (6/74) Loss to followup: 8.1% (6/74)</td>
<td>N/A</td>
</tr>
<tr>
<td>Bayraktar 1993&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Serum transaminase elevation &gt;2x ULN for &gt;6 months; HCV, HIV negative; HBsAg and HBeAg positive; chronic active hepatitis (per liver histology)</td>
<td>Decompensated cirrhosis</td>
<td>Screened: NR Eligible: NR Enrolled: unclear Analyzed: 35</td>
<td>Withdrawals: none reported Loss to followup: none reported (unclear if results for all enrolled patients reported)</td>
<td>N/A</td>
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<tr>
<td>Bozkaya 2005&lt;sup&gt;53&lt;/sup&gt;</td>
<td>ALT &gt;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 &lt;20 g per week; BMI &lt;30 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Presence of non-alcoholic steatohepatitis and significant liver steatosis; high BMI; high alcohol intake; drug-related toxicity</td>
<td>Screened: 390</td>
<td>Eligible: 55</td>
<td>Enrolled: 55</td>
<td>Analyzed: 55</td>
</tr>
<tr>
<td>Chan 2007&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Age &gt;18 years; positive HBsAg for &gt;6 months prior to screening; detectable HBV DNA by non-PCR based assay; significantly increased ALT levels (ALT 1.5 to 10 times ULN on &gt;2 occasions in the previous 6 months or ALT above ULN with &gt;1 flareup of ALT &gt;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 &gt;100,000 copies/ml</td>
<td>Hepatocellular carcinoma; ALT &gt;10 times ULN at screening; decompensated liver disease; complications of liver cirrhosis; co-infection 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 &gt;1.5 times ULN; anti-nuclear antibody titre &gt;1:160; serum amylase or lipase level &gt;2 times ULN, hemoglobin &lt;11 g/dl; white cell count &lt;3x10&lt;sup&gt;9&lt;/sup&gt;/l; platelet count &lt;100x10&lt;sup&gt;9&lt;/sup&gt;/l; pregnant or lactating women</td>
<td>Screened: 443</td>
<td>Eligible: 139</td>
<td>Enrolled: 139</td>
<td>Analyzed: 136</td>
</tr>
<tr>
<td>Author, year</td>
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<tr>
<td>Dienstag 1999&lt;sup&gt;55&lt;/sup&gt;</td>
<td>18 years of age; detectable serum HBsAg for at least 6 months, serum HBeAg for at least one month, and ALT levels 1.3 to 10 times the upper limit of normal for at least three months; evidence of chronic hepatitis on liver biopsy; and detectable levels of HBV DNA</td>
<td>Previous antiviral therapy for hepatitis B; any treatment with antiviral drugs, immunomodulatory drugs, or cortico-steroids within the previous 6 months; bilirubin level &gt;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/mm³; a neutrophil count of less than 1500 cells/mm³; a platelet count of less than 100,000 cells/mm³; presence of a confounding illness or other type of liver disease; pregnant or breastfeeding</td>
<td>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</td>
<td>Withdrawals: 6 (2 patients withdrew before receiving treatment, 4 others excluded because they did not meet inclusion criteria)</td>
<td>Adjustments for odds ratios: ALT, HBV DNA, HAI score, race, age, sex, weight, and the presence of cirrhosis</td>
<td></td>
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<tr>
<td>Hadziyannis 1990&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Chronic, active hepatitis; HBsAg positive; HBeAg negative/serum HBV DNA positive for &gt;1 year</td>
<td>Decompensated cirrhosis; use of corticosteroids, immunosuppressive drugs or antivirals with 6 months</td>
<td>Screened: NR Eligible: NR Enrolled: 50 Analyzed: 35 (at 12 months)</td>
<td>Withdrawals: NR Loss to followup: unclear; results presented for 35/50 enrolled patients</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Hadziyannis 2003&lt;sup&gt;46&lt;/sup&gt;</td>
<td>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 10⁵ 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, 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</td>
<td>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</td>
<td>Withdrawals: 2.4% (3/123) vs. 1.6% (1/61) Loss to followup: 0.8% (1/123) vs. 0% (0/61)</td>
<td>N/A</td>
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<td>Jonas 2008&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Creatinine no more than 1.5 mg/dL, adequate blood count.</td>
<td>Chemotherapeutic agents; serum alphafetoprotein 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</td>
<td>Screened: 293 Eligible: 173 Analyzed: 170</td>
<td>Note: only 12-17 year old age group included, n=83</td>
<td>A vs. B Withdrawals: 5% (3/56) vs. 0% (0/27) Loss to followup: none</td>
</tr>
<tr>
<td>Lai 1997&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Chronic HBsAg carriers; HBV DNA levels &gt;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</td>
<td>NR</td>
<td>Screened: NR Eligible: NR Enrolled: 42 Analyzed: 42</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Lai 1998&lt;sup&gt;20&lt;/sup&gt;</td>
<td>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 &lt;10 times the upper limit of normal for at least the previous 3 months</td>
<td>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</td>
<td>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</td>
<td>A vs. B vs. C Withdrawals: 6% (8/142) vs. 3% (4/143) vs. 4% (3/73)</td>
<td>N/A</td>
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<td>Lampertico 1997&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Age 18-65 years; chronic active HBV, with or without cirrhosis; HBsAg and anti-Hbe in serum for ≥1 year; serum ALT &gt;2x ULN; detectable serum HBV DNA in year preceding study</td>
<td>HCV, HDV or HIV positive; pregnant or lactating; drug abuse' alcoholism; antiviral or immunosuppressive therapy in 12 months preceding study; platelet counts &lt;100,000/mL; white blood cell counts &lt;3,000/mL; serum markers of autoimmunity; renal failure; history of hepatic decompensation; other serious medical illness</td>
<td>Screened: NR Eligible: NR Enrolled: 42 Analyzed: unclear</td>
<td>Withdrawals: 6/42 (14%) Loss to followup: 3/42 (7%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Liaw 2004&lt;sup&gt;76&lt;/sup&gt;</td>
<td>Patients &gt;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</td>
