

# ***Evidence Synthesis***

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## **Number 110**

### **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.<sup>1</sup> The 2004 USPSTF recommendation was based on an evidence review with literature searches conducted through 2001.<sup>2</sup>

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.<sup>1</sup> 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.<sup>1</sup> 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).<sup>3,4</sup> 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).<sup>5</sup> 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 immunoglobulin M (IgM) antibody to the HBV core antigen (anti-HBc).<sup>6,7</sup> 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).<sup>6,7</sup> The presence of HBV e antigen (HBeAg) is usually associated with high levels of HBV DNA in serum and high infectivity.<sup>8,9</sup> 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.<sup>10</sup> Due to underreporting, the actual number of cases is estimated to be 6.5 times higher than the number of reported cases.<sup>10</sup> From 2000 to 2010, the incidence of acute HBV infection declined among all age groups.<sup>11</sup> 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.<sup>11</sup>

As of 2008, an estimated 704,000 people in the United States were chronically infected with HBV.<sup>12</sup> 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.<sup>13</sup>

## Etiology and Natural History

HBV is spread through percutaneous or mucous membrane exposure to blood or blood containing bodily fluids (serum, semen or saliva).<sup>6,9,14</sup> 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.<sup>5</sup> 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.<sup>15</sup> 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.<sup>9,15</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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.<sup>17,18</sup> 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  $\geq 2$  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.<sup>19-21</sup> Regions of the world with very high HBV prevalence ( $\geq 8\%$ ) include most of Asia, most of Africa, Australasia with the exception of Australia and New Zealand, and parts of South America.<sup>15</sup> Persons at higher risk for acute HBV infection include men, black persons, and those 30 to 39 years of age.<sup>11</sup> 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%).<sup>9, 11, 15, 22, 23</sup> 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.<sup>6</sup>

## 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.<sup>15</sup> 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.<sup>6, 9</sup> Vaccination results in  $\geq 90$  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.<sup>6, 9</sup> As of 2011, universal vaccination of children has been implemented in over 190 countries, with 81 countries

targeting newborns.<sup>24, 25</sup> The widespread implementation of universal vaccination strategies throughout the world has been credited with marked decreases in HBV incidence, particularly among younger persons.<sup>26</sup>

## 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.<sup>27, 28</sup> Drugs for HBV infection are broadly categorized as either interferons or nucleoside/nucleotide analogues.<sup>21, 28-30</sup> The interferons affect viral replication as well as immune modulation.<sup>8, 27</sup> 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).<sup>27</sup> Biopsy may be performed in some patients to establish the degree of liver inflammation and fibrosis.<sup>27, 28</sup> 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.<sup>27, 28</sup>

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.<sup>21, 29</sup> 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.<sup>15, 27, 28</sup> 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.<sup>27, 28</sup>

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.<sup>27</sup> 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.<sup>15</sup> 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.<sup>15,27</sup>

## Recommendations of Other Groups

The CDC<sup>15</sup> and the American Association for the Study of Liver Diseases (AASLD)<sup>27</sup> 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;<sup>15</sup> 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.<sup>27</sup> The Institute of Medicine (IOM) endorses screening in high risk groups.<sup>31</sup>

## Chapter 2. Methods

### Key Questions and Analytic Framework

Using the methods developed by the USPSTF,<sup>32,33</sup> 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.<sup>3</sup>

This review differs from the prior brief USPSTF evidence update<sup>2</sup> in that it included key questions on the benefits and harms of antiviral treatment, benefits of education or behavior change counseling, and the association between improvements in intermediate and clinical

outcomes; and 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)<sup>27</sup> 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<sup>32, 33</sup> 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.<sup>32, 33</sup>

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 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.<sup>34</sup> 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 ( $\geq 2\%$ ) 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**).<sup>35</sup> 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  $\geq 8\%$ ). Independent predictors of HBV infection in this cohort were medium (prevalence,  $\geq 2\%$  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 ( $\geq 2\%$  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];  $I^2=18\%$ ).<sup>36</sup> Pooled results from one other good-quality<sup>37</sup> and two fair-quality trials<sup>38, 39</sup> 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,<sup>40-43</sup> eight trials interferon alfa-2b injection versus no treatment,<sup>44-51</sup> nine trials lamivudine versus placebo<sup>52-60</sup> and one study of tenofovir versus placebo.<sup>61</sup> 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.<sup>62</sup> Nine trials<sup>40, 41, 45-47, 49, 55, 58, 61</sup> 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.<sup>41-44, 47-51, 55-57, 59-61</sup> Two trials restricted inclusion to adolescents<sup>41, 61</sup> 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.<sup>40, 44-46, 48, 50, 51, 54, 55, 57, 58</sup> In trials that did not report the prevalence of baseline cirrhosis, patients with decompensated liver disease were generally excluded.<sup>41-43, 49, 52, 56, 59-62</sup> Study duration ranged from 8 weeks to 3 years. Twelve trials<sup>40-44, 47, 48, 53, 57, 58, 60, 61</sup> reported outcomes on antiviral therapy, three trials<sup>52, 56, 59</sup> reported outcomes following discontinuation of antiviral therapy, and seven trials<sup>45, 46, 49-51, 54, 55</sup> reported both. Two trials were rated good-quality,<sup>49, 61</sup> four trials poor-quality,<sup>44, 45, 52, 53</sup> 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**).<sup>42-44, 48, 50, 51, 55, 59-61</sup> One trial reported no HBeAg loss in either treated or control groups.<sup>56</sup> 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];  $I^2=5\%$ )<sup>44, 48, 50, 51</sup> than for lamivudine (three trials; RR, 1.7 [95% CI, 1.0 to 3.0];  $I^2=0\%$ ),<sup>55, 59, 60</sup> adefovir (two trials; RR, 1.8 [95% CI, 0.8 to 4];  $I^2=58\%$ )<sup>42, 43</sup> or tenofovir (1 trial; RR, 1.4 [95% CI, 0.6 to 3.4]),<sup>61</sup> though estimates were imprecise and based on only one or two trials for drugs other than interferon. The adefovir risk estimate had the most statistical heterogeneity. It was based on two trials: a longer duration trial<sup>42</sup> (72 weeks) found adefovir associated with an increased likelihood of HBeAg loss versus placebo (RR, 2.5 [95% CI, 1.5 to 4.2]) and a shorter duration trial<sup>43</sup> (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];  $I^2=5\%$ ).<sup>42-44, 48, 50, 51, 55, 59-61</sup> Stratifying all antiviral trials according to duration resulted in similar estimates for studies  $\leq 1$  year duration (six trials; RR, 2.0 [95% CI, 1.3 to 3.2];  $I^2=27\%$ )<sup>42-44, 48, 59, 60</sup> and those of more than one year duration (four trials; RR, 2.1 [95% CI, 1.4 to 3.1];  $I^2=0\%$ ).<sup>50, 51, 55, 61</sup> Removing one poor-quality trial<sup>44</sup> also had no effect on the overall estimate (eight trials; RR, 2.1 [95% CI, 1.6 to 2.8];  $I^2=0\%$ ).<sup>42, 43, 48, 50, 51, 55, 60, 61</sup>

*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];  $I^2=0\%$ )<sup>44, 46, 48-52, 54, 55, 58, 61</sup> (**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];  $I^2=0\%$ ).<sup>44, 46, 48-51</sup> 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];  $I^2=0\%$ ).<sup>52, 54, 55, 58</sup> The estimate for tenofovir was imprecise and based on one trial (RR, 3.1 [95% CI, 0.13 to 75]).<sup>61</sup>

Estimates were similar for trials of HBeAg-positive patients (seven trials; RR, 2.6 [95% CI, 1.1 to 6.1];  $I^2=0\%$ )<sup>44, 48-51, 55, 61</sup> and HBeAg-negative patients (four trials; RR, 1.9 [95% CI, 0.5 to 7.8];  $I^2=0\%$ ).<sup>46, 52, 54, 58</sup> 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];  $I^2=0\%$ ),<sup>46, 50, 51, 54, 55, 58, 61</sup> or when excluding two poor-quality<sup>44, 52</sup> trials (nine trials; RR, 2.2 [95% CI, 1.0 to 5.0];  $I^2=0\%$ ).<sup>46, 48-51, 54, 55, 58, 61</sup> 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];  $I^2=0$ ).<sup>44, 48, 50, 51, 55, 58, 61</sup>

**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**).<sup>38-42, 46, 51-53, 55, 58, 59</sup> Estimates were similar for adefovir (four trials; RR, 2.9 [95% CI, 2.3 to 3.6];  $I^2=0\%$ ),<sup>40-43</sup> lamivudine (five trials; RR, 2.4 [95% CI, 1.6 to 3.6];  $I^2=54\%$ ),<sup>53-55, 57, 60</sup> and tenofovir (one trial; RR, 2.0 [95% CI, 1.4 to 2.9]).<sup>61</sup> The estimate for interferon alfa-2b was imprecise (two trials; RR, 5.0 [95% CI, 0.6 to 40];  $I^2=28\%$ ).<sup>44, 48</sup> 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];  $I^2=11\%$ )<sup>41-44, 48, 55, 57, 60, 61</sup> or negative patients (three trials; RR, 2.0 [95% CI, 1.4 to 2.9];  $I^2=26\%$ ),<sup>40, 53, 54</sup> studies of more than 1 year duration (five trials; RR, 2.4 [95% CI, 1.6 to 3.5];  $I^2=57\%$ ),<sup>48, 54, 55, 57, 61</sup> or after excluding two poor-quality<sup>44, 53</sup> studies (10 trials; RR, 2.5 [95% CI, 2.0 to 3.0];  $I^2=31\%$ ).<sup>40-43, 48, 54, 55, 57, 60, 61</sup> 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];  $I^2=0\%$ ).<sup>38-42, 46, 51-53, 55, 58, 59</sup>

**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**).<sup>40, 43, 48, 50, 54, 55, 59-61</sup> 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];  $I^2=46\%$ ).<sup>54, 55, 59, 60</sup> 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];  $I^2=0\%$ ),<sup>40, 43</sup> interferon alfa-2b (two trials; RR, 7.5 [95% CI, 1.4 to 40];  $I^2=0\%$ ),<sup>48, 50</sup> and tenofovir (one trial; RR, 97 [95% CI, 6.1 to 1526]),<sup>61</sup> 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];  $I^2=64\%$ )<sup>40, 43, 48, 50, 54, 55, 59-61</sup> or to studies of more than 1 year duration (four trials; RR, 8.4 [95% CI, 1.5 to 49];  $I^2=76\%$ )<sup>50, 54, 55, 61</sup> 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.<sup>43, 48, 50, 55, 59-61</sup> 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]<sup>40</sup> and 4.8 [95% CI, 0.62 to 36]<sup>54</sup>). 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**).<sup>40, 42, 46, 51, 54, 55, 57</sup> 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]<sup>40</sup> and 2.1 [95% CI, 1.5 to 2.8])<sup>42</sup> and lamivudine (three trials; RR, 2.3 [95% CI, 1.7 to 3.2];  $I^2=0\%$ ).<sup>54, 55, 57</sup> 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]<sup>46</sup> and 4.0

[95% CI, 0.5 to 33]<sup>51</sup>).

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];  $I^2=0\%$ )<sup>46, 51, 54, 55, 57</sup> or when results were stratified for HBeAg positive (four trials; RR, 2.2 [95% CI, 1.8 to 2.7];  $I^2=0\%$ )<sup>42, 51, 55, 57</sup> and HBeAg negative (three trials; RR, 2.1 [95% CI, 1.4 to 3];  $I^2=0\%$ )<sup>40, 46, 54</sup> patients. No trial was rated poor-quality.

**Composite Intermediate Outcomes.** Composite intermediate outcomes were reported in 10 trials (**Table 5**).<sup>45-47, 49, 50, 54, 57, 58, 61, 63</sup> 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**).<sup>45, 46, 54, 58, 61, 63</sup> 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];  $I^2=21\%$ ).<sup>45, 46, 54, 58, 61, 63</sup> 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]<sup>63</sup> and 78 [95% CI, 4.9 to 1236]<sup>61</sup>). 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];  $I^2=78\%$ )<sup>45, 46, 54, 58</sup> or after excluding one poor-quality trial (RR, 9.3 [95% CI, 1.6 to 55];  $I^2=83\%$ ).<sup>45</sup> 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];  $I^2=88\%$ ).<sup>46, 54, 61</sup>

The composite intermediate outcome of clearance of HBeAg plus suppression of HBV DNA was evaluated in four trials.<sup>49, 50, 57, 59</sup> 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]<sup>49</sup> and 11 [95% CI, 1.5 to 75]<sup>50</sup>) and lamivudine was more effective than placebo in one larger (n=358) trial (RR, 3.3 [95% CI, 1.1 to 10])<sup>57</sup> but not in another, smaller (n=42) trial (RR, 2.5 [95% CI, 0.17 to 38]).<sup>59</sup> 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]).<sup>61</sup>

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

Four trials (in six publications) compared entecavir versus lamivudine,<sup>64-69</sup> two trials pegylated interferon alfa 2a versus lamivudine,<sup>70, 71</sup> and two trials (reported in one publication)<sup>72</sup> tenofovir versus adefovir (**Appendix B5**). Duration of followup ranged from 48 to 96 weeks. Five trials predominantly enrolled HBeAg positive patients (78% to 100%).<sup>64-66, 68-70, 72</sup> and the remaining three trials<sup>67, 71, 72</sup> 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<sup>64, 67, 70, 71</sup> 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];  $I^2=94\%$ )<sup>64, 67-69</sup> and histological (two trials; RR, 1.2 [95% CI,

1.1 to 1.3];  $I^2=0\%$ )<sup>64, 67</sup> 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]),<sup>70</sup> HBsAg loss or seroconversion (two trials; RR, 16 [95% CI, 2.2 to 121];  $I^2=0\%$ ),<sup>70, 71</sup> ALT normalization (two trials; RR, 1.4 [95% CI, 1.2 to 1.6];  $I^2=0\%$ ),<sup>70, 71</sup> virological improvement (two trials; RR, 2.8 [95% CI, 1.9 to 4.4];  $I^2=0\%$ ),<sup>70, 71</sup> and histological improvement (two trials; RR, 1.2 [95% CI, 1.0 to 1.4];  $I^2=0\%$ ).<sup>70, 71</sup> 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).<sup>64, 67-69</sup> There were no clear differences between tenofovir versus adefovir on various intermediate outcomes, in part due to imprecise estimates.<sup>72</sup> 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).<sup>41, 43, 46, 49, 51, 54, 55, 57, 73, 75, 76</sup> Three trials evaluated interferon alfa-2b,<sup>46, 49, 51</sup> two trials interferon alfa-2a,<sup>73, 75</sup> two trials adefovir<sup>41, 43</sup> and four trials lamivudine.<sup>54, 55, 57, 76</sup> One trial was rated good-quality<sup>49</sup> and the remainder fair-quality<sup>41, 43, 46, 51, 54, 55, 57, 73, 75, 76</sup> (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<sup>57, 76</sup> and adefovir.<sup>43</sup> One of the lamivudine trials followed patients for 1 year<sup>57</sup> and the other for a median of 32 months.<sup>76</sup> The placebo-controlled phase of the adefovir trial was 12 weeks.<sup>43</sup> The two longest duration trials followed patients for 7 years

after completing 18 weeks or 6 months of interferon alfa-2a therapy.<sup>73, 75</sup> 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<sup>46</sup> and one trial of lamivudine<sup>54</sup> 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<sup>41, 43, 49</sup> or cirrhosis.<sup>75</sup> One study enrolled adolescents.<sup>41</sup>

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<sup>41, 43</sup> and two trials of lamivudine<sup>55, 57</sup> recorded no deaths. Although pooled estimates for incident cirrhosis (three trials; RR, 0.70 [95% CI, 0.33 to 1.46];  $I^2=0\%$ ) (**Figure 9**)<sup>51, 73, 75</sup> hepatocellular carcinoma (five trials; RR, 0.57 [95% CI, 0.32 to 1.04];  $I^2=2\%$ ) (**Figure 10**),<sup>46, 54, 73, 75, 76</sup> and mortality (five trials; RR, 0.55 [95% CI, 0.18 to 1.71];  $I^2=43\%$ ) (**Figure 11**)<sup>49, 51, 73, 75, 76</sup> all favored antiviral therapy over placebo, none of the differences were statistically significant. Excluding trials with less than 2 years of followup<sup>46, 54, 73, 75, 76</sup> 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.<sup>76</sup> This trial was discontinued early (median followup, 2.7 years) after reaching a pre-specified stopping threshold on a composite primary outcome (hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or liver-related mortality). For hepatocellular cancer, it reported a relative risk for lamivudine versus placebo of 0.52 (95% CI, 0.27 to 1.02), or 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, **Table 7**)—were similar (adjusted HR, 0.5 [95% CI, 0.6 to 0.7]).<sup>76</sup>

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**).<sup>64-67, 70, 71</sup> All trials were rated good-quality.

The two trials of entecavir versus lamivudine were of similar design, except that one enrolled HBeAg-positive patients<sup>64-66</sup> and the other HBeAg-negative patients.<sup>67</sup> 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<sup>70, 71</sup> 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<sup>70</sup> enrolled HBeAg positive patients and the other<sup>71</sup> 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.<sup>77</sup>

## **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**).<sup>40-42, 44-52, 54-62, 76</sup> Data were available for adefovir (three trials),<sup>40-42</sup> interferon alfa-2b (eight trials),<sup>44-51</sup> lamivudine (nine trials),<sup>52, 54-60, 76</sup> telbivudine (one trial),<sup>62</sup> and tenofovir (one trial).<sup>61</sup> 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.<sup>40, 44-48, 50, 51, 54, 55, 57, 58, 76</sup> The trials that did not report cirrhosis information excluded patients with decompensated liver disease.<sup>41, 42, 49, 52, 56, 59-62</sup> One of the lamivudine trials<sup>52</sup> and two of the interferon alfa-2b trials<sup>44, 45</sup> were rated poor-quality, two trials were rated good-quality,<sup>49, 61</sup> and the remainder fair-quality (**Appendix B6**).<sup>40-42, 46-48, 50, 51, 54-60, 62, 76</sup> Eight trials were conducted in the United States, Europe, Australia, or New Zealand,<sup>41, 45-47, 49, 55, 58, 61</sup> 11 were conducted in regions with high HBV prevalence<sup>44, 48, 50-52, 54, 56, 57, 59, 60, 62</sup> and three were conducted in countries with both low and high HBV prevalence.<sup>40, 42, 76</sup>

*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];  $I^2=0\%$ )<sup>40, 42, 54-62, 76</sup> (**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];  $I^2=0\%$ )<sup>54-60, 76</sup> and adefovir (two trials; RR, 1.0 [95% CI, 0.4 to 2.1];  $I^2=31\%$ ).<sup>40, 42</sup> Results were also consistent for telbivudine (RR, 1.1 [95% CI, 0.9 to 1.3])<sup>62</sup> and tenofovir (RR, 0.5 [95% CI, 0.2 to 1.3]),<sup>61</sup> but based on only one trial each.

Four lamivudine studies<sup>54, 55, 56, 59</sup> 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, 0.8 [95% CI, 0.6 to 1.03];  $I^2=0\%$ ). There were no poor-quality trials.

Three trials<sup>45, 50, 51</sup> 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**).<sup>40-42, 46, 48, 49, 52, 58, 60</sup> 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];  $I^2=0\%$ ),<sup>52, 58, 60</sup> adefovir (three trials; RR, 2.9 [95% CI, 0.5 to 16];  $I^2=0\%$ ),<sup>40-42</sup> and interferon alfa-2b (three trials; RR, 4.8 [95% CI, 0.9 to 26];  $I^2=0\%$ )<sup>46, 48, 49</sup> though estimates for individual drugs were imprecise and did not reach statistical significance.

Removing one poor-quality trial<sup>52</sup> 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.<sup>44, 47, 51</sup>

*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**).<sup>40, 57, 58, 60-62, 76</sup> 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];  $I^2=14\%$ ).<sup>57, 58, 60, 76</sup> adefovir (one trial; RR, 1.0 [95% CI, 0.9 to 1.2]),<sup>40</sup> and tenofovir (one trial; RR, 0.95 [95% CI, 0.8 to 1.1]),<sup>61</sup> 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]).<sup>62</sup> 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)<sup>64, 67, 68</sup> or between tenofovir versus adefovir (two trials)<sup>72</sup> 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.<sup>70, 71</sup>

## **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**).<sup>80-89</sup> 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),<sup>80-82, 88</sup> two studies evaluated biochemical remission (normalization of serum transaminase levels),<sup>83, 87</sup> one study evaluated HBeAg clearance,<sup>86</sup> one study evaluated histological response (improvement in biopsy findings),<sup>84</sup> and two studies evaluated composite intermediate outcomes (virological response plus HBeAg clearance,<sup>89</sup> or virological plus biochemical response<sup>85</sup>). The clinical outcomes also varied. Three studies evaluated death,<sup>82, 83, 89</sup> two studies hepatocellular carcinoma,<sup>80, 88</sup> 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<sup>83, 84, 86, 89</sup> and the remainder on HBeAg negative patients.<sup>80-82, 85, 87, 88</sup> 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<sup>80, 82, 88</sup>, in the remainder patients received interferon. Two studies only included patients with cirrhosis,<sup>80, 83</sup> one study excluded patients with cirrhosis,<sup>81</sup> and in the other studies, the proportion of patients with cirrhosis ranged from 12 to 60 percent. Seven studies were rated fair-quality<sup>80-82, 85, 86, 88, 89</sup> and three studies poor-quality (**Appendix B8**).<sup>83, 84, 87</sup> 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]),<sup>83</sup> one study evaluated a composite intermediate outcome (virological response plus HBeAg clearance: adjusted HR, 0.59 [95% CI, 0.20 to 1.67])<sup>89</sup> 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]).<sup>82</sup> For hepatocellular carcinoma, one study evaluated maintenance of virological remission (no virological breakthrough) (adjusted HR, 0.10 [95% CI, 0.01 to 0.77])<sup>80</sup> and one study evaluated achieving virological remission during therapy (adjusted HR, 0.77 [95% CI, 0.35 to 1.69])<sup>88</sup> in HBeAg negative patients. For composite clinical outcomes, one study evaluated HBeAg loss (adjusted HR, 0.06 [95% CI, 0.01 to 0.61])<sup>86</sup> 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])<sup>84</sup> 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])<sup>89</sup> and three studies evaluated virological (adjusted HR, 0.24 [95% CI, 0.06 to 0.96]),<sup>81</sup> biochemical (0.48 [95% CI, 0.23 to 1.0]),<sup>88</sup> or a composite intermediate outcome (virological plus biochemical response: adjusted HR, 0.53 [95% CI, 0.29 to 0.91])<sup>85</sup> 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.<sup>2</sup> 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%).<sup>4</sup> 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.<sup>35</sup> 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.<sup>41, 43, 46, 49, 51, 54, 55, 57, 73, 75, 76</sup> 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];  $I^2=2\%$ ),<sup>46, 54, 73, 75, 76</sup> 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.<sup>76</sup> 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.<sup>90</sup> Although other reviews<sup>91-96</sup> 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];  $I^2=4\%$ ),<sup>42-44, 48, 50, 51, 55, 59-61</sup> HBsAg loss or seroconversion (12 trials; RR, 2.4 [95% CI, 1.2 to 4.9];  $I^2=0\%$ ),<sup>44, 46, 48-52, 54, 55, 58, 61</sup> ALT normalization (12 trials; RR, 2.5 [95% CI, 2.1 to 3.0];  $I^2=27\%$ ),<sup>38-42, 46, 51-53, 55, 58, 59</sup> reduction in HBV DNA (nine trials; RR, 7.2 [95% CI, 3.2 to 16];  $I^2=58\%$ ),<sup>40, 43, 48, 50, 54, 55, 59-61</sup> histological improvement (seven trials; RR, 2.1 [95% CI, 1.8 to 2.6];  $I^2=0\%$ ),<sup>40, 42, 46, 51, 54, 55, 57</sup> 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.<sup>90, 97-100</sup>

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.<sup>80-89</sup>

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];  $I^2=0\%$ ),<sup>40-42, 46, 48, 49, 52, 58, 60</sup> but trials found no difference in risk of serious adverse events (12 trials; RR, 0.8 [95% CI, 0.6 to 1.1];  $I^2=0\%$ )<sup>40, 42, 54-62, 76</sup> or experiencing any adverse event (seven trials; RR, 0.96 [95% CI, 0.9 to 1.0];  $I^2=0\%$ ).<sup>40, 57, 58, 60-62, 76</sup> 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,<sup>70, 71</sup> consistent with the known high prevalence of adverse events with interferon-based therapies.<sup>101</sup> 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.<sup>26, 102, 103</sup> 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.<sup>104, 105</sup> 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.<sup>77</sup> 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.

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

## 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.<sup>108, 109</sup> Substantial reductions in prevalence have been observed among United States adolescents and younger adults (up to 50 years of age).<sup>109</sup> In addition universal HBV vaccination has been adopted in over 190 countries<sup>24</sup> and epidemiological data indicating declining HBV prevalence globally.<sup>110</sup> 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.<sup>111</sup> 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.<sup>112</sup> 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.<sup>113</sup> However, research on combination therapies and new investigational agents, including drugs with novel viral targets,<sup>112, 114</sup> is ongoing.

## Relevance for Priority Populations

HBV infection is more prevalent in the United States among persons originating from countries with high prevalence,<sup>115</sup> such as most of Asia and the western Pacific. Black persons are also at higher risk of HBV infection.<sup>11</sup> 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.<sup>109</sup>

## 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)<sup>116</sup> 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<sup>117</sup>) 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.<sup>118</sup>

## 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

1. United States Preventive Services Task Force. Screening for hepatitis B virus infection. 2004. Available at: <http://www.uspreventiveservicestaskforce.org/uspstf/uspshpb.htm>.
2. Research Triangle Institute - University of North Carolina (RTI-UNC). Screening for hepatitis B virus infection: a brief evidence update for the United States Preventive Services Task Force. 2004. Available at: <http://www.uspreventiveservicestaskforce.org/3rduspstf/hepbscr/hepbup.pdf>.
3. Lin K, Vickery J. Screening for hepatitis B virus infection in pregnant women: evidence for the United States Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* 2009;150(12):874-6.
4. United States Preventive Services Task Force. Screening for hepatitis B virus infection in pregnancy. *Ann Intern Med.* 2009;150:869-73.
5. Lin KW, Kirchner JT. Hepatitis B. *Am Fam Physician.* 2004;69(1):75-82.
6. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR* 2006;55(RR-16):1-33; quiz CE1-4.
7. Centers for Disease Control and Prevention. Interpretation of hepatitis B serologic test results. Available at: <http://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf>.
8. Dusheiko G, Antonakopoulos N. Current treatment of hepatitis B. *Gut.* 2008;57(1):105-24.
9. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep.* 2005;54(RR-16):1-31.
10. Centers for Disease Control and Prevention. Viral Hepatitis Statistics & Surveillance: Disease Burden from Viral Hepatitis A, B, and C in the United States. 2013. Available at: <http://www.cdc.gov/hepatitis/Statistics/index.htm>.
11. Centers for Disease Control and Prevention. Viral hepatitis surveillance - United States, 2010. Available at: <http://www.cdc.gov/hepatitis/Statistics/2010Surveillance/Commentary.htm>.
12. Ioannou GN. Hepatitis B virus in the United States: infection, exposure, and immunity rates in a nationally representative survey. *Ann Intern Med.* 2011;154(5):319-28.
13. Centers for Disease Control and Prevention. Viral Hepatitis Statistics & Surveillance: Table 3.5. Number and rate of deaths with hepatitis B listed as a cause of death, by demographic characteristic and year — United States, 2006–2010. 2013. Available at: <http://www.cdc.gov/hepatitis/Statistics/2011Surveillance/Table3.5.htm>.
14. Centers for Disease Control and Prevention. Hepatitis B General Fact Sheet. 2010. Available at: <http://www.cdc.gov/hepatitis/hbv/pdfs/hepbgeneralfactsheet.pdf>.
15. Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR* 2008;57(RR-8):1-20.
16. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: Special



- emphasis on disease progression and prognostic factors. *J Hepatol.* 2008;48(2):335-52.
17. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *J Am Med Assoc.* 2006;295(1):65-73.
  18. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology.* 2006;130(3):678-86.
  19. Kowdley KV, Wang CC, Welch S, et al. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. *Hepatology.* 2012;56(2):422-33.
  20. Mitchell T, Armstrong GL, Hu DJ, et al. The increasing burden of imported chronic hepatitis B—United States, 1974–2008. *PLoS ONE.* 2011;6(12):e27717.
  21. Sorrell MF, Belongia EA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis B. *Ann Intern Med.* 2009;150:104-10.
  22. Quaglio G, Lugoboni F, Mezzelani P, et al. Hepatitis vaccination among drug users. *Vaccine.* 2006;24(15):2702-9.
  23. Wasley A, Grytdal S, Gallagher K. Surveillance for acute viral hepatitis--United States, 2006. *MMWR Surveill Summ.* 2008;57(2):1-24.
  24. World Health Organization. WHO Vaccine Preventable Diseases Monitoring System. 2013. Available at: [http://apps.who.int/immunization\\_monitoring/en/globalsummary/diseaseresult.cfm](http://apps.who.int/immunization_monitoring/en/globalsummary/diseaseresult.cfm).
  25. Centers for Disease C, Prevention. Implementation of newborn hepatitis B vaccination--worldwide, 2006. *MMWR.* 2008;57(46):1249-52.
  26. Zanetti AR, Van Damme P, Shouval D. The global impact of vaccination against hepatitis B: A historical overview. *Vaccine.* 2008;26(49):6266-73.
  27. Lok AS, McMahon BJ. American Association for the Study of Liver Diseases (AASLD) Practice Guideline Update: Chronic hepatitis B: Update 2009. *Hepatology.* 2009;50:661.
  28. Keeffe EB, Dieterich DT, Han S-HB, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol.* 2008;6(12):1315-41.
  29. Hoofnagle JH, Doo E, Liang TJ, et al. Management of hepatitis B: summary of a clinical research workshop. *Hepatology.* 2007;45(4):1056-75.
  30. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology.* 2007;45(2):507-39.
  31. Institute of Medicine. Report Brief January 2010: Hepatitis and liver cancer: a national strategy for prevention and control of hepatitis B and C. 2010. Available at: <http://www.iom.edu/Reports/2010/Hepatitis-and-Liver-Cancer-A-National-Strategy-for-Prevention-and-Control-of-Hepatitis-B-and-C.aspx/>.
  32. Harris R, P., Helfand M, Wolff SH, et al. Current methods of the United States Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001;20(3S):21-35.
  33. United States Preventive Services Task Force. Procedure manual. AHRQ Publication No. 08-05118-EF. 2008. Available at: <http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm>.
  34. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *Br Med J.* 2003;327(7414):557-60.
  35. Spenatto N, Boulinguez S, Mularczyk M, et al. Hepatitis B screening: Who to target? A French sexually transmitted infection clinic experience. *J Hepatol.* 2013;58(4):690-7.

36. Chen W, Gluud C. Vaccines for preventing hepatitis B in health-care workers. *Cochrane Database Syst Rev*. 2009(1).
37. Szmunes W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *N Engl J Med*. 1980;303(15):833-41.
38. Coutinho RA, Lelie N, Albrecht-Van Lent P, et al. Efficacy of a heat inactivated hepatitis B vaccine in male homosexuals: outcome of a placebo controlled double blind trial. *Br Med J Clin Res Ed*. 1983;286(6374):1305-8.
39. Francis DP, Hadler SC, Thompson SE, et al. The prevention of hepatitis B with vaccine. Report of the centers for disease control multi-center efficacy trial among homosexual men. *Ann Intern Med*. 1982;97(3):362-6.
40. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med*. 2003;348(9):800-7.
41. Jonas MM, Kelly D, Pollack H, et al. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. *Hepatology*. 2008;47(6):1863-71.
42. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med*. 2003;348(9):808-16.
43. Zeng M, Mao Y, Yao G, et al. A double-blind randomized trial of adefovir dipivoxil in Chinese subjects with HBeAg-positive chronic hepatitis B. *Hepatology*. 2006;44(1):108-16.
44. Bayraktar Y, Uzunalimoglu B, Arslan S, et al. Effects of recombinant alpha interferon on chronic active hepatitis B: preliminary results. *Gut*. 1993;34(2 Suppl):S101.
45. Hadziyannis S, Bramou T, Makris A, et al. Interferon alfa-2b treatment of HBeAg negative/serum HBV DNA positive chronic active hepatitis type B. *J Hepatol*. 1990;11 Suppl 1:S133-6.
46. Lampertico P, Del Ninno E, Manzin A, et al. A randomized, controlled trial of a 24-month course of interferon alfa 2b in patients with chronic hepatitis B who had hepatitis B virus DNA without hepatitis B e antigen in serum. *Hepatology*. 1997;26(6):1621-5.
47. Muller R, Baumgarten R, Markus R, et al. Treatment of chronic hepatitis B with interferon alfa-2b. *J Hepatol*. 1990;11(1): S137-140.
48. Perez V, Tanno H, Villamil F, et al. Recombinant interferon alfa-2b following prednisone withdrawal in the treatment of chronic type B hepatitis. *J Hepatol*. 1990;11 Suppl 1:S113-7.
49. Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. The Hepatitis Interventional Therapy Group. *N Engl J Med*. 1990;323(5):295-301.
50. Sarin SK, Guptan RC, Thakur V, et al. Efficacy of low-dose alpha interferon therapy in HBV-related chronic liver disease in Asian Indians: a randomized controlled trial. *J Hepatol*. 1996;24(4):391-6.
51. Waked I, Amin M, Abd el Fattah S, et al. Experience with interferon in chronic hepatitis B in Egypt. *J Chemother*. 1990;2(5):310-8.
52. Ali HY. Trial of lamivudine in hepatitis B surface antigen carriers with persistent hepatitis B core IgM antibody. *Saudi Med J*. 2003;24(9):996-9.
53. Bozkaya H, Yurdaydin C, Idilman R, et al. Lamivudine treatment in HBeAg-negative

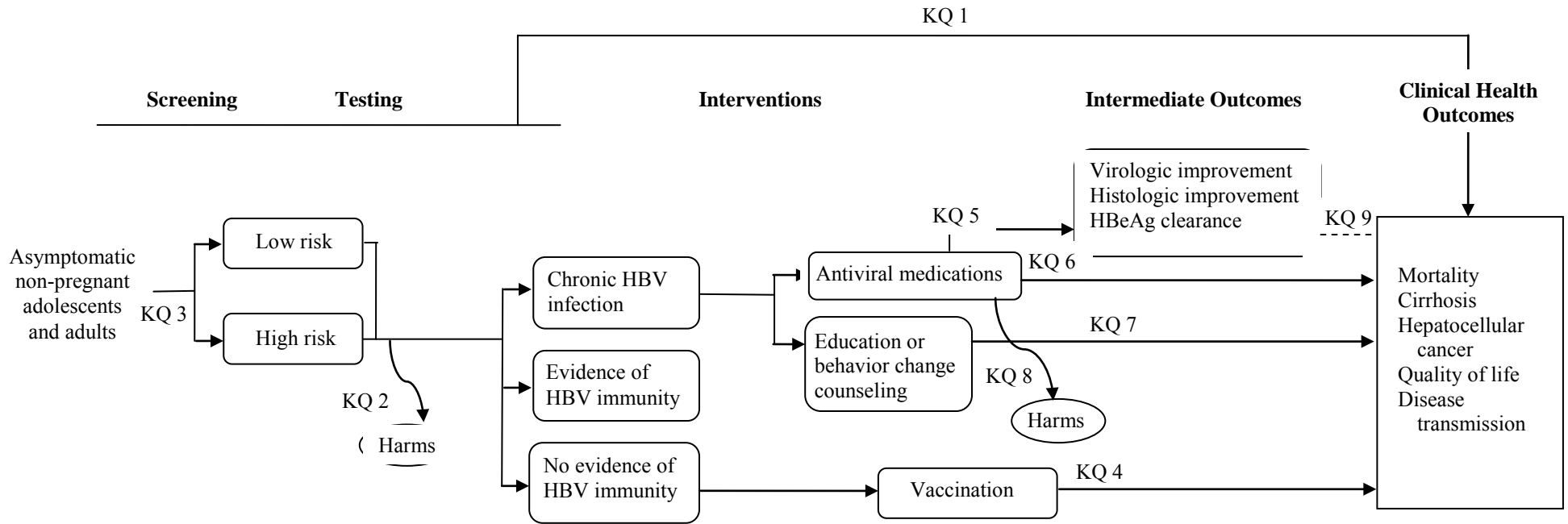
- chronic hepatitis B patients with low level viraemia. *Antivir Ther.* 2005;10(2):319-25.
54. Chan HL-Y, Wang H, Niu J, et al. Two-year lamivudine treatment for hepatitis B e antigen-negative chronic hepatitis B: a double-blind, placebo-controlled trial. *Antivir Ther.* 2007;12(3):345-53.
  55. Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med.* 1999;341(17):1256-63.
  56. Lai CL, Ching CK, Tung AK, et al. Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers: a placebo-controlled trial. *Hepatology.* 1997;25(1):241-4.
  57. Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med.* 1998;339(2):61-8.
  58. Tassopoulos NC, Volpes R, Pastore G, et al. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Lamivudine Precore Mutant Study Group. *Hepatology.* 1999;29(3):889-96.
  59. Yalcin K, Degertekin H, Kokoglu OF, et al. A three-month course of lamivudine therapy in HBeAg-positive hepatitis B patients with normal aminotransferase levels. *Turk J Gastroenterol.* 2004;15(1):14-20.
  60. Yao G, Wang B, Cui Z, et al. A randomized double-blind placebo-controlled study of lamivudine in the treatment of patients with chronic hepatitis B virus infection. *Chin Med J.* 1999;112(5):387-91.
  61. Murray KF, Szenborn L, Wysocki J, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. *Hepatology.* 2012;56(6):2018-26.
  62. Lai C-L, Lim SG, Brown NA, et al. A dose-finding study of once-daily oral telbivudine in HBeAg-positive patients with chronic hepatitis B virus infection. *Hepatology.* 2004;40(3):719-26.
  63. Jonas MM, Block JM, Haber BA, et al. Treatment of children with chronic hepatitis B virus infection in the United States: Patient selection and therapeutic options. *Hepatology.* 2010;52(6):2192-205.
  64. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med.* 2006;354(10):1001-10.
  65. Gish RG, Lok AS, Chang TT, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology.* 2007;133(5):1437-44.
  66. Chang TT, Chao YC, Gorbakov VV, et al. Results of up to 2 years of entecavir vs lamivudine therapy in nucleoside-naïve HBeAg-positive patients with chronic hepatitis B. *J Viral Hepat.* 2009;16(11):784-9.
  67. Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med.* 2006;354(10):1011-20.
  68. Lai C-L, Rosmawati M, Lao J, et al. Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection. *Gastroenterology.* 2002;123(6):1831-8.
  69. Ren F-Y, Piao D-M, Piao X-X. A one-year trial of entecavir treatment in patients with HBeAg-positive chronic hepatitis B. *World J Gastroenterol.* 2007;13(31):4264-7.
  70. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med.* 2005;352(26):2682-95.

71. Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med.* 2004;351(12):1206-17.
72. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med.* 2008;359(23):2442-55.
73. Lin SM, Sheen IS, Chien RN, et al. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology.* 1999;29(3):971-5.
74. Liaw YF, Lin SM, Chen TJ, et al. Beneficial effect of prednisolone withdrawal followed by human lymphoblastoid interferon on the treatment of chronic type B hepatitis in Asians: a randomized controlled trial. *J Hepatol.* 1994;20(2):175-80.
75. Mazzella G, Saracco G, Festi D, et al. Long-term results with interferon therapy in chronic type B hepatitis: a prospective randomized trial. *Am J Gastroenterol.* 1999;94(8):2246-50.
76. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med.* 2004;351(15):1521-31.
77. Yu H-b, Liu E-q, Lu S-m, et al. Treatment with peginterferon versus interferon in Chinese patients with hepatitis B. *Biomed Pharmacother.* 2010;64(8):559-64.
78. Yao GB. Management of hepatitis B in China. *J Med Virol.* 2000;61(3):392-7.
79. Yao GB, Zhu M, Cui ZY, et al. A 7-year study of lamivudine therapy for hepatitis B virus e antigen-positive chronic hepatitis B patients in China. *J Dig Dis.* 2009;10(2):131-7.
80. Andreone P, Gramenzi A, Cursaro C, et al. High risk of hepatocellular carcinoma in anti-HBe positive liver cirrhosis patients developing lamivudine resistance. *J Viral Hepat.* 2004;11(5):439-42.
81. Baltayiannis G, Katsanos K, Karayiannis P, et al. Interferon- $\alpha$  therapy in HBeAg-negative chronic hepatitis B: a long-term prospective study from north-western Greece. *Aliment Pharmacol Ther.* 2006;24(3):525-33.
82. Di Marco V, Marzano A, Lampertico P, et al. Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. *Hepatology.* 2004;40(4):883-91.
83. Fattovich G, Giustina G, Realdi G, et al. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alfa. European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology.* 1997;26(5):1338-42.
84. Hui CK, Leung N, Shek WH, et al. Changes in liver histology as a "surrogate" end point of antiviral therapy for chronic HBV can predict progression to liver complications. *J Clin Gastroenterol.* 2008;42(5):533-8.
85. Lampertico P, Del Ninno E, Vigano M, et al. Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. *Hepatology.* 2003;37(4):756-63.
86. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med.* 1996;334(22):1422-7.
87. Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. *J Hepatol.* 2001;34(2):306-13.
88. Papatheodoridis GV, Manolakopoulos S, Touloumi G, et al. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic

- 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.
89. Lau DT, Everhart J, Kleiner DE, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology*. 1997;113(5):1660-7.
  90. Shamliyan TA, Johnson JR, MacDonald R, et al. Systematic review of the literature on comparative effectiveness of antiviral treatments for chronic hepatitis B infection. *J Gen Intern Med*. 2011;26(3):326-39.
  91. Miyake Y, Kobashi H, Yamamoto K. Meta-analysis: the effect of interferon on development of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *J Gastroenterol*. 2009;44(5):470-5.
  92. Zhang QQ, An X, Liu YH, et al. Long-term nucleos(t)ide analogues therapy for adults with chronic hepatitis B reduces the risk of long-term complications: a meta-analysis. *Virology*. 2011;8:72.
  93. Lai C-L, Yuen M-F. Prevention of hepatitis b virus-related hepatocellular carcinoma with antiviral therapy. *Hepatology*. 2013;57(1):399-408.
  94. Wong GLH, Yiu KKL, Wong VWS, et al. Meta-analysis: reduction in hepatic events following interferon-alfa therapy of chronic hepatitis B. *Aliment Pharmacol Ther*. 2010;32(9):1059-68.
  95. Jin H, Pan N, Mou Y, et al. Long-term effect of interferon treatment on the progression of chronic hepatitis B: bayesian meta-analysis and meta-regression. *Hepatol Res*. 2011(41):512-23.
  96. Papatheodoridis GV, Lampertico P, Manolakopoulos S, et al. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol*. 2010;53(2):348-56.
  97. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology*. 2010;139(4):1218-29.
  98. Liang J, Tang YF, Wu FS, et al. Entecavir versus lamivudine for the treatment of chronic hepatitis B: a systematic review. *Pharmazie*. 2012;67(11):883-90.
  99. Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naïve patients with chronic hepatitis B. *Value Health*. 2010;13(8):934-45.
  100. Zhao SH, Liu EQ, Cheng DX, et al. Comparison of entecavir and adefovir for the treatment of chronic hepatitis B. *Braz J Infect Dis*. 2012;16(4):366-72.
  101. Chou R, Hartung D, Rahman B, et al. Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. *Ann Intern Med*. 2013;158:114-23.
  102. Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med*. 1997;336(26):1855-9.
  103. Lim SG, Mohammed R, Yuen M-F, et al. Prevention of hepatocellular carcinoma in hepatitis B virus infection. *J Gastroenterol Hepatol*. 2009;24(8):1352-7.
  104. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care*. 2012;28(02):138-44.

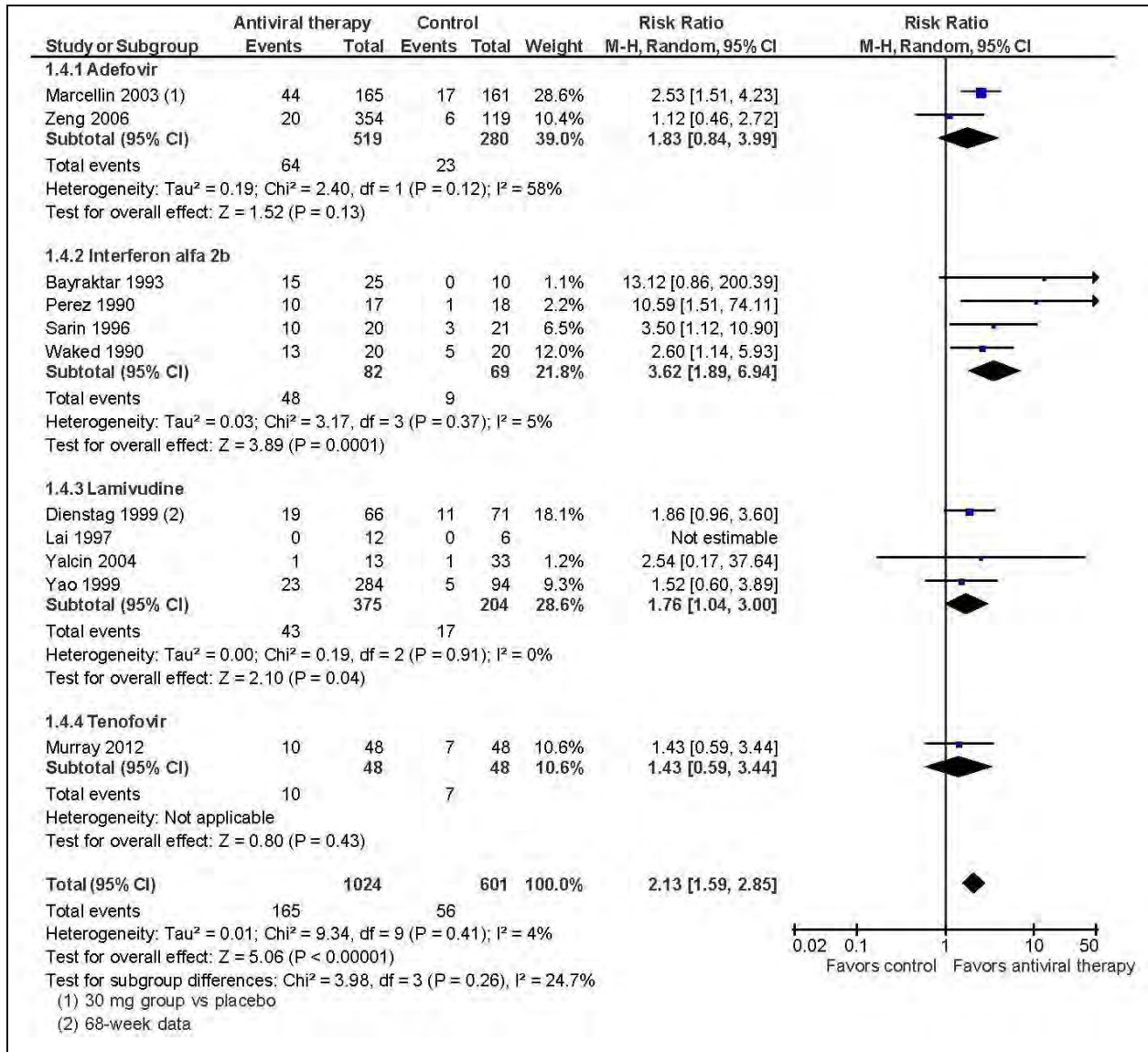
105. Pham B, Klassen TP, Lawson ML, et al. Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary. *J Clin Epidemiol*. 2005;58(8):769-76.
106. Zhang B-H, Yang B-H, Tang Z-Y. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2004;130(7):417-22.
107. Chen JG, Parkin DM, Chen QG, et al. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. *J Med Screen*. 2003;10(4):204-9.
108. Centers for Disease Control and Prevention. Surveillance for acute viral hepatitis - United States, 2007. *MMWR Surveill Summ*. 2009;58(SS-3):Available at: <http://www.cdc.gov/mmwr/pdf/ss/ss5803.pdf>.
109. Wasley A, Kruszon-Moran D, Kuhnert W, et al. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. *J Infect Dis*. 2010;202(2):192-201.
110. Ott JJ, Stevens GA, Groeger J, et al. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*. 2012;30(12):2212-9.
111. Cox N, Tillmann H. Emerging pipeline drugs for hepatitis B infection. *Expert Opin Emerg Drugs*. 2011;16(4):713-29.
112. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):661-2.
113. Kwon H, Lok AS. Hepatitis B therapy. *Nat Rev Gastroenterol Hepatol*. 2011;8(5):275-84.
114. Grimm D, Thimme R, Blum HE. HBV life cycle and novel drug targets. *Hepatol Int*. 2011;5(2):644-53.
115. Centers for Disease Control and Prevention. Screening for chronic hepatitis B among Asian/Pacific Islander populations --- New York City, 2005. *MMWR*. 2006;55(18):505-9.
116. Lin SY, Chang ET, So SK. Why we should routinely screen Asian American adults for hepatitis B: a cross-sectional study of Asians in California. *Hepatology*. 2007;46(4):1034-40.
117. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505.
118. Lai CL, Yuen MF. The natural history and treatment of chronic hepatitis B: a critical evaluation of standard treatment criteria and end points. *Ann Intern Med*. 2007;147(1):58-61.

**Figure 1. Analytic Framework**



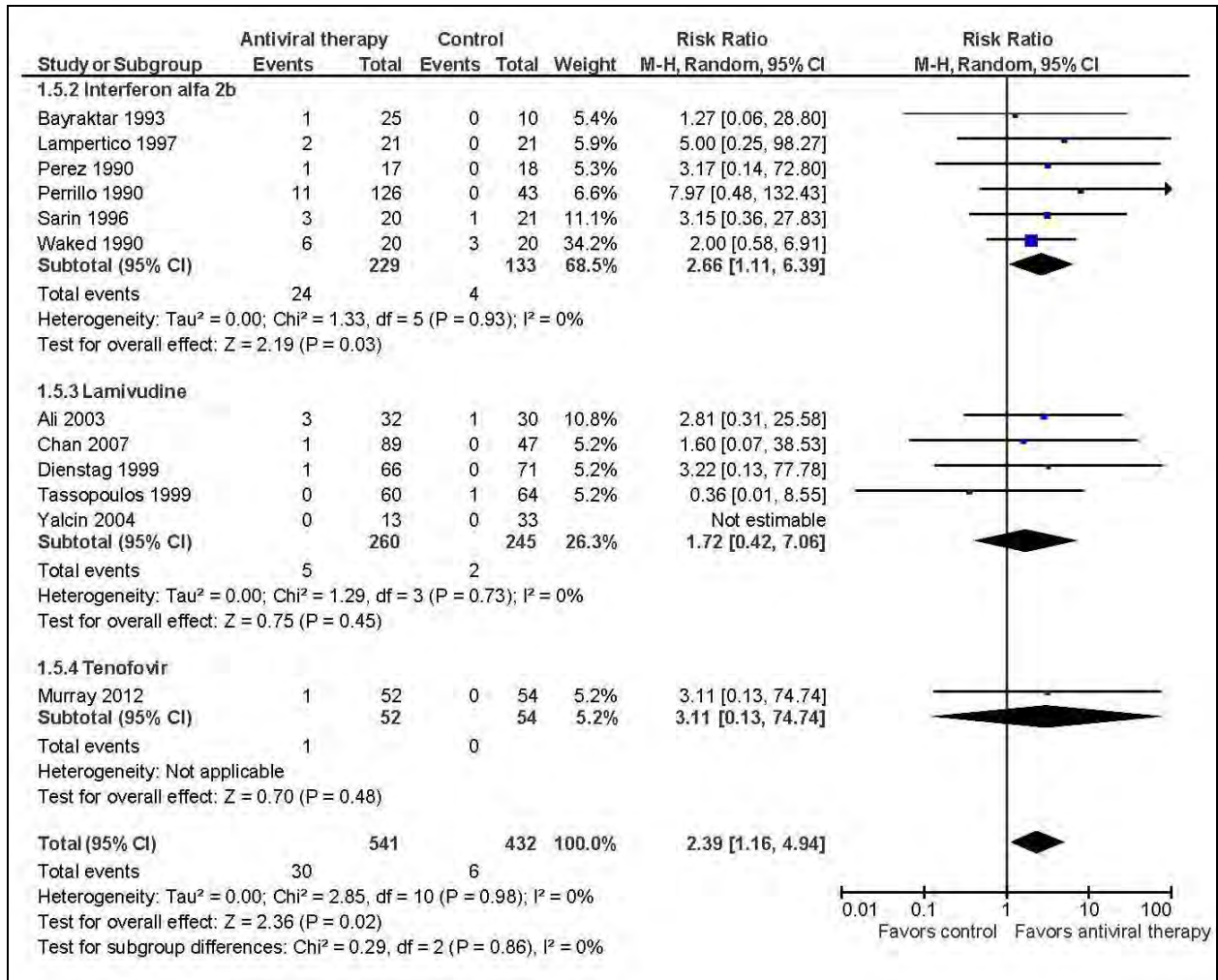
HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; KQ, key question.

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

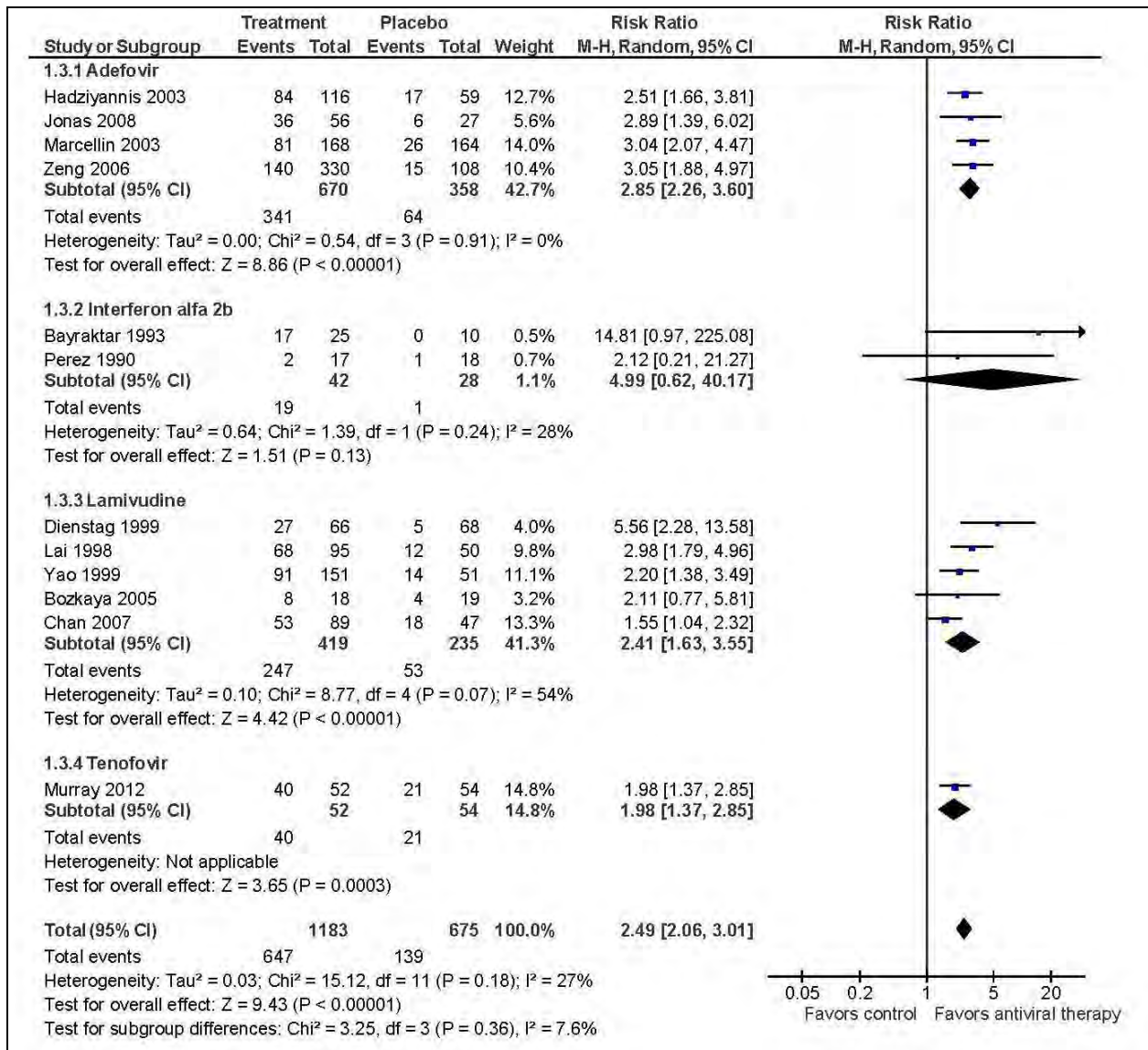




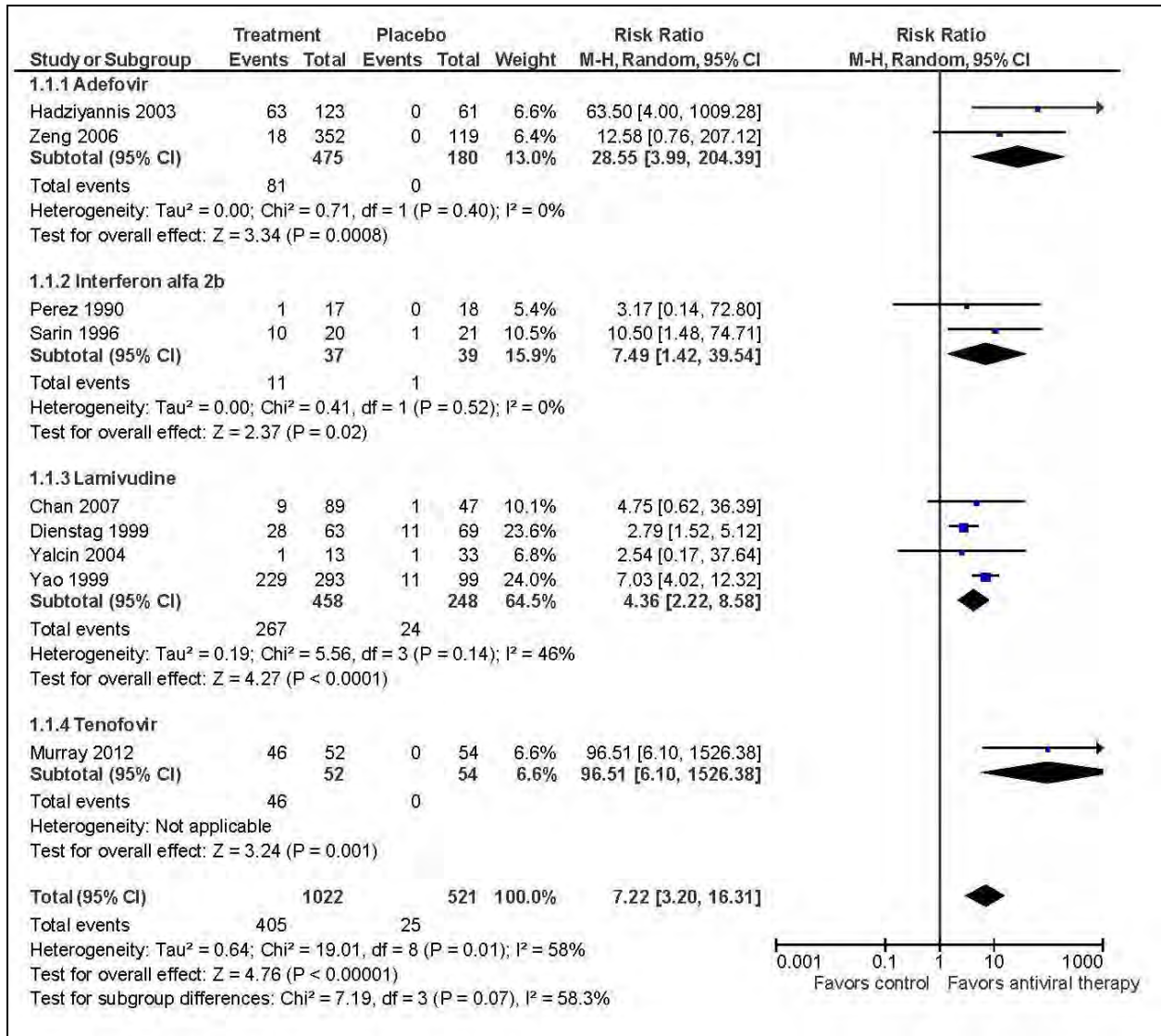
**Figure 3. HBsAg Loss, Antiviral Therapy Versus Placebo or No Treatment**



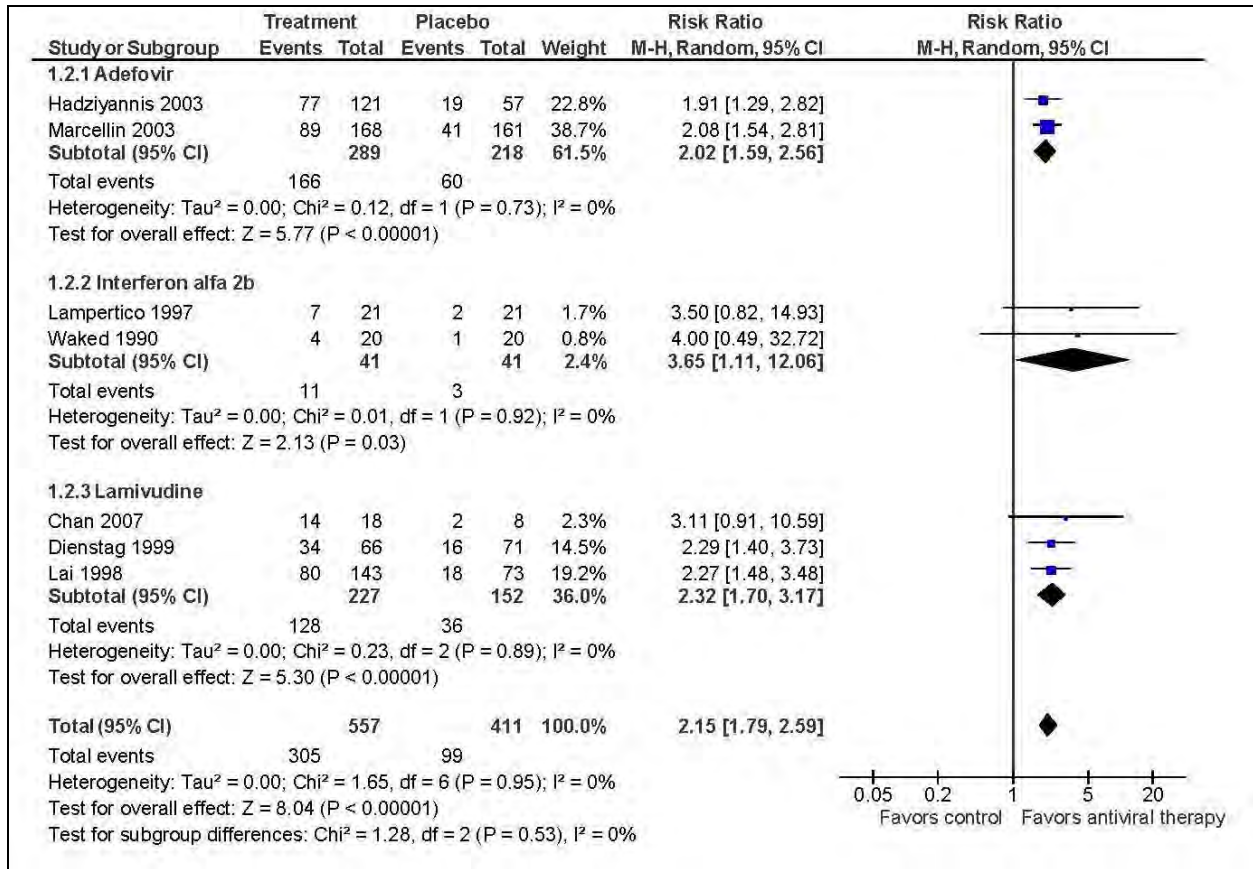
**Figure 4. ALT Normalization, Antiviral Therapy Versus Placebo or No Treatment**



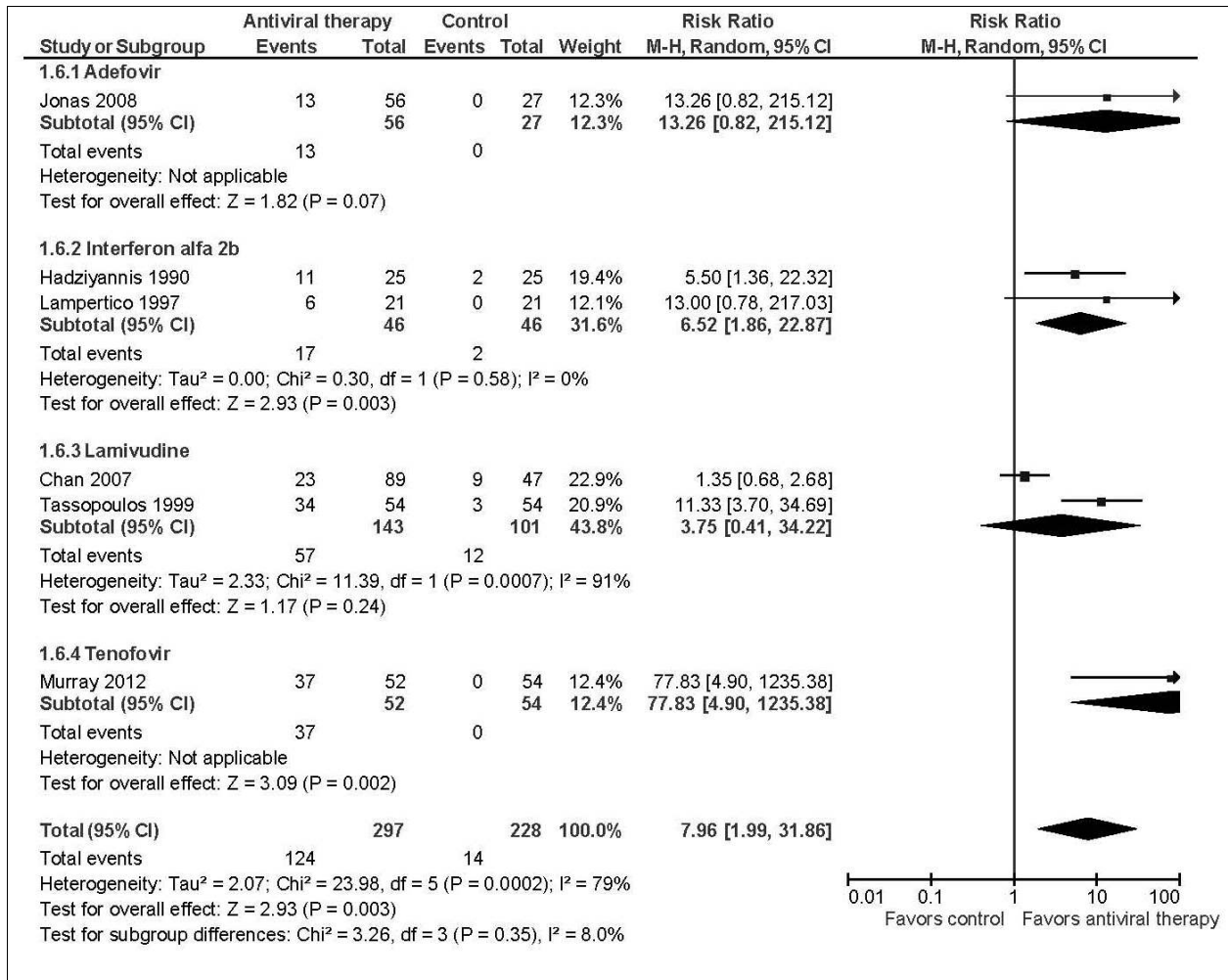
**Figure 5. HBV DNA Loss, Antiviral Therapy Versus Placebo or No Treatment**



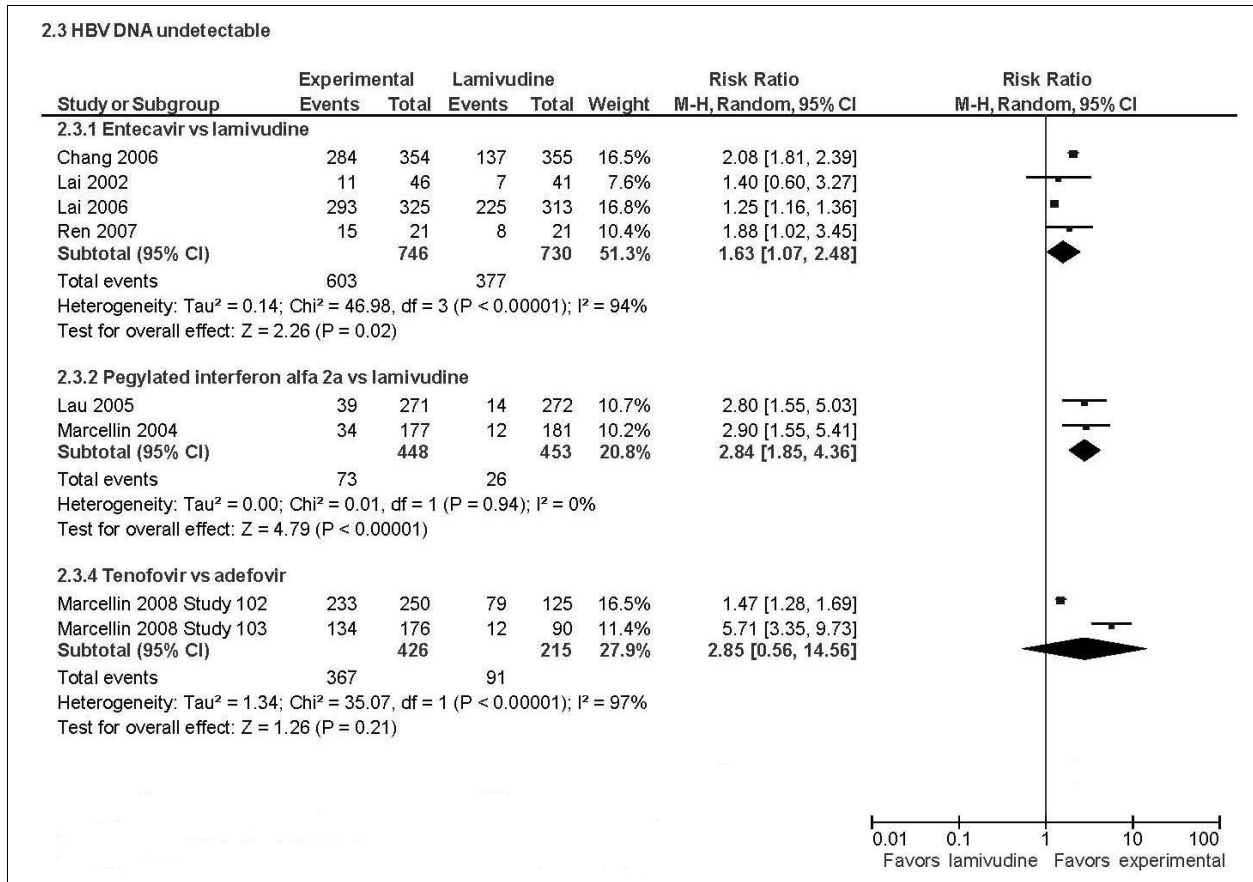
**Figure 6. Histologic Improvement, Antiviral Therapy Versus Placebo or No Treatment**



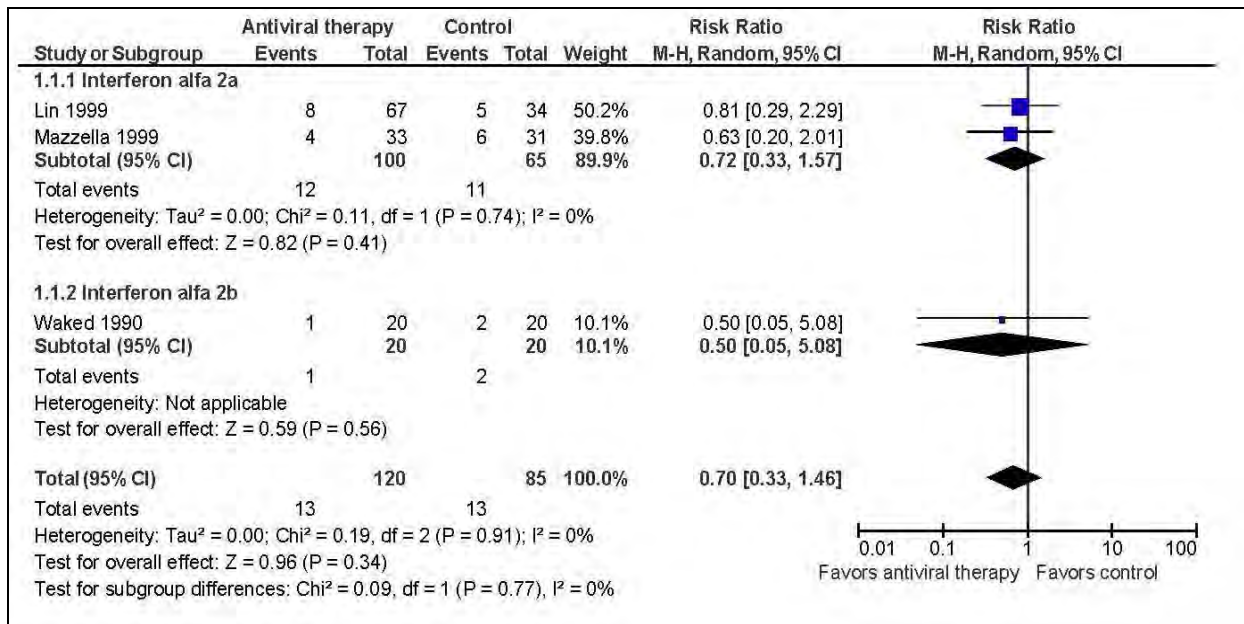
**Figure 7. HBV DNA Loss Plus ALT Normalization, Antiviral Therapy Versus Placebo or No Treatment**