<td>Evidence of hepatocellular carcinoma, serum ALT &gt;10 times ULN, hepatic decompensation, autoimmune hepatitis, coinfection with HCV, HDV, or HIV, serious concurrent illness, amylase or lipase &gt;2 times ULN, elevated creatinine level, hemoglobin &lt; 8 g per cubic deciliter, white cell count &lt;15000 per cubic millimeter, platelet count &lt;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.</td>
<td>Screened: NR Eligible: NR Enrolled: 651 Analyzed: 651</td>
<td>Per-protocol withdrawals: 21% (135/651) Withdrawals for other reasons: 8% (52/651)</td>
<td>HR adjusted for country, sex, baseline alanine aminotransferase level, Child-Pugh score, and Ishak fibrosis score; CI unadjusted for interim analyses</td>
</tr>
<tr>
<td>Lin 1999&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Age 16-65 years; heterosexual male; HBsAg and HBeAg positive; elevated ALT (&lt;40 U/l); liver biopsy within 3 months of study entry showing chronic active hepatitis or chronic lobular hepatitis; presence of serum HBV-DNA</td>
<td>Immunosuppressive or antiviral therapy use; HDV infection; IV drug abuse; decompensated liver disease; other serious medical illness; AFP &gt;100 ng/ml</td>
<td>Screened: NR Eligible: NR Enrolled: 120 Analyzed: 101</td>
<td>NR</td>
<td>Age, baseline ALT, baseline HBV-DNA, preexisting cirrhosis AFP level, duration of hepatitis, treatment regimen</td>
</tr>
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<tr>
<td>Marcellin 200342</td>
<td>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.</td>
<td>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.</td>
<td>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</td>
<td>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)</td>
<td>Loss to followup for total group: Unclear</td>
</tr>
<tr>
<td>Mazzella 199975</td>
<td>HBsAg, HBeAg and HBV-DNA positive; elevated ALT; histologic evidence of chronic active or persistent hepatitis</td>
<td>Age &lt;18 or &gt;65 years; pregnancy; histologically proven cirrhosis; HDV or HIV antibodies; history of drug abuse</td>
<td>Screened: NR Eligible: NR Enrolled: 64 Analyzed: 64</td>
<td>NR</td>
<td>N/A</td>
</tr>
<tr>
<td>Muller 199077</td>
<td>Age 18-65 years; HBsAg and HBV DNA positive for ≥6 months</td>
<td>HDV or HIV positive; decompensated cirrhosis; chronic renal insufficiency; use of hemodialysis or immunosuppressive agents; previous organ transplantation; poor physical condition</td>
<td>Screened: NR Eligible: NR Enrolled: 58 Analyzed: 55</td>
<td>Withdrawals: 3/58 (5%) Loss to followup: none reported</td>
<td>N/A</td>
</tr>
<tr>
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<tr>
<td>Murray 2012*</td>
<td>Age 12 to &lt;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</td>
<td>Previous tenofovir use; HCV, HDV or HIV co-infection; history of significant bone disease, decompensated liver disease, or renal disease; evidence of hepatocellular carcinoma</td>
<td>Screened: 149 Eligible: NR Enrolled: 106 Analyzed: 101</td>
<td>Withdrawals: 5/106 (5%)</td>
<td>Loss to followup: none reported</td>
</tr>
<tr>
<td>Perez 1990*</td>
<td>Age ≥18 years; HBsAg, HBeAg and HBV DNA for at least 6 months; ALT &gt;1.3 ULN; compensated liver disease with prolonged prothrombin &lt;3 seconds; normal serum albumin and bilirubin; no history of hepatic encephalopathy, bleeding esophageal varices or ascites</td>
<td>HDV or HIV positive; low hematocrit (&lt;35%), platelets (&lt;100,000/mm^3), white blood cells (&lt;4,000/mm^3), granulocytes (&lt;1,500/mm^3)</td>
<td>Screened: NR Eligible: NR Enrolled: 35 Analyzed: 35</td>
<td>Withdrawals: none reported</td>
<td>Loss to followup: none reported</td>
</tr>
<tr>
<td>Perrillo 1990*</td>
<td>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)</td>
<td>Corticosteroid or antiviral therapy during previous 12 months; pregnancy; serious medical illness; low hematocrit, platelet (&lt;70x10^9), white cell (&lt;3x10^9) and granulocyte (&lt;1.5x10^9) counts; elevated serum creatinine; alcoholism; drug abuse; other potential causes of liver disease; HDV or HIV positive</td>
<td>Screened: 545 Eligible: 169 Enrolled: 169 Analyzed: 169</td>
<td>Withdrawals: 4/169 (2%)</td>
<td>Loss to followup 2/169 (1%)</td>
</tr>
<tr>
<td>Sarin 1996*</td>
<td>Age &lt;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 Antiviral therapy within 12 months; pregnancy; platelet count &lt;70,000/cmm; white cell count &lt;3,000/cmm; elevated serum creatinine</td>
<td>Screened: NR Eligible: NR Enrolled: 41 Analyzed: 41</td>
<td>Withdrawals: none reported</td>
<td>Loss to followup: none reported</td>
<td>N/A</td>
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<tr>
<td>Tassopoulos 1999&lt;sup&gt;58&lt;/sup&gt;</td>
<td>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 &gt; 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 &gt;3 months before screening with no value falling in reference range during intervening period</td>
<td>HCV, HDV, HIV positive; presence of decompensated liver disease; evidence of autoimmune hepatitis; interferon treatment within previous 6 months</td>
<td>Screened: 260 Eligible: 125 Enrolled: 125 Analyzed: 124</td>
<td>A vs. B: Withdrawals: 12% (7/60) vs. 6.3% (4/64) Per-protocol withdrawals at week 26 (HBV DNA &gt;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</td>
<td>N/A</td>
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<tr>
<td>Waked 1990&lt;sup&gt;77&lt;/sup&gt;</td>
<td>HBsAg positive for &gt;6 months; elevated aminotransferase; histologically active liver disease; normal blood count; normal renal function; compensated liver disease</td>
<td>Normal aminotransferase; chronic persistant hepatic; inactive cirrhosis or normal histology; serum albumin &lt;3 gm/dL; serum bilirubin &gt;4 mg/dL; serum creatinine &gt;1/5 mg/dL; history of encephalopathy, ascites of bleeding esophageal varices; HDV infection; male homosexuality; pregnancy; corticosteroid or antiviral therapy with preceding 12 months; inadequate blood counts; asymptomatic heart disease of ECG evidence of ischemic heart disease</td>
<td>Screened: NR Eligible: NR Enrolled: 40 Analyzed: 35</td>
<td>Withdrawals: 5/40 (13%) Loss to followup: 1/40 (3%)</td>
<td>N/A</td>
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<td>Yalcin 2004[47]</td>
<td>Adult patients with no previous antiretroviral treatment; HBsAg positive for &gt;6 months; positive HBeAg; serum HBV DNA &gt;1 pg/ml; persistently normal ALT values on at least 3 occasions in the previous 6 months; histological evidence of absent or minimal changes in liver biopsy; negative urine or serum pregnancy test for women of childbearing age; all men with partners of childbearing age and premenopausal women required to use reliable contraception during study and 6 months after treatment completion</td>
<td>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</td>
<td>Screened: 53  Eligible: 46  Enrolled: 46  Analyzed: 46</td>
<td>Withdrawals: 0 vs. 3% (1/33)  Loss to followup: None</td>
<td>N/A</td>
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<tr>
<td>Yao 1999[46]</td>
<td>Aged 16 to 65 years; HBeAg and HBsAg positive in the 6 months prior to screening; detectable HBV DNA at screening; ALT levels &lt;10 times the upper limit of normal at screening</td>
<td>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 &gt;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</td>
<td>Screened: 440  Eligible: 429  Enrolled: 429  Analyzed: 429</td>
<td>A vs. B  Withdrawals: 2.8% (9/322) vs. 1.8% (2/110)</td>
<td>N/A</td>
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## Appendix B5. Treatment Trials Evidence Table

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<tr>
<td>Zeng, 200663</td>
<td>At least 18 years old with detectable HBsAg for previous 6 months, detectable HBeAg, HBV DNA $&gt;10^6$ copies/mL, ALT level more that 1 xULN, and ALT more than 2 xULN sometime in previous 6 months</td>
<td>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</td>
<td>Screened: NR Eligible: NR Enrolled: 480 Analyzed: 480</td>
<td>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</td>
<td>N/A</td>
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<td>Chang 200665, Gish 200765, Chang 200966</td>
<td>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</td>
<td>HCV, HDV or HIV coinfection, other liver disease, use of antiviral agents within 24 weeks of randomization, prior lamivudine use lasting &gt;12 weeks, AFP &gt;100mg/ml, history of ascites requiring diuretics or paracentesis, previous entecavir treatment</td>
<td>Screened: 1,056 Eligible: NR Enrolled: 715 Analyzed: 709</td>
<td>Withdrawals: unclear; 10/715 (1%) withdrew due to AEs Loss to follow up: 54/715 (8%)</td>
<td>N/A</td>
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<tr>
<td>Lai 200268</td>
<td>Age ≥16 years, HBsAg positive, HBeAg positive or HBeAg negative and anti-HBeAg positive, HBV DNA $&gt;40$ Meq/mL, ALT $&lt;10x$ ULN, compensated liver disease</td>
<td>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</td>
<td>Screened: 431 Eligible: NR Enrolled: 185 Analyzed: 169 (87 A vs B)</td>
<td>Withdrawals: 8/185 (4%) Loss to followup: NR</td>
<td>N/A</td>
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<tr>
<td>Lai 200669</td>
<td>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</td>
<td>HCV, HDV or HIV coinfection, other liver disease, use of antiviral agents within 24 weeks of randomization, prior lamivudine use lasting &gt;12 weeks, AFP &gt;100ng/ml, history of ascites requiring diuretics or paracentesis, previous entecavir treatment</td>
<td>Screened: 1,468 Eligible: 694 Enrolled: 648 Analyzed: 638</td>
<td>Withdrawals: 31/638 (5%) Loss to follow-up: NR</td>
<td>N/A</td>
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<tr>
<td>Lau 2005&lt;sup&gt;5&lt;/sup&gt;</td>
<td>HBsAg positive for at least 6 months, anti-HBs negative, HBeAg positive, HBV DNA &gt; 500,000 copies/mL, ALT &gt; 1 and &lt; 10x ULN, chronic HBV confirmed by liver biopsy</td>
<td>Decompensated liver disease, coexisting serious medical or psychiatric illness, neutrophil count &lt; 1500/mL&lt;sup&gt;3&lt;/sup&gt;, platelet count &lt; 90,000/mL&lt;sup&gt;3&lt;/sup&gt;, creatinine &gt; 1.5x ULN, history of alcohol or drug abuse, HIV, HCV or HDV coinfection, HBV treatment within 6 months of study</td>
<td>Screened: NR Eligible: NR Enrolled: n=543 (excluding 271 patients randomized to peg interferon + lamivudine combination therapy) Analyzed: 543</td>
<td>Withdrawals: 70/543 (13%) Loss to followup: NR</td>
<td>N/A</td>
</tr>
<tr>
<td>Marcellin 2004&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Adults, HBeAg negative, anti-HBe antibody and HBsAg positive, HBV DNA &gt; 100,000 copies/mL, serum ALT &gt; 1 and &lt; 10x ULN, HBV positive confirmed by liver biopsy within previous 24 months, evidence of prominent necroinflammatory activity</td>
<td>Decompensated liver disease, coexisting serious medical or psychiatric illness, neutrophil count &lt; 1500/mL&lt;sup&gt;3&lt;/sup&gt;, platelet count &lt; 90,000/mL&lt;sup&gt;3&lt;/sup&gt;, creatinine &gt; 1.5x ULN, history of alcohol or drug abuse, HIV, HCV or HDV coinfection, HBV treatment within 6 months</td>
<td>Screened: Not reported Eligible: Not reported Enrolled: 552 Analyzed: 537</td>
<td>Withdrawals: 38/358 (11%) Loss to followup: not reported</td>
<td>N/A</td>
</tr>
<tr>
<td>Marcellin 2008&lt;sup&gt;72&lt;/sup&gt; Study 102 (HBeAg negative at baseline)</td>
<td>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 &gt; 1 to &lt; 10x ULN, HBV DNA &gt; 10&lt;sup&gt;5&lt;/sup&gt; copies/mL, &lt; 12 weeks treatment with any nucleoside or nucleotide or use of lamivudine or emtricitabine for at least 12 weeks</td>
<td>HIV, HCV or HDV infection, evidence of HCC, creatinine clearance &lt; 70 ml/minute, hemoglobin &lt; 8 g/dL, neutrophil count &lt; 1000/mL&lt;sup&gt;3&lt;/sup&gt;, liver decompensation or failure</td>
<td>Screened: 846 Eligible: 382 Enrolled: 375 Analyzed: 375</td>
<td>Withdrawals: 10/375 (3%) Loss to followup: 1/375 (0.3%)</td>
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<tr>
<td>Study 103 (HBeAg positive at baseline)</td>
<td>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 &gt; 2 to &lt; 10x ULN, HBV DNA &gt; 10&lt;sup&gt;6&lt;/sup&gt; copies/mL, &lt; 12 weeks treatment with any nucleoside or nucleotide</td>
<td>Screened: 603 Eligible: 272 Enrolled: 266 Analyzed: 266</td>
<td>Withdrawals: 15/266 (6%) Loss to followup: none reported</td>
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Screening for Hepatitis B Virus Infection 129 Pacific Northwest EPC
### Appendix B5. Treatment Trials Evidence Table

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<tr>
<td>Ren 2007</td>
<td>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, detectable HBsAg, HBV DNA positive, serum ALT 1.3-10 X ULN</td>
<td>HIV, HCV of 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 &gt;100 ng/mL, history of ascites requiring diuretics or paracentesis, previous treatment with entecavir or adefovir</td>