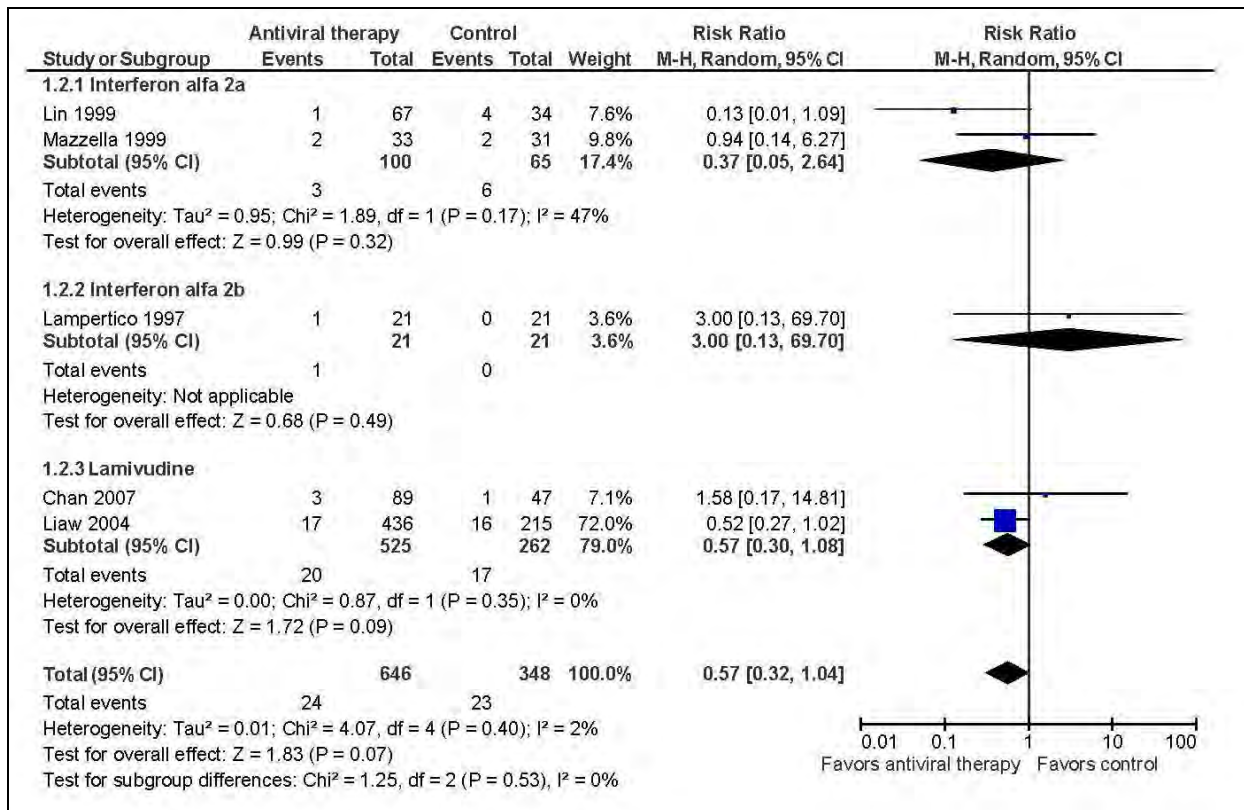
**Figure 8. HBV DNA Loss, Head-to-Head Studies of Antiviral Therapy**



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



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





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

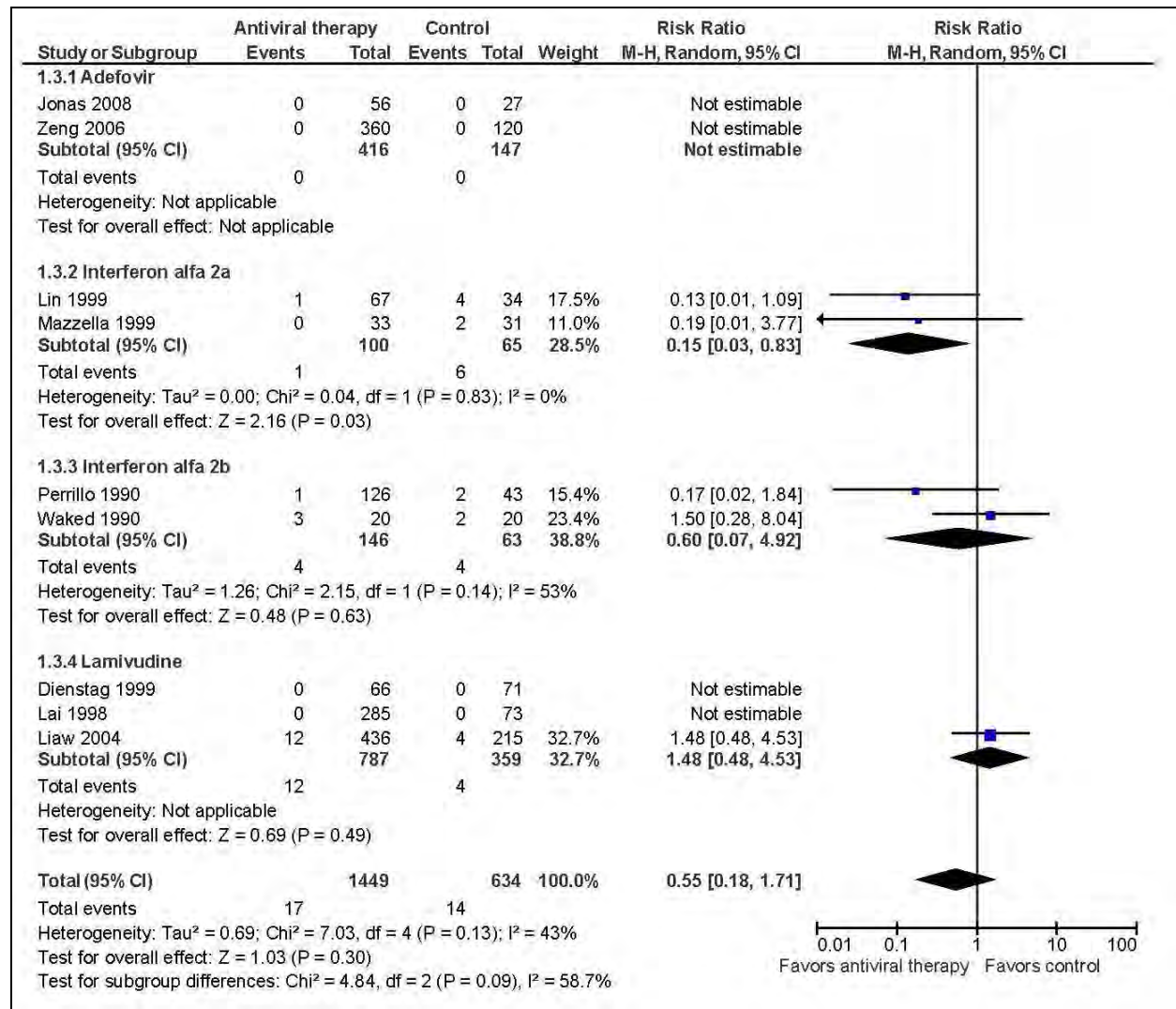


Figure 12. Serious Adverse Events, Antiviral Therapy Versus Placebo or No Treatment

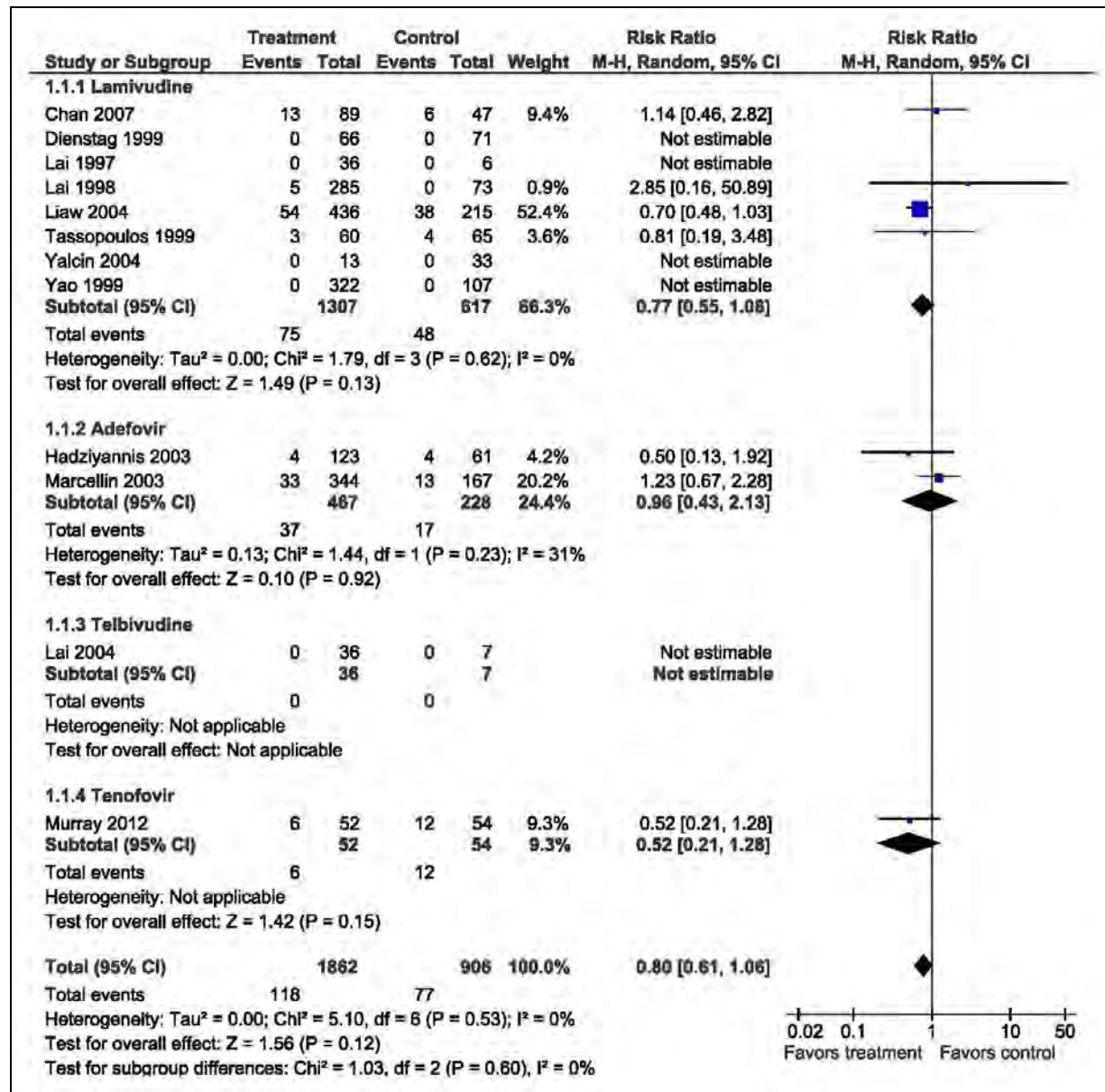


Figure 13. Withdrawals Due to Adverse Events, Antiviral Therapy Versus Placebo or No Treatment

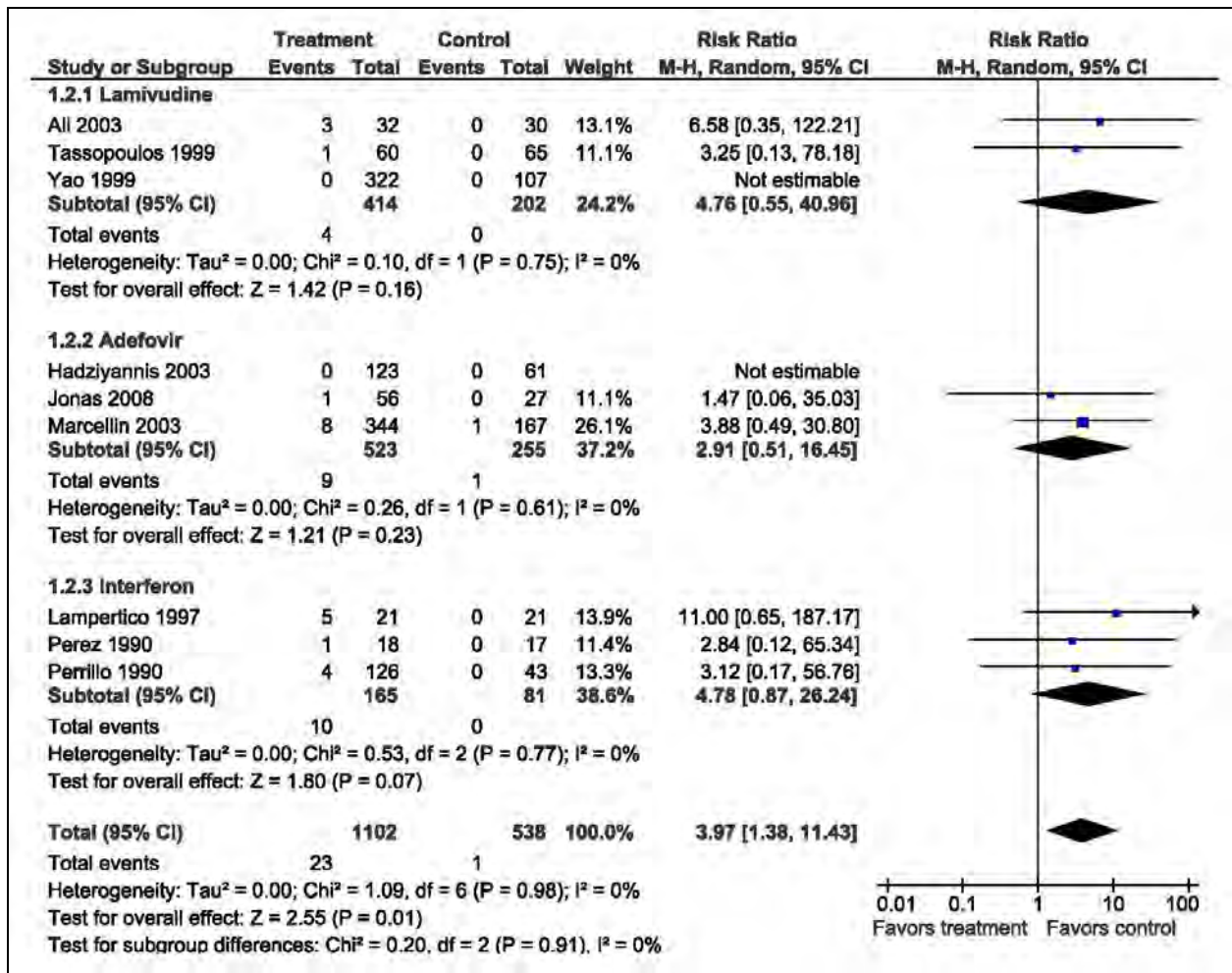
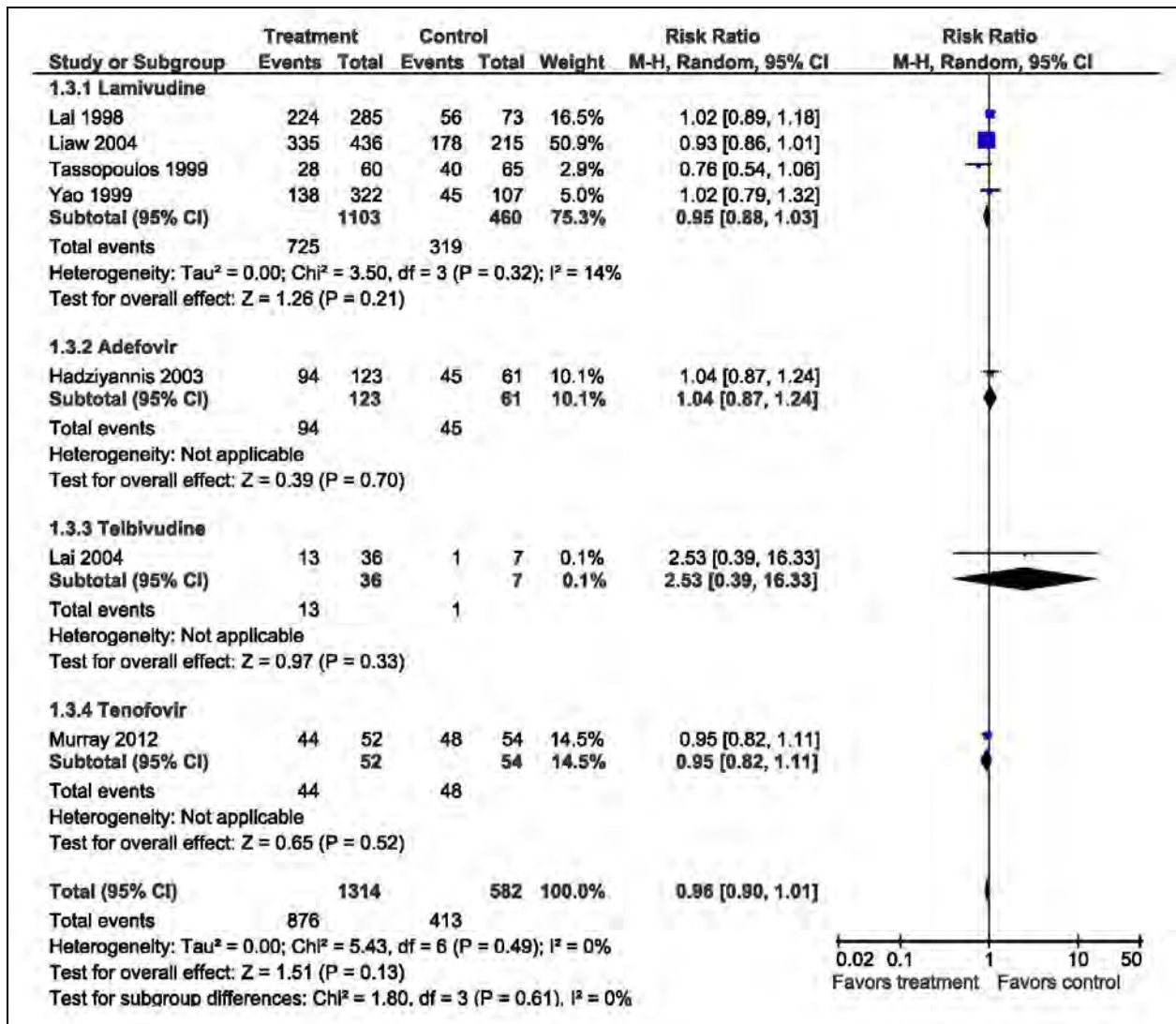


Figure 14. Any Adverse Events, Antiviral Therapy Versus Placebo or No Treatment



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

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

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<sup>a</sup> Hepatitis B surface antigen.

<sup>b</sup> Antibody to hepatitis B core antigen.

<sup>c</sup> Immunoglobulin M.

<sup>d</sup> Antibody to HBsAg.

<sup>e</sup> Negative test result.

<sup>f</sup> Positive test result.

<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.

<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).

<sup>i</sup> Milli-International units per milliliter.

**Table 2. Alternative Screening Strategies: Study Characteristics**

<b>Author, Year Country</b>	<b>Study design</b>	<b>Sample size</b>	<b>Setting Population characteristics</b>	<b>HBV Screening Strategies</b>	<b>Quality</b>
Spennato, 2013 <sup>35</sup> 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 $\geq 8\%$ ) country of birth: 7.2%	A: Screen all B: Screening those born in moderate or high prevalence ( $\geq 2\%$ ) 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**

Author, Year Country	HBV Prevalence	Screening Strategy	Proportion screened	Sensitivity	Specificity	Number needed to screen to identify one case of HBV infection
Spennato, 2013 <sup>35</sup> France	0.8% (49/6194)	A: Screen all B: Screening those born in moderate or high prevalence ( $\geq 2\%$ ) 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	A: 100% (6194/6194) B: 12% (761/6011) C: 64% (3949/6194) D: 73% (4504/6194) E: 84% (5205/6194)	A: 100% (49/49) B: 31% (15/48) C: 98% (48/49) D: 84% (41/49) E: 94% (46/49)	A: 0% (0/6145) B: 87% (5217/5963) C: 37% (2244/6145) D: 27% (1682/6145) E: 16% (986/6145)	A: 126 B: 16 C: 82 D: 110 E: 113

HBV, hepatitis B virus.

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

Author, year	Study design Duration	Country	Population	HBeAg status	Cirrhosis	Intermediate outcomes reported	Quality
<b>Adefovir vs Placebo</b>							
Hadziyannis 2003 <sup>40</sup>	RCT 48 weeks	Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore	n=185 Mean age 46 years 83% male	Negative	11%	ALT normalization Virologic improvement Histologic improvement	Fair
Jonas 2008 <sup>41</sup>	RCT 48 weeks	Germany, Poland, Spain, United Kingdom, United States	n=83 Mean age 14 years 75% male	Positive	NR	ALT normalization Composite outcomes	Fair
Marcellin 2003 <sup>42</sup>	RCT 48 weeks	Australia, Canada, France, Germany, Italy, Malaysia, The Phillipines, Singapore, Spain, Taiwan, Thailand, United Kingdom, United States <sup>a</sup>	n=515 Mean age 35 years 74% male	Positive	NR	HBeAg loss/seroconversion ALT normalization Histologic improvement	Fair
Zeng 2006 <sup>43</sup>	RCT 12 weeks	China	n=480 Mean age 32 years 83% male	Positive	NR	HBeAg loss/seroconversion ALT normalization Virologic improvement	Fair
<b>Interferon Alfa 2b vs No Treatment</b>							
Bayraktar 1993 <sup>44</sup>	Controlled trial 6 months	Turkey	n=35 Mean age 36 years 71% male	Positive	29%	HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization	Poor
Hadziyannis 1990 <sup>45</sup>	RCT 14-16 weeks treatment + 2 year followup	Greece	n=50 Mean age 49 years 94% male	Negative	44%	Composite outcomes	Poor
Lampertico 1997 <sup>46</sup>	Open label RCT 3 years	Italy	n=42 Mean age 46 years 86% male	Negative	17%	HBsAg loss/seroconversion Histologic improvement Composite outcomes	Fair
Muller 1990 <sup>47</sup>	RCT 10 months	Germany	n=58 Mean age NR; range 18-65 years 79% male	Positive	5%	Composite outcomes	Fair



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

Author, year	Study design Duration	Country	Population	HBeAg status	Cirrhosis	Intermediate outcomes reported	Quality
Perez 1990 <sup>48</sup>	RCT 24 weeks (control phase)	Argentina	n=35 Mean age 39 years 77% male	Positive	14%	HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement	Fair
Perrillo 1990 <sup>49</sup>	RCT 10 months	United States	n=169 Mean age 40 years 85% male	Positive	NR	HBsAg loss/seroconversion Composite outcomes	Good
Sarin 1996 <sup>50</sup>	RCT 16 months	India	n=41 Mean age 35 years 94% male	Positive	44%	HBeAg loss/seroconversion HBsAg loss/seroconversion Virologic improvement Composite outcomes	Fair
Waked 1990 <sup>51</sup>	RCT 16 months	Egypt	n=40 Mean age 36 years 78% male	Positive	40%	HBeAg loss/seroconversion HBsAg loss/seroconversion Histologic improvement	Fair
<b>Lamivudine vs Placebo</b>							
Ali 2003 <sup>52</sup>	RCT 12 months	Iraq	n=74 Mean age NR % male NR	Negative	NR	HBsAg loss/seroconversion	Poor
Bozkaya 2005 <sup>53</sup>	Controlled trial 12 months (control phase)	Turkey	n=55 Mean age 36 years 60% male	Negative	NR <sup>b</sup>	ALT normalization	Poor
Chan 2007 <sup>a54</sup>	RCT 30 months	China	n=139 Mean age 39 years 84% male	Negative	27%	HBsAg loss/seroconversion ALT normalization Virologic improvement Histologic improvement Composite outcomes	Fair
Dienstag 1999 <sup>55</sup>	RCT 16 months	United States	n=137 Median age 39 years 83% male	Positive	10%	HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement Histologic improvement	Fair
Lai, 1997 <sup>56</sup>	RCT 8 weeks	Hong Kong	n=42 Mean age 32 years 64% male	Positive	NR	HBeAg loss/seroconversion	Fair

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

Author, year	Study design Duration	Country	Population	HBeAg status	Cirrhosis	Intermediate outcomes reported	Quality
Lai 1998 <sup>57</sup>	RCT 1 year	Hong Kong, Taiwan, Singapore	n=358 Median age 31 years 73% male	Positive	5%	ALT normalization Histologic improvement Composite outcomes	Fair
Tassopoulos 1999 <sup>58</sup>	RCT 24 weeks	Greece	n=125 Median age 43 years 80% male	Negative	15%	HBsAg loss/seroconversion Composite outcomes	Fair
Yalcin 2004 <sup>59</sup>	RCT 1 year	Turkey	n=46 Mean age 24 years 54% male	Positive	NR	HBeAg loss/seroconversion HBsAg loss/seroconversion Virologic improvement Composite outcomes	Fair
Yao, 1999 <sup>60</sup>	RCT 12 weeks	China	n=429 Mean age 32 years 73% male	Positive	NR	HBeAg loss/seroconversion ALT normalization Virologic improvement	Fair
<b>Tenofovir vs Placebo</b>							
Murray 2012 <sup>61</sup>	RCT 72 weeks	United States, Bulgaria, France, Poland, Romania, Spain, Turkey	n=106 Mean age 15 years 73% male	Positive	NR	HBeAg loss/seroconversion HBsAg loss/seroconversion ALT normalization Virologic improvement Composite outcomes	Good

<sup>a</sup>Patient population was 60% Asian.

<sup>b</sup>24% had fibrosis.

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

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

Author, year	Results	Quality
<b>Adefovir vs Placebo</b>		
Jonas 2008 <sup>63</sup>	HBV DNA <1000 copies/mL + ALT normalization: 13/56 (23%) vs. 0/27 (0%); RR 13, 95% CI 0.8 to 215	Fair
<b>Interferon Alfa 2b vs No Treatment</b>		
Hadziyannis 1990 <sup>45</sup>	HBV DNA undetectable and ALT normalization: 11/25 (44%) vs 2/25 (8%); <b>RR 5.5, 95% CI 1.4 to 22</b> HBV DNA and ALT reduced by >50% from baseline: 3/25 (12%) vs 6/25 (24%); RR 0.5, 95% CI 0.1 to 1.8	Poor
Lampertico 1997 <sup>46</sup>	Loss of HBV DNA + ALT normalization: 6/21 (29%) vs 0/21 (0%); RR 13, 95% CI 0.8 to 217 Loss of HBsAg and/or HBV DNA: 7/21 (33%) vs 0/21 (0%); RR 15, 95% CI 0.9 to 247	Fair
Muller 1990 <sup>47</sup>	Loss of HBsAg, HBeAg, HBV DNA and ALT normalization: 1/30 (3%) vs 0/28 (0%); RR 2.8, 95% CI 0.1 to 66 Loss of HBeAg, HBV DNA and ALT normalization, : 8/30 (27%) vs 0/28 (0%); RR 15, 95% CI 0.9 to 248	Fair
Perrillo 1990 <sup>48</sup>	Loss of HBeAg + HBV DNA: 38/126 (26%) vs 3/43 (7%); <b>RR 4.6, 95% CI 1.5 to 14</b>	Good
Sarin 1996 <sup>50</sup>	Loss of HBeAg and HBV DNA: 10/20 (50%) vs 1/21 (5%); <b>RR 11, 95% CI 1.5 to 75</b>	Fair
<b>Lamivudine vs Placebo</b>		
Lai, 1998 <sup>57</sup>	HBeAg seroconversion + HBV DNA undetectable: 39/275 (14%) vs 3/70 (4%) <b>RR 3.31, 95% CI 1.05 to 10.40</b>	Fair
Chan, 2007 <sup>54</sup>	HBV DNA <10,000 copies/ml and ALT normalization at 24 months (time on treatment): 50/89 (56%) vs 5/47 (11%); <b>reported adjusted OR<sup>a</sup> 11, 95% CI 3.8 to 30; RR 5.3, 95% CI 2.3 to 12</b> HBV DNA <10,000 copies/ml and ALT normalization at 30 months (6 months after treatment cessation): 23/89 (26%) vs 9/47 (19%); RR 1.3, 95% CI 0.7 to 2.7	Fair
Tassopoulos 1999 <sup>58</sup>	HBV DNA <2.5 pg/mL and ALT normalization: 34/54 (63%) vs 3/54 (6%); <b>RR 11, 95% CI 3.7 to 35</b>	Fair
Yalcin 2004 <sup>59</sup>	HBeAg seroconversion + HBV DNA loss: 1/13 (8%) vs 1/33 (3%); RR 2.5, 95% CI 0.17 to 38	Fair
<b>Tenofovir vs Placebo</b>		
Murray 2012 <sup>61</sup>	HBV DNA <400 copies/mL + ALT normalization: 37/52 (71%) vs 0/54 (0%); <b>RR 77, 95% CI 5 to 1235</b> HBV DNA <400 copies/mL + ALT normalization + HBeAg loss: 11/52 (21%) vs 0/54 (0%); <b>RR 24, 95% CI 1.4 to 395</b> HBV DNA <400 copies/mL + ALT normalization + HBsAg loss: 8/52 (15%) vs 0/54 (0%); <b>RR 18 (95% CI 1.0 to 298)</b>	Good

<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**

<b>Outcome</b>	<b>Entecavir vs lamivudine</b>	<b>Pegylated interferon alfa 2a vs lamivudine</b>	<b>Tenofovir vs adefovir</b>
HBeAg loss/seroconversion	RR 1.2 (95% CI 0.9 to 1.5, I <sup>2</sup> =0%); 3 trials <sup>64, 68, 69</sup>	RR 1.6 (95% CI 1.2 to 2.1); 1 trial <sup>70</sup>	RR 1.2 (95% CI 0.7 to 2.1); 1 trial <sup>72</sup>
HBsAg loss/seroconversion	RR 1.8 (95% CI 0.9 to 3.9); 1 trial <sup>64</sup>	RR 16 (95% CI 2.2 to 121, I <sup>2</sup> =0%); 2 trials <sup>70, 71</sup>	RR 5.7 (95% CI 0.3 to 103); 1 trial <sup>72</sup>
ALT normalization	RR 1.1 (95% CI 1.0 to 1.2, I <sup>2</sup> =0%); 4 trials <sup>64, 67-69</sup>	RR 1.4 (95% CI 1.2 to 1.6, I <sup>2</sup> =0%); 2 trials <sup>70, 71</sup>	RR 1.1 (95% CI 0.9 to 1.4, I <sup>2</sup> =73%); 2 trials <sup>72</sup>
Virological improvement	RR 1.6 (95% CI 1.1 to 2.5, I <sup>2</sup> =94%); 4 trials <sup>64, 67-69</sup>	RR 2.8 (95% CI 1.9 to 4.4, I <sup>2</sup> =0%); 2 trials <sup>70, 71</sup>	RR 2.9 (95% CI 0.6 to 15, I <sup>2</sup> =97%); 2 trials <sup>72</sup>
Histological improvement	RR 1.2 (95% CI 1.1 to 1.3, I <sup>2</sup> =0%); 2 trials <sup>64, 67</sup>	RR 1.2 (CI 1.0 to 1.4, 0%); 2 trials <sup>70, 71</sup>	RR 1.1 (95% CI 1.0 to 1.2, I <sup>2</sup> =0%); 2 trials <sup>72</sup>

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**

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

<sup>a</sup>Cirrhotics excluded from study.

<sup>b</sup>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.  
HBeAg, hepatitis B e antigen; N/A, not applicable; NR, not reported; RCT, randomized controlled trial.

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

Drug Author, year	Duration Followup	Time period for harms data	N Country	Cirrhosis	Serious adverse events Treatment vs. control/no treatment	Withdrawal due to adverse events Treatment vs. control/no treatment	Any adverse events Treatment vs. control/no treatment	Quality	Notes
<b>Adefovir vs Placebo</b>									
Hadziyannis 2003 <sup>40</sup>	11 months + 1 month followup	Both	n=185 Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore	11% cirrhosis	3% (4/123) vs. 7% (4/61) RR 0.5 (95% CI 0.1 to 1.9)	0% (0/123) vs. 0% (0/61) RR 0.5 (95% CI 0.0 to 25)	76% (94/123) vs. 74% (45/61) RR 1.0 (95% CI 0.9 to 1.2)	Fair	Any adverse event refers to those reported by at least 5% of patients
Jonas 2008 <sup>41</sup>	11 months	Time-on-treatment	n=83 United States and Europe	% cirrhosis NR <sup>a</sup>	NR separately for relevant age group	1.7% (1/56) vs. 0% (0/27) RR 1.5 (95% CI 0.1 to 35)	NR separately for relevant age group	Fair	
Marcellin 2003 <sup>42</sup>	11 months + 1 month followup	Both	n=515 North America, Europe, Australia, and Southeast Asia	% cirrhosis NR <sup>a</sup>	10% (33/344) vs. 8% (13/167) RR 1.2 (95% CI 0.7 to 2.3)	2.3% (8/344) vs. <1% (1/167) RR 3.9 (95% CI 0.5 to 31)	NR	Fair	N values calculated Combined treatment arms
<b>Interferon Alfa 2b vs No Treatment</b>									
Bayraktar 1993 <sup>44</sup>	6 months	Time-on-treatment	n=35 Turkey	29% cirrhosis	NR	0% (0/25) <sup>b</sup>	NR	Poor	Results reported for treated group only
Hadziyannis 1990 <sup>45</sup>	1 year + 1 year followup	Unclear*	n=50 Greece	44% cirrhosis	0% (0/25) <sup>b</sup>	NR	NR	Poor	Results reported for treated group only
Lampertico 1997 <sup>46</sup>	2 years + 1 year followup	Time-on-treatment	n=42 Italy	17% cirrhosis	NR	24% (5/21) vs 0% (0/21) RR 11 (95% 0.65 to 187)	NR	Fair	
Muller 1990 <sup>47</sup>	4 months + 6 months followup	Time-on-treatment	n=58 Germany	5% cirrhosis	NR	3.7% (1/27) <sup>b</sup>	NR	Fair	Results reported for treated group only
Perez 1990 <sup>48</sup>	6 months (2nd phase) + 6 month followup	Time-on-treatment	n=35 Argentina	14% cirrhosis	NR	6% (1/18) vs. 0% (0/17) RR 2.7 (95% CI 0.1 to 62)	NR	Fair	
Perrillo 1990 <sup>49</sup>	4 months + 6 month followup	Time-on-treatment	n=169 United States	% cirrhosis NR <sup>a</sup>	NR	3% (4/126) vs 0% (0/43) RR 3.12 (95% CI 0.17 to 57)	NR	Good	

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

Drug Author, year	Duration Followup	Time period for harms data	N Country	Cirrhosis	Serious adverse events Treatment vs. control/no treatment	Withdrawal due to adverse events Treatment vs. control/no treatment	Any adverse events Treatment vs. control/no treatment	Quality	Notes
Sarin 1996 <sup>50</sup>	4 months + 1 year followup	Unclear*	n=41 India	44% cirrhosis	0% (0/20) <sup>b</sup>	NR	NR	Fair	Results reported for treated group only
Waked 1990 <sup>51</sup>	4 months + 1 year followup	Time-on-treatment	n=40 Egypt	40% cirrhosis	0% (0/20) <sup>b</sup>	0% (0/20) <sup>b</sup>	NR	Fair	Results reported for treated group only Serious adverse effects inferred
<b>Lamivudine vs Placebo</b>									
Ali 2003 <sup>52</sup>	6 months + 1 year followup	Unclear	n=74 Iraq	% cirrhosis NR <sup>a</sup>	NR	9.4% (3/32) vs. 0% (0/30) RR 6.6 (95% CI 0.4 to 122)	NR	Poor	
Chan 2007 <sup>54</sup>	2 years + 6 months followup	Unclear	n=139 China	27% cirrhosis	15% (13/89) vs. 13% (6/47) RR 1.1 (95% CI 0.5 to 2.8)	NR	NR	Fair	
Dienstag 1999 <sup>55</sup>	1 year + 4 months followup	Unclear	n=143 United States	10% cirrhosis	0% (0/66) vs 0% (0/71) RR 1.1 (95% CI 0.0 to 53)	NR	NR	Fair	Results inferred
Lai 1997 <sup>56</sup>	1 month + 1 month followup	Unclear	n=42 Hong Kong	% cirrhosis NR <sup>a</sup>	0% (0/36) vs. 0% (0/6) RR 0.2 (95% CI 0.0 to 8.8)	NR	NR	Fair	Combined treatment arms
Lai 1998 <sup>57</sup>	1 year	Time-on-treatment	n=358 Hong Kong, Taiwan, Singapore	5% cirrhosis	1.8% (5/285) vs. 0% (0/73) RR 2.9 (95% CI 0.2 to 51)	NR	78.6% (224/285) vs. 77% (56/73) RR 1.0 (95% CI 0.9 to 1.2)	Fair	Combined treatment arms
Liaw 2004 <sup>76</sup>	2.7 years median + ≤1 year followup	Time-on-treatment	n=651 Several countries in Asia, Australia, New Zealand	33% cirrhosis	12% (54/436) vs. 18% (38/215) RR 0.7 (95% CI 0.5 to 1.0)	NR	77% (335/436) vs. 83% (178/215) RR 0.9 (95% CI 0.9 to 1.0)	Fair	Any adverse event refers to those that occurred in greater than 10% of patients
Tassopoulos 1999 <sup>58</sup>	6 months	Time-on-treatment	n=125 Greece	15% cirrhosis	5% (3/60) vs. 6% (4/65) RR 0.8 (95% CI 0.2 to 3.5)	2% (1/60) vs. 0% (0/65) RR 3.2 (95% CI 0.1 to 78)	47% (28/60) vs. 62% (40/65) RR 0.8 (95% CI 0.5 to 1.1)	Fair	

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

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

<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**

<b>Outcomes</b>	<b>Entecavir vs lamivudine</b>	<b>Pegylated interferon alfa 2a vs lamivudine</b>	<b>Tenofovir vs adefovir</b>
Serious adverse events	RR 0.9 (95% CI 0.6 to 1.3, I <sup>2</sup> =0%); 2 trials <sup>64, 67</sup>	RR 2.1 (95% CI 1.0 to 4.5, I <sup>2</sup> =0%); 2 trials <sup>70, 71</sup>	RR 1.0 (95% CI 0.5 to 1.8); 2 trials (one publication, results pooled) <sup>72</sup>
Withdrawals due to adverse events	RR 0.5 (95% CI 0.1 to 1.9, I <sup>2</sup> =43%); 3 trials <sup>64, 67, 68</sup>	RR 7.6 (95% CI 1.1 to 52, I <sup>2</sup> =38%); 2 trials <sup>70, 71</sup>	Not reported
Any adverse event	RR 1.0 (95% CI 0.9 to 1.1, I <sup>2</sup> =34%); 3 trials <sup>64, 67, 68</sup>	RR 1.7 (95% CI 1.5 to 2.0, I <sup>2</sup> =55%); 2 trials <sup>70, 71</sup>	RR 1.0 (95% CI 0.9 to 1.1); 2 trials (one publication, results pooled) <sup>72</sup>

CI, confidence interval; RR, relative risk.