<td>Screened: Not reported Eligible: Not reported Enrolled: 61 Analyzed: unclear of efficacy, 61 for harms</td>
<td>Withdrawals: 1/61 (2%) Loss to followup: None reported</td>
<td>N/A</td>
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<tr>
<th>Author, year</th>
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<th>Clinical health outcomes</th>
<th>Adverse events</th>
<th>Quality</th>
<th>Funding source</th>
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<tbody>
<tr>
<td>All 2003</td>
<td>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 doesn’t match other text and table about antibody development and HBsAg loss</td>
<td>NR</td>
<td>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)</td>
<td>Poor</td>
<td>NR</td>
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</table>

| Bayraktar 1993 | 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 |

<p>| Bozkaya 2005 | 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 |</p>
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</table>
| Chan 2007  | A vs. B               | 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 0.7 to 3.8)  
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 | Fair | Glaxo-Smith Kline |
| Dienstag 1999 | A vs. B  
One-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% | Mortality: None  
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 |
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<tr>
<td>Hadziyannis</td>
<td>(62/63) vs. 33% (23/69); RR 2.95 (95% CI 2.11-4.13)</td>
<td>Likelihood of histologic response: OR 7.5, 95% CI 2.7-20.9</td>
<td>Interferon alfa 2b (no results presented for untreated group)</td>
<td>Poor</td>
<td>NR</td>
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<tr>
<td>199045</td>
<td>Likelihood of HBeAg seroconversion: OR 9.7, 95% CI 1.7-56.1</td>
<td></td>
<td>Serious adverse events 0/25 (0%)</td>
<td>NR</td>
<td>NR</td>
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<td>4-month outcomes (time on treatment)</td>
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<td>Complete treatment response: 10/25 (40%) vs 0/25 (0%); RR 21 (95% CI 1.30 to 340)</td>
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<td>Partial treatment response: 7/25 (28%) vs 4/25 (16%); RR 1.75 (95% CI 0.59 to 5.24)</td>
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<td>12-month outcomes (post-treatment)</td>
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<td>Complete treatment response: 11/25 (44%) vs 2/25 (8%); RR 5.5 (95% CI 1.36 to 22)</td>
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<td>Partial treatment response: 3/25 (12%) vs 6/25 (24%); RR 0.5 (95% CI 0.14 to 1.78)</td>
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<td>Hadziyannis</td>
<td>A vs. B</td>
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<tr>
<td>200340</td>
<td>64% (77/121) vs. 33% (19/57); RR 1.9 (95% CI 1.3 to 2.8)</td>
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<td>Gilead Sciences</td>
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<td></td>
<td>HBV DNA undetectable: 51% (63/123) vs. 0% (0/61); RR 64 (95% CI 4.0 to 1009)</td>
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<td>ALT normalization: 72% (84/116) vs. 29% (17/59); RR 2.5 (95% CI 1.7 to 3.8)</td>
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<tr>
<td>Jonas</td>
<td>A vs. B</td>
<td>Mortality: None</td>
<td></td>
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<td>Gilead Sciences</td>
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<tr>
<td>200831</td>
<td>HBV DNA &lt;1000 copies/mL and ALT normalization: 23% (13/56) vs. 0% (0/27); RR 13 (95% CI 0.8 to 215.1)</td>
<td></td>
<td>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)</td>
<td>Fair</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Author, year</td>
<td>Intermediate outcomes</td>
<td>Clinical health outcomes</td>
<td>Adverse events</td>
<td>Quality</td>
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</table>
| Lai 1997<sup>56</sup> | 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 |
| Lai 1998<sup>57</sup> | 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% (76/73)  
RR 1.0 (95% CI 0.9 to 1.2) (combined treatment arms) | Fair | Glaxo Wellcome Research and Development |
| Lampertico 1997<sup>46</sup> | 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% CI 0.65 to 187) | Fair | Istituto Superiore di Sanità (Italian National Health Service) |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Liaw 2004&lt;sup&gt;17&lt;/sup&gt;</td>
<td>NR</td>
<td>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 Mortality during double-blind phase: &lt;1% (2/436) vs. 0Hepatocellular 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)</td>
<td>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 &gt;10% of patients in a treatment group</td>
<td>Fair</td>
<td>Glaxo-SmithKline; some authors received funding by industry</td>
</tr>
<tr>
<td>Lin 1999&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Not relevant&lt;sup&gt;8&lt;/sup&gt;</td>
<td>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: 8/67 (12%) vs 5/34 (15%); RR 0.81 (95% CI 0.29 to 2.29)</td>
<td>Not relevant&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Fair</td>
<td>The Prosperous Foundation (Taipei, Taiwan)</td>
</tr>
</tbody>
</table>

<sup>17</sup> Liaw 2004, <sup>18</sup> Lin 1999, <sup>8</sup> Not relevant
### Appendix B5. Treatment Trials Evidence Table

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<th>Funding source</th>
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<tbody>
<tr>
<td>Marcellin 2003⁴²</td>
<td>A vs. B vs. C</td>
<td>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)</td>
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<td>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)</td>
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<td>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)</td>
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<td></td>
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<td>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)</td>
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<td>A + B vs. C</td>
<td>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. &lt;1% (1/167) RR 3.9 (95% CI 0.5 to 31)</td>
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<td>Fair</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Mazzella 1999⁷³</td>
<td>Not relevant⁹</td>
<td>A vs. B</td>
<td>Mortality: 0/33 (0%) vs 2/31 (6%); RR 0.19 (95% CI 0.01 to 3.77)</td>
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<td>Fair</td>
<td>NR</td>
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<td></td>
<td></td>
<td>Hepatocellular cancer: 2/33 (3%) vs 2/31 (6%); RR 0.94 (95% CI 0.14 to 6.27)</td>
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<td>Incident cirrhosis: 4/33 (12%) vs 6/31 (19%); RR 0.63 (95% CI 0.2 to 2.01)</td>
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<td>Muller 1990⁷⁷</td>
<td>A vs. B</td>
<td>Complete response: 1/30 (3%) vs 0/28 (0%); RR 2.81 (95% CI 0.12 to 66)</td>
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<td>Partial response: 8/30 (27%) vs 3/28 (0%); RR 2.49 (95% CI 0.73 to 8.45)</td>
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<td></td>
<td>Interferon alfa 2b (no results presented for untreated group) Withdrawals due to adverse events 3.7% (1/27)</td>
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<td>Fair</td>
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## Appendix B5. Treatment Trials Evidence Table

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<tr>
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<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Murray 2012&lt;sup&gt;11&lt;/sup&gt;</td>
<td>A vs. B</td>
<td>Viral load achieved: 46/52 (89%) vs 0/54 (0%); RR 97 (95% CI 6 to 1526)</td>
<td>A vs. B</td>
<td>Serious adverse events</td>
<td>Good</td>
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<tr>
<td></td>
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<td>Viral load undetectable: 44/52 (85%) vs 0/54 (0%); RR 92 (95% CI 6 to 1462)</td>
<td></td>
<td>12% (6/52) vs 22% (12/54)</td>
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<td>ALT normalization, patients &gt;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)</td>
<td></td>
<td>RR 0.5 (95% CI 0.2 to 1.3)</td>
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<td>ALT normalization, all patients: 40/52 (77%) vs 21/54 (39%); RR 1.98 (95% CI 1.37 to 2.85)</td>
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<td>Any adverse event 85% (44/52) vs 89% (48/54)</td>
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<td>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)</td>
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<td>RR 0.95 (95% CI 0.8 to 1.1)</td>
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<td>HBsAg loss: 1/52 (2%) vs 0/54 (0%); RR 3.11 (95% CI 0.13 to 75)</td>
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<td>Composite outcomes</td>
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<td>Viral load achieved + ALT normalization: 37/52 (71%) vs 0/54 (0%); RR 77 (95% CI 5 to 1235)</td>
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<td>Viral load achieved + ALT normalization + HBeAg loss: 11/52 (21%) vs 0/54 (0%); RR 24 (95% CI 1.44 to 395)</td>
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<td>Viral load achieved + ALT normalization + HBsAg loss: 8/52 (15%) vs 0/54 (0%); RR 18 (95% CI 1.04 to 298)</td>
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<tr>
<td>Perez 1990&lt;sup&gt;16&lt;/sup&gt;</td>
<td>A vs. B</td>
<td>HBeAG loss: 10/17 (59%) vs 1/18 (6%); RR 11 (95% CI 1.59 to 78)</td>
<td>A vs. B</td>
<td>Withdrawals due to adverse events</td>
<td>Fair</td>
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<td>HBsAG loss: 1/17 (6%) vs 0/18 (0%); RR 3.17 (95% CI 0.14 to 73)</td>
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<td>6% (1/18) vs. 0% (0/17)</td>
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<td>HBV DNA loss: 1/17 (6%) vs 0/18 (0%); RR 3.17 (95% CI 0.14 to 73)</td>
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<td>RR 2.7 (95% CI 0.1 to 62)</td>
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<td>ALT normalization: 2/17 (12%) vs 1/18 (6%); RR 2.12 (95% CI 0.21 to 21)</td>
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<tr>
<td>Perrillo 1990&lt;sup&gt;17&lt;/sup&gt;</td>
<td>A vs B vs C vs D vs no treatment</td>
<td>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)</td>
<td>A + B + C (all arms) vs C (no treatment)</td>
<td>Mortality: 1/126 (0.8%) vs 2/43 (5%); RR 0.17 (95% CI 0.02 to 1.84)</td>
<td>Good</td>
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<td>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)</td>
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<td>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)</td>
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<tbody>
<tr>
<td>Sarin 199667</td>
<td>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)</td>
<td>NR</td>
<td>Interferon alfa 2b (no results presented for untreated group) Serious adverse events 0% (0/20)</td>
<td>Fair</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Tassopoulos 199958</td>
<td>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</td>
<td>NR</td>
<td>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)</td>
<td>Fair</td>
<td>Glaxo Wellcome Research and Development</td>
</tr>
<tr>
<td>Waked 199077</td>
<td>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)</td>
<td>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)</td>
<td>Interferon alfa 2b (no results presented for untreated group) Withdrawals due to adverse events 0% (0/20)</td>
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<td>NR</td>
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</table>
| **Yalcin 2004** | 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)  
Loss of HBV DNA: 100% (13/13) vs. 0% (0/33); RR 66 (95% CI 4.2 to 1029)  
Month 12 (treatment plus post-treament 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** | 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% (14/51); RR 2.20 (95% CI 1.38-3.49) | 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             |
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</table>
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% (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 |
| Head-to-head | | | | | |
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 |

[^6]: Pacific Northwest EPC
## Appendix B5. Treatment Trials Evidence Table

<table>
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<th>Author, year</th>
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<tr>
<td>Lai 2002&lt;sup&gt;66&lt;/sup&gt;</td>