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

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

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

Author, year Country	Study design	Intermediate outcome evaluated Proportion of patients with intermediate outcome	Treatment Duration of followup	Characteristics of HBV infection	Age Sex Race	Number receiving antiviral treatment Lost to followup	Quality
Lau 1997 <sup>63</sup> USA	Cohort (originally enrolled in RCTs)	Response (sustained loss of HBV DNA and clearance of HBeAg within 1 year of starting treatment): 30%	Interferon alfa Mean 6.2 years	HBeAg positive: All ALT (median): 154 Serum HBV DNA (mq/mL): 4843 Cirrhosis: 17%	Mean age: 41 years Male: 83% Race: 94% white, 6% black	n=103 Lost to followup: 8 (7.8%); assumed to be alive and without liver- related complications	Fair
Niederrau 1996 <sup>86</sup> Europe	Prospective cohort	Loss of HBeAg after therapy: 51%	Interferon alfa 2b Mean 50 months	HBeAg positive: All HBsAg clearance: 9.7% ALT: NR AST: NR HBV DNA: NR Fibrosis stage: NR Cirrhosis: NR (Child- Pugh class B or C excluded)	Mean age: NR Female: NR Race: NR	n=103 Lost to followup: None	Fair
Papatheodoridis 2001 <sup>87</sup> Greece	Cohort (unclear if prospective or retrospective)	Sustained biochemical response (normalization of ALT at the end of interferon therapy and persistently normal ALT levels throughout the post-treatment followup period): 27%	Interferon alfa Mean 6.0 years	HBeAg positive: Excluded ALT (median): 112 Serum HBV DNA (median, pg/ml): 4.4 Cirrhosis: 27%	Mean age: 47 years Male: 83% Race: NR	n=209 Lost to followup: 9 (4.3%)	Poor
Papatheodoridis 2011 <sup>88</sup> Greece	Retrospective cohort	Virological remission (HBV DNA <200 IU/ml throughout therapy): 28%	Lamivudine Median 4.7 years	HBeAg positive: Excluded ALT (median): 98 Serum HBV DNA (median, x10 <sup>3</sup> IU/ml): 400 Cirrhosis: 26%	Mean age: 54 years Male: 72% Race: NR	n=818 Lost to followup: 180 (22%)	Fair

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**

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

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

Author, year Country	Confounders adjusted for in analysis	Death	Hepatocellular carcinoma	Composite outcomes	Quality
<b>HBeAg Negative Patients</b>					
Andreone 2004 <sup>80</sup> Italy	Age Sex Child-Pugh class ALT HBV viral load Albumin Bilirubin Prothrombin activity Alpha-fetoprotein Previous interferon therapy Smoking status Months of treatment All patients HBeAg negative	NR	No virological breakthrough vs. breakthrough: adjusted HR 0.10 (95% CI 0.01 to 0.77)	NR	Fair
Baltayiannis 2006 <sup>81</sup> Greece	Age Gender Alcohol use ALT >200 IU/L at baseline HBV-DNA >10,000 copies/ml at baseline Histologic grade >9 Histologic stage >2 All patients HBeAg negative	NR	NR	Virological response at 6 months vs. no virological response: adjusted HR 0.24 (95% CI 0.06 to 0.96) <sup>d</sup>	Fair
Di Marco 2004 <sup>82</sup> Italy	Age Sex HBV DNA level ALT Hepatic flare after virological breakthrough Previous interferon therapy Cirrhosis All patients HBeAg negative	No virological breakthrough vs. breakthrough: adjusted HR 0.34 (95% CI 0.15 to 0.80)	NR	NR	Fair

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

Author, year Country	Confounders adjusted for in analysis	Death	Hepatocellular carcinoma	Composite outcomes	Quality
Lampertico 2003 <sup>85</sup> Italy	Age Sex ALT HBV viral load IgM anti-HBc level Necroinflammatory grade Fibrosis stage All patients HBeAg negative	NR	NR	Sustained virological and biochemical response vs. no sustained response: adjusted HR 0.13 (95% CI 0.03 to 0.55) <sup>e</sup>	Fair
Papatheodoridis 2001 <sup>87</sup> Greece	Cirrhosis Age All patients HBeAg negative	NR	NR	Death or liver transplantation Sustained biochemical response vs. no sustained biochemical response: adjusted HR 0.48 (95% CI 0.23 to 1.0) Severe clinical complications <sup>f</sup> Sustained biochemical response vs. no sustained biochemical response: adjusted HR 0.53 (95% CI 0.29 to 0.91)	Poor
Papatheodoridis 2011 <sup>88</sup> Greece	Age Sex Liver disease severity ALT AST Bilirubin Albumin Hemoglobin Platelet count HBV DNA Interferon alfa in the past All patients HBeAg negative	NR	Virological remission under therapy vs. no virological remission: adjusted HR 0.77 (95% CI 0.35 to 1.69) <sup>g</sup>	NR	Fair

<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 12. Associations Between Intermediate Outcomes and Final Health Outcomes**

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

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

<sup>a</sup> Study performed in HBeAg-negative patients.

**Table 13. Summary of Evidence**

<b>Key Question</b>	<b>Number and type of studies identified for update</b>	<b>Limitations</b>	<b>Consistency</b>	<b>Applicability</b>	<b>Summary of findings</b>	<b>Overall quality</b>
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?	No studies	No studies	N/A	N/A	No evidence	No evidence
2. What are the harms of screening for HBV infection (e.g., labeling, anxiety, and harms of confirmatory tests, including biopsy)?	No studies	No studies	N/A	N/A	No evidence	No evidence
3. How well do different screening strategies identify individuals with HBV infection (e.g., strategies that target persons from high prevalence countries, men who have sex with men, injection drug users, immunization history, or other risk factors)?	One cross-sectional study	Evidence only available from one study with methodologic limitations	N/A	Study conducted in high-risk sexually transmitted disease clinic attendees	One study found screening targeted at persons born in countries with higher chronic HBV prevalence, men, and unemployed persons identified 98% (48/49) of infections; number needed to screen to identify one case of HBV infection of 82.	Poor
4. In non-pregnant adolescents and adults with no evidence of HBV immunity on screening, how effective is HBV vaccination for improving clinical outcomes?	No studies with evidence on long-term clinical outcomes	No evidence on long-term clinical outcomes	Moderate	Studies conducted in high-risk populations (health-care workers or MSM) and/or children	Vaccination is associated with decreased risk of HBV acquisition in 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.	Fair
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)?	30 RCTs	Study duration and patient characteristics varied widely  Few good-quality studies	High	About half the studies conducted outside of the United States/Europe and about 1/3 enrolled HBeAg negative patients	Antiviral treatment was more effective than placebo or no treatment for HBeAg loss or seroconversion (10 trials, RR 2.1, 95% CI 1.6 to 2.9, I <sup>2</sup> =4%), HBsAg loss/seroconversion (12 trials, RR 2.4, 95% CI 1.2 to 4.9, I <sup>2</sup> =0%), ALT normalization (12 trials, RR 2.5, 95% CI 2.1 to 3.0, I <sup>2</sup> =27%), loss of HBV DNA (9 trials, RR 7.2, 95% CI 3.2 to 16; I <sup>2</sup> =58%) and histologic improvement (7 trials, RR 2.1, 95% CI 1.8 to 2.6; I <sup>2</sup> =0%). Results were generally consistent across specific antiviral drugs.	Fair



**Table 13. Summary of Evidence**

Key Question	Number and type of studies identified for update	Limitations	Consistency	Applicability	Summary of findings	Overall quality
					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.	
6. In non-pregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving health outcomes?	16 RCTs	Many studies were small, with few events  Only one good-quality study	Moderate	About half of the studies conducted outside of the United States/Europe and about 1/3 enrolled HBeAg negative patients	Estimates for incident cirrhosis (3 trials, RR 0.70, 95% CI 0.33 to 1.46, I <sup>2</sup> =0%), hepatocellular carcinoma (5 trials, RR 0.57, 95% CI 0.32 to 1.04, I <sup>2</sup> =2%), and mortality (5 trials, RR 0.55, 95% CI 0.18 to 1.71, I <sup>2</sup> =43%) all favored antiviral therapy over placebo though differences were not statistically significant.  There were too few clinical events in head-to-head trials of entecavir or pegylated interferon alfa 2a versus lamivudine or pegylated interferon versus non-pegylated interferon to determine effects on clinical outcomes.	Fair
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?	No studies	No evidence	N/A	N/A	No evidence	No evidence

**Table 13. Summary of Evidence**

Key Question	Number and type of studies identified for update	Limitations	Consistency	Applicability	Summary of findings	Overall quality
8. What are the harms associated with antiviral treatment for HBV infection?	29 RCTs	Many studies were small, with few events	High	Many studies conducted outside of the United States/Europe	<p>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, <math>I^2=0\%</math>) or any adverse events (7 trials, RR 0.96, 95% CI 0.9 to 1.0, <math>I^2=0\%</math>). 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, <math>I^2=0\%</math>). Results were generally consistent across specific antiviral drugs.</p> <p>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, <math>I^2=0\%</math>) and withdrawal due to adverse events (RR 7.6, 95% CI 1.1 to 52, <math>I^2=38\%</math>) versus lamivudine.</p>	Fair
KQ 9. Do improvements in intermediate outcomes improve final health outcomes?	10 observational studies	<p>High variability in patient characteristics and outcomes evaluated</p> <p>No studies were good quality; three were poor quality and failed to address important confounders</p>	Moderate	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.	Ten observational studies found an association between various intermediate outcomes and clinical outcomes (death, hepatocellular carcinoma, or a composite clinical outcome), but variability in patient populations, intermediate and clinical outcomes evaluated, and methodological limitations make it difficult to draw strong conclusions. In some studies, results were not statistically significant.	Poor

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

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

### PsycINFO

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

## Vaccination and Clinical Outcomes - Key Question 4

### Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

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

### EBM Reviews - Cochrane Central Register of Controlled Trials

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

## Treatment (Key Questions 5, 6, 7)

### Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

- 1 Hepatitis B/dt, th or Hepatitis B, Chronic/dt, th
- 2 Hepatitis B virus/de
- 3 (hepatitis b or hbv).mp.
- 4 th.fs.

## Appendix A1. Search Strategies

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

### EBM Reviews - Cochrane Central Register of Controlled Trials

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

## Education or Counseling Supplemental Search – Key Question 7

### PsycINFO

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

## Harms of Treatment – Key Question 8

### Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

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

## Appendix A1. Search Strategies

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

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

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)

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

### Systematic Reviews – All Key Questions

EBM Reviews - Cochrane Database of Systematic Reviews

- 1 (hepatitis b or hbv).ti.
- 2 limit 1 to full systematic reviews
- 3 limit 1 to recently updated reviews
- 4 limit 1 to new reviews
- 5 or/2-4

Ovid MEDLINE(R) without Revisions

- 1 Hepatitis B virus/ or Hepatitis B/ or Hepatitis B, Chronic/ or hepatitis b.mp.
- 2 limit 1 to yr="2008 -Current"
- 3 limit 2 to evidence based medicine reviews
- 4 meta-analysis.mp. or exp Meta-Analysis/
- 5 (cochrane or medline).tw.
- 6 search\$.tw.
- 7 4 or 5 or 6
- 8 "Review Literature as Topic"/ or systematic review.mp.
- 9 7 or 8
- 10 2 and 9
- 11 3 or 10
- 12 limit 11 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
- 13 limit 12 to english language

## Appendix A2. Inclusion and Exclusion Criteria per Key Question

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

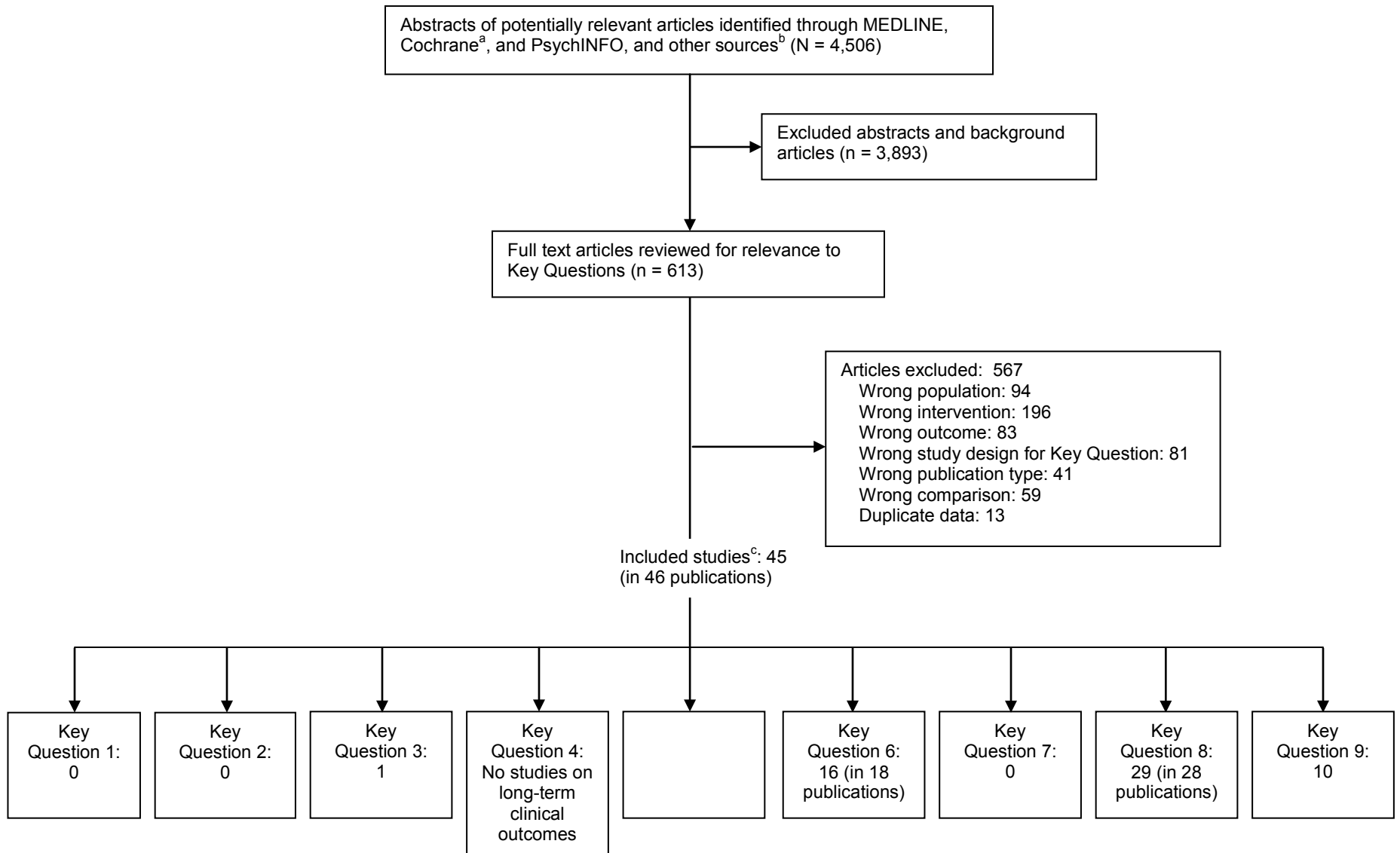
## Appendix A2. Inclusion and Exclusion Criteria per Key Question

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

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.



**Appendix A3. Literature Flow Diagram**



<sup>a</sup> Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

<sup>b</sup> Other sources include reference lists of relevant articles.

<sup>c</sup> Some studies are included for more than one Key Question.

## Appendix A4. Excluded Studies

### Wrong Population

Failure of specific immunotherapy in fulminant type B hepatitis. *Ann Intern Med.* 1977; 86(3):272-7.

Implementation of newborn hepatitis B vaccination--worldwide, 2006. *MMWR Morb Mortal Wkly Rep.* 2008; 57(46):1249-52.

Akhter MN, Stout C, Twiehaus JM. Hepatitis B screening and vaccination in a facility for the mentally retarded. *Mo Med.* 1985; 82(7):345-

Arulrajan A, Tyrie C, Phillips K, O'Connell S. Hepatitis B screening and immunization for people with a mental handicap in Southampton: Costs and benefits. *J Intellect Disabil Res.* 1992; 36(3):259-64.

Bayliss MS, Gandek B, Bungay KM, Sugano D, Hsu MA, Ware JE, Jr. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. *Qual Life Res.* 1998; 7(1):39-55.

Campos-Outcalt D. Hepatitis B virus screening in a high-risk college population. *J Am Coll Health.* 1985; 34(3):120-2.

Carreno V, Marcellin P, Hadziyannis S, Salmeron J, Diago M, Kitis GE, et al. Retreatment of chronic hepatitis B e antigen-positive patients with recombinant interferon alfa-2a. The European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology.* 1999; 30(1):277-82.

Cavanaugh JS, Awi D, Mendy M, Hill AVS, Whittle H, McConkey SJ. Partially randomized, non-blinded trial of DNA and MVA therapeutic Vaccines based on hepatitis B virus surface protein for chronic HBV infection. *PLoS ONE.* 2011; 6(2):e14626.

Chang MH. Impact of hepatitis B vaccination on hepatitis B disease and nucleic acid testing in high-prevalence populations. *J Clin Virol.* 2006; 36 Suppl 1:S45-50.

Chen DK, Yim C, O'Rourke K, Krajden M, Wong DK, Heathcote EJ. Long-term follow-up of a randomized trial of interferon therapy for chronic hepatitis B in a predominantly homosexual male population. *J Hepatol.* 1999; 30(4):557-63.

Chien R-N, Lin C-H, Liaw Y-F. The effect of lamivudine therapy in hepatic decompensation during

acute exacerbation of chronic hepatitis B. *J Hepatol.* 2003; 38(3):322-7.

Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med.* 2013; 158(11):807-20.

De Maria E, Gabrielli GB, Casaril M, Galiotto M, Dagradi R, Squarzone S, et al. Chronic viral hepatitis and interferon treatment: clinical experience in a series of 200 Italian patients. *J Chemother.* 1998; 10(2):173-5.

Denburg A, Rashid M, Brophy J, Curtis T, Malloy P, Audley J, et al. Initial health screening results for Karen refugees: a retrospective review. *Can Commun Dis Rep.* 2007; 33(13):16-22.

Dhillon S, Moore C, Li SD, Aziz A, Kakar A, Dosanjh A, et al. Efficacy of high-dose intra-dermal hepatitis B virus Vaccine in previous vaccination non-responders with chronic liver disease. *Dig Dis Sci.* 2012; 57(1):215-20.

Dore GJ, Cooper DA, Pozniak AL, DeJesus E, Zhong L, Miller MD, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfecting with HIV-1 and hepatitis B virus. *J Infect Dis.* 2004; 189(7):1185-92.

Etemadi J, Somi MH, Ardalan MR, Hashemi SSR, Soltani GG, Shoja MM. Prevalence and risk factors of hepatitis B infection among hemodialysis patients in Tabriz: a multicenter report. *Saudi J Kidney Dis Transpl.* 2012; 23(3):609-13.

Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2002. *Semin Dial.* 2005; 18(1):52-61.

Fisher A, Musini VM, Bassett K. Antiviral treatments for lamivudine-resistant chronic hepatitis B adult patients. *Cochrane Database Syst Rev.* 2009(4).

Flink HJ, Hansen BE, Heathcote EJ, Feinman SV, Simsek H, Karayalcin S, et al. Successful treatment with peginterferon alfa-2b of HBeAg-positive HBV non-responders to standard interferon or lamivudine. *Am J Gastroenterol.* 2006; 101(11):2523-9.

Fowler A, Sudhanva M, Zuckerman M. Hepatitis B screening in HIV-infected individuals. *AIDS.* 2005; 19(12):1338-9.

## Appendix A4. Excluded Studies

- Gilson RJ, Chopra KB, Newell AM, Murray-Lyon IM, Nelson MR, Rice SJ, et al. A placebo-controlled phase I/II study of adefovir dipivoxil in patients with chronic hepatitis B virus infection. *J Viral Hepat.* 1999 ; 6(5):387-95.
- Guenoc X, Narbonne V, Jousse-Joulin S, Devauchelle-Pensec V, Dougados M, Daures JP, et al. Is screening for hepatitis B and hepatitis C useful in patients with recent-onset polyarthritis? The ESPOIR cohort study. *J Rheumatol.* 2009; 36(7):1407-13.
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med.* 2005; 352(26):2673-81.
- Hashimoto Y, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, et al. Clinical and virological effects of long-term (over 5 years) lamivudine therapy. *J Med Virol.* 2010; 82(4):684-91.
- Hezode C, Chevaliez S, Bouvier-Alias M, Roudot-Thoraval F, Brillet R, Zafrani E-S, et al. Efficacy and safety of adefovir dipivoxil 20 mg daily in HBeAg-positive patients with lamivudine-resistant hepatitis B virus and a suboptimal virological response to adefovir dipivoxil 10 mg daily. *J Hepatol.* 2007; 46(5):791-6.
- Idilman R, Cinar K, Seven G, Bozkus Y, Elhan A, Bozdayi M, et al. Hepatitis B surface antigen seroconversion is associated with favourable long-term clinical outcomes during lamivudine treatment in HBeAg-negative chronic hepatitis B patients. *J Viral Hepat.* 2012; 19(3):220-6.
- Jonas MM, Little NR, Gardner SD, Alonso EM, Alvarez F, Areias J, et al. Long-term lamivudine treatment of children with chronic hepatitis B: Durability of therapeutic responses and safety. *J Viral Hepat.* 2008; 15(1):20-7.
- Kanda Y, Shigeno K, Kinoshita N, Nakao K, Yano M, Matsuo H. Sudden hearing loss associated with interferon. *Lancet.* 1994; 343(8906):1134-5.
- Kim JH, Yim HJ, Jung ES, Jung YK, Seo YS, Yeon JE, et al. Virologic and biochemical responses to clevudine in patients with chronic HBV infection-associated cirrhosis: data at week 48. *J Viral Hepat.* 2011; 18(4):287-93.
- Kim WR, Terrault NA, Pedersen RA, Therneau TM, Edwards E, Hindman AA, et al. Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. *Gastroenterology.* 2009; 137(5):1680-6.
- Kumar M, Satapathy S, Monga R, Das K, Hissar S, Pande C, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. *Hepatology.* 2007; 45(1):97-101.
- Kundu SS, Kundu AK, Pal NK. Interferon-alpha in the treatment of acute prolonged hepatitis B virus infection. *J Assoc Physicians India.* 2000; 48(7):671-3.
- Manegold C, Hannoun C, Wywiol A, Dietrich M, Polywka S, Chiwakata CB, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis.* 2001; 32(1):144-8.
- Manolakopoulos S, Karatapanis S, Elefsiniotis J, Mathou N, Vlachogiannakos J, Iliadou E, et al. Clinical course of lamivudine monotherapy in patients with decompensated cirrhosis due to HBeAg negative chronic HBV infection. *Am J Gastroenterol.* 2004; 99(1):57-63.
- Matsue K, Aoki T, Odawara J, Fujiwara H, Iwama K-i, Kimura S-i, et al. High risk of hepatitis B-virus reactivation after hematopoietic cell transplantation in hepatitis B core antibody-positive patients. *Eur J Haematol.* 2009 ; 83(4):357-64.
- Matthews GV, Avihingsanon A, Lewin SR, Amin J, Rerknimitr R, Petcharapirat P, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfecting antiretroviral naive individuals in Thailand. *Hepatology.* 2008 ; 48(4):1062-9.
- Mazzella G, Accogli E, Sottili S, Festi D, Orsini M, Salzetta A, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. *J Hepatol.* 1996; 24(2):141-7.
- McCaughan G, Angus P, Bowden S, Shaw T, Breschkin A, Sheil R, et al. Retransplantation for precore mutant-related chronic hepatitis B infection: prolonged survival in a patient receiving sequential ganciclovir/famciclovir therapy. *Liver Transpl Surg.* 1996; 2(6):472-4.
- McDonald EM, Mann AH, Thomas HC. Interferons as mediators of psychiatric morbidity. *An*

## Appendix A4. Excluded Studies

investigation in a trial of recombinant alpha-interferon in hepatitis-B carriers. *Lancet*. 1987; 2(8569):1175-8.

McGory RW, Ishitani MB, Oliveira WM, Stevenson WC, Dickson RC, Caldwell SH, et al. Effects of fialuridine on hepatitis B immune globulin pharmacokinetics following orthotopic liver transplant for chronic hepatitis B viral-induced cirrhosis. *Transplant Proc*. 1995; 27(1):1213-4.

McPhee SJ, Nguyen T, Euler GL, Mock J, Wong C, Lam T, et al. Successful promotion of hepatitis B vaccinations among Vietnamese-American children ages 3 to 18: results of a controlled trial. *Pediatrics*. 2003; 111(6 Pt 1):1278-88.

Medeiros RH, Figueiredo AEP, Poli-de-Figueiredo CE, d'Avila DO, de los Santos CA. Low response to intradermal hepatitis B vaccination in incident hemodialysis patients. *J Bras Nefrol*. 2011; 33(1):45-9.

Mederacke I, Yurdaydin C, Groshennig A, Erhardt A, Cakaloglu Y, Yalcin K, et al. Renal function during treatment with adefovir plus peginterferon alfa-2a vs either drug alone in hepatitis B/D co-infection. *J Viral Hepat*. 2012; 19(6):387-95.

Micozkadioglu H, Zumurtdal A, Torun D, Sezer S, Ozdemir FN, Haberal M. Low dose intradermal vaccination is superior to high dose intramuscular vaccination for hepatitis B in unresponsive hemodialysis patients. *Ren Fail*. 2007; 29(3):285-8.

Mittal SK, Rao S, Kumari S, Aggarwal V, Prakash C, Thirupuram S. Simultaneous administration of hepatitis B Vaccine with other E.P.I. Vaccines. *Indian J Pediatr*. 1994; 61(2):183-8.

Mitwalli A. Responsiveness to hepatitis B Vaccine in immunocompromised patients by doubling the dose scheduling. *Nephron*. 1996; 73(3):417-20.

Mok Q, Underhill G, Wonke B, Aldouri M, Kelsey M, Jefferies D. Intradermal hepatitis B Vaccine in thalassaemia and sickle cell disease. *Arch Dis Child*. 1989; 64(4):535-40.

Molina J, Bartolome J, Moraleta G, Ruiz-Moreno M, Rua MJ, Moreno A, et al. Persistence of hepatitis B virus DNA after reduction of viral replication in serum and liver. *J Med Virol*. 1992 ; 38(1):11-5.

Monteon FJ, Contreras AM, Espinoza L, Vazquez G, Aguilar S, Cueva L. Interferon alfa-2b in renal

transplant recipients with viral chronic hepatitis: a pilot study. *Transplant Proc*. 1996; 28(6):3306-8.

Moses SE, Lim ZY, Sudhanva M, Devereux S, Ho AYL, Pagliuca A, et al. Lamivudine prophylaxis and treatment of hepatitis B Virus-exposed recipients receiving reduced intensity conditioning hematopoietic stem cell transplants with alemtuzumab. *J Med Virol*. 2006; 78(12):1560-3.

Mu S-C, Wang G-M, Jow G-M, Chen B-F. Impact of universal vaccination on intrafamilial transmission of hepatitis B virus. *J Med Virol*. 2011; 83(5):783-90.

Nagamatsu H, Itano S, Nagaoka S, Akiyoshi J, Matsugaki S, Kurogi J, et al. Prophylactic lamivudine administration prevents exacerbation of liver damage in HBe antigen positive patients with hepatocellular carcinoma undergoing transhepatic arterial infusion chemotherapy. *Am J Gastroenterol*. 2004; 99(12):2369-75.

Nam S-W, Bae S-H, Lee S-W, Kim Y-S, Kang S-B, Choi J-Y, et al. Short-term overlap lamivudine treatment with adefovir dipivoxil in patients with lamivudine-resistant chronic hepatitis B. *World J Gastroenterol*. 2008; 14(11):1781-4.

Nardiello S, Gargiulo M, Pizzella T, Digilio L, Di Ottavio L, Galanti B. Relation of changes in hepatitis B virus replication markers to the outcome of interferon treatment in patients with chronic hepatitis. *J Chemother*. 1992; 4(2):95-8.

Narkewicz MR, Smith D, Silverman A, Vierling J, Sokol RJ. Clearance of chronic hepatitis B virus infection in young children after alpha interferon treatment. *J Pediatr*. 1995; 127(5):815-8.

Neudorf-Grauss R, Bujanover Y, Dinari G, Broide E, Neveh Y, Zahavi I, et al. Chronic hepatitis B virus in children in Israel: clinical and epidemiological characteristics and response to interferon therapy. *Isr Med Assoc J*. 2000; 2(2):164-8.

Niederhauser C, Mansouri Taleghani B, Graziani M, Stolz M, Tinguely C, Schneider P. Blood donor screening: how to decrease the risk of transfusion-transmitted hepatitis B virus? *Swiss Med Wkly*. 2008; 138(9-10):134-41.

Nikolaidis N, Vassiliadis T, Giouleme O, Tziomalos K, Grammatikos N, Patsiaoura K, et al. Effect of lamivudine treatment in patients with decompensated cirrhosis due to anti-HBe positive/HBeAg-negative

## Appendix A4. Excluded Studies

- chronic hepatitis B. *Clin Transplant*. 2005; 19(3):321-6.
- Novack L, Sarov B, Goldman-Levi R, Yahalom V, Safi J, Soliman H, et al. Impact of pooling on accuracy of hepatitis B virus surface antigen screening of blood donations. *Trans R Soc Trop Med Hyg*. 2008; 102(8):787-92.
- Ozgenç F, Arikian C, Sertoz RY, Nart D, Aydogdu S, Yagci RV. Effect of long-term lamivudine in chronic hepatitis B virus-infected children. *Antivir Ther*. 2004; 9(5):729-32.
- Pallier C, Rodriguez C, Brillet R, Nordmann P, Hezode C, Pawlotsky J-M. Complex dynamics of hepatitis B virus resistance to adefovir. *Hepatology*. 2009; 49(1):50-9.
- Pan CQ, Hu KQ, Yu AS, Chen W, Bunchorntavakul C, Reddy KR. Response to tenofovir monotherapy in chronic hepatitis B patients with prior suboptimal response to entecavir. *J Viral Hepat*. 2012; 19(3):213-9.
- Papaevangelou G, Roumeliotou-Karayannis A, Tassopoulos N, Kolaitis N, Contoyannis P, Krugman S. Post-exposure hepatitis B vaccination of sexual partners of acute viral hepatitis patients. *The Journal of infection*. 1983; 7(1):63-7.
- Park JW, Kim HS, Seo DD, Jang JS, Shin WG, Kim KH, et al. Long-term efficacy of entecavir in adefovir-refractory chronic hepatitis B patients with prior lamivudine resistance. *J Viral Hepat*. 2011 ; 18(10):e475-81.
- Park SJ, Paik SW, Choi MS, Lee JH, Koh KC, Kim SJ, et al. Is lamivudine with 1-week HBIg as effective as long-term high-dose HBIg in HBV prophylaxis after liver transplantation? *Transplant Proc*. 2002; 34(4):1252-4.
- Patterson SJ, George J, Strasser SI, Lee AU, Sievert W, Nicoll AJ, et al. Tenofovir disoproxil fumarate rescue therapy following failure of both lamivudine and adefovir dipivoxil in chronic hepatitis B. *Gut*. 2011; 60(2):247-54.
- Pei S-N, Chen C-H, Lee C-M, Wang M-C, Ma M-C, Hu T-H, et al. Reactivation of hepatitis B virus following rituximab-based regimens: a serious complication in both HBsAg-positive and HBsAg-negative patients. *Ann Hematol*. 2010; 89(3):255-62.
- Perrillo RP, Wright T, Rakela J, Levy G, Schiff E, Gish R, et al. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology*. 2001; 33(2):424-32.
- Perz JF, Elm JL, Jr., Fiore AE, Huggler JI, Kuhnert WL, Effler PV. Near elimination of hepatitis B virus infections among Hawaii elementary school children after universal infant hepatitis B vaccination. *Pediatrics*. 2006; 118(4):1403-8.
- Porres JC, Mora I, Gutierrez J, Bartolome J, Quiroga JA, Bas C, et al. Antiviral effect of recombinant gamma interferon in chronic hepatitis B virus infection: a pilot study. *HepatoGastroenterology*. 1988; 35(1):5-9.
- Preziati D, La Rosa L, Covini G, Marcelli R, Rescalli S, Persani L, et al. Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. *Eur J Endocrinol*. 1995; 132(5):587-93.
- Qin H, Li H, Xing M, Wu C, Li G, Song J. Nutritional support treatment for severe chronic hepatitis and posthepatitic cirrhosis. *J Huazhong Univ Sci Technolog Med Sci*. 2006; 26(2):217-20.
- Roumeliotou-Karayannis A, Papaevangelou G, Tassopoulos N, Richardson SC, Krugman S. Post-exposure active immunoprophylaxis of spouses of acute viral hepatitis B patients. *Vaccine*. 1985; 3(1):31-4.
- Schiff ER, Dienstag JL, Karayalcin S, Grimm IS, Perrillo RP, Husa P, et al. Lamivudine and 24 weeks of lamivudine/interferon combination therapy for hepatitis B e antigen-positive chronic hepatitis B in interferon nonresponders. *J Hepatol*. 2003; 38(6):818-26.
- Schmilovitz-Weiss H, Ben-Ari Z, Sikuler E, Zuckerman E, Sbeit W, Ackerman Z, et al. Lamivudine treatment for acute severe hepatitis B: a pilot study.[Erratum appears in *Liver Int*. 2005; 25(1):196]. *Liver Int*. 2004; 24(6):547-51.
- Sherman M, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianciara J, et al. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. *Gastroenterology*. 2006; 130(7):2039-49.
- Summers PR, Biswas MK, Pastorek JG, 2nd, Pernoll ML, Smith LG, Bean BE. The pregnant hepatitis B

## Appendix A4. Excluded Studies

carrier: evidence favoring comprehensive antepartum screening. *Obstet Gynecol.* 1987; 69(5):701-4.