<td>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)</td>
<td>None reported</td>
<td>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)</td>
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<td>Not reported</td>
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<td>Lai 2006&lt;sup&gt;67&lt;/sup&gt;</td>
<td>A vs B (time on treatment) Histologic improvement (among patients with adequate baseline biopsy specimen and Knodell necro-inflammatory 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 (&lt;300 copies/mL): 293/325 (90%) vs 225/313 (72%); RR 1.3 (95% CI 1.2 to 1.4) ALT normalization (&lt;1 x ULN): 253/325 (78%) vs 222/313 (71%); RR 1.1 (95% CI 1.0 to 1.2)</td>
<td>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</td>
<td>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)</td>
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<td>Bristol Myers Squibb</td>
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### Appendix B5. Treatment Trials Evidence Table

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<td>Lau 2005</td>
<td>A vs B HBeAg loss/seroconversion: Time on treatment, loss: 81/271 (30%) vs 59/272 (22%); Time on treatment, seroconversion: 72/271 (27%) vs 55/272 (20%); Time on treatment + follow-up, loss: 91/271 (34%) vs 57/272 (21%); Time on treatment + follow-up, seroconversion: 87/271 (32%) vs 52/272 (19%); HBsAg loss/seroconversion: 8/271 (3%) vs 0/272 (0%); HBV DNA loss: Time on treatment: 68/271 (25%) vs 108/272 (40%); Time on treatment + follow-up: 39/271 (14%) vs 14/272 (5%); ALT normalization: Time on treatment: 105/271 (39%) vs 168/272 (62%); Time on treatment + follow-up: 111/271 (41%) vs 76/272 (28%); 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%); ALT normalization + HBV DNA &lt;100,000 copies/ml: Time on treatment: 27/271 (10%) vs 50/272 (18%); Time on treatment + follow-up: 62/271 (23%) vs 28/272 (10%);</td>
<td>A vs B Mortality: 0/271 (0%) vs 1/272 (0.4%); Serious adverse events: 12/271 (12%) vs 5/272 (2%);</td>
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<td>Roche Pharmaceuticals</td>
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<td>Marcellin 2004</td>
<td>A vs B HBsAg loss/seroconversion: Time on treatment + follow-up, loss: 7/177 (4%) vs 0/181 (0%); HBV DNA loss: Time on treatment: 112/177 (63%) vs 133/181 (73%); Time on treatment + follow-up: 34/177 (19%) vs 12/181 (7%); ALT normalization: Time on treatment: 67/177 (38%) vs 132/181 (73%); Time on treatment + follow-up: 105/177 (59%) vs 80/181 (44%); Histologic improvement: Time on treatment + follow-up: 85/177 (48%) vs 72/181 (40%); ALT normalization + HBV DNA &lt;400 copies/ml: Time on treatment: 47/177 (27%) vs 109/181 (60%); Time on treatment + follow-up: 26/177 (15%) vs 11/181 (6%);</td>
<td>A vs B Mortality: 1/177 (1%) vs 0/181 (0%);</td>
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Screening for Hepatitis B Virus Infection 141 Pacific Northwest EPC
### Appendix B5. Treatment Trials Evidence Table

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<tr>
<td>Marcellin 2008/72 Study 102 (HBeAg negative at baseline)</td>
<td>A vs B &lt;br&gt;HBsAg loss: 0/250 (0%) vs 0/125 (0%); RR not estimable&lt;br&gt;HBV DNA loss (&lt;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) &lt;br&gt;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) &lt;br&gt;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) &lt;br&gt;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</td>
<td>No deaths in either group; 3 cases of HCC but results not reported according to study group</td>
<td>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)</td>
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<td>Study 103 (HBeAg positive at baseline)</td>
<td>A vs B &lt;br&gt;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) &lt;br&gt;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) &lt;br&gt;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) &lt;br&gt;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) &lt;br&gt;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) &lt;br&gt;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</td>
<td>No deaths in either group</td>
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## Appendix B5. Treatment Trials Evidence Table

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| Ren 2007<sup>a</sup> | 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 |

<sup>a</sup> Non-FDA approved; included for clinical outcomes (Key Question 6) only.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ARD, adjusted relative difference between groups; BMI, body mass index; CI, confidence interval; 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

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<th>Loss to follow-up: differential/high?</th>
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<td>Inclusion criteria</td>
<td>Number receiving antiviral treatment Lost to followup</td>
<td>Age Sex Race</td>
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<tr>
<td>Andreone 2004&lt;sup&gt;80&lt;/sup&gt; Italy</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>No virological breakthrough vs. breakthrough (all cases of breakthrough had lamivudine resistance) No virological breakthrough=HBV DNA became undetectable on treatment and remained undetectable</td>
<td>Lamivudine</td>
<td>Median 3.5 years</td>
<td>HBeAg negative chronic HBV infection with elevated ALT and compensated cirrhosis Excluded: HCC, HDV, HCV, HIV</td>
<td>n=22 Lost to followup: Unclear</td>
<td>Mean age: 53 years Male: 82% Race: NR</td>
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<tr>
<td>Baltayiannis 2006&lt;sup&gt;81&lt;/sup&gt; Greece</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Virological response at 6 months vs. no virological response Virological response=HBV DNA &lt;10,000 copies/ml at 6 months of treatment</td>
<td>Interferon alfa</td>
<td>6 years</td>
<td>HBeAg-negative chronic HBV infection with elevated ALT and histologic evidence of chronic hepatitis Excluded: HCC, HCV, HDV, HIV</td>
<td>n=63 Lost to followup: 1 (1.6%)</td>
<td>Mean age: 51 years Male: 63% Race: NR</td>
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<tr>
<td>Di Marco 2004&lt;sup&gt;62&lt;/sup&gt; Italy</td>
<td>Retrospective cohort</td>
<td>No virological breakthrough vs. breakthrough No virological breakthrough=HBV DNA &lt;105 copies/ml throughout followup after achieving undetectability</td>