Sun H-C, Tang Z-Y, Wang L, Qin L-X, Ma Z-C, Ye Q-H, et al. Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. *J Cancer Res Clin Oncol.* 2006; 132(7):458-65.

Toccaceli F, Rosati S, Scuderi M, Iacomi F, Picconi R, Laghi V. Leukocyte and platelet lowering by some interferon types during viral hepatitis treatment. *HepatoGastroenterology.* 1998; 45(23):1748-52.

Tsubota A, Arase Y, Suzuki Y, Suzuki F, Hosaka T, Akuta N, et al. Benefit of lamivudine therapy and factors associated with clinical outcome in spontaneous severe acute exacerbation of chronic hepatitis B virus infection. *Intervirology.* 2004; 47(6):335-41.

Tsubota A, Arase Y, Suzuki Y, Suzuki F, Sezaki H, Hosaka T, et al. Lamivudine monotherapy for spontaneous severe acute exacerbation of chronic hepatitis B. *J Gastroenterol Hepatol.* 2005; 20(3):426-32.

van Bommel F, de Man RA, Wedemeyer H, Deterding K, Petersen J, Buggisch P, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. *Hepatology.* 2010; 51(1):73-80.

van Bommel F, Zollner B, Sarrazin C, Spengler U, Huppe D, Moller B, et al. Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. *Hepatology.* 2006; 44(2):318-25.

van der Eijk AA, Hansen BE, Niesters HGM, Janssen HLA, van de Ende M, Schalm SW, et al. Viral dynamics during tenofovir therapy in patients infected with lamivudine-resistant hepatitis B virus mutants. *J Viral Hepat.* 2005; 12(4):364-72.

Van Thiel DH, Friedlander L, Kania RJ, Molloy PJ, Hassanein T, Wahlstrom E, et al. Lamivudine treatment of advanced and decompensated liver disease due to hepatitis B. *HepatoGastroenterology.* 1997; 44(15):808-12.

Vassilopoulos D, Apostolopoulou A, Hadziyannis E, Papatheodoridis GV, Manolakopoulos S, Koskinas J, et al. Long-term safety of anti-TNF treatment in

patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis.* 2010; 69(7):1352-5.

Wong DK, Yim C, Naylor CD, Chen E, Sherman M, Vas S, et al. Interferon alfa treatment of chronic hepatitis B: randomized trial in a predominantly homosexual male population. *Gastroenterology.* 1995; 108(1):165-71.

Wong VW-S, Wong GL-H, Tsang SW-C, Hui AY, Chim AM-L, Yiu KK-L, et al. Long-term follow-up of lamivudine treatment in patients with severe acute exacerbation of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B. *Antivir Ther.* 2008; 13(4):571-9.

Yagci M, Ozkurt ZN, Yegin ZA, Aki Z, Sucak GT, Haznedar R. Hepatitis B virus reactivation in HBV-DNA negative and positive patients with hematological malignancies. *Hematology.* 2010; 15(4):240-4.

Yao FY, Bass NM. Lamivudine treatment in patients with severely decompensated cirrhosis due to replicating hepatitis B infection. *J Hepatol.* 2000; 33(2):301-7.

Yildiz O, Aygen B, Demirturk N, Demirdal T, Inan D, Yildirmak T, et al. Lamivudine resistance mutations in patients infected with hepatitis B virus genotype D. *World J Gastroenterol.* 2011; 17(45):4987-92.

Yu J-W, Sun L-J, Zhao Y-H, Kang P, Li S-C. The study of efficacy of lamivudine in patients with severe acute hepatitis B. *Dig Dis Sci.* 2010; 55(3):775-83.

Zhang C-H, Xu G-L, Jia W-D, Li J-S, Ma J-L, Ge Y-S. Effects of interferon treatment on development and progression of hepatocellular carcinoma in patients with chronic virus infection: a meta-analysis of randomized controlled trials. *Int J Cancer.* 2011; 129(5):1254-64.

## Wrong Intervention

Steroids in chronic B-hepatitis. A randomized, double-blind, multinational trial on the effect of low-dose, long-term treatment on survival. A trial group of the European Association for the Study of the Liver. *Liver.* 1986; 6(4):227-32.

Akarca US, Ersoz G, Gunsar F, Karasu Z, Saritas E, Yuce G, et al. Interferon-lamivudine combination is

## Appendix A4. Excluded Studies

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

Alberti A, Fattovich G, Pontisso P, Brollo L, Belussi F, Ruol A. Interferon treatment of anti-HBe positive and HBV DNA positive chronic hepatitis B. *Chemioterapia.* 1988; 7(3):15-9.

Alexander GJ, Brahm J, Fagan EA, Smith HM, Daniels HM, Eddleston AL, et al. Loss of HBsAg with interferon therapy in chronic hepatitis B virus infection. *Lancet.* 1987; 2(8550):66-9.

Alexander GJ, Fagan EA, Guarner P, Rolando N, Brahm J, Eddleston AL, et al. A controlled trial of 6 months thrice weekly lymphoblastoid interferon versus no therapy in chronic hepatitis B virus infection. A preliminary analysis of the first 32 patients. *J Hepatol.* 1986; 3(2):S183-S8.

Alexander GJ, Fagan EA, Hegarty JE, Yeo J, Eddleston AL, Williams R. Controlled clinical trial of acyclovir in chronic hepatitis B virus infection. *J Med Virol.* 1987; 21(1):81-7.

Ambrosch F, Andre FE, Delem A, D'Hondt E, Jonas S, Kunz C, et al. Simultaneous vaccination against hepatitis A and B: results of a controlled study. *Vaccine.* 1992; 10 Suppl 1:S142-5.

Anderson MG, Harrison TJ, Alexander G, Zuckerman AJ, Murray-Lyon IM. Randomised controlled trial of lymphoblastoid interferon for chronic active hepatitis B. *Gut.* 1987; 28(5):619-22.

Anderson MG, Harrison TJ, Alexander GJ, Zuckerman AJ, Murray-Lyon IM. Randomised controlled trial of lymphoblastoid interferon for chronic active hepatitis B. *J Hepatol.* 1986; 3(2).

Badamchian M, Goldstein AL, Szein MB. Immune and neuroendocrine modulation with thymosins: current status of recent clinical trials in the United States. *Int J Neurosci.* 1990; 51(3-4):365-7.

Bahrani H, Daryani NE, Haghpanah B, Moayyeri A, Moghadam KF, Mirmomen S, et al. Effects of indomethacin on viral replication markers in asymptomatic carriers of hepatitis B: a randomized, placebo-controlled trial. *Am J Gastroenterol.* 2005; 100(4):856-61.

Barbara L, Mazzella G, Baraldini M, Gasbarrini G, Giungi F, Malavolti M, et al. A randomised controlled trial with human lymphoblastoid interferon

vs no treatment in chronic hepatitis B virus infection. Preliminary results. *J Hepatol.* 1986; 3(2).

Barbaro G, Zechini F, Pellicelli AM, Francavilla R, Scotto G, Bacca D, et al. Long-term efficacy of interferon alpha-2b and lamivudine in combination compared to lamivudine monotherapy in patients with chronic hepatitis B. An Italian multicenter, randomized trial. *J Hepatol.* 2001; 35(3):406-11.

Bassendine MF, Chadwick RG, Salmeron J, Shipton U, Thomas HC, Sherlock S. Adenine arabinoside therapy in HBsAg-positive chronic liver disease: a controlled study. *Gastroenterology.* 1981; 80(5 pt 1):1016-22.

Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. *Lancet.* 1981; 2(8256):1129-33.

Benvegnu L, Chemello L, Noventa F, Fattovich G, Pontisso P, Alberti A. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. *Cancer.* 1998; 83(5):901-9.

Berk L, Schalm SW, de Man RA, Heytink RA, Berthelot P, Brechot C, et al. Failure of acyclovir to enhance the antiviral effect of alpha lymphoblastoid interferon on HBe-seroconversion in chronic hepatitis B. A multi-centre randomized controlled trial. *J Hepatol.* 1992; 14(2-3):305-9.

Bissett J, Eisenberg M, Gregory P, Robinson WS, Merigan TC. Recombinant fibroblast interferon and immune interferon for treating chronic hepatitis B virus infection: patients' tolerance and the effect on viral markers. *J Infect Dis.* 1988; 157(5):1076-80.

Blum AL, Berthet P, Doelle W, Goebell H, Kortum K, Pelloni S, et al. Treatment of acute viral hepatitis with (+)-cyanidanol-3. *Lancet.* 1977; 2(8049):1153-5.

Bodenheimer HC, Jr., Schaffner F, Vernace S, Hirschman SZ, Goldberg JD, Chalmers T. Randomized controlled trial of quinacrine for the treatment of HBsAg-positive chronic hepatitis. *Hepatology.* 1983; 3(6):936-8.

Brissot P, Jacquelinet C, Jouanolle H, David V, Guyader D, Gueguen M, et al. Short-term prednisolone followed by recombinant human alpha-interferon alone or combined with adenine-arabinoside in chronic hepatitis B. A prospective and randomized trial. *J Hepatol.* 1991; 12(2):181-9.

## Appendix A4. Excluded Studies

- Brook MG, Chan G, Yap I, Karayiannis P, Lever AM, Jacyna M, et al. Randomised controlled trial of lymphoblastoid interferon alfa in Europid men with chronic hepatitis B virus infection. *BMJ*. 1989; 299(6700):652-6.
- Brook MG, Main J, Yap I, Chan G, Karayiannis P, Crossey M, et al. Short report: prednisolone withdrawal followed by lymphoblastoid interferon in the therapy of adult patients with presumed childhood-acquired chronic hepatitis B virus infection. *Aliment Pharmacol Ther*. 1993; 7(3):331-6.
- Brook MG, McDonald JA, Karayiannis P, Caruso L, Forster G, Harris JR, et al. Randomised controlled trial of interferon alfa 2A (rbe) (Roferon-A) for the treatment of chronic hepatitis B virus (HBV) infection: factors that influence response. *Gut*. 1989; 30(8):1116-22.
- Capalbo M, Palmisano L, Bonino F, Pellas C, Maset J. Intramuscular natural beta interferon in the treatment of chronic hepatitis B: a multicentre trial. Italian Hepatitis B Study Group. *Ital J Gastroenterol*. 1994; 26(5):238-41.
- Carreno V, Moreno A, Galiana F, Bartolome FJ. Alpha- and gamma-interferon versus alpha-interferon alone in chronic hepatitis B. A randomized controlled study. *J Hepatol*. 1993; 17(3):321-5.
- Carreno V, Porres JC, Mora I, Gutiez J, Quiroga JA, Ramon y Cajal S, et al. A controlled study of treatment with recombinant interferon alpha in chronic hepatitis B virus infection: induction and maintenance schedules. *Antiviral Res*. 1987 ; 8(3):125-37.
- Caselmann WH, Eisenburg J, Hofschneider PH, Koshy R. Beta- and gamma-interferon in chronic active hepatitis B. A pilot trial of short-term combination therapy. *Gastroenterology*. 1989; 96(2 Pt 1):449-55.
- Chan HL, Heathcote EJ, Marcellin P, Lai CL, Cho M, Moon YM, et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. *Ann Intern Med*. 2007; 147(11):745-54.
- Chan HL, Hui AY, Wong VW, Chim AM, Wong ML, Sung JJ. Long-term follow-up of peginterferon and lamivudine combination treatment in HBeAg-positive chronic hepatitis B. *Hepatology*. 2005; 41(6):1357-64.
- Chan HL, Leung NW, Hui AY, Wong VW, Liew CT, Chim AM, et al. A randomized, controlled trial of combination therapy for chronic hepatitis B: comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone. *Ann Intern Med*. 2005; 142(4):240-50.
- Chan HLY, Chen YC, Gane EJ, Sarin SK, Suh DJ, Piratvisuth T, et al. Randomized clinical trial: efficacy and safety of telbivudine and lamivudine in treatment-naive patients with HBV-related decompensated cirrhosis. *J Viral Hepat*. 2012 ; 19(10):732-43.
- Chan HL-Y, Wong VW-S, Chim AM-L, Choi PC-L, Chan H-Y, Hui AY, et al. Virological response to different combination regimes of peginterferon alpha-2b and lamivudine in hepatitis B e antigen positive chronic hepatitis B. *Antivir Ther*. 2007; 12(5):815-23.
- Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006; 295(1):65-73.
- Chung HT, Lok AS, Lai CL. Re-evaluation of alpha-interferon treatment of chronic hepatitis B using polymerase chain reaction. *J Hepatol*. 1993; 17(2):208-14.
- Cohen M. The efficacy of a peptide-nucleic acid solution (Reticulose) for the treatment of hepatitis A and hepatitis B--a preliminary controlled human clinical trial. *J R Soc Health*. 1992; 112(6):266-70.
- Combarrous F, Fouque D, Chossegros P, Bouliou R, Laville M, Zech P. Neurologic side-effects of ganciclovir. *Clin Nephrol*. 1994 ; 42(4):279-80.
- Csatary LK, Telegdy L, Gergely P, Bodey B, Bakacs T. Preliminary report of a controlled trial of MTH-68/B virus Vaccine treatment in acute B and C hepatitis: a phase II study. *Anti Cancer Res*. 1998; 18(2B):1279-82.
- De Man RA, Schalm SW, Heijtkink RA, Berk L, Den Ouden J, ten Kate FJ, et al. Long-term follow-up of antiviral combination therapy in chronic hepatitis B. *Am J Med*. 1988; 85(2A):150-4.
- Dehghan Nayeri N, Asadi Noghabi AA, Molaei S. The effect of telephone consultation on the quality of life of patients receiving interferon therapy: a quasi-experimental study. *Telemed J E Health*. 2012; 18(6):459-63.



## Appendix A4. Excluded Studies

- Di Bisceglie AM, Fong TL, Fried MW, Swain MG, Baker B, Korenman J, et al. A randomized, controlled trial of recombinant alpha-interferon therapy for chronic hepatitis B. *Am J Gastroenterol*. 1993; 88(11):1887-92.
- Dienstag JL, Stevens CE, Bhan AK, Szmuness W. Hepatitis B Vaccine administered to chronic carriers of hepatitis b surface antigen. *Ann Intern Med*. 1982; 96(5):575-9.
- Dusheiko GM, Paterson AC, Pitcher L, Kassianides C, DiBisceglie AM, Song E, et al. Recombinant leucocyte interferon treatment of chronic hepatitis B. An analysis of two therapeutic trials. *J Hepatol*. 1986; 3 Suppl 2:S199-207.
- Economou M, Manolakopoulos S, Trikalinos T-A, Filis S, Bethanis S, Tzourmakliotis D, et al. Interferon-alpha plus lamivudine vs lamivudine reduces breakthroughs, but does not affect sustained response in HBeAg negative chronic hepatitis B. *World J Gastroenterol*. 2005; 11(37):5882-7.
- Eyigung CP, Yilmaz S, Gul C, Sengul A, Hacibektasoglu A, Van Thiel DH. A comparative trial of two surface subunit recombinant hepatitis B Vaccines vs a surface and PreS subunit Vaccine for immunization of healthy adults. *J Viral Hepat*. 1998; 5(4):265-9.
- Fan X-H, Geng J-Z, Wang L-F, Zheng Y-Y, Lu H-Y, Li J, et al. De novo combination therapy with lamivudine and adefovir dipivoxil in chronic hepatitis B patients. *World J Gastroenterol*. 2011; 17(43):4804-9.
- Fattovich G, Brollo L, Boscaro S, Pontisso P, Giustina G, Criscuolo D, et al. Long-term effect of low dose recombinant interferon therapy in patients with chronic hepatitis B. *J Hepatol*. 1989; 9(3):331-7.
- Fattovich G, Brollo L, Pontisso P, Pornaro E, Rugge M, Alberti A, et al. Levamisole therapy in chronic type B hepatitis. Results of a double-blind randomized trial. *Gastroenterology*. 1986; 91(3):692-6.
- Fattovich G, Farci P, Rugge M, Brollo L, Mandas A, Pontisso P, et al. A randomized controlled trial of lymphoblastoid interferon-alpha in patients with chronic hepatitis B lacking HBeAg. *Hepatology*. 1992; 15(4):584-9.
- Fattovich G, Giustina G, Alberti A, Guido M, Pontisso P, Favarato S, et al. A randomized controlled trial of thymopentin therapy in patients with chronic hepatitis B. *J Hepatol*. 1994; 21(3):361-6.
- Fattovich G, Giustina G, Brollo L, Guido M, Pontisso P, Noventa F, et al. Therapy for chronic hepatitis B with lymphoblastoid interferon-alpha and levamisole. *Hepatology*. 1992; 16(5):1115-9.
- Feverly J, Elewaut A, Michielsens P, Nevens F, Van Eyken P, Adler M, et al. Efficacy of interferon alfa-2b with or without prednisone withdrawal in the treatment of chronic viral hepatitis B. A prospective double-blind Belgian-Dutch study. *J Hepatol*. 1990; 11(1).
- Flink HJ, Sprengers D, Hansen BE, van Zonneveld M, de Man RA, Schalm SW, et al. Flares in chronic hepatitis B patients induced by the host or the virus? Relation to treatment response during Peg-interferon {alpha}-2b therapy. *Gut*. 2005; 54(11):1604-9.
- Flink HJ, van Zonneveld M, Hansen BE, de Man RA, Schalm SW, Janssen HL. Treatment with Peg-interferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. *Am J Gastroenterol*. 2006; 101(2):297-303.
- Flisiak R, Prokopowicz D. Effect of misoprostol on the course of viral hepatitis B. *HepatoGastroenterology*. 1997; 44(17):1419-25.
- Garcia G, Smith CI, Weissberg JI, Eisenberg M, Bissett J, Nair PV, et al. Adenine arabinoside monophosphate (vidarabine phosphate) in combination with human leukocyte interferon in the treatment of chronic hepatitis B. A randomized, double-blinded, placebo-controlled trial. *Ann Intern Med*. 1987; 107(3):278-85.
- Hoofnagle JH, Davis GL, Pappas SC, Hanson RG, Peters M, Avigan MI, et al. A short course of prednisolone in chronic type B hepatitis. Report of a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1986; 104(1):12-7.
- Hoofnagle JH, Hanson RG, Minuk GY, Pappas SC, Schafer DF, Dusheiko GM, et al. Randomized controlled trial of adenine arabinoside monophosphate for chronic type B hepatitis. *Gastroenterology*. 1984; 86(1):150-7.
- 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

- interferon in patients with chronic hepatitis B. *Gastroenterology*. 1988; 95(5):1318-25.
- Itoh S, Marutani K, Matsuo S. Changes in ultrastructure of hepatocytes and liver test results before, during, and after treatment with interferon-beta in patients with HB(e)Ag-positive chronic active hepatitis. *Dig Dis Sci*. 1992; 37(8):1260-7.
- Jain S, Thomas HC, Oxford JS, Sherlock S. Trial of ribavirin for the treatment of HBsAg positive chronic liver disease. *J Antimicrob Chemother*. 1978; 4(4):367-73.
- Janssen HL, Berk L, Heijtkink RA, ten Kate FJ, Schalm SW. Interferon-alpha and zidovudine combination therapy for chronic hepatitis B: results of a randomized, placebo-controlled trial. *Hepatology*. 1993; 17(3):383-8.
- Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet*. 2005; 365(9454):123-9.
- Kaygusuz I, Ozturk Kaygusuz T, Ozturk A, Kilic SS, Karlidag T, Keles E, et al. Effects of interferon-alpha2b on hearing. *Int J Audiol*. 2004; 43(8):438-41.
- Kim YJ, Cho HC, Sinn DH, Gwak G-Y, Choi MS, Koh KC, et al. Frequency and risk factors of renal impairment during long-term adefovir dipivoxil treatment in chronic hepatitis B patients. *J Gastroenterol Hepatol*. 2012; 27(2):306-12.
- Kleiner DE, Gaffey MJ, Sallie R, Tsokos M, Nichols L, McKenzie R, et al. Histopathologic changes associated with fialuridine hepatotoxicity. *Mod Pathol*. 1997; 10(3):192-9.
- Krogsgaard K. The long-term effect of treatment with interferon-alpha 2a in chronic hepatitis B. The Long-Term Follow-up Investigator Group. The European Study Group on Viral Hepatitis (EUROHEP). Executive Team on Anti-Viral Treatment. *J Viral Hepat*. 1998; 5(6):389-97.
- Lai CL, Leung N, Teo EK, Tong M, Wong F, Hann HW, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology*. 2005; 129(2):528-36.
- Lam ET, Lam CL, Lai CL, Yuen MF, Fong DY, So TM. Health-related quality of life of Southern Chinese with chronic hepatitis B infection. *Health Qual Life Outcomes*. 2009; 7:52.
- Lau JY, Lai CL, Wu PC, Chung HT, Lok AS, Lin HJ. A randomised controlled trial of recombinant interferon-gamma in Chinese patients with chronic hepatitis B virus infection. *J Med Virol*. 1991; 34(3):184-7.
- Lee HS, Chung YH, Lee K, Byun KS, Paik SW, Han JY, et al. A 12-week clevudine therapy showed potent and durable antiviral activity in HBeAg-positive chronic hepatitis B. *Hepatology*. 2006; 43(5):982-8.
- Lee SD, Tong MJ, Wu JC, Lin HC, Tsai YT, Lo KJ. A randomised double-blind placebo-controlled trial of prednisolone therapy in HBeAg and HBV DNA positive Chinese patients with chronic active hepatitis B. *J Hepatol*. 1991; 12(2):246-50.
- Lee SU, Choi KH, Ha BJ, Suh SY, Han BH, Ku JY, et al. Effect of adenine arabinoside and alpha-interferon in patients with HBeAg-positive chronic active hepatitis. *Korean J Intern Med*. 1990; 5(1):1-4.
- Liaw YF, Lin SM, Chen TJ, Chien RN, Sheen IS, Chu CM. Beneficial effect of prednisolone withdrawal followed by human lymphoblastoid interferon on the treatment of chronic type B hepatitis in Asians: a randomized controlled trial. *J Hepatol*. 1994; 20(2):175-80.
- Liaw YF, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. *Hepatology*. 2011; 54(1):91-100.
- Lim SG, Krastev Z, Ng TM, Mechkov G, Kotzev IA, Chan S, et al. Randomized, double-blind study of emtricitabine (FTC) plus clevudine versus FTC alone in treatment of chronic hepatitis B. *Antimicrob Agents Chemother*. 2006; 50(5):1642-8.
- Lim SG, Ng TM, Kung N, Krastev Z, Volfova M, Husa P, et al. A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B. *Arch Intern Med*. 2006; 166(1):49-56.
- Lin SM, Tai DI, Chien RN, Sheen IS, Chu CM, Liaw YF. Comparison of long-term effects of lymphoblastoid interferon alpha and recombinant

## Appendix A4. Excluded Studies

- interferon alpha-2a therapy in patients with chronic hepatitis B. *J Viral Hepat.* 2004; 11(4):349-57.
- Liu JP, McIntosh H, Lin H. Chinese medicinal herbs for asymptomatic carriers of hepatitis B virus infection. *Cochrane Database Syst Rev.*2009(1).
- Liu JP, Wang J. Acupuncture for chronic hepatitis B virus infection. *Cochrane Database Syst Rev.*2009(1).
- Lok AS, Lai CL, Wu PC. Interferon therapy of chronic hepatitis B virus infection in Chinese. *J Hepatol.* 1986; 3(2):S209-15.
- Lok AS, Lai CL, Wu PC, Leung EK. Long-term follow-up in a randomised controlled trial of recombinant alpha 2-interferon in Chinese patients with chronic hepatitis B infection. *Lancet.* 1988; 2(8606):298-302.
- Lok AS, Wilson LA, Thomas HC. Neurotoxicity associated with adenine arabinoside monophosphate in the treatment of chronic hepatitis B virus infection. *J Antimicrob Chemother.* 1984; 14(1):93-9.
- Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med.* 2012; 156(4):271-8.
- Main J, Brown JL, Howells C, Galassini R, Crossey M, Karayiannis P, et al. A double blind, placebo-controlled study to assess the effect of famciclovir on virus replication in patients with chronic hepatitis B virus infection. *J Viral Hepat.* 1996; 3(4):211-5.
- Manolakopoulos S, Striki A, Deutsch M, Mela M, Ketikoglou I, Tzourmakliotis D, et al. Long-term adefovir plus lamivudine therapy does not decrease creatinine clearance in HBeAg-negative chronic hepatitis B patients. *Liver Int.* 2011; 31(10):1525-32.
- Manzillo G, Piccinino F, Sagnelli E, Izzo CM, Pasquale G, Maio G, et al. Treatment of HBsAg-positive chronic active hepatitis with corticosteroids and/or azathioprine. A prospective study. *Ric Clin Lab.* 1983; 13(2):261-8.
- Marcellin P, Lau GKK, Zeuzem S, Heathcote EJ, Pockros PJ, Reddy KR, et al. Comparing the safety, tolerability and quality of life in patients with chronic hepatitis B vs chronic hepatitis C treated with peginterferon alpha-2a. *Liver Int.* 2008; 28(4):477-85.
- Marcellin P, Mommeja-Marin H, Sacks SL, Lau GKK, Sereni D, Bronowicki J-P, et al. A phase II dose-escalating trial of clevudine in patients with chronic hepatitis B. *Hepatology.* 2004; 40(1):140-8.
- Marcellin P, Ouzan D, Degos F, Brechot C, Metman EH, Degott C, et al. Randomized controlled trial of adenine arabinoside 5'-monophosphate in chronic active hepatitis B: comparison of the efficacy in heterosexual and homosexual patients. *Hepatology.* 1989; 10(3):328-31.
- Marcellin P, Pouteau M, Lorient MA, Boyer N, Degos F, Cales P, et al. Adenine arabinoside 5'-monophosphate in patients with chronic hepatitis B: comparison of the efficacy in patients with high and low viral replication. *Gut.* 1995; 36(3):422-6.
- Martin J, Bosch O, Moraleta G, Bartolome J, Quiroga JA, Carreno V. Pilot study of recombinant human granulocyte-macrophage colony-stimulating factor in the treatment of chronic hepatitis B. *Hepatology.* 1993 ; 18(4):775-80.
- Martin P, Hann HW, Westerberg S, Munoz SJ, Rubin R, Maddrey WC. Interferon-alpha2b therapy is efficacious in Asian-Americans with chronic hepatitis B infection: a prospective controlled trial. *Dig Dis Sci.* 1998; 43(4):875-9.
- Mazzella G, Saracco G, Rizzetto M, Amed MA, Gonzalez Quintela A, Rosina F, et al. Human lymphoblastoid interferon for the treatment of chronic hepatitis B. A randomized controlled trial. *Am J Med.* 1988; 85(2A):141-2.
- Mazzella G, Villanova N, Abdu-Ahmed M, Barbara L, Saracco G, Rizzetto M, et al. Treatment of chronic hepatitis B with human lymphoblastoid interferon: results of a controlled trial. *Chemioterapia.* 1988; 7(3):12-4.
- Mellerup MT, Krogsgaard K, Gluud C. Glucocorticosteroids for viral hepatitis B. *Cochrane Database Syst Rev.* 2009(1).
- Mellerup MT, Krogsgaard K, Mathurin P, Gluud C, Poynard T. Sequential combination of glucocorticosteroids and alfa interferon versus alfa interferon alone for HBeAg-positive chronic hepatitis B. *Cochrane Database Syst Rev.*2009(1).
- Mendez-Navarro J, Corey KE, Zheng H, Barlow LL, Jang JY, Lin W, et al. Hepatitis B screening, prophylaxis and re-activation in the era of rituximab-based chemotherapy. *Liver Int.* 2011; 31(3):330-9.

## Appendix A4. Excluded Studies

- Merchant RC, Keshavarz R. Patterns in the offering of hepatitis B prophylaxis by US emergency department physicians. *Infect Control Hosp Epidemiol.* 2006; 27(7):764-6.
- Mihm U, Gartner BC, Faust D, Hofmann WP, Sarrazin C, Zeuzem S, et al. Viral kinetics in patients with lamivudine-resistant hepatitis B during adefovir-lamivudine combination therapy. *J Hepatol.* 2005; 43(2):217-24.
- Milazzo F, Galli M, Fassio PG, Cargnel A, Pugliese A, Tovo PA, et al. Attempted treatment of fulminant viral hepatitis with human fibroblast interferon. *Infection.* 1985; 13(3):130-3.
- Milne A, Hopkirk N, Lucas CR, Waldon J, Foo Y. Failure of New Zealand hepatitis B carriers to respond to *Phyllanthus amarus*. *N Z Med J.* 1994; 107(980):243.
- Mitsui F, Tsuge M, Kimura T, Kitamura S, Abe H, Saneto H, et al. Importance of serum concentration of adefovir for Lamivudine-adevovir combination therapy in patients with lamivudine-resistant chronic hepatitis B. *Antimicrob Agents Chemother.* 2010; 54(8):3205-11.
- Morrison DS, Gilchrist G. Prison admission health screening as a measure of health needs. *Health Bull (Edinb).* 2001; 59(2):114-9.
- Moschos M, Manesis E, Panagakis E, Brouzas D, Hadziyannis S, Theodossiadis G. The effect of low-dose interferon treatment on visual evoked potentials. *Doc Ophthalmol.* 1997; 94(3):215-21.
- Moucari R, Boyer N, Ripault MP, Castelnau C, Mackiewicz V, Dauvergne A, et al. Sequential therapy with adefovir dipivoxil and pegylated interferon alfa-2a for HBeAg-negative patients. *J Viral Hepat.* 2011; 18(8):580-6.
- Muller R, Klein H, Vido I, Niehoff G, Lautz HU, Gebel M, et al. Antiviral treatment in chronic hepatitis B. Data of 5 prospectively controlled randomized trials. *J Hepatol.* 1986; 3 Suppl 2:S217-23.
- Mutchnick MG, Appelman HD, Chung HT, Aragona E, Gupta TP, Cummings GD, et al. Thymosin treatment of chronic hepatitis B: a placebo-controlled pilot trial. *Hepatology.* 1991; 14(3):409-15.
- Mutimer D, Naoumov N, Honkoop P, Marinos G, Ahmed M, de Man R, et al. Combination alpha-interferon and lamivudine therapy for alpha-interferon-resistant chronic hepatitis B infection: results of a pilot study. *J Hepatol.* 1998; 28(6):923-9.
- Nair PV, Tong MJ, Kempf R, Co R, Lee SD, Venturi CL. Clinical, serologic, and immunologic effects of human leukocyte interferon in HBsAg-positive primary hepatocellular carcinoma. *Cancer.* 1985; 56(5):1018-22.
- Niederau C, Heintges T, Niederau M, Stremmel W, Strohmeyer G. Prospective randomized controlled trial of sequential treatment with corticoids and alpha-interferon versus treatment with interferon alone in patients with chronic active hepatitis B. *Eur J Med.* 1992; 1(7):396-402.
- Niro GA, Fontana R, Gioffreda D, Fiorella S, Accadia L, Iacobellis A, et al. Sequential treatment with lamivudine and alpha-interferon in anti-HBe-positive chronic hepatitis B patients: a pilot study. *Dig Liver Dis.* 2007; 39(9):857-63.
- Papadopoulos VP, Chrysagis DN, Protopapas AN, Goulis IG, Dimitriadis GT, Mimidis KP. Peginterferon alfa-2b as monotherapy or in combination with lamivudine in patients with HBeAg-negative chronic hepatitis B: a randomised study. *Med Sci Monit.* 2009; 15(2):CR56-61.
- Pastore G, Santantonio T, Milella M, Monno L, Mariano N, Moschetta R, et al. Anti-HBe-positive chronic hepatitis B with HBV-DNA in the serum response to a 6-month course of lymphoblastoid interferon. *J Hepatol.* 1992; 14(2-3):221-5.
- Pastore G, Santantonio T, Monno L, Milella M, Luchena N, Angarano G. Permanent inhibition of viral replication induced by low dosage of human leukocyte interferon in patients with chronic hepatitis B. *HepatoGastroenterology.* 1988; 35(2):57-61.
- Perez V, Findor J, Tanno H, Sorda J. A controlled trial of high dose interferon, alone and after prednisone withdrawal, in the treatment of chronic hepatitis B: long term follow up. *Gut.* 1993; 34(2 Suppl):S91-4.
- Perrillo R, Hann HW, Mutimer D, Willems B, Leung N, Lee WM, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology.* 2004; 126(1):81-90.
- Perrillo RP. The use of corticosteroids in conjunction with antiviral therapy in chronic hepatitis B with

## Appendix A4. Excluded Studies

ongoing viral replication. *J Hepatol.* 1986; 3 Suppl 2:S57-64.

Perrillo RP, Regenstein FG, Bodicky CJ, Campbell CR, Sanders GE, Sunwoo YC. Comparative efficacy of adenine arabinoside 5' monophosphate and prednisone withdrawal followed by adenine arabinoside 5' monophosphate in the treatment of chronic active hepatitis type B. *Gastroenterology.* 1985; 88(3):780-6.

Perrillo RP, Regenstein FG, Peters MG, DeSchryver-Kecskemeti K, Bodicky CJ, Campbell CR, et al. Prednisone withdrawal followed by recombinant alpha interferon in the treatment of chronic type B hepatitis. A randomized, controlled trial. *Ann Intern Med.* 1988; 109(2):95-100.

Peters MG, Hann Hw H, Martin P, Heathcote EJ, Buggisch P, Rubin R, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology.* 2004; 126(1):91-101.

Petersen J, Ratziu V, Buti M, Janssen HLA, Brown A, Lampertico P, et al. Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: an international multicenter cohort study. *J Hepatol.* 2012; 56(3):520-6.

Piccolo P, Lenci I, Demelia L, Bandiera F, Piras MR, Antonucci G, et al. A randomized controlled trial of pegylated interferon-alpha2a plus adefovir dipivoxil for hepatitis B e antigen-negative chronic hepatitis B. *Antivir Ther.* 2009; 14(8):1165-74.

Pol S, Couillin I, Michel ML, Driss F, Nalpas B, Carnot F, et al. Immunotherapy of chronic hepatitis B by anti HBV Vaccine. *Acta Gastroenterol Belg.* 1998; 61(2):228-33.

Pol S, Nalpas B, Driss F, Michel ML, Tiollais P, Denis J, et al. Efficacy and limitations of a specific immunotherapy in chronic hepatitis B. *J Hepatol.* 2001; 34(6):917-21.

Porres JC, Carreno V, Mora I, Gutiez J, Moreno A, Ramon y Cajal S, et al. Different doses of recombinant alpha interferon in the treatment of chronic hepatitis B patients without antibodies against the human immunodeficiency virus. *HepatoGastroenterology.* 1988; 35(6):300-3.

Qian MYY, Yuwei J R, Angus P, Schelleman T, Johnson L, Gow P. Efficacy and cost of a hepatocellular carcinoma screening program at an

Australian teaching hospital. *J Gastroenterol Hepatol.* 2010; 25(5):951-6.

Realdi G, Fattovich G, Pastore G, Caredda F, Noventa F, Santantonio T, et al. Problems in the management of chronic hepatitis B with interferon: experience in a randomized, multicentre study. *J Hepatol.* 1990; 11 Suppl 1:S129-32.

Reichen J, Bianchi L, Frei PC, Male PJ, Lavanchy D, Schmid M. Efficacy of steroid withdrawal and low-dose interferon treatment in chronic active hepatitis B. Results of a randomized multicenter trial. Swiss Association for the Study of the Liver. *J Hepatol.* 1994; 20(2):168-74.

Ren F-Y, Jin H, Piao X-X, Piao F-S. Ribavirin and IFN-alpha combination therapy induces CD4+ T-cell proliferation and Th1 cytokine secretion in patients with chronic hepatitis B. *World J Gastroenterol.* 2007; 13(41):5440-5.

Robson SC, Brice E, van Rensburg C, Kannemeyer J, Hift RJ, Kirsch RE. Safety and efficacy of interferon alpha-2b following prednisone withdrawal in the treatment of chronic viral hepatitis B. A case-controlled, randomised study. *S Afr Med J.* 1992; 82(5):317-20.

Rodriguez-Inigo E, Bartolome J, Lopez-Alcorocho JM, Contonat T, Oliva H, Carreno V. Activation of liver disease in healthy hepatitis B surface antigen carriers during interferon-alpha treatment. *J Med Virol.* 1997; 53(1):76-80.

Romeo F, Palmisano L, Arcoria D. Thymostimulin in the treatment of hepatitis B surface antigen-positive chronic active hepatitis. Controlled clinical trial--two years follow-up. *Arzneimittelforschung.* 1987; 37(4):450-6.