<td>Lamivudine</td>
<td>4 years</td>
<td>HBeAg-negative chronic HBV infection with histologic evidence of chronic hepatitis Excluded: HCC, HCV, HDV, HIV</td>
<td>n=656 Lost to followup: NR 40 patients had no virological response and excluded from analysis</td>
<td>Mean age: 49 years Male: 83% Race: NR</td>
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<tr>
<td>Fattovich 1997&lt;sup&gt;83&lt;/sup&gt; Italy</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Biochemical remission vs. no remission Biochemical remission = normalization of ALT levels</td>
<td>Interferon alfa</td>
<td>Mean 7 years</td>
<td>HBeAg-positive, HBsAg-positive chronic HBV infection with compensated cirrhosis and AST or ALT &gt;1.5 times ULN Excluded: HCC, HDV</td>
<td>n=40 Lost to followup: NR for treated subgroup</td>
<td>Mean age: 47 years Male: 85% Race: 100% white</td>
<td></td>
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<tr>
<td>Hui 2008&lt;sup&gt;84&lt;/sup&gt; China (Hong Kong)</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Histological response in HAI score vs. no histological response Histological response = improvement of 2 points or more on HAI score after end of treatment</td>
<td>Interferon alfa</td>
<td>2a or 2b Median 9.9 years</td>
<td>HBeAg-positive chronic HBV infection Excluded: HDV, HCV, HIV</td>
<td>n=89 Lost to followup: NR</td>
<td>Mean age: 30 years Male: 78% Race: NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lampertico 2003&lt;sup&gt;85&lt;/sup&gt; Italy</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>Sustained virological and biochemical response vs. no sustained response Sustained virological and biochemical response = normalization of serum ALT and clearance of HBV DNA</td>
<td>Interferon alfa</td>
<td>2b 5.7 years</td>
<td>HBeAg-negative chronic HBV infection with Ishak &gt;3 fibrosis or Ishak &lt;3 fibrosis with at least one ALT &gt;200 IU/L during the past 12 months Excluded: HCV, HCV, HIV</td>
<td>n=101 Lost to followup: 4 (4.0%)</td>
<td>Mean age: 46 years Male: 87% Race: NR</td>
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</tbody>
</table>
## Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Comparison</th>
<th>Treatment Duration of followup</th>
<th>Inclusion criteria</th>
<th>Number receiving antiviral treatment</th>
<th>Lost to followup</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau 1997[59] United States</td>
<td>Cohort (originally enrolled in RCT's)</td>
<td>Response vs. non-response Response=Sustained loss of HBV DNA and clearance of HBeAg within 1 year of starting treatment</td>
<td>Interferon alfa Mean 6.2 years</td>
<td>HBeAg-positive chronic HBV infection with elevated AST and/or ALT Excluded: HDV, HIV after 1988</td>
<td>n=103 Lost to followup: 8 (7.8%); assumed to be alive and without liver-related complications</td>
<td></td>
<td>Mean age: 41 years</td>
<td>Male: 83%</td>
<td>Race: 94% white, 6% black</td>
</tr>
<tr>
<td>Niederau 1996[86] Europe</td>
<td>Prospective cohort</td>
<td>Loss of HBeAg after therapy vs. no loss</td>
<td>Interferon alfa 2b Mean 4.2 years</td>
<td>HBeAg-positive chronic HBV infection, ALT &gt;2 times upper limit of normal and histologic evidence of active hepatitis Excluded: HDV, HIV, advanced cirrhosis</td>
<td>n=103 Lost to followup: None</td>
<td></td>
<td>Mean age: NR</td>
<td>Female: NR</td>
<td>Race: NR</td>
</tr>
<tr>
<td>Papatheodoridis 2001[87] Greece</td>
<td>Cohort (unclear if prospective or retrospective)</td>
<td>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 posttreatment followup period</td>
<td>Interferon alfa Mean 6 years</td>
<td>HBeAg-negative chronic HBV infection with elevated ALT and histologic evidence of chronic hepatitis Excluded: decompensated liver disease, HCC, HCV, HDV, HIV</td>
<td>n=209 Lost to followup: 9 (4.3%)</td>
<td></td>
<td>Mean age: 47 years</td>
<td>Male: 83%</td>
<td>Race: NR</td>
</tr>
<tr>
<td>Papatheodoridis 2011[88] Greece</td>
<td>Retrospective cohort</td>
<td>Virological remission vs. no virological remission Virological remission=HBV DNA &lt;200 IU/ml throughout therapy</td>
<td>Lamivudine Median 4.7 years</td>
<td>HBeAg-negative chronic HBV infection with at least two of the following: elevated ALT, HBV DNA &gt;2000 IU/ml, or histologic evidence of chronic hepatitis Excluded: HDV, HCV, HIV, HCC diagnosed before or within first 6 months of treatment</td>
<td>n=818 Lost to followup: 180 (22%)</td>
<td></td>
<td>Mean age: 54 years</td>
<td>Male: 72%</td>
<td>Race: NR</td>
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</tbody>
</table>
### Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Characteristics of HBV infection</th>
<th>Proportion of patients with intermediate outcome</th>
<th>Confounders adjusted for in analysis</th>
<th>Results (by clinical outcome)</th>
<th>Quality</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baltayiannis 2006&lt;sup&gt;81&lt;/sup&gt; Greece</td>
<td>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</td>
<td>Virological response at 6 months: 35% (22/63)</td>
<td>Age Gender Alcohol use ALT &gt;200 IU/L at baseline HBV-DNA &gt;10,000 copies/mL at baseline Histologic grade &gt;9 Histologic stage &gt;2 All patients HBeAg negative</td>
<td>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)</td>
<td>Fair</td>
<td>NR</td>
</tr>
<tr>
<td>Di Marco 2004&lt;sup&gt;12&lt;/sup&gt; Italy</td>
<td>HBeAg positive: Excluded HBsAg clearance: NR ALT &gt;2 times ULN: 65% AST: NR Serum HBV-DNA: NR Fibrosis stage: NR Cirrhosis on histology: 25%</td>
<td>No virological breakthrough: 39% (240/616)</td>
<td>Age Sex HBV DNA level ALT Hepatic flare after virological breakthrough Previous interferon therapy Cirrhosis All patients HBeAg negative</td>
<td>Death No virological breakthrough vs. breakthrough: adjusted HR 0.34 (95% CI 0.15 to 0.80)</td>
<td>Fair</td>
<td>NR</td>
</tr>
<tr>
<td>Fattovich 1997&lt;sup&gt;83&lt;/sup&gt; Italy</td>
<td>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%</td>
<td>Biochemical remission: 28% (11/40)</td>
<td>Age Sex Symptoms Hepatic stigmata Splenomegaly AST ALT AST/ALT ratio Bilirubin Albumin Gamma-globulins Platelets HBeAg clearance ALT normalization All patients HBeAg positive</td>
<td>Death Biochemical remission vs. no remission: adjusted HR 0.09 (95% CI 0.01 to 0.71)</td>
<td>Poor</td>
<td>NR</td>
</tr>