Rumi M, Romeo R, De Filippi F, Marcelli R, Del Ninno E, van Eyken P, et al. A multicentre randomized clinical trial of recombinant alpha-2a interferon therapy in patients with chronic hepatitis B. *Ital J Gastroenterol.* 1993; 25(3):117-20.

Ryu HJ, Lee JM, Ahn SH, Kim DY, Lee MH, Han K-H, et al. Efficacy of adefovir add-on lamivudine rescue therapy compared with switching to entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. *J Med Virol.* 2010; 82(11):1835-42.

## Appendix A4. Excluded Studies

- Saconato H, Atallah AN, Souza GM, Parise ER. Thymosin alpha1 for chronic hepatitis B. *Cochrane Database Syst Rev*.2009(1).
- Saconato H, Souza GM, Atallah AN, Parise ER. Foscarnet for chronic hepatitis B. *Cochrane Database Syst Rev*.2009(1).
- Sagnelli E, Piccinino F, Manzillo G, Felaco FM, Filippini P, Maio G, et al. Effect of immunosuppressive therapy on HBsAg-positive chronic active hepatitis in relation to presence or absence of HBeAg and anti-HBe. *Hepatology*. 1983; 3(5):690-5.
- Sangfelt P, Uhnoo I, Hollander A, Lindh G, Weiland O. Lamivudine and famciclovir combination therapy with or without addition of interferon-alpha-2b for HBeAg-positive chronic hepatitis B: a pilot study. *Scand J Infect Dis*. 2002; 34(7):505-11.
- Santantonio T, Niro GA, Sinisi E, Leandro G, Insalata M, Guastadisegni A, et al. Lamivudine/interferon combination therapy in anti-HBe positive chronic hepatitis B patients: a controlled pilot study. *J Hepatol*. 2002; 36(6):799-804.
- Saracco G, Mazzella G, Rosina F, Cancellieri C, Lattore V, Raise E, et al. A controlled trial of human lymphoblastoid interferon in chronic hepatitis B in Italy. *Hepatology*. 1989; 10(3):336-41.
- Sarin SK, Kumar M, Kumar R, Kazim SN, Guptan RC, Sakhuja P, et al. Higher efficacy of sequential therapy with interferon-alpha and lamivudine combination compared to lamivudine monotherapy in HBeAg positive chronic hepatitis B patients. *Am J Gastroenterol*. 2005; 100(11):2463-71.
- Saruc M, Ozden N, Turkel N, Ayhan S, Hock LM, Tuzcuoglu I, et al. Long-term outcomes of thymosin-alpha 1 and interferon alpha-2b combination therapy in patients with hepatitis B e antigen (HBeAg) negative chronic hepatitis B. *J Pharm Sci*. 2003; 92(7):1386-95.
- Schalm SW. Treatment of chronic hepatitis B with a combination of acyclovir and human lymphoblastoid interferon. *Chemioterapia*. 1988; 7(3):26-9.
- Schalm SW, Heathcote J, Cianciara J, Farrell G, Sherman M, Willems B, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. *Gut*. 2000; 46(4):562-8.
- Schalm SW, Heijtkink RA. Spontaneous disappearance of viral replication and liver cell inflammation in HBsAg-positive chronic active hepatitis: results of a placebo vs. interferon trial. *Hepatology*. 1982; 2(6):791-4.
- Schalm SW, Heytink RA, van Buuren HR, de Man RA. Acyclovir enhances the antiviral effect of interferon in chronic hepatitis B. *Lancet*. 1985; 2(8451):358-60.
- Schattner A, Revel M. Interferon treatment for hepatitis. *Isr J Med Sci*. 1989; 25(7):357-9.
- Scotto G, Palumbo E, Fazio V, Cibelli DC, Saracino A, Angarano G. Efficacy and tolerability of lamivudine alone versus lamivudine plus alpha-interferon for treatment of chronic active hepatitis B in patients with a precore-mutant variant. *Infez Med*. 2006; 14(3):145-51.
- Scully LJ, Shein R, Karayiannis P, McDonald JA, Thomas HC. Lymphoblastoid interferon therapy of chronic HBV infection. A comparison of 12 vs. 24 weeks of thrice weekly treatment. *J Hepatol*. 1987; 5(1):51-8.
- Senturk H, Tabak F, Ozaras R, Erdem L, Canbakan B, Mert A, et al. Efficacy of pre-S-containing HBV Vaccine combined with lamivudine in the treatment of chronic HBV infection. *Dig Dis Sci*. 2009; 54(9):2026-30.
- Shi M, Wang RS, Zhang H, Zhu YF, Han B, Zhang Y, et al. Sequential treatment with lamivudine and interferon-alpha monotherapies in hepatitis B e antigen-negative Chinese patients and its suppression of lamivudine-resistant mutations. *J Antimicrob Chemother*. 2006; 58(5):1031-5.
- Sjogren MH, Hoofnagle JH, Waggoner JG. Effect of corticosteroid therapy on levels of antibody to hepatitis B core antigen in patients with chronic type B hepatitis. *Hepatology*. 1987; 7(3):582-5.
- Smith CI, Kitchen LW, Scullard GH, Robinson WS, Gregory PB, Merigan TC. Vidarabine monophosphate and human leukocyte interferon in chronic hepatitis B infection. *JAMA*. 1982; 247(16):2261-5.
- Soloway RD, Summerskill WH, Baggenstoss AH, Geall MG, Gitnick GL, Elveback IR, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of

## Appendix A4. Excluded Studies

- treatments and early prognosis. *Gastroenterology*. 1972; 63(5):820-33.
- Song JW, Zhang G, Lin JG, Tang WX, Lin JS. [Clinical study of lamivudine and interferon combinate administration to inhibit hepatitis B virus replication]. *Zhonghua Gan Zang Bing Za Zhi*. 2004 ; 12(10):593-6.
- Sun X, Qin W, Zhou R, Wang L, Li Y, Zhao L. Effect of conventional interferon- in patients with HBeAg-positive chronic hepatitis B: a systematic review and meta-analysis. *J Evid Based Med*. 2010; 3(4):220-5.
- Suzuki H, Yamamoto S, Hirayama C, Takino T, Fujisawa K, Oda T. Cianidanol therapy for HBe-antigen-positive chronic hepatitis: a multicentre, double-blind study. *Liver*. 1986; 6(1):35-44.
- Takkenberg B, Terpstra V, Zaaier H, Weegink C, Dijkgraaf M, Jansen P, et al. Intrahepatic response markers in chronic hepatitis B patients treated with peginterferon alpha-2a and adefovir. *J Gastroenterol Hepatol*. 2011 ; 26(10):1527-35.
- Tanaka H, Shiota G, Kawasaki H. Interferon-alpha therapy alters glucose metabolism in patients with chronic hepatitis B. *J Med*. 1997; 28(5-6):325-34.
- Tangkijvanich P, Thong-ngam D, Mahachai V, Kladchareon N, Suwangool P, Kullavanijaya P. Long-term effect of interferon therapy on incidence of cirrhosis and hepatocellular carcinoma in Thai patients with chronic hepatitis B. *Southeast Asian J Trop Med Public Health*. 2001; 32(3):452-8.
- Tassopoulos NC, Koutelou MG, Polychronaki H, Paraloglou-Ioannides M, Hadziyannis SJ. Recombinant interferon-alpha therapy for acute hepatitis B: a randomized, double-blind, placebo-controlled trial. *J Viral Hepat*. 1997; 4(6):387-94.
- Teran JC, Mullen KD, Hoofnagle JH, McCullough AJ. Decrease in serum levels of markers of hepatic connective tissue turnover during and after treatment of chronic hepatitis B with interferon-alpha. *Hepatology*. 1994; 19(4):849-56.
- Teuber G, Dienes HP, Meyer Zum Buschenfelde KH, Gerken G. Long-term follow-up of patients with chronic hepatitis B after interferon treatment. *Z Gastroenterol*. 1996; 34(4):230-6.
- Thomas HC, Lok AS, Carreno V, Farrell G, Tanno H, Perez V, et al. Comparative study of three doses of interferon-alpha 2a in chronic active hepatitis B. The International Hepatitis Trial Group. *J Viral Hepat*. 1994; 1(2):139-48.
- Tine F, Liberati A, Craxi A, Almasio P, Pagliaro L. Interferon treatment in patients with chronic hepatitis B: a meta-analysis of the published literature. *J Hepatol*. 1993; 18(2):154-62.
- Trepo C, Rougier P, Bizollon T, Poupon R, Zarski JP, Quinton A, et al. Combination therapy with ARA-AMP and interferon of chronic active hepatitis B. Interim analysis of an ongoing study. *J Hepatol*. 1991; 13(1):S3.
- Truong BX, Seo Y, Kato M, Hamano K, Ninomiya T, Katayama M, et al. Long-term follow-up of Japanese patients with chronic hepatitis B treated with interferon-alpha. *Int J Mol Med*. 2005; 16(2):279-84.
- van Zonneveld M, Flink HJ, Verhey E, Senturk H, Zeuzem S, Akarca US, et al. The safety of pegylated interferon alpha-2b in the treatment of chronic hepatitis B: predictive factors for dose reduction and treatment discontinuation. *Aliment Pharmacol Ther*. 2005; 21(9):1163-71.
- van Zonneveld M, Zondervan PE, Cakaloglu Y, Simon C, Akarca US, So TM, et al. Peg-interferon improves liver histology in patients with HBeAg-positive chronic hepatitis B: no additional benefit of combination with lamivudine. *Liver Int*. 2006; 26(4):399-405.
- Vandepapeliere P, Lau GKK, Leroux-Roels G, Horsmans Y, Gane E, Tawandee T, et al. Therapeutic vaccination of chronic hepatitis B patients with virus suppression by antiviral therapy: a randomized, controlled study of co-administration of HBsAg/AS02 candidate *Vaccine* and lamivudine. *Vaccine*. 2007; 25(51):8585-97.
- Waked I, Amin M, Abd-el Fattah SA, Osman L, Sabbour M. Interferon in chronic active hepatitis B. Preliminary results. *Chemioterapia*. 1988; 7(3):198-202.
- Wang X-Y, Zhang X-X, Yao X, Jiang J-H, Xie Y-H, Yuan Z-H, et al. Serum HBeAg sero-conversion correlated with decrease of HBsAg and HBV DNA in chronic hepatitis B patients treated with a therapeutic *Vaccine*. *Vaccine*. 2010; 28(51):8169-74.
- Weimar W, Heijtkink RA, ten Kate FJ, Schalm SW, Masurel N, Schellekens H, et al. Double-blind study

## Appendix A4. Excluded Studies

of leucocyte interferon administration in chronic HBsAg-positive hepatitis. *Lancet*. 1980; 1(8164):336-8.

Weller IV. A randomised controlled trial of adenine arabinoside 5'-monophosphate (ARA-AMP) in chronic hepatitis B virus infection. *J Hepatol*. 1986; 3 Suppl 2:S107-10.

Weller IV, Carreno V, Fowler MJ, Monjardino J, Makinen D, Varghese Z, et al. Acyclovir in hepatitis B antigen-positive chronic liver disease: inhibition of viral replication and transient renal impairment with iv bolus administration. *J Antimicrob Chemother*. 1983; 11(3):223-31.

Weller IV, Lok AS, Mindel A, Karayiannis P, Galpin S, Monjardino J, et al. Randomised controlled trial of adenine arabinoside 5'-monophosphate (ARA-AMP) in chronic hepatitis B virus infection. *Gut*. 1985; 26(7):745-51.

Whitfield K, Stoeckl SL, Skoog M, Lindschou Hansen J, Mumtaz K, Gluud C. Levamisole for chronic hepatitis B. *Cochrane Database Syst Rev*.2010(11).

Williams SJ, Craig PI, Cooksley WG, Bye WA, Bilous M, Grierson JM, et al. Randomised controlled trial of recombinant human interferon -alpha A for chronic active hepatitis B. *Aust N Z J Med*. 1990; 20(1):9-19.

Wong DK, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med*. 1993; 119(4):312-23.

Wu T, Roger H, Xie L, Liu G, Hao B. Bicyclol for chronic hepatitis B. *Cochrane Database Syst Rev*. 2006(4):CD004480.

Wu T, Xie L, Liu GJ, Hao B, Harrison RA. Bicyclol for chronic hepatitis B. *Cochrane Database Syst Rev*.2009(1).

Xia Y, Han M, Liu PJ, Gluud C. Glycyrrhizin for chronic hepatitis B virus infection. *Cochrane Database Syst Rev*.2011(1).

Xia Y, Liu PJ, Gluud C. Glycyrrhizin versus antiviral drugs for chronic hepatitis B virus infection. *Cochrane Database Syst Rev*.2011(2).

Yalcin K, Danis R, Degertekin H, Alp MN, Tekes S, Budak T. The lack of effect of therapeutic

vaccination with a pre-S2/S HBV Vaccine in the immune tolerant phase of chronic HBV infection. *J Clin Gastroenterol*. 2003; 37(4):330-5.

Yalcin K, Degertekin H, Yildiz F, Celik Y. Comparison of 12-month courses of interferon-alpha-2b-lamivudine combination therapy and interferon-alpha-2b monotherapy among patients with untreated chronic hepatitis B. *Clin Infect Dis*. 2003; 36(12):1516-22.

Yang H-J, Lee J-H, Kim YJ, Yoon J-H, Lee H-S. Antiviral efficacy of combination therapy with entecavir and adefovir for entecavir/lamivudine-resistant hepatitis B virus with or without adefovir resistance. *J Med Virol*. 2012; 84(3):424-30.

Yang Y-F, Zhao W, Zhong Y-D, Yang Y-J, Shen L, Zhang N, et al. Comparison of the efficacy of thymosin alpha-1 and interferon alpha in the treatment of chronic hepatitis B: a meta-analysis. *Antiviral Res*. 2008; 77(2):136-41.

Yeh CT, Sheen IS, Chen TC, Hsieh SY, Chu CM, Liaw YF. Orlon modulates the therapeutic effect of interferon to eliminate preferentially the hepatitis B virus precore stop mutant. *J Hepatol*. 2000; 32(5):829-36.

Yokosuka O, Omata M, Imazeki F, Hirota K, Mori J, Uchiyama K, et al. Combination of short-term prednisolone and adenine arabinoside in the treatment of chronic hepatitis B. A controlled study. *Gastroenterology*. 1985; 89(2):246-51.

Yoo BC, Kim JH, Chung YH, Lee KS, Paik SW, Ryu SH, et al. Twenty-four-week clevudine therapy showed potent and sustained antiviral activity in HBsAg-positive chronic hepatitis B. *Hepatology*. 2007; 45(5):1172-8.

Yoo BC, Kim JH, Kim T-H, Koh KC, Um S-H, Kim YS, et al. Clevudine is highly efficacious in hepatitis B e antigen-negative chronic hepatitis B with durable off-therapy viral suppression. *Hepatology*. 2007 ; 46(4):1041-8.

You J, Zhuang L, Cheng H-Y, Yan S-M, Qiao Y-W, Huang J-H, et al. A randomized, controlled, clinical study of thymosin alpha-1 versus interferon-alpha in [corrected] patients with chronic hepatitis B lacking HBsAg in China [corrected].[Erratum appears in *J Chin Med Assoc*. 2005; 68(3):154]. *J Chin Med Assoc*. 2005; 68(2):65-72.



## Appendix A4. Excluded Studies

Zarski JP, Causse X, Cohard M, Cougnard J, Trepo C. A randomized, controlled trial of interferon alfa-2b alone and with simultaneous prednisone for the treatment of chronic hepatitis B. French Multicenter Group. *J Hepatol*. 1994; 20(6):735-41.

Zavaglia C, Severini R, Tinelli C, Franzone JS, Airoldi A, Tempini S, et al. A randomized, controlled study of thymosin-alpha1 therapy in patients with anti-HBe, HBV-DNA-positive chronic hepatitis B. *Dig Dis Sci*. 2000; 45(4):690-6.

Zheng MH, Shi KQ, Dai ZJ, Ye C, Chen YP. A 24-week, parallel-group, open-label, randomized clinical trial comparing the early antiviral efficacy of telbivudine and entecavir in the treatment of hepatitis B e antigen-positive chronic hepatitis B virus infection in adult Chinese patients. *Clin Ther*. 2010; 32(4):649-58.

### Wrong Outcome

Alavian S-M, Mansouri S, Abouzari M, Assari S, Bonab MS, Miri S-M. Long-term efficacy of hepatitis B vaccination in healthcare workers of Oil Company Hospital, Tehran, Iran (1989-2005). *Eur J Gastroenterol Hepatol*. 2008; 20(2):131-4.

Brooks EA, Lacey LF, Payne SL, Miller DW. Economic evaluation of lamivudine compared with interferon-alpha in the treatment of chronic hepatitis B in the United States. *Am J Manag Care*. 2001; 7(7):677-82.

Brunetto MR, Giarin M, Saracco G, Oliveri F, Calvo P, Capra G, et al. Hepatitis B virus unable to secrete e antigen and response to interferon in chronic hepatitis B. *Gastroenterology*. 1993; 105(3):845-50.

Butler LM, Mills PK, Yang RC, Chen MS, Jr. Hepatitis B knowledge and vaccination levels in California Hmong youth: implications for liver Cancer prevention strategies. *Asian Pac J Cancer Prev*. 2005; 6(3):401-3.

Carrouee-Durantel S, Durantel D, Werle-Lapostolle B, Pichoud C, Naesens L, Neyts J, et al. Suboptimal response to adefovir dipivoxil therapy for chronic hepatitis B in nucleoside-naive patients is not due to pre-existing drug-resistant mutants. *Antivir Ther*. 2008; 13(3):381-8.

Chang ET, Sue E, Zola J, So SK. 3 For Life: a model pilot program to prevent hepatitis B virus infection and liver Cancer in Asian and Pacific Islander

Americans. *Am J Health Promot*. 2009; 23(3):176-81.

Chen MS, Jr., Fang DM, Stewart SL, Ly MY, Lee S, Dang JH, et al. Increasing hepatitis B screening for hmong adults: results from a randomized controlled community-based study. *Cancer Epidemiol Biomarkers Prev*. 2013; 22(5):782-91.

Cox AD, Cox D, Cyrier R, Graham-Dotson Y, Zimet GD. Can self-prediction overcome barriers to Hepatitis B vaccination? A randomized controlled trial. *Health Psychol*. 2012; 31(1):97-105.

Degos F, Duhamel G, Brechot C, Nalpas B, Courouce AM, Tron F, et al. Hepatitis B vaccination in chronic alcoholics. *J Hepatol*. 1986; 2(3):402-9.

Dufour A, Remis RS, Alary M, Otis J, Masse B, Turmel B, et al. Factors associated with hepatitis B vaccination among men having sexual relations with men in Montreal, Quebec, Canada. Omega Study Group. *Sex Transm Dis*. 1999; 26(6):317-24.

Farrell M, Battersby M, Strang J. Screening for hepatitis B and vaccination of injecting drug users in NHS drug treatment services. *Br J Addict*. 1990; 85(12):1657-9.

Foster T, Hon H, Kanwal F, Han S, Spiegel B. Screening high risk individuals for hepatitis B: physician knowledge, attitudes, and beliefs. *Dig Dis Sci*. 2011; 56(12):3471-87.

Franson TR, Ksobiech LJ, Simonsen H. Prevalence of Hepatitis B carriers in a mental health in-patient facility: Implications for employee screening and vaccination. *Psychiatr Hosp*. 1986 Spr; 17(2):81-3.

Gjeruldsen SR, Myrvang B, Opjordsmoen S. A 25-year follow-up study of drug addicts hospitalised for acute hepatitis: present and past morbidity. *Eur Addict Res*. 2003; 9(2):80-6.

Gralnek IM, Hays RD, Kilbourne A, Rosen HR, Keeffe EB, Artinian L, et al. Development and evaluation of the Liver Disease Quality of Life instrument in persons with advanced, chronic liver disease--the LDQOL 1.0. *Am J Gastroenterol*. 2000; 95(12):3552-65.

Grytdal SP, Liao Y, Chen R, Garvin CC, Grigg-Saito D, Kagawa-Singer M, et al. Hepatitis B testing and vaccination among Vietnamese- and Cambodian-Americans. *J Community Health*. 2009; 34(3):173-80.

## Appendix A4. Excluded Studies

- Gunn RA, Murray PJ, Ackers ML, Hardison WG, Margolis HS. Screening for chronic hepatitis B and C virus infections in an urban sexually transmitted disease clinic: rationale for integrating services. *Sex Transm Dis.* 2001; 28(3):166-70.
- Hagan H, Thiede H, McGough JP, Alexander ER. Hepatitis B vaccination among research participants, Seattle, Washington. *Am J Public Health.* 2002; 92(11):1756.
- Hagedorn H, Dieperink E, Dingmann D, Durfee J, Ho SB, Isenhardt C, et al. Integrating hepatitis prevention services into a substance use disorder clinic. *J Subst Abuse Treat.* 2007; 32(4):391-8.
- Hamlyn E, McAllister J, Winston A, Sinclair B, Amin J, Carr A, et al. Is screening for sexually transmitted infections in men who have sex with men who receive non-occupational HIV post-exposure prophylaxis worthwhile? [Erratum appears in *Sex Transm Infect.* 2006 ; 82(5):422]. *Sex Transm Infect.* 2006; 82(1):21-3.
- Hann HW, Han SH, Block TM, Harris M, Maa JF, Fisher RT, et al. Symptomatology and health attitudes of chronic hepatitis B patients in the USA. *J Viral Hepat.* 2008; 15(1):42-51.
- Hann H-WL, Hann RS, Maddrey WC. Hepatitis B virus infection in 6,130 unvaccinated Korean-Americans surveyed between 1988 and 1990. *Am J Gastroenterol.* 2007; 102(4):767-72.
- Havel RD, Wright MP. Automated interviewing for hepatitis B risk assessment and vaccination referral. *Am J Prev Med.* 1997; 13(5):392-5.
- Hsu CE, Zhang G, Yan FA, Shang N, Le T. What made a successful hepatitis B program for reducing liver Cancer disparities: an examination of baseline characteristics and educational intervention, infection status, and missing responses of at-risk Asian Americans. *J Community Health.* 2010; 35(3):325-35.
- Hutchinson SJ, Wadd S, Taylor A, Bird SM, Mitchell A, Morrison DS, et al. Sudden rise in uptake of hepatitis B vaccination among injecting drug users associated with a universal Vaccine programme in prisons. *Vaccine.* 2004; 23(2):210-4.
- Hwang JP, Huang C-H, Yi JK. Knowledge about hepatitis B and predictors of hepatitis B vaccination among Vietnamese American college students. *J Am Coll Health.* 2008; 56(4):377-82.
- Kim S-Y, Billah K, Lieu TA, Weinstein MC. Cost Effectiveness of Hepatitis B Vaccination at HIV Counseling and Testing Sites. *Am J Prev Med.* 2006; 30(6):498-506.
- Kose S, Turken M, Cavdar G, Tatar B, Senger SS. Evaluation of vaccination results in high-risk patients included in hepatitis B vaccination program. *Human Vaccines.* 2010; 6(11):903-5.
- Kumar A, Lalani S, Afridi AAK, Khuwaja AK. Screening of hepatitis B and C among people visiting general practice clinics in a rural district of Sindh, Pakistan. *J Ayub Med Coll Abbottabad.* 2010; 22(4):143-5.
- Kung AW, Jones BM, Lai CL. Effects of interferon-gamma therapy on thyroid function, T-lymphocyte subpopulations and induction of autoantibodies. *J Clin Endocrinol Metab.* 1990; 71(5):1230-4.
- Kweon YO, Goodman ZD, Dienstag JL, Schiff ER, Brown NA, Burchardt E, et al. Decreasing fibrogenesis: an immunohistochemical study of paired liver biopsies following lamivudine therapy for chronic hepatitis B. *J Hepatol.* 2001; 35(6):749-55.
- Lai C-L, Lim SG, Brown NA, Zhou X-J, Lloyd DM, Lee Y-M, et al. A dose-finding study of once-daily oral telbivudine in HBeAg-positive patients with chronic hepatitis B virus infection. *Hepatology.* 2004; 40(3):719-26.
- Lampertico P, Manzin A, Rumi MG, Paolucci S, Del Ninno E, Clementi M, et al. Hepatitis B virus precore mutants in HBeAg carriers with chronic hepatitis treated with interferon. *J Viral Hepat.* 1995; 2(5):251-6.
- Li W-C, Wang M-R, Kong L-B, Ren W-G, Zhang Y-G, Nan Y-M. Peginterferon alpha-based therapy for chronic hepatitis B focusing on HBsAg clearance or seroconversion: a meta-analysis of controlled clinical trials. *BMC Infect Dis.* 2011; 11:165.
- Ma GX, Fang CY, Shive SE, Toubbeh J, Tan Y, Siu P. Risk perceptions and barriers to Hepatitis B screening and vaccination among Vietnamese immigrants. *J Immigr Minor Health.* 2007; 9(3):213-20.
- Ma GX, Gao W, Tan Y, Chae WG, Rhee J. A community-based participatory approach to a hepatitis B intervention for Korean Americans. *Prog Community Health Partnersh.* 2012; 6(1):7-16.

## Appendix A4. Excluded Studies

- Ma GX, Lee S, Wang M, Tan Y, Gao W, Ma X, et al. Role of sociocultural factors in hepatitis B screening among Asian Americans. *South Med J*. 2011; 104(7):466-72.
- Ma GX, Shive SE, Toubbeh JI, Tan Y, Wu D. Knowledge, attitudes, and behaviors of Chinese hepatitis B screening and vaccination. *Am J Health Behav*. 2008; 32(2):178-87.
- Ma S-W, Li Y-Y, Zhang G-W, Huang X, Sun J, Li C, et al. Complementarity-determining region 3 size spectratypes of T cell receptor beta chains in CD8+ T cells following antiviral treatment of chronic hepatitis B. *Antimicrob Agents Chemother*. 2011; 55(2):888-94.
- Mahoney FJ, Stewart K, Hu H, Coleman P, Alter MJ. Progress toward the elimination of hepatitis B virus transmission among health care workers in the United States. *Arch Intern Med*. 1997; 157(22):2601-5.
- Margolis HS, Handsfield HH, Jacobs RJ, Gangi JE. Evaluation of office-based intervention to improve prevention counseling for patients at risk for sexually acquired hepatitis B virus infection. Hepatitis B-WARE Study Group. *Am J Obstet Gynecol*. 2000; 182(1 Pt 1):1-6.
- Marinho RT, Moura MC, Pedro M, Ramalho FJ, Velosa JF. Hepatitis B vaccination in hospital personnel and medical students. *J Clin Gastroenterol*. 1999; 28(4):317-22.
- Morimitsu Y, Kleiner DE, Jr., Conjeevaram HS, Hsia CC, Di Bisceglie AM, Tabor E. Expression of transforming growth factor alpha in the liver before and after interferon alfa therapy for chronic hepatitis B. *Hepatology*. 1995 ; 22(4 Pt 1):1021-6.
- Moskovitz DN, Osiowy C, Giles E, Tomlinson G, Heathcote EJ. Response to long-term lamivudine treatment (up to 5 years) in patients with severe chronic hepatitis B, role of genotype and drug resistance. *J Viral Hepat*. 2005; 12(4):398-404.
- Muhlbacher A, Zdunek D, Melchior W, Michl U. Is infective blood donation missed without screening for antibody to hepatitis B core antigen and/or hepatitis B virus DNA? *Vox Sang*. 2001; 81(2):139.
- Mustufa MA, Memon AA, Nasim S, Shahid A, Omar SM. Exposure to risk factors for hepatitis B and C viruses among primary school teachers in Karachi. *J Infect Dev Ctries*. 2010 ; 4(10):616-20.
- Nakazawa T, Shibuya A, Takeuchi A, Shibata Y, Hidaka H, Okuwaki Y, et al. Viral level is an indicator of long-term outcome of hepatitis B virus e antigen-negative carriers with persistently normal serum alanine aminotransferase levels. *J Viral Hepat*. 2011; 18(7):e191-9.
- Nam SW, Jung JJ, Bae SH, Choi JY, Yoon SK, Cho SH, et al. Clinical outcomes of delayed clearance of serum HBsAg in patients with chronic HBV infection. *Korean J Intern Med*. 2007; 22(2):73-6.
- Nguyen TT, McPhee SJ, Stewart S, Gildengorin G, Zhang L, Wong C, et al. Factors associated with hepatitis B testing among Vietnamese Americans. *J Gen Intern Med*. 2010; 25(7):694-700.
- Ozars R, Tabak F, Tahan V, Ozturk R, Akin H, Mert A, et al. Correlation of quantitative assay of HBsAg and HBV DNA levels during chronic HBV treatment. *Dig Dis Sci*. 2008; 53(11):2995-8.
- Paik Y-H, Han K-H, Hong SP, Lee HW, Lee KS, Kim S-O, et al. The clinical impact of early detection of the YMDD mutant on the outcomes of long-term lamivudine therapy in patients with chronic hepatitis B. *Antivir Ther*. 2006; 11(4):447-55.
- Pal J, Czompoly T, Nyarady Z, Marczinovits I, Janaky T, Kele Z, et al. Determination of the fine epitope specificity of an anti-hepatitis B virus X protein monoclonal antibody using microanalytical and molecular biological methods. *Mol Immunol*. 2003; 40(5):241-6.
- Park GJH, Katelaris PH, Jones DB, Seow F, Lin BPC, Le Couteur DG, et al. The C-caffeine breath test distinguishes significant fibrosis in chronic hepatitis B and reflects response to lamivudine therapy. *Aliment Pharmacol Ther*. 2005; 22(5):395-403.
- Paul RG, Roodman ST, Campbell CR, Bodicky CJ, Perrillo RP. HLA class I antigen expression as a measure of response to antiviral therapy of chronic hepatitis B. *Hepatology*. 1991; 13(5):820-5.
- Petit MA, Zoulim F, Berthillon P, Capel F, Li J, Dauguet C, et al. PreS1 antigen/antibody patterns following interferon therapy in acute and chronic hepatitis B. *J Hepatol*. 1994; 20(1):47-56.
- Plaitano S, Saggiocca L, Mele A, Bove C, Protano D, Adamo B, et al. Hepatitis B mass immunization of adolescents: a pilot study in a community. *Eur J Epidemiol*. 1993; 9(3):307-10.

## Appendix A4. Excluded Studies

- Pollicino T, Isgro G, Di Stefano R, Ferraro D, Maimone S, Brancatelli S, et al. Variability of reverse transcriptase and overlapping S gene in hepatitis B virus isolates from untreated and lamivudine-resistant chronic hepatitis B patients. *Antivir Ther.* 2009; 14(5):649-54.
- Poynard T, Ngo Y, Marcellin P, Hadziyannis S, Ratziu V, Benhamou Y, et al. Impact of adefovir dipivoxil on liver fibrosis and activity assessed with biochemical markers (FibroTest-ActiTest) in patients infected by hepatitis B virus. *J Viral Hepat.* 2009; 16(3):203-13.
- Rein DB, Lesesne SB, Leese PJ, Weinbaum CM. Community-based hepatitis B screening programs in the United States in 2008. *J Viral Hepat.* 2010; 17(1):28-33.
- Robinson T, Bullen C, Humphries W, Hornell J, Moyes C. The New Zealand Hepatitis B Screening Programme: screening coverage and prevalence of chronic hepatitis B infection. *N Z Med J.* 2005; 118(1211):U1345.
- Scully LJ, Brown D, Lloyd C, Shein R, Thomas HC. Immunological studies before and during interferon therapy in chronic HBV infection: identification of factors predicting response. *Hepatology.* 1990; 12(5):1111-7.
- Sellers J, Zimic-Vincetic M, Howard M, Mahony JB, Chernesky MA. Predictors of positivity for hepatitis B and the derivation of a selective screening rule in a Canadian sexually transmitted disease clinic. *J Clin Virol.* 1998; 11(1):85-91.
- Shindo M, Hamada K, Nishioji K, Muramatsu A, Oda Y, Okuno T. The predictive value of liver fibrosis in determining the effectiveness of interferon and lamivudine therapies for chronic hepatitis B. *J Gastroenterol.* 2004; 39(3):260-7.
- Singal AK, Fontana RJ. Meta-analysis: oral anti-viral agents in adults with decompensated hepatitis B virus cirrhosis. *Aliment Pharmacol Ther.* 2012; 35(6):674-89.
- Spiegel BM, Bolus R, Han S, Tong M, Esrailian E, Talley J, et al. Development and validation of a disease-targeted quality of life instrument in chronic hepatitis B: the hepatitis B quality of life instrument, version 1.0. *Hepatology.* 2007; 46(1):113-21.
- Svrtlih N, Pavic S, Terzic D, Delic D, Simonovic J, Gvozdenovic E, et al. Reduced quality of life in patients with chronic viral liver disease as assessed by SF12 questionnaire. *J Gastrointest Liver Dis.* 2008; 17(4):405-9.
- Tan NC, Cheah SL, Teo EK, Yang LH. Patients with chronic hepatitis B infection: what is their quality of life? *Singapore Med J.* 2008; 49(9):682-7.
- Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology.* 2009; 49(5):1503-14.
- ter Borg MJ, van Zonneveld M, Zeuzem S, Senturk H, Akarca US, Simon C, et al. Patterns of viral decline during PEG-interferon alpha-2b therapy in HBeAg-positive chronic hepatitis B: relation to treatment response. *Hepatology.* 2006; 44(3):721-7.
- van der Eijk AA, Niesters HG, Hansen BE, Heijink RA, Janssen HL, Schalm SW, et al. Quantitative HBV DNA levels as an early predictor of nonresponse in chronic HBe-antigen positive hepatitis B patients treated with interferon-alpha. *J Viral Hepat.* 2006; 13(2):96-103.
- van der Plas SM, Hansen BE, de Boer JB, Stijnen T, Passchier J, de Man RA, et al. The Liver Disease Symptom Index 2.0; validation of a disease-specific questionnaire. *Qual Life Res.* 2004 ; 13(8):1469-81.
- van der Sande MAB, Waight PA, Mendy M, Zaman S, Kaye S, Sam O, et al. Long-term protection against HBV chronic carriage of Gambian adolescents vaccinated in infancy and immune response in HBV booster trial in adolescence. *PLoS ONE.* 2007; 2(8):e753.
- Villa E, Lei B, Taliani G, Graziosi A, Critelli R, Luongo M, et al. Pretreatment with pegylated interferon prevents emergence of lamivudine mutants in lamivudine-naïve patients: a pilot study. *Antivir Ther.* 2009; 14(8):1081-7.
- 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.
- Westh H, Hoffmann S, Christiansen E, Worm AM. Hepatitis B core antibody screening in a high prevalence group: comparison of three enzyme immunoassays using receiver operating characteristic analysis. *J Virol Methods.* 1996; 56(1):13-8.

## Appendix A4. Excluded Studies

Westland CE, Yang H, Delaney WEt, Gibbs CS, Miller MD, Wulfsohn M, et al. Week 48 resistance surveillance in two phase 3 clinical studies of adefovir dipivoxil for chronic hepatitis B. *Hepatology*. 2003; 38(1):96-103.

Williams SJ, Farrell GC. Serial antipyrine clearance studies detect altered hepatic metabolic function during spontaneous and interferon-induced changes in chronic hepatitis B disease activity. *Hepatology*. 1989; 10(2):192-7.

Wong VW-S, Wong GL-H, Chim AM-L, Choi PC-L, Chan AW-H, Tsang SW-C, et al. Surrogate end points and long-term outcome in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol*. 2009 ; 7(10):1113-20.

Yeh C-T, Sheen IS, Chen T-C, Hsieh S-Y, Chu C-M, Liaw Y-F. Prednisolone modulates the therapeutic effect of interferon to eliminate preferentially the hepatitis B virus precore stop mutant. *J Hepatol*. 2000; 32(5):829-36.

Yen Y-H, Lu S-N, Chen C-H, Wang J-H, Wu C-M, Hung C-H, et al. Changes in serum hepatitis B e antigen (HBeAg) levels associated with the emergence of YMDD mutants in HBeAg non-seroconverted patients during lamivudine therapy. *Liver Int*. 2007; 27(10):1349-55.

Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut*. 1999; 45(2):295-300.

Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: The effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. *Hepatology*. 2001; 34(1):139-45.

Zhao H, Kurbanov F, Wan MB, Yin YK, Niu JQ, Hou JL, et al. Genotype B and younger patient age associated with better response to low-dose therapy: a trial with pegylated/nonpegylated interferon-alpha-2b for hepatitis B e antigen-positive patients with chronic hepatitis B in China. *Clin Infect Dis*. 2007; 44(4):541-8.

### Wrong Study Design for Key Question

Amin J, Dore GJ, O'Connell DL, Bartlett M, Tracey E, Kaldor JM, et al. Cancer incidence in people with

hepatitis B or C infection: a large community-based linkage study. *J Hepatol*. 2006; 45(2):197-203.

Asahina Y, Izumi N, Uchihara M, Noguchi O, Nishimura Y, Inoue K, et al. Core promoter/pre-core mutations are associated with lamivudine-induced HBeAg loss in chronic hepatitis B with genotype C. *J Hepatol*. 2003; 39(6):1063-9.

Bayraktar Y, Koseoglu T, Somner C, Kayhan B, Temizer A, Uzunalimoglu B, et al. The use of deferoxamine infusions to enhance the response rate to interferon-alpha treatment of chronic viral hepatitis B. *J Viral Hepat*. 1996; 3(3):129-35.

Bolukbas C, Bolukbas FF, Kendir T, Akbayir N, Ince AT, Abut E, et al. The effectiveness of lamivudine treatment in cirrhotic patients with HBV precore mutations: a prospective, open-label study. *Dig Dis Sci*. 2006; 51(7):1196-202.

Brunetto MR, Oliveri F, Coco B, Leandro G, Colombatto P, Gorin JM, et al. Outcome of anti-HBe positive chronic hepatitis B in alpha-interferon treated and untreated patients: a long term cohort study. *J Hepatol*. 2002; 36(2):263-70.

Chang TT, Lai CL, Kew Yoon S, Lee SS, Coelho HS, Carrilho FJ, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology*. 2010; 51(2):422-30.

Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Chronic hepatitis B virus infection and mortality from non-liver causes: results from the Haimen City cohort study. *Int J Epidemiol*. 2005; 34(1):132-7.

Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol*. 2006; 101(8):1797-803.

Cianciara J, Laskus T. Development of transient autoimmune hepatitis during interferon treatment of chronic hepatitis B. *Dig Dis Sci*. 1995; 40(8):1842-4.

Crook PD, Jones ME, Hall AJ. Mortality of hepatitis B surface antigen-positive blood donors in England and Wales. *Int J Epidemiol*. 2003; 32(1):118-24.

Da Villa G, Piccinino F, Scolastico C, Fusco M, Piccinino R, Sepe A. Long-term epidemiological survey of hepatitis B virus infection in a hyperendemic area (Afragola, southern Italy): results

## Appendix A4. Excluded Studies

- of a pilot vaccination project. *Res Virol.* 1998; 149(5):263-70.
- Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. *Value Health.* 2010; 13(8):922-33.
- Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naïve patients with chronic hepatitis B. *Value Health.* 2010; 13(8):934-45.
- di Marco V, di Stefano G, Ferraro D, Almasio P, Bonura C, Giglio M, et al. HBV-DNA suppression and disease course in HBV cirrhosis patients on long-term lamivudine therapy. *Antivir Ther.* 2005; 10(3):431-9.
- Dienstag JL, Goldin RD, Heathcote EJ, Hann HW, Woessner M, Stephenson SL, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology.* 2003; 124(1):105-17.
- Dienstag JL, Wei LJ, Xu D, Kreter B. Cross-study analysis of the relative efficacies of oral antiviral therapies for chronic hepatitis B infection in nucleoside-naïve patients. *Clin Drug Investig.* 2007; 27(1):35-49.
- Eun JR, Lee HJ, Kim TN, Lee KS. Risk assessment for the development of hepatocellular carcinoma: according to on-treatment viral response during long-term lamivudine therapy in hepatitis B virus-related liver disease. *J Hepatol.* 2010; 53(1):118-25.
- Evans AA, Chen G, Ross EA, Shen FM, Lin WY, London WT. Eight-year follow-up of the 90,000-person Haimen City cohort: I. Hepatocellular carcinoma mortality, risk factors, and gender differences. *Cancer Epidemiol Biomarkers Prev.* 2002; 11(4):369-76.
- Fornaciari G, Bassi C, Beltrami M, Castagnetti E, Maccari S, Plancher AC. Hemolytic anemia secondary to interferon treatment for chronic B hepatitis. *J Clin Gastroenterol.* 1991 ; 13(5):596-7.
- Gaia S, Marzano A, Smedile A, Barbon V, Abate ML, Olivero A, et al. Four years of treatment with lamivudine: clinical and virological evaluations in HBe antigen-negative chronic hepatitis B. *Aliment Pharmacol Ther.* 2004; 20(3):281-7.
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology.* 2006; 131(6):1743-51.
- Hutton DW, Tan D, So SK, Brandeau ML. Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B. *Ann Intern Med.* 2007; 147(7):460-9.
- Hwang JP, Mohseni M, Gor BJ, Wen S, Guerrero H, Vierling JM. Hepatitis B and hepatitis C prevalence and treatment referral among Asian Americans undergoing community-based hepatitis screening. *Am J Public Health.* 2010; 100 Suppl 1:S118-24.
- Hynicka LM, Yunker N, Patel PH. A review of oral antiretroviral therapy for the treatment of chronic hepatitis B. *Ann Pharmacother.* 2010; 44(7-8):1271-86.
- Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Fukuda M, et al. Interferon decreases hepatocellular *Carcinogenesis* in patients with cirrhosis caused by the hepatitis B virus: a pilot study. *Cancer.* 1998; 82(5):827-35.
- International Interferon-alpha Hepatocellular Carcinoma Study Group. Effect of interferon-alpha on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study. International Interferon-alpha Hepatocellular Carcinoma Study Group.[Erratum appears in *Lancet* 1998; 352(9135):1230]. *Lancet.* 1998; 351(9115):1535-9.
- Kaiser T, Moessner J, Patel K, McHutchison JG, Tillmann HL. Life threatening liver disease during treatment with monoclonal antibodies. *BMJ.* 2009; 338:b508.
- Kaymakoglu S, Danalioglu A, Demir K, Karaca C, Akyuz F, Onel D, et al. Long-Term Results of Interferon Alpha Monotherapy in Patients with HBeAg-Negative Chronic Hepatitis B. *Dig Dis Sci.* 2007; 52(3):727-31.
- Kurihara T, Imazeki F, Yokosuka O, Fukai K, Kanda T, Kawai S, et al. Effect of lamivudine in HBeAg-positive chronic hepatitis B: discordant effect on HBeAg and HBV DNA according to pretreatment ALT level. *World J Gastroenterol.* 2005; 11(22):3346-50.

## Appendix A4. Excluded Studies

- Lai C-L, Yuen M-F. Prevention of hepatitis b virus-related hepatocellular carcinoma with antiviral therapy. *Hepatology*. 2013; 57(1):399-408.
- Lin S-M, Yu M-L, Lee C-M, Chien R-N, Sheen IS, Chu C-M, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. *J Hepatol*. 2007; 46(1):45-52.
- Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology*. 2007; 45(2):507-39.
- Lugoboni F, Migliozi S, Mezzelani P, Pajusco B, Ceravolo R, Quaglio G. Progressive decrease of hepatitis B in a cohort of drug users followed over a period of 15 years: the impact of anti-HBV vaccination. *Scand J Infect Dis*. 2004; 36(2):131-3.
- Manesis EK, Hadziyannis SJ. Interferon  $\alpha$  Treatment and Retreatment of Hepatitis B e Antigen-Negative Chronic Hepatitis B. *Gastroenterology*. 2001; 121(1):101-9.
- Manesis EK, Moschos M, Brouzas D, Kotsiras J, Petrou C, Theodosiadis G, et al. Neurovisual impairment: a frequent complication of alpha-interferon treatment in chronic viral hepatitis. *Hepatology*. 1998; 27(5):1421-7.
- Manolakopoulos S, Bethanis S, Elefsiniotis J, Karatapanis S, Triantos C, Sourvinos G, et al. Lamivudine monotherapy in HBeAg-negative chronic hepatitis B: prediction of response-breakthrough and long-term clinical outcome. *Aliment Pharmacol Ther*. 2006; 23(6):787-95.
- Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013; 381(9865):468-75.
- Marino D, Boso C, Crivellari G, Mazzarotto R, Stragliotto S, Farinati F, et al. Fatal HBV-related liver failure during lamivudine therapy in a patient with non-Hodgkin's lymphoma. *Tumori*. 2008; 94(5):748-9.
- Matsumoto A, Tanaka E, Rokuhara A, Kiyosawa K, Kumata H, Omata M, et al. Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: a multicenter retrospective study of 2795 patients. *Hepatol Res*. 2005; 32(1):173-84.
- Mauracher E. Low dose interferon alfa-2b for chronic hepatitis B in Asian countries. *Gut*. 1993; 34(2 Suppl):S99-100.
- McKenzie R, Fried MW, Sallie R, Conjeevaram H, Di Bisceglie AM, Park Y, et al. Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. *N Engl J Med*. 1995; 333(17):1099-105.
- McMahon BJ, Alberts SR, Wainwright RB, Bulkow L, Lanier AP. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. *Arch Intern Med*. 1990; 150(5):1051-4.
- McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis*. 1985; 151(4):599-603.
- McMahon BJ, Bulkow LR, Singleton RJ, Williams J, Snowball M, Homan C, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology*. 2011; 54(3):801-7.
- McMahon BJ, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. *Ann Intern Med*. 2001; 135(9):759-68.
- Milkiewicz P, Yim C, Pache I, Heathcote J. Diffuse skin reaction in patient with hepatitis B, treated with two different formulations of pegylated interferon. *Can J Gastroenterol*. 2005; 19(11):677-8.
- Miranda-Guardiola F, Fernandez-Llama P, Badia JR, Botey A, Estruch R, Darnell A, et al. Acute renal failure associated with alpha-interferon therapy for chronic hepatitis B. *Nephrol Dial Transplant*. 1995; 10(8):1441-3.
- Miyake Y, Kobashi H, Yamamoto K. Meta-analysis: the effect of interferon on development of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *J Gastroenterol*. 2009; 44(5):470-5.
- Muqit MKM, Stanga PE, Vilar FJ, Patton N. Presumed entecavir-induced ocular toxicity. *Eye (Lond)*. 2011; 25(12):1665-8.

## Appendix A4. Excluded Studies

- Murakami CS, Zeller K, Bodenheimer HC, Jr., Lee WM. Idiopathic thrombocytopenic purpura during interferon-alpha 2B treatment for chronic hepatitis. *Am J Gastroenterol.* 1994; 89(12):2244-5.
- Nevens F, Goubau P, Van Eyken P, Desmyter J, Desmet V, Fevery J. Treatment of decompensated viral hepatitis B-induced cirrhosis with low doses of interferon alpha. *Liver.* 1993; 13(1):15-9.
- Nishizaki Y, Morizane T, Kojima S, Sakuma K, Koyama A, Shiozawa H, et al. Predictive factors for the response to lamivudine in HBV-infected patients with chronic hepatitis and cirrhosis. *Tokai J Exp Clin Med.* 2006; 31(3):121-4.
- Ojetti V, Gasbarrini A, Migneco A, Flore R, Santoliquido A, De Martini D, et al. Lamivudine-induced muscle mitochondrial toxicity. *Dig Liver Dis.* 2002; 34(5):384-5.
- Papatheodoridis GV, Dimou E, Dimakopoulos K, Manolakopoulos S, Rapti I, Kitis G, et al. Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. *Hepatology.* 2005; 42(1):121-9.
- Papatheodoridis GV, Petraki K, Cholongitas E, Kanta E, Ketikoglou I, Manesis EK. Impact of interferon-alpha therapy on liver fibrosis progression in patients with HBeAg-negative chronic hepatitis B. *J Viral Hepat.* 2005; 12(2):199-206.
- Perrillo R, Tamburro C, Regenstein F, Balart L, Bodenheimer H, Silva M, et al. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. *Gastroenterology.* 1995; 109(3):908-16.
- Piao C-Y, Fujioka S-i, Iwasaki Y, Fujio K, Kaneyoshi T, Araki Y, et al. Lamivudine treatment in patients with HBV-related hepatocellular carcinoma--using an untreated, matched control cohort. *Acta Med Okayama.* 2005 ; 59(5):217-24.
- Porres JC, Carreno V, Ruiz M, Marron JA, Bartolome J. Interferon antibodies in patients with chronic HBV infection treated with recombinant interferon. *J Hepatol.* 1989; 8(3):351-7.
- Poynard T, Zoulim F, Ratziu V, Degos F, Imbert-Bismut F, Deny P, et al. Longitudinal assessment of histology surrogate markers (FibroTest-ActiTest) during lamivudine therapy in patients with chronic hepatitis B infection. *Am J Gastroenterol.* 2005; 100(9):1970-80.
- Salkic N, Zerem E, Zildzic M, Basic M. Reversible peg-interferon-induced unilateral sensorineural hearing loss during hepatitis B treatment. *Turk J Gastroenterol.* 2009; 20(2):156.
- Sata M, Yano Y, Yoshiyama Y, Ide T, Kumashiro R, Suzuki H, et al. Mechanisms of thrombocytopenia induced by interferon therapy for chronic hepatitis B. *J Gastroenterol.* 1997; 32(2):206-10.
- Schalm SW, Summerskill WH, Gitnick GL, Elveback LR. Contrasting features and responses to treatment of severe chronic active liver disease with and without hepatitis BS antigen. *Gut.* 1976 ; 17(10):781-6.
- Senturk H, Baysal B, Tahan V, Zerdali H, Ozaras R, Tabak F, et al. Long-Term Effect of Interferon Therapy in Patients with HBeAg Positive Chronic Hepatitis B Infection. *Dig Dis Sci.* 2011 2011/01/01; 56(1):208-12.
- Shakil AO, Di Bisceglie AM, Hoofnagle JH. Seizures during alpha interferon therapy. *J Hepatol.* 1996; 24(1):48-51.
- Sun L-J, Yu J-W, Zhao Y-H, Kang P, Li S-C. Influential factors of prognosis in lamivudine treatment for patients with acute-on-chronic hepatitis B liver failure. *J Gastroenterol Hepatol.* 2010; 25(3):583-90.
- Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou-Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology.* 1987; 92(6):1844-50.
- Thio CL, Seaberg EC, Skolasky R, Jr., Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet.* 2002; 360(9349):1921-6.
- Thomas HC, Karayiannis P, Brook G. Treatment of hepatitis B virus infection with interferon. Factors predicting response to interferon. *J Hepatol.* 1991; 13(1).
- Van Thiel DH, Friedlander L, Fagioli S, Wright HI, Irish W, Gavalier 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

events following interferon-alfa therapy of chronic hepatitis B. *Aliment Pharmacol Ther.* 2010; 32(9):1059-68.

Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DKH, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology.* 2010; 139(4):1218-29.

Wu CF, Yu MW, Lin CL, Liu CJ, Shih WL, Tsai KS, et al. Long-term tracking of hepatitis B viral load and the relationship with risk for hepatocellular carcinoma in men. *Carcinogenesis.* 2008; 29(1):106-12.

Yang YF, Zhao W, Zhong YD, Xia HM, Shen L, Zhang N. Interferon therapy in chronic hepatitis B reduces progression to cirrhosis and hepatocellular carcinoma: a meta-analysis. *J Viral Hepat.* 2009; 16(4):265-71.

Yu MW, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst.* 2005; 97(4):265-72.

Yuen MF, Yuan HJ, Wong DK, Yuen JC, Wong WM, Chan AO, et al. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut.* 2005; 54(11):1610-4.

Yuen M-F, Sablon E, Libbrecht E, Van De Velde H, Wong DK-H, Fung J, et al. Significance of viral load, core promoter/precore mutations and specific sequences of polymerase gene in HBV-infected patients on 3-year lamivudine treatment. *Antivir Ther.* 2006; 11(6):779-86.

Zeng M, Yimin M, Guangbi Y, Jinlin H, Hao W, Hong R, et al. Five years of treatment with adefovir dipivoxil in Chinese patients with HBeAg-positive chronic hepatitis B. *Liver Int.* 2012; 32(1):137-46.

Zhao S, Tang L, Fan X, Chen L. Telbivudine for chronic hepatitis B. *Cochrane Database Syst Rev.* 2010(9).

Zhao SH, Liu EQ, Cheng DX, Li YF, Wang YL, Chen YL, et al. Comparison of entecavir and adefovir for the treatment of chronic hepatitis B. *Braz J Infect Dis.* 2012; 16(4):366-72.

Schiano TD, Lissos TW, Ahmed A, Siano C, Zaitman D, Cohn G, et al. Lamivudine-stavudine-

induced liver failure in hepatitis B cirrhosis. *Am J Gastroenterol.* 1997; 92(9):1563-4.

Dogan UB, Kara B, Gumurdulu Y, Soyulu A, Akin MS. Comparison of the efficacy of tenofovir and entecavir for the treatment of nucleos(t)ide-naive patients with chronic hepatitis B. *Turk J Gastroenterol.* 2012; 23(3):247-52.

### Wrong Publication Type

Bouchard MJ, Navas-Martin S. Hepatitis B and C virus hepatoCarcinogenesis: lessons learned and future challenges. *Cancer Lett.* 2011; 305(2):123-43.

Brahams D. Deaths in US fialuridine trial. *Lancet.* 1994; 343(8911):1494-5.

Buffington J, Mast EE. Pre vaccination screening for hepatitis B among sexually active adolescents and young adults. *Clin Infect Dis.* 1998; 27(6):1562-3.

Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *JAMA.* 2003; 289(8):959-62.

Chien RN, Liaw YF. Nucleos(t)ide analogues for hepatitis B virus: strategies for long-term success. *Best Pract Res Clin Gastroenterol.* 2008; 22(6):1081-92.

De Clercq E. The discovery of antiviral agents: ten different compounds, ten different stories. *Med Res Rev.* 2008; 28(6):929-53.

Eun JR, Lee HJ, Lee S, Kim TN, Jang BIK, Choi JW, et al. The effect of lamivudine and adefovir dipivoxil on preventing hepatocellular carcinoma in HBV-related liver cirrhosis. *Hepatology.* 2007; 46:664A-5A.

Fung J, Ching-Lung L, Seto W-K, Yuen M-F. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. *J Antimicrob Chemother.* 2011; 66:2715-25.

Gentilcore E, Marzano A, Smedile A, Rizzetto M. Ineffectiveness of hepatitis B vaccination in lamivudine-treated cirrhotics. *J Hepatol.* 2004; 40(2):357-8.

Ghany M, Liang TJ. Drug targets and molecular mechanisms of drug resistance in chronic hepatitis B. *Gastroenterology.* 2007; 132(4):1574-85.

Gish RG, Gadano AC. Chronic hepatitis B: current epidemiology in the Americas and implications for management. *J Viral Hepat.* 2006; 13(12):787-98.

## Appendix A4. Excluded Studies

- Grady GF. Strategies for prevention of hepatitis B as a sexually transmitted disease. *Sex Transm Dis.* 1981; 8(4 suppl):344-8.
- Grime P. Blood-borne virus screening in health care workers: Is it worthwhile? *Occup Med.* 2007; 57(8):544-6.
- Hadziyannis SJ. Lymphoblastoid interferon in controlled trials of chronic hepatitis B virus infection. *Hepatology.* 1988; 8(3):696-8.
- Herzenberg H. Interferon alfa-2b for chronic hepatitis B. *N Engl J Med.* 1991; 324(7):493-4.
- Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology.* 2007; 45(4):1056-75.
- Ibrahim N, Yaseen AlSabbagh EM, Qintar M, Samra M, Shahrour Y. Interferon beta for chronic hepatitis B. *Cochrane Database Syst Rev.*2010(6).
- Imanishi J, Kishida T. Clinical trials with interferon in Japan. *Tex Rep Biol Med.* 1981; 41:647-52.
- Liaw YF. Impact of hepatitis B therapy on the long-term outcome of liver disease. *Liver Int.* 2011; 31 Suppl 1:117-21.
- Liaw YF, Lin SM, Sheen IS, Chen TJ, Chu CM. Treatment of chronic type B hepatitis in Southeast Asia. *Am Med J.* 1988; 85(2A):147-9.
- Lok ASF, Lai CL, Wu PC, Lau JY, Leung EK, Wong LS. Treatment of chronic hepatitis B with interferon: experience in Asian patients. *Semin Liver Dis.* 1989; 9(4):249-53.
- Martelli CM, Turchi M, Souto FJ, Saez-Alquezar A, Andrade AL, Zicker F. Anti-HBc testing for blood donations in areas with intermediate hepatitis B endemicity. *Pan American Journal of Public Health.* 1999; 6(1):69-73.
- Muller R, Baumgarten R, Markus R, Schulz M, Wittenberg H, Hintsche-Kilger B, et al. Low dose alpha interferon treatment in chronic hepatitis B virus infection. *Gut.* 1993; 34(2 Suppl):S97-8.
- Mumtaz K, Hamid S, Jafri W. Pegylated interferon for chronic hepatitis B. *Cochrane Database Syst Rev.*2009(1).
- Mumtaz K, Khan HS, Bhatti IO, Hamid S, Jafri W. Interferon alpha for chronic hepatitis B. *Cochrane Database Syst Rev.*2010(6).
- Mumtaz K, Subhan A, Hamid S, Jafri W. Lamivudine for chronic hepatitis B in adults. *Cochrane Database Syst Rev.*2009(1).
- Murofushi T, Takeuchi N, Ozeki H, Mizuno M. Acute vestibular dysfunction associated with interferon-alpha therapy. *Eur Arch Otorhinolaryngol.* 1998; 255(2):77-8.
- Njei B, Kumar S, Kongnyuy EJ. Adefovir dipivoxil versus other antiviral drugs for chronic hepatitis B. *Cochrane Database Syst Rev.*2011(12).
- Njei B, Kumar S, Kongnyuy EJ. Adefovir dipivoxil for chronic hepatitis B. *Cochrane Database Syst Rev.*2011(12).
- Pablo K, Rooks P, Nevin R. Benefits of serologic screening for hepatitis B immunity in military recruits. *J Infect Dis.* 2005; 192(12):2180-1; author reply 1.
- Perez-Roldan F, Gonzalez-Carro P, Villafanez-Garcia MC. Adefovir dipivoxil for chemotherapy-induced activation of hepatitis B virus infection. *N Engl J Med.* 2005; 352(3):310-1.
- Propst A, Propst T, Dietze O, Kathrein H, Judmeier G, Vogel W. Development of granulomatous hepatitis during treatment with interferon-alpha 2b. *Dig Dis Sci.* 1995 ; 40(10):2117-8.
- Puliyel JM, Taneja V, Jindal K, Thomas N. Hepatitis B leading to hepatocellular carcinoma: calculating the risk. *Indian J Gastroenterol.* 2001; 20(6):251-2.
- Quaglio G, Lugoboni F, Mezzelani P, Des Jarlais DC, Lechi A. Hepatitis vaccination among drug users. *Vaccine.* 2006; 24(15):2702-9.
- Rizzetto M, Volpes R, Smedile A. Response of pre-core mutant chronic hepatitis B infection to lamivudine. *J Med Virol.* 2000; 61(3):398-402.
- Rizzetto M, Zanetti AR. Progress in the prevention and control of viral hepatitis type B: closing remarks. *J Med Virol.* 2002; 67(3):463-6.
- Seeff LB, Beebe GW, Hoofnagle JH, Norman JE, Buskell-Bales Z, Waggoner JG, et al. A serologic follow-up of the 1942 epidemic of post-vaccination

## Appendix A4. Excluded Studies

hepatitis in the United States Army. *N Engl J Med*. 1987; 316(16):965-70.

Tron F. Hepatitis B *Vaccine*: clinical experience. IARC Sci Publ. 1984(63):279-95.

van der Veen YJJ, de Zwart O, Mackenbach J, Richardus JH. Cultural tailoring for the promotion of hepatitis B screening in Turkish Dutch: a protocol for a randomized controlled trial. *BMC Public Health*. 2010; 10:674.

Weimar W, Heijntink RA, Schalm SW, van Blankenstein M, Schellekens H, Masurel N, et al. Fibroblast interferon in HBsAg-positive chronic active hepatitis. *Lancet*. 1977; 2(8051):1282.

Woo GW, Krahn M, Prichett S. Entecavir for chronic hepatitis B. *Cochrane Database Syst Rev*. 2009(1).

### Wrong Comparison

Akuta N, Suzuki F, Suzuki Y, Sezaki H, Hosaka T, Someya T, et al. Favorable efficacy of long-term lamivudine therapy in patients with chronic hepatitis B: an 8-year follow-up study. *J Med Virol*. 2005; 75(4):491-8.

Alderman EM, Shapiro A, Spigland I, Coupey SM, Bashir M, Fox AS. Are there risk factors for hepatitis B infection in inner-city adolescents that justify prevaccination screening? *J Adolesc Health*. 1998; 22(5):389-93.

Andreone P, Cursaro C, Gramenzi A, Zavagliz C, Rezakovic I, Altomare E, et al. A randomized controlled trial of thymosin-alpha1 versus interferon alfa treatment in patients with hepatitis B e antigen antibody--and hepatitis B virus DNA--positive chronic hepatitis B. *Hepatology*. 1996 ; 24(4):774-7.

Ascione A, Ascione T, Lanza AG, Utech W, Di Costanzo GG, Macri M. Factors influencing outcome of lamivudine in anti-HBe-positive chronic hepatitis B. *HepatoGastroenterology*. 2006; 53(72):919-23.

Bosch O, Moraleda G, Castillo I, Carreno V. Treatment of chronic hepatitis B with recombinant interferon alpha versus recombinant interferon alpha plus levamisole. *J Hepatol*. 1993; 19(3):437-41.

Chang M-H, You S-L, Chen C-J, Liu C-J, Lee C-M, Lin S-M, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B *Vaccinees*: a 20-year follow-up study. *J Natl Cancer Inst*. 2009; 101(19):1348-55.

Da Silva LC, Pinho JR, Sitnik R, Da Fonseca LE, Carrilho FJ. Efficacy and tolerability of long-term therapy using high lamivudine doses for the treatment of chronic hepatitis B. *J Gastroenterol*. 2001; 36(7):476-85.

Da Villa G. Successful mass vaccination against hepatitis B virus in a hyperendemic area in Italy. *Res Virol*. 1993; 144(4):255-8.

Dai C-Y, Yu M-L, Hsieh M-Y, Lee L-P, Hou N-J, Huang J-F, et al. Early response to lamivudine therapy in clinically non-cirrhotic chronic hepatitis B patients with decompensation. *Liver Int*. 2007; 27(10):1364-70.

Del Poggio P, Zaccanelli M, Oggionni M, Colombo S, Jamoletti C, Puhalo V. Low-dose tenofovir is more potent than adefovir and is effective in controlling HBV viremia in chronic HBeAg-negative hepatitis B. *World J Gastroenterol*. 2007; 13(30):4096-9.

Demirturk N, Usluer G, Ozgunes I, Colak H, Kartal ED, Dincer S. Comparison of different treatment combinations for chronic hepatitis B infection. *J Chemother*. 2002; 14(3):285-9.

Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M. A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med*. 1995; 333(25):1657-61.

Dooley JS, Davis GL, Peters M, Waggoner JG, Goodman Z, Hoofnagle JH. Pilot study of recombinant human alpha-interferon for chronic type B hepatitis. *Gastroenterology*. 1986; 90(1):150-7.

Eisenberg M, Rosno S, Garcia G, Konrad MW, Gregory PB, Robinson WS, et al. Preliminary trial of recombinant fibroblast interferon in chronic hepatitis B virus infection. *Antimicrob Agents Chemother*. 1986; 29(1):122-6.

Gonzalez-Mateos F, Garcia-Monzon C, Garcia-Buey L, Garcia-Sanchez A, Pajares JM, Moreno-Otero R. Long-term effect of interferon alpha alone or after prednisone withdrawal in chronic hepatitis B. Interim report and review of the literature. *HepatoGastroenterology*. 1995; 42(6):893-9.

Hope RL, Weltman M, Dingley J, Fiatarone J, Hope AH, Craig PI, et al. Interferon alfa for chronic active hepatitis B. Long term follow-up of 62 patients: outcomes and predictors of response. *Med J Aust*. 1995; 162(1):8-11.

## Appendix A4. Excluded Studies

- Kim HJ, Park DI, Park JH, Cho YK, Sohn CI, Jeon WK, et al. Comparison between clevudine and entecavir treatment for antiviral-naive patients with chronic hepatitis B. *Liver Int.* 2010; 30(6):834-40.
- Krogsgaard K, Marcellin P, Trepo C, Berthelot P, Sanchez-Tapias JM, Bassendine M, et al. Prednisolone withdrawal therapy enhances the effect of human lymphoblastoid interferon in chronic hepatitis B. INTERPRED Trial Group. *J Hepatol.* 1996; 25(6):803-13.
- Kurashige N, Ohkawa K, Hiramatsu N, Yakushijin T, Mochizuki K, Oze T, et al. Lamivudine-to-entecavir switching treatment in type B chronic hepatitis patients without evidence of lamivudine resistance. *J Gastroenterol.* 2009; 44(8):864-70.
- Kurokawa M, Hiramatsu N, Oze T, Yakushijin T, Miyazaki M, Hosui A, et al. Long-term effect of lamivudine treatment on the incidence of hepatocellular carcinoma in patients with hepatitis B virus infection. *J Gastroenterol.* 2012; 47(5):577-85.
- Lai C-L, Gane E, Liaw Y-F, Hsu C-W, Thongsawat S, Wang Y, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med.* 2007; 357(25):2576-88.
- Lai C-L, Yuen M-F, Hui C-K, Garrido-Lestache S, Cheng CT-K, Lai Y-P. Comparison of the efficacy of lamivudine and famciclovir in Asian patients with chronic hepatitis B: results of 24 weeks of therapy. *J Med Virol.* 2002; 67(3):334-8.
- Liaw YF, Sheen IS, Lee CM, Akarca US, Papatheodoridis GV, Suet-Hing Wong F, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. *Hepatology.* 2011; 53(1):62-72.
- Leung NW, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, et al. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology.* 2001; 33(6):1527-32.
- Liaw YF, Jia JD, Chan HLY, Han KH, Tanwandee T, Chuang WL, et al. Shorter durations and lower doses of peginterferon alfa-2a are associated with inferior hepatitis B e antigen seroconversion rates in hepatitis B virus genotypes B or C. *Hepatology.* 2011; 54(5):1591-9.
- Liaw YF, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, et al. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *Gastroenterology.* 2000; 119(1):172-80.
- Lok AS, Novick DM, Karayiannis P, Dunk AA, Sherlock S, Thomas HC. A randomized study of the effects of adenine arabinoside 5'-monophosphate (short or long courses) and lymphoblastoid interferon on hepatitis B virus replication. *Hepatology.* 1985; 5(6):1132-8.
- Ma H, Yang R-F, Wei L. Quantitative serum HBsAg and HBeAg are strong predictors of sustained HBeAg seroconversion to pegylated interferon alfa-2b in HBeAg-positive patients. *J Gastroenterol Hepatol.* 2010 ; 25(9):1498-506.
- Marcellin P, Bonino F, Lau GKK, Farci P, Yurdaydin C, Piratvisuth T, et al. Sustained response of hepatitis B e antigen-negative patients 3 years after treatment with peginterferon alpha-2a. *Gastroenterology.* 2009; 136(7):2169-79.e1-4.
- Mazur W, Krol F, Cianciara J, Nazzal K, Gladysz A, Juszczyk J, et al. A multi-center open study to determine the effect of lamivudine on HBV DNA clearance and to assess the safety of the regimen in patients with chronic hepatitis B infection. *Med Sci Monit.* 2002; 8(4):CR257-62.
- Mellerrup MT, Krogsgaard K, Mathurin P, Gluud C, Poynard T. Sequential combination of glucocorticosteroids and alfa interferon versus alfa interferon alone for HBeAg-positive chronic hepatitis B. *Cochrane Database Syst Rev.* 2002(2):CD000345.
- Mihm U, Sarrazin C, Herrmann E, Teuber G, von Wagner M, Kronenberger B, et al. Response predictors and results of a long-term treatment with lamivudine in patients with chronic hepatitis B. *Z Gastroenterol.* 2003; 41(3):249-54.
- Minuk GY, German GB, Bernstein C, Benarroch A, Gauthier T, Sekla L. A pilot study of steroid withdrawal followed by oral acyclovir in the treatment of chronic type B hepatitis. *Clin Invest Med.* 1992; 15(6):506-12.
- Montesano R. Hepatitis B immunization and hepatocellular carcinoma: The Gambia Hepatitis Intervention Study. *J Med Virol.* 2002; 67(3):444-6.
- Munoz R, Castellano G, Fernandez I, Alvarez MV, Manzano ML, Marcos MS, et al. A pilot study of

## Appendix A4. Excluded Studies

- beta-interferon for treatment of patients with chronic hepatitis B who failed to respond to alpha-interferon. *J Hepatol.* 2002; 37(5):655-9.
- Musch E, Hogemann B, Gerritzen A, Fischer HP, Wiese M, Kruis W, et al. Phase II clinical trial of combined natural interferon-beta plus recombinant interferon-gamma treatment of chronic hepatitis B. *HepatoGastroenterology.* 1998; 45(24):2282-94.
- Nevens F, Main J, Honkoop P, Tyrrell DL, Barber J, Sullivan MT, et al. Lamivudine therapy for chronic hepatitis B: a six-month randomized dose-ranging study. *Gastroenterology.* 1997 ; 113(4):1258-63.
- Oliveri F, Santantonio T, Bellati G, Colombatto P, Mels GC, Carriero L, et al. Long term response to therapy of chronic anti-HBe-positive hepatitis B is poor independent of type and schedule of interferon. *Am J Gastroenterol.* 1999; 94(5):1366-72.
- Omata M, Imazeki F, Yokosuka O, Ito Y, Uchiumi K, Mori J, et al. Recombinant leukocyte a interferon treatment in patients with chronic hepatitis B virus infection. Pharmacokinetics, tolerance, and biologic effects. *Gastroenterology.* 1985; 88(4):870-80.
- Pradeep Kumar S, Medhi S, Asim M, Das BC, Gondal R, Kar P. Evaluation of adefovir & lamivudine in chronic hepatitis B: correlation with HBV viral kinetic, hepatic-necro inflammation & fibrosis. *Indian J Med Res.* 2011; 133:50-6.
- Roushan MR, Samie H, Amiri MJS. Efficacy of hepatitis B Vaccine in susceptible spouses of chronic hepatitis B virus infected individuals at the time of marriage. *Saudi Med J.* 2007; 28(4):540-3.
- Saruc M, Yuceyar H, Kucukmetin N, Demir MA, Kandiloglu AR. Combination thymosin-alpha 1 and interferon-alpha 2b in the treatment of anti-HBe-positive chronic hepatitis B in Turkey. *HepatoGastroenterology.* 2002; 49(45):798-802.
- Schiff E, Simsek H, Lee WM, Chao Y-C, Sette H, Jr., Janssen HLA, et al. Efficacy and safety of entecavir in patients with chronic hepatitis B and advanced hepatic fibrosis or cirrhosis.[Erratum appears in *Am J Gastroenterol.* 2009; 104(2):540]. *Am J Gastroenterol.* 2008; 103(11):2776-83.
- Scullard GH, Pollard RB, Smith JL, Sacks SL, Gregory PB, Robinson WS, et al. Antiviral treatment of chronic hepatitis B virus infection. I. Changes in viral markers with interferon combined with adenine arabinoside. *J Infect Dis.* 1981; 143(6):772-83.
- Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. *Health Technol Assess.* 2006; 10(28):iii-iv, xi-xiv, 1-183.
- Smith CI, Weissberg J, Bernhardt L, Gregory PB, Robinson WS, Merigan TC. Acute Dane particle suppression with recombinant leukocyte A interferon in chronic hepatitis B virus infection. *J Infect Dis.* 1983; 148(5):907-13.
- Suh DJ, Um SH, Herrmann E, Kim J-H, Lee YS, Lee HJ, et al. Early viral kinetics of telbivudine and entecavir: results of a 12-week randomized exploratory study with patients with HBeAg-positive chronic hepatitis B. *Antimicrob Agents Chemother.* 2010; 54(3):1242-7.
- Sypsa V, Hadjipaschali E, Hatzakis A. Prevalence, risk factors and evaluation of a screening strategy for chronic hepatitis C and B virus infections in healthy company employees. *Eur J Epidemiol.* 2001; 17(8):721-8.
- Villeneuve JP, Condreay LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, et al. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology.* 2000; 31(1):207-10.
- Wolters LM, van Nunen AB, Niesters HG, de Man RA. Contrasting patterns of response to lamivudine monotherapy in chronic hepatitis B patients. *Scand J Gastroenterol Suppl.* 2000(232):74-8.
- Yao GB, Zhu M, Wang YM, Xu DZ, Tan DM, Chen CW, et al. [A double-blind, double-dummy, randomized, controlled study of entecavir versus lamivudine for treatment of chronic hepatitis B]. *Zhonghua Nei Ke Za Zhi.* 2006; 45(11):891-5.
- Zavaglia C, Bottelli R, Bellati G, Asti L, Mondazzi L, Iamoni G, et al. Treatment of chronic hepatitis B (HBeAg-HBV DNA-positive) with lymphoblastoid alpha interferon with or without corticosteroids: short- and long-term follow-up. *Ital J Gastroenterol.* 1996; 28(6):324-31.
- Zhao H, Si CW, Wei L, Wan MB, Ying YK, Hou JL, et al. [A multicenter, randomized, open-label study of the safety and effectiveness of pegylated interferon alpha 2b and interferon alpha 2b in treating HBeAg positive chronic hepatitis B patients]. *Zhonghua Gan Zang Bing Za Zhi.* 2006; 14(5):323-6.

## Appendix A4. Excluded Studies

Zheng Y, Zhao L, Wu T, Guo S, Chen Y, Zhou T. Efficacy of consensus interferon in treatment of HBeAg-positive chronic hepatitis B: a multicentre, randomized controlled trial. *Viol J*. 2009; 6:99.

Zhu M, Xu B, Yao GB. [Durability of HBeAg seroconversion in lamivudine treatment of chronic hepatitis B patients]. *Zhonghua Gan Zang Bing Za Zhi*. 2005; 13(7):534-6.

Zollner B, Petersen J, Schafer P, Schroter M, Laufs R, Sterneck M, et al. Subtype-dependent response of hepatitis B virus during the early phase of lamivudine treatment. *Clin Infect Dis*. 2002; 34(9):1273-7.

Zollner B, Schafer P, Feucht HH, Schroter M, Petersen J, Laufs R. Correlation of hepatitis B virus load with loss of e antigen and emerging drug-resistant variants during lamivudine therapy. *J Med Virol*. 2001; 65(4):659-63.

Zylberberg H, Jiang J, Pialoux G, Driss F, Carnot F, Dubois F, et al. Alpha-interferon for chronic active hepatitis B in human immunodeficiency virus-infected patients. *Gastroenterol Clin Biol*. 1996; 20(11):968-71.

Rakela J, Wood JR, Czaja AJ, O'Brien PC, Taswell HF, Bowyer BA, et al. Long-term versus short-term treatment with recombinant interferon alfa-2a in patients with chronic hepatitis B: a prospective, randomized treatment trial. *Mayo Clin Proc*. 1990; 65(10):1330-5.

### Duplicate Data

Chang T-T, Lai C-L, Chien R-N, Guan R, Lim S-G, Lee C-M, et al. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol*. 2004; 19(11):1276-82.

Cooksley H, Chokshi S, Maayan Y, Wedemeyer H, Andreone P, Gilson R, et al. Hepatitis B virus e antigen loss during adefovir dipivoxil therapy is associated with enhanced virus-specific CD4+ T-cell reactivity. *Antimicrob Agents Chemother*. 2008; 52(1):312-20.

Izzedine H, Hulot JS, Launay-Vacher V, Marcellini P, Hadziyannis SJ, Currie G, et al. Renal safety of adefovir dipivoxil in patients with chronic hepatitis B: two double-blind, randomized, placebo-controlled studies. *Kidney Int*. 2004; 66(3):1153-8.

Lim SG, Marcellin P, Tassopoulos N, Hadziyannis S, Chang TT, Tong M, et al. Clinical trial: Effects of

adefovir dipivoxil therapy in Asian and Caucasian patients with chronic hepatitis B. *Aliment Pharmacol Ther*. 2007; 26(10):1419-28.

Lok AS, Ma OC, Lau JY. Interferon alfa therapy in patients with chronic hepatitis B virus infection. Effects on hepatitis B virus DNA in the liver. *Gastroenterology*. 1991; 100(3):756-61.

Lok ASF, Lai C-L, Leung N, Yao G-B, Cui Z-Y, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology*. 2003; 125(6):1714-22.

Perrillo RP, Lai CL, Liaw YF, Dienstag JL, Schiff ER, Schalm SW, et al. Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. *Hepatology*. 2002; 36(1):186-94.

Sung JY, Tsoi KKF, Wong VWS, Li KCT, Chan HLY. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2008; 28(9):1067-77.

Yao GB. Management of hepatitis B in China. *J Med Virol*. 2000; 61(3):392-7.

Yao GB, Zhu M, Cui ZY, Wang BE, Yao JL, Zeng MD. A 7-year study of lamivudine therapy for hepatitis B virus e antigen-positive chronic hepatitis B patients in China. *J Dig Dis*. 2009; 10(2):131-7.

Yuen MF, Chow DH, Tsui K, Wong BC, Yuen JC, Wong DK, et al. Liver histology of Asian patients with chronic hepatitis B on prolonged lamivudine therapy. *Aliment Pharmacol Ther*. 2005; 21(7):841-9.

Yuen M-F, Seto W-K, Chow DH-F, Tsui K, Wong DK-H, Ngai VW-S, et al. Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. *Antivir Ther*. 2007; 12(8):1295-303.

Zhang QQ, An X, Liu YH, Li SY, Zhong Q, Wang J, et al. Long-term nucleos(t)ide analogues therapy for adults with chronic hepatitis B reduces the risk of long-term complications: a meta-analysis. *Viol J*. 2011; 8:72.

## **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.

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



## Appendix B1. Screening Strategies Evidence Table

Author, year Country	Eligibility	N	Baseline characteristics	Screening strategy	HBsAg positive	Results	Funding source	Quality	Comments
Spennato 2013 <sup>35</sup> France	STD clinic attendees in France	6,194	Age 20-29 years: 62% Female: 56% Self-reported injection drug use: 0.7% High endemic area (prevalence $\geq 8\%$ ) country of birth: 7.2%	A: Screen all B: Screening those born in moderate or high prevalence ( $\geq 2\%$ ) country C: Same as B, plus men and unemployed D: Screen those born in moderate or high prevalence country, transfusion history or blood contacts, tattoos, body piercing, more than two sexual partners during the last year, hepatitis among sexual partners or household members, or intravenous or intranasal drug use; no screening for patients who reported prior HBV vaccination E: Same as D, except prior vaccination history not considered	0.8% (49/6194)	<b>A vs. B vs. C vs. D vs. E</b> Proportion screened: 100% (6194/6194) vs. 12% (761/6011) vs. 64% (3949/6194) vs. 73% (4504/6194) vs. 84% (5205/6194) Sensitivity: 100% (49/49) vs. 31% (15/48) vs. 98% (48/49) vs. 84% (41/49) vs. 94% (46/49) Specificity: 0% (0/6145) vs. 87% (5217/5963) vs. 37% (2244/6145) vs. 27% (1682/6145) vs. 16% (986/6145) Number needed to screen to identify one case of HBV infection: 126 vs. 16 vs. 82 vs. 110 vs. 113	Not stated	Fair	Proportion screened, and number needed to screen calculated from prevalence and sensitivity/specificity provided in the article. 183 patients did not have information on birth country (1 HBV case). No cases in patients with history of injection drug use. Prevalence in country of origin (adjusted OR 15.8 for medium prevalence, OR 44 for high prevalence), male sex (adjusted OR 2.4), unemployed (adjusted OR 3.2), and not vaccinated (adjusted OR 2.9) independent predictors. Blood transfusion, tattoos, body piercing, number of sex partners, men having sex with men, intranasal drug use not predictive. AUROC 0.92 for strategy C.

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**

<b>Study, year</b>	<b>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</b>	<b>Did the study evaluate a representative spectrum?</b>	<b>Did the study report the proportion of eligible patients who met inclusion criteria who underwent screening?</b>	<b>Was there a high rate of non-screening among eligible patients?</b>	<b>Did the study describe methods for ascertaining risk factors?</b>	<b>Did the study prospectively compare different pre-defined screening strategies?</b>	<b>Quality</b>
Spenatto 2013 <sup>35</sup>	Yes	Yes	Yes	No (19%)	Yes	No	Fair

**Appendix B3. Vaccination Studies Evidence Table**

<b>Author, year</b>	<b>Study design</b>	<b>No. of centers Country</b>	<b>Prevalence of Hepatitis B, if reported</b>	<b>Study duration Mean followup</b>	<b>Baseline demographics</b>	<b>Eligibility criteria</b>	<b>Exclusion criteria</b>
<b><i>Trials</i></b>							
Coutinho 1983 <sup>38</sup>	RCT	Netherlands Centers NR	Low prevalence country; among 2946 male homosexuals, 60% had evidence of past or present infection; among 316 at-risk men, annual attack rate of 28%	21.5 months	Vaccine vs. placebo Age, mean: 31 vs. 30 years 100% male ALT: see eligibility	Male homosexuals between 16 and 50 years of age, negative for HBsAg, anti-HBsAg, and anti-HBc, with ALT <50 IU/l, no serious illness, and >2 different male sexual partners in the preceeding 6 months	See eligibility criteria
Szmunes 1980 <sup>37</sup>	RCT	United States Centers NR	In over 10,000 homosexual men tested, 68% had evidence of past or present infection	24 months	Vaccine vs. placebo Age, mean: 29 vs. 29 years 100% male 86% vs. 88% White ALT: see eligibility	HBV-negative persons who were exclusively or predominantly homosexual, with no recent symptoms of hepatitis, negative for HBsAg, anti-HBs, and anti-HBc, and with ALT<50 IU in a blood specimen from preceeding 2 weeks	See eligibility criteria
Francis 1982 <sup>39</sup>	RCT	United States 5 centers	Not reported	18 months	Vaccine vs. placebo Age, mean: 30 vs. 29 years 100% male 88% vs. 91% White ALT: see eligibility	Men aged ≥18 years with homosexual preference who were negative for HBV serological markers (negative HBsAg, anti-HBc, anti-HBs) and had normal ALT (<53 IU)	See eligibility criteria
<b><i>Systematic Review</i></b>							
<b>Author, year</b>	<b>Purpose of study</b>	<b>Databases searched, date of last search</b>	<b>Number of studies</b>	<b>Types of studies included/ limitations of primary studies</b>	<b>Methods for rating methodological quality of primary studies</b>	<b>Methods for synthesizing results of primary studies</b>	<b>Number of patients</b>
Chen 2009 <sup>36</sup>	Assess the harms/ benefits of HBV vaccine in health-care workers	Cochrane Hepato - Biliary Group Controlled Trials Registry, Cochrane Library, MEDLINE, EMBASE through February 2003	21 total; 4 placebo-controlled	4 PCTs; all included studies conducted in high-risk population and were rated low quality	Assessment of method of allocation and concealment, blinding and attrition	Random and fixed effects models applied	HBV vaccine: 1365 Placebo: 1332

## Appendix B3. Vaccination Studies Evidence Table

Author, year	Number screened Number eligible Number enrolled Number analyzed	Withdrawals Loss to followup	Adjusted variables for statistical analysis (for observational studies)	Interventions	Results	Funding source
<b>Trials</b>						
Coutinho 1983 <sup>38</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) <u>Infection at 21.5 months</u> Hepatitis B (ALT $\geq$ 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
Szmunes 1980 <sup>37</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) <u>Infection at 18 months</u> Hepatitis B (ALT $\geq$ 90 IU only): 7 vs. 45 HBV events with ALT $\geq$ 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>39</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) <u>Infection at 18 months</u> 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
<b>Systematic Review</b>						
Author, year	Interventions	Results				
Chen 2009 <sup>36</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, I <sup>2</sup> =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

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to follow-up: differential/high?	Analyze people in the groups in which they were randomized?	Quality	
<b><i>Trials</i></b>												
Coutinho 1983 <sup>38</sup>	Unclear; method not described	Unclear	Yes; only significant difference on history of jaundice	Yes	Yes	Unclear; described as double-blind	Unclear; described as double-blind	Unclear	No/No	Yes	Fair	
Szmunes 1980 <sup>37</sup>	Unclear; method not described	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Good	
Francis 1982 <sup>39</sup>	Unclear; method not described	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	No/No	Yes	Fair	
<b><i>Systematic Review</i></b>												
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 <sup>36</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline demographics
<b>Placebo-controlled</b>					
Ali 2003 <sup>52</sup>	RCT	1 site Iraq	24 months duration; 6-12 months of treatment and followup (variable based on efficacy measures) Mean followup: NR	A. Lamivudine 100 mg daily (n=32) B. Placebo (n=30)	Age range: 25-45 years Male: NR Race: NR Baseline liver function: NR HBV markers: see eligibility Prior HBV treatment: NR
Bayraktar 1993 <sup>44</sup>	Controlled trial	Unclear (likely single site) Turkey	Study duration: 6 months Mean duration of followup: NR	A. Interferon alfa 2b 5 MU IM 3x/week (n=25) B. No treatment (n=10)	A vs. B Mean age 35 vs 36 years 72% vs 70% male Race NR 20% vs 30% cirrhosis
Bozkaya 2005 <sup>53</sup>	Non-randomized controlled trial	1 site Turkey	1 year treatment; 6 months post-treatment followup (for those in treatment group) Mean followup: NR	A: Lamivudine 100 mg daily (n=18) B: Untreated group with raised ALT (n=19) C: Untreated group with normal ALT (n=18)	A vs. B vs. C Age, mean: 32 vs. 39 vs. 38 years Male: 94% vs. 68% vs. 17% Race: NR ALT, median (range): 64 (38-186) vs. 48 (35-168) vs. 17 (11-30) IU/l HBV-DNA, median (range): $1.2 \times 10^3$ ( $1 \times 10^2$ - $9.7 \times 10^4$ ) vs. $4.2 \times 10^3$ ( $1 \times 10^2$ - $3.6 \times 10^5$ ) vs. $2.5 \times 10^3$ ( $1 \times 10^2$ - $5.2 \times 10^5$ ) copies/ml HAI, median (range): 4.5 (1.0-16.0) vs. 4.0 (1.0-8.0) vs. 2.0 (1.0-4.0) Presence of fibrosis: 33% vs. 24% vs. 0 Prior HBV treatment: No patients
Chan 2007 <sup>54</sup>	RCT	8 sites China	24 months of treatment; 6 months followup Mean followup: NR	A. Lamivudine 100 mg daily (n=89) B. Placebo (n=47)	A vs. B Age, mean: 39 vs. 39 years Male: 84% vs. 83% Race: NR Cirrhosis: 31% vs. 21% ALT, mean: 2.1 vs. 2.6 x ULN Necroinflammatory score, median: 5 vs. 5 Fibrosis score, median: 2 vs. 2 HBV DNA, mean: 5.7 vs. 5.6 log copies/ml HBeAg positive: 6% vs. 6% Prior HBV treatment: NR, but allowed (see eligibility criteria)

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Study design</b>	<b>Number of sites Country</b>	<b>Study duration Mean followup</b>	<b>Interventions</b>	<b>Baseline demographics</b>
Dienstag 1999 <sup>55</sup>	RCT	34 sites United States	Study duration: 68 weeks Treatment duration: 52 weeks Post-treatment followup: 16 weeks	A. Lamivudine 100 mg daily (n=66) B. Placebo (n=71)	A vs. B Median age: 40 vs. 38 years Sex: 86% vs. 80% male Race: 59% vs. 56% White, 24% vs. 17% Asian, 15% vs. 18% Black Cirrhosis: 6% vs. 14% Median HAI score: 10 vs. 11 Median serum HBV DNA: 102.2 vs. 56.5 pg/ml Median serum ALT: 125 vs. 135 IU/l Median serum bilirubin: 0.7 vs. 0.7 mg/dl Median serum albumin: 3.9 vs. 3.8 g/dl
Hadziyannis 1990 <sup>45</sup>	RCT	Unclear (likely single site) Greece	Study duration: 1 year (2 year followup for some patients) Mean duration of followup: NR	A. Interferon alfa 2b 3 MU 3x/week for 14-16 weeks (n=25) B. No treatment (n=25)	A vs. B Mean age 49 vs 48 years 92% vs 96% male Race NR 40% vs 48% cirrhosis 96% vs 100% anti-HBe positive Mean serum HBV DNA 26 vs 24 pg/mL Mean serum ALT 1203 vs 175 IU/L
Hadziyannis 2003 <sup>40</sup>	RCT	32 sites; Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore	48 weeks duration and followup; Safety analysis included all events that occurred within 30 days of drug discontinuation	A. Adefovir 10 mg daily (n=123) B. Placebo (n=62)	A vs. B Age, mean: 46 vs. 45 years Male: 83% vs. 82% Race: 67% vs. 66% white; 4% vs. 2% black; 29% vs. 33% Asian ALT x ULN, mean: 3.5 vs. 3.6 HBV DNA, mean: 6.9 vs. 6.9 log copies/ml Knodell necroinflammatory activity score, mean: 7.7 vs 7.1 Knodell fibrosis score, mean: 1.9 vs 1.8 Cirrhosis: 11% vs. 10% Prior interferon alfa treatment: 39% vs. 46% Prior lamivudine treatment: 8% vs. 7% Prior famciclovir treatment: 6% vs. 11% Note: some patients had received more than one medication

## Appendix B5. Treatment Trials Evidence Table

Author, year	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline demographics
Jonas 2008 <sup>41</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 log <sub>10</sub> 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>56</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>57</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**

<b>Author, year</b>	<b>Study design</b>	<b>Number of sites Country</b>	<b>Study duration Mean followup</b>	<b>Interventions</b>	<b>Baseline demographics</b>
Liaw 2004 <sup>16</sup>	RCT	41 sites Australia, China, Malaysia, New Zealand, the Phillipines, Singapore, Taiwan, Thailand	Maximum 5 years (blinded phase terminated by data safety and monitoring board at second interim analysis because results showed efficacy) Treatment duration, median (range): 32.4 (0 -42) months Mean followup: NR	A. Lamivudine 100 mg daily (n=436) B. Placebo (n=215)	A vs. B Age, median: 43 vs. 44 years Male: 85% vs. 85% Race: Asian 98% vs. 98% Child-Pugh score 5: 78% vs. 73% 6: 17% vs. 19% >7: 5% vs. 8% Ishak fibrosis score 4: 40% vs. 35% 5: 29% vs. 26% 6: 31% vs. 39% HBV DNA, median (range): 11.7 (<0.7- 109,800) vs. 21.5 (<0.7-4234) mEq/ml HBV DNA >0.7 mEq/ml: 79% vs. 81% HBeAg positive: 58% vs. 58% ALT, median (range): 70 (14-959) vs. 68 (7- 821) U/LALT >1 x ULN: 78% vs. 80% Prior HBV treatment: NR, but allowed (see eligibility criteria)
Lin 1999 <sup>3</sup>	RCT	Single site China	18 weeks treatment + mean 7 years followup (range 1 to 11 years)	A. Interferon alfa 2a 4-5 MU/m <sup>2</sup> (n=67) B. Placebo (n=34)	A vs. B Mean age 32 vs 32 years 100% male (both groups) 100% Chinese (both groups) 10% vs 15% cirrhosis Mean ALT 227 vs 256 U/L Mean AFP 9 vs 11 mg/ml
Marcellin 2003 <sup>42</sup>	RCT	78 sites North America, Europe, Australia, and Southeast Asia	48 weeks duration and followup; Safety analysis included all events that occurred within 30 days of drug discontinuation	A. Adefovir 10 mg daily (n=172) B. Adefovir 30 mg daily (n=173) C. Placebo (n=170)	A vs. B vs. C Age, mean: 34 vs. 34 vs. 37 years Male: 76% vs. 75% vs. 71% Race: 35% vs. 37% vs. 36% white, 5% vs. 3% vs. 2% black, 60% vs. 58 vs. 60% Asian, 1% vs. 2% vs. 2% other ALT (xULN), mean: 3.4 vs 3.0 vs. 3.4 HBV DNA, mean: 8.25 vs. 8.22 vs. 8.12 log copies/mL Total Knodell score, mean: 9.01 vs. 9.55 vs. 9.65 Knodell necroinflammatory score, mean: 7.37 vs. 7.84 vs. 7.83 Knodell fibrosis score, mean: 1.64 vs. 1.71 vs. 1.83

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline demographics
					HBeAg positive: 100% Prior interferon alfa treatment: 24.9% (123/494)
Mazzella 1999 <sup>75</sup>	RCT	Single site Italy	6 months treatment + 7 years followup	A. Interferon alfa 2a, mean dose 648 MU (n=33) B. No treatment (n=31)	A vs B Mean age 36 vs 41 years 76% vs 81% male Race NR 0% cirrhosis (both groups) Mean ALT 106 vs 144 U/L
Muller 1990 <sup>47</sup>	RCT	Unclear (likely single site) Germany	Study duration: 4 months Mean duration of followup: NR	A. Interferon alfa 2b 3 MU SC 3x/week (n=30) B. No treatment (n=28)	A vs. B Mean age NR; range 18-65 years 79% male Race NR 5% cirrhosis 96% vs 96% HBeAg positive
Murray 2012 <sup>61</sup>	RCT	21 sites United States, Bulgaria, France, Poland, Romania, Spain, Turkey	72 weeks	A. Tenofovir 300 mg qd B. placebo	A vs. B Mean age 15 years both groups (SD 1; range 12-17 years) 73% vs 65% male 94% vs 91% White 1% vs 0% Black 1% vs 1% Asian 1% vs 4% other 92% vs 89% HBeAg positive 83% vs 87% prior HBV treatment Mean HBV DNA 8.01 vs 8.24 log <sub>10</sub> copies/mL Normal ALT 33% vs 22% Mean ALT 101 U/L
Perez 1990 <sup>48</sup>	RCT	Unclear (likely single site) Argentina	Study duration: 24 weeks (control phase) Mean duration of followup: NR	A. Prednisone run-in + interferon alfa 2b 10 MU SC 3x/week (n=17) B. No treatment (n=18)	A vs. B Mean age 39 years 71% vs 83% male Race NR Mean HBV DNA 570 vs 480 U/L Mean ALT 160 vs 109 pg/mL
Perrillo 1990 <sup>49</sup>	RCT	Multicenter (number of sites NR) United States	Study duration: 16 weeks (+ 6 months post-treatment observation) Mean duration of followup: NR	A. Prednisone run-in + interferon alfa 2b 5 MU qd (n=44) B. Placebo run-in + interferon alfa 2b, 1 MU qd (n=41) C. Placebo run-in + interferon alfa 2b 5 MU qd (n=41) D. No treatment (n=43)	A vs. B vs. C vs. D Mean age 40 vs 41 vs 41 vs 43 years 86% vs 80% vs 88% vs 84% male Race NR Mean HBV DNA 117 vs 127 vs 176 vs 146 pg/mL Mean serum ALT 152 vs 183 vs 182 vs 168 U/L

## Appendix B5. Treatment Trials Evidence Table

Author, year	Study design	Number of sites Country	Study duration Mean followup	Interventions	Baseline demographics
Sarin 1996 <sup>50</sup>	RCT	Unclear (likely single site) India	Study duration: 4 months + 12 months post-treatment followup Mean duration of followup: NR	A. Interferon alfa 2b 3 MU SC 3x/week (n=20) B. No treatment (n=21)	A vs. B Mean age 32 vs 37 years 80% vs 81% male Race NR 45% vs 43% cirrhosis
Tassopoulos 1999 <sup>58</sup>	RCT	1 site Greece	A vs. B Followed for up to 52 weeks (unblinding at week 26 and further participation based on week 24 sera results) Median exposure, (range): 366 (55-425) vs. 189 (11-257) days	A. Lamivudine 100 mg daily (n=60) B. Placebo (n=64) Note: Comparison data only available up to week 26	A vs. B Age, median: 42 vs. 44 years Male: 83% vs. 77% Race: NR Cirrhosis: 14% vs. 16% (table 1 states 18% (10/64) of persons in placebo group had cirrhosis) Knodell score, median (range): 5 (1-9) vs. 7 (2-10) Abnormal ALT: 97% vs. 95% ALT x ULN, median (range): 3.2 (0.6-16.4) vs. 3.3 (0.7-12.5) HBV DNA positive: 92% vs. 86% HBV DNA, median (range): 255.0 (1.3-18,000) vs. 95.5 (1.3-3900) pg/mL HBeAg negative: 98% vs. 98% anti-HBeAg positive: 98% vs. 100% HBsAg positive: 100% vs. 100% Prior HBV treatment: NR, but allowed (see eligibility criteria)
Waked 1990 <sup>51</sup>	RCT	Unclear (likely single site) Egypt	Study duration: 16 weeks (+ 12 months post-treatment observation) Mean duration of followup: NR	A. Interferon alfa 2b5 MU SC 2x/week (n=12) or daily (n=8) B. No treatment (n=20)	Mean age 36 years 78% male Race NR 40% cirrhosis
Yalcin 2004 <sup>59</sup>	RCT	One site Turkey	Duration: 12 months Active treatment: 12 weeks	A. Lamivudine 100 mg daily (n=13) B. Control (n=33)	A vs. B Age, mean: 23 vs. 25 years Male: 54% vs. 56% Race: NR HBV DNA, median: 4116 vs. 4094 pg/ml ALT, median: 27 vs. 30 IU/L HBeAg positive: 100% in both groups Inflammation score, median: 1 vs. 2 Fibrosis score, median: 0 in both groups

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Study design</b>	<b>Number of sites Country</b>	<b>Study duration Mean followup</b>	<b>Interventions</b>	<b>Baseline demographics</b>
Yao 1999 <sup>60</sup>	RCT	Multiple sites (number NR) China	Blinded treatment duration: 12 weeks Open-label treatment: 9 months	A. Lamivudine 100 mg daily (n=322) B. Placebo (n=107)	A vs. B Age: 32 vs. 31 years (unclear if this is mean or median) Male: 74% vs. 69% Race: NR, conducted in China HBV DNA: 96.9 vs. 91.9 pg/mL (unclear if this is mean or median) ALT: 1.7 vs. 1.5 times upper limit of normal (unclear if this is mean or median)
Zeng, 2006 <sup>43</sup>	RCT	Seven cities China	52 weeks; Only first 12 weeks met inclusion criteria	A. Adefovir 10 mg daily for first 12 weeks, open label adefovir 10 mg daily for next 28 weeks, adefovir 10 mg daily for remaining 12 weeks (n=240) B. Adefovir 10 mg daily for first 12 weeks, open label adefovir 10 mg daily for next 28 weeks, placebo for remaining 12 weeks (n=120) C. Placebo for first 12 weeks, open label adefovir 10 mg daily for next 28 weeks, adefovir 10 mg daily for remaining 12 weeks (n=120) Note: only data from first 12 weeks included; during this time, there were two treatment groups adefovir (A+B above) vs. placebo (C above)	A vs. B vs. C Age, mean: 31 vs. 32 vs. 32 years Male: 84% vs. 82% vs. 82% Race: 100% Chinese Cirrhosis: None ALT (xULN), mean: 3.9 vs. 3.3 vs. 3.8 HBV DNA, mean: 8.6 vs. 8.5 vs. 8.6 log10copies/mL HBeAg positive: 99% vs. 96% vs. 99% Prior lamivudine treatment: 35% vs. 32% vs. 27%
<b>Head-to-head</b>					
Chang 2006 <sup>64</sup> , Gish 2007 <sup>65</sup> , Chang 2009 <sup>66</sup>	RCT	137 centers North America, Asia, Australia, South America	96 weeks (52 weeks treatment + additional 44 weeks for partial responders; results for responders, partial responders and non-responders included in results)	A. Entecavir 0.5 mg qd B. Lamivudine 100 mg qd	A vs B n=354 vs 355 Mean age 35 vs 35 years 77% vs 74% male 58% vs 57% Asian 40% vs 40% White 2% vs 2% Black <1% vs 1% other 98% vs 99% HBeAg positive 2% vs 2% cirrhosis

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Study design</b>	<b>Number of sites Country</b>	<b>Study duration Mean followup</b>	<b>Interventions</b>	<b>Baseline demographics</b>
Lai 2002 <sup>68</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  <i>Dose ranging study; results for 0.01 and 0.1 mg not abstracted</i>	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>67</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>70</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

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Study design</b>	<b>Number of sites Country</b>	<b>Study duration Mean followup</b>	<b>Interventions</b>	<b>Baseline demographics</b>
Marcellin 2008 <sup>72</sup> Study 102 (HBeAg negative at baseline)	RCT	106 centers 15 countries in Europe, North America, Australia and New Zealand	48 weeks (time on treatment)	A. Tenofovir 300 mg qd B. Adefovir 10 mg qd	n=375 Mean age 44 years 77% male 65% White 25% Asian 3% Black 7% other 0% HBeAg positive 20% cirrhosis
Study 103 (HBeAg positive at baseline)					n=266 Mean age 34 years 69% male 52% White 36% Asian 7% Black 5% other 100% HBeAg negative 20% cirrhosis
Ren 2007 <sup>69</sup>	RCT	Single center (?) China	48 weeks (time on treatment)	A. Entecavir 0.5 mg qd B. Lamivudine 100 mg qd	n=42 (excluding 19 patients who previously failed lamivudine treatment and were switched to entecavir) Mean age 32 years 55% male 100% Asian (?) 100% HBeAg positive (?) Cirrhosis not reported

<b>Author, year</b>	<b>Eligibility criteria</b>	<b>Exclusion criteria</b>	<b>Number screened, eligible, enrolled, analyzed</b>	<b>Withdrawals (Number, %) Loss to followup (Number, %)</b>	<b>Adjusted variables for statistical analysis</b>
<b>Placebo-controlled</b>					
Ali 2003 <sup>52</sup>	HBsAg/anti-HBe positive with persistent anti-HBc IgM; asymptomatic	NR	Screened: NR Eligible: NR Enrolled: 74 Analyzed: 62	Withdrawals: 8.1% (6/74) Loss to followup: 8.1% (6/74)	N/A
Bayraktar 1993 <sup>44</sup>	Serum transaminase elevation >2x ULN for >6 months; HCV, HIV negative; HBsAg and HBeAg positive; chronic active hepatitis (per liver histology)	Decompenstated cirrhosis	Screened: NR Eligible: NR Enrolled: unclear Analyzed: 35	Withdrawals: none reported Loss to followup: none reported (unclear if results for all enrolled patients reported)	N/A

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (Number, %) Loss to followup (Number, %)	Adjusted variables for statistical analysis
Bozkaya 2005 <sup>53</sup>	ALT >1 x ULN; undetectable HBV-DNA by hybrid capture assay during monthly/bi-monthly assessments during year prior to entry into study; alcohol intake absent or <20 g per week; BMI <30 kg/m <sup>2</sup>	Presence of non-alcoholic steatohepatitis and significant liver steatosis; high BMI; high alcohol intake; drug-related toxicity	Screened: 390 Eligible: 55 Enrolled: 55 Analyzed: 55	NR	N/A
Chan 2007 <sup>54</sup>	Age >18 years; positive HBsAg for >6 months prior to screening; detectable HBV DNA by non-PCR based assay; significantly increased ALT levels (ALT 1.5 to 10 times ULN on >2 occasions in the previous 6 months or ALT above ULN with >1 flareup of ALT >200 IU/l in past 12 months); liver biopsy in past 12 months showing evidence of active hepatitis; once PCR-based HBV DNA assay was available, inclusion modified to HBV DNA >100,000 copies/ml	Hepatocellular carcinoma; ALT >10 times ULN at screening; decompensated liver disease; complications of liver cirrhosis; coinfection with HCV, HDV, or HIV; serious medical or psychiatric illness; use of immunosuppressive or immunomodulatory therapy within the previous 6 months; treatment with antiviral agent within the previous 6 months; history of hypersensitivity to nucleoside analogues; serum creatinine >1.5 times ULN; anti-nuclear antibody titre >1:160; serum amylase or lipase level >2 times ULN, hemoglobin <11 g/dl; white cell count <3x10 <sup>9</sup> /l; platelet count <100x10 <sup>9</sup> /l; pregnant or lactating women	Screened: 443 Eligible: 139 Enrolled: 139 Analyzed: 136	Withdrawals during treatment: 18% (25/136) Withdrawals post-treatment: 18% (19/105) Post randomization exclusions: 2.2% (3/139) Missing data: 6.6% (9/136)	OR adjusted for baseline HBV DNA and ALT levels

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (Number, %) Loss to followup (Number, %)	Adjusted variables for statistical analysis
Dienstag 1999 <sup>55</sup>	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	Previous antiviral therapy for hepatitis B; any treatment with antiviral drugs, immunomodulatory drugs, or cortico-steroids within the previous 6 months; bilirubin level >2.5 mg/dl; prothrombin time more than 3 seconds longer than normal; albumin level of less than 3.5 g/dl; history of ascites, variceal hemorrhage, or hepatic encephalopathy; co-infection with HCV, HDV, or HIV; a nuclear antibody titer of more than 1:160; a creatine level of more than 1.5 mg/dl; a hemoglobin level of less than 11 g/dl; a white-cell count of less than 3000 cells/mm <sup>3</sup> ; a neutrophil count of less than 1500 cells/mm <sup>3</sup> ; a platelet count of less than 100,000 cells/mm <sup>3</sup> ; presence of a confounding illness or other type of liver disease; pregnant or breastfeeding	Screened: 217 Eligible: NR Enrolled: 143 Analyzed: 137 *143 enrolled but 6 excluded at the baseline visit because they did not have 6 months of serum HBsAg	Withdrawals: 6 (2 patients withdrew before receiving treatment, 4 others excluded because they did not meet inclusion criteria)	Adjustments for odds ratios: ALT, HBV DNA, HAI score, race, age, sex, weight, and the presence of cirrhosis
Hadziyannis 1990 <sup>45</sup>	Chronic, active hepatitis; HBsAg positive; HBeAg negative/serum HBV DNA positive for >1 year	Decompensated cirrhosis; use of corticosteroids, immunosuppressive drugs or antivirals with 6 months	Screened: NR Eligible: NR Enrolled: 50 Analyzed: 35 (at 12 months)	Withdrawals: NR Loss to followup: unclear; results presented for 35/50 enrolled patients	N/A
Hadziyannis 2003 <sup>40</sup>	Age 16-65 years of age with HBeAg negative chronic HBV and compensated liver disease. Chronic HBV defined as HBsAg for at least 6 months, undetectable HBeAg, detectable anti-HBe, HBV DNA of at least 10 <sup>5</sup> 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	Screened: 391 Eligible: 235 Enrolled: 185 Analyzed: 178 for histologic outcomes Note: one patient in group B never received treatment and was excluded, baseline n=123 in group A, 61 in group B	Withdrawals: 2.4% (3/123) vs. 1.6% (1/61) Loss to followup: 0.8% (1/123) vs. 0% (0/61)	N/A



**Appendix B5. Treatment Trials Evidence Table**

Author, year	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (Number, %) Loss to followup (Number, %)	Adjusted variables for statistical analysis
	creatinine no more than 1.5 mg/dL, adequate blood count.	chemotherapeutic agents; serum alpha-fetoprotein of at least 50 ng/mL, evidence of a hepatic mass, liver disease not due to HBV, prior therapy for more than 12 weeks with a nucleoside or nucleotide analogue with activity against HBV, seropositivity for HIV, HCV, or HDV			
Jonas 2008 <sup>41</sup>	HBsAg present for at least 6 months prior to randomization, positive HBeAg at screening, HBV DNA >1 x 10 <sup>5</sup> copies/mL by PCR, ALT >1.5 xULN, compensated liver disease, adequate renal function, adequate hematologic function, negative serologic tests for HIV, HDV, HCV, and alpha-fetoprotein <50 ng/mL	Treatment for chronic HBV in previous 6 months, evidence of other liver diseases, received bone marrow transplant or organ transplants, received immunosuppressive, nephrotoxic, or hepatotoxic medications within 2 months of enrollment	Screened: 293 Eligible: 173 Enrolled: 173 Analyzed: 170 Note: only 12-17 year old age group included, n=83	A vs. B Withdrawals: 5% (3/56) vs. 0% (0/27) Loss to followup: none	N/A
Lai 1997 <sup>56</sup>	Chronic HBsAg carriers; HBV DNA levels >10 pg/mL for at least 3 months; stable serum ALT and AST levels of less than 2 times the upper limit of normal range for at least 3 months; no antiviral, investigational, or biological modifier drugs in the past 6 months; no evidence of liver decompensation, renal impairment, or pancytopenia; tested negative for antibodies against HCV, HDV, and HIV	NR	Screened: NR Eligible: NR Enrolled: 42 Analyzed: 42	None	N/A
Lai 1998 <sup>57</sup>	Aged 16 to 70 years; detectable serum HBsAg and HBeAg for at least the previous 6 months; serum HBV DNA levels of at least 5 pg/mL; ALT levels <10 times the upper limit of normal for at least the previous 3 months	HCV, HDV, or HIV infection; decompensated liver disease; evidence of autoimmune hepatitis; received an investigational drug in the previous 30 days; received any antiviral, immunomodulator, cytotoxic agents, or corticosteroids in the previous 6 months; or received lamivudine in the previous 3 months	Screened: NR Eligible: NR Enrolled: 358 Analyzed: 357 Note: 1 patient in placebo group excluded due to no evidence of HBsAg for 6 months prior to enrollment	A vs. B vs. C Withdrawals: 6% (8/142) vs. 3% (4/143) vs. 4% (3/73)	N/A

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Eligibility criteria</b>	<b>Exclusion criteria</b>	<b>Number screened, eligible, enrolled, analyzed</b>	<b>Withdrawals (Number, %) Loss to followup (Number, %)</b>	<b>Adjusted variables for statistical analysis</b>
Lampertico 1997 <sup>46</sup>	Age 18-65 years; chronic active HBV, with or without cirrhosis; HBsAg and anti-Hbe in serum for ≥1 year; serum ALT >2x ULN