<tr>
<td>Hui 2008&lt;sup&gt;84&lt;/sup&gt; China (Hong Kong)</td>
<td>HBeAg positive: All HBsAg clearance: NR ALT (mean): 113 AST: NR Serum HBV-DNA &gt;105 copies/ml: 100% Fibrosis stage (mean, Ishak): 2 Cirrhosis: 12%</td>
<td>Histological response in HAI score: 40% (36/89) Histological response in fibrosis stage: 18% (16/89)</td>
<td>Fibrosis HBV DNA level All patients HBeAg positive</td>
<td>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)</td>
<td>Poor</td>
<td>Reports no funding received</td>
</tr>
</tbody>
</table>
## Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Characteristics of HBV infection</th>
<th>Proportion of patients with intermediate outcome</th>
<th>Confounders adjusted for in analysis</th>
<th>Results (by clinical outcome)</th>
<th>Quality</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lampertico 2003&lt;sup&gt;85&lt;/sup&gt; Italy</td>
<td>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%</td>
<td>Sustained virological and biochemical response: 30% (30/101)</td>
<td>Age Sex ALT HBV viral load IgM anti-HBc level Necroinflammatory grade Fibrosis stage All patients HBeAg negative</td>
<td>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)</td>
<td>Fair</td>
<td>Fondazione Italiana Ricerca Cancro and the consorzio Inter-universitario Trapianti d'Organo (Rome)</td>
</tr>
<tr>
<td>Lau 1997&lt;sup&gt;89&lt;/sup&gt; United States</td>
<td>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%</td>
<td>Response: 30% (31/103)</td>
<td>Cirrhosis Age Sex ALT AST All patients HBeAg positive</td>
<td>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)</td>
<td>Fair</td>
<td>NR</td>
</tr>
<tr>
<td>Niederau 1996&lt;sup&gt;88&lt;/sup&gt; Europe</td>
<td>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)</td>
<td>HBeAg loss: 51% (53/103)</td>
<td>Age Sex Baseline HBV DNA Baseline ALT Duration of hepatitis Preexisting cirrhosis All patients HBeAg positive</td>
<td>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)</td>
<td>Fair</td>
<td>Van Meeteren Foundation</td>
</tr>
</tbody>
</table>
## Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Characteristics of HBV infection</th>
<th>Proportion of patients with intermediate outcome</th>
<th>Confounders adjusted for in analysis</th>
<th>Results (by clinical outcome)</th>
<th>Quality</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papatheodoridis 2001</td>
<td>Greece</td>
<td>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%</td>
<td>Sustained biochemical response: 27% (57/209)</td>
<td>Cirrhosis Age All patients HBeAg negative</td>
<td>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)</td>
<td>Poor</td>
<td>NR</td>
</tr>
<tr>
<td>Papatheodoridis 2011</td>
<td>Greece</td>
<td>HBeAg positive: Excluded HBsAg clearance: NR ALT (median): 88 AST (median): 68 Serum HBV DNA (median, x103 IU/ml): 400 Fibrosis stage: NR Cirrhosis: 26%</td>
<td>Virological remission: 28% (228/818)</td>
<td>Age Sex Liver disease severity ALT AST Bilirubin Albumin Hemoglobin Platelet count HBV DNA Interferon alfa in the past All patients HBeAg negative</td>
<td>Hepatocellular carcinoma Virological remission under therapy vs. no virological remission: adjusted HR 0.77 (95% CI 0.35 to 1.69)</td>
<td>Fair</td>
<td>Hellenic Center for Disease Control and Prevention</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?</th>
<th>Did the study use accurate methods for ascertaining intermediate outcomes?</th>
<th>Were outcome assessors and/or data analysts blinded to treatment?</th>
<th>Did the article report the number of patients who met inclusion criteria excluded due to missing data or loss to followup?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreone 2004&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
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</tr>
<tr>
<td>Baltayiannis 2006&lt;sup&gt;81&lt;/sup&gt;</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Di Marco 2004&lt;sup&gt;82&lt;/sup&gt;</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
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<tr>
<td>Fattovich 1997&lt;sup&gt;83&lt;/sup&gt;</td>
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<td>Yes</td>
<td>Unclear</td>
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<tr>
<td>Hui 2008&lt;sup&gt;84&lt;/sup&gt;</td>
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<td>Yes</td>
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<tr>
<td>Lampertico 2003&lt;sup&gt;85&lt;/sup&gt;</td>
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<td>No</td>
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<tr>
<td>Lau 1997&lt;sup&gt;86&lt;/sup&gt;</td>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Niederau 1996&lt;sup&gt;87&lt;/sup&gt;</td>
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<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
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<tr>
<td>Papatheodoridis 2001&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
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<tr>
<td>Papatheodoridis 2011&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Did the study perform appropriate statistical analyses on potential confounders, or appropriately account for them (should evaluate at least age, sex, fibrosis stage, HBV viral load, HBeAg status)?</th>
<th>Is there important (overall or differential) exclusion of patients due to missing data or loss to followup?</th>
<th>Were outcomes prespecified and defined, and ascertained using accurate methods?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreone 2004&lt;sup&gt;80&lt;/sup&gt;</td>
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<td>Unclear</td>
<td>Yes</td>
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<tr>
<td>Baltayiannis 2006&lt;sup&gt;81&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
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<td>Di Marco 2004&lt;sup&gt;82&lt;/sup&gt;</td>
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<td>Unclear</td>
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<td>Fattovich 1997&lt;sup&gt;83&lt;/sup&gt;</td>
<td>No</td>
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<tr>
<td>Hui 2008&lt;sup&gt;84&lt;/sup&gt;</td>
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<tr>
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<td>Yes</td>
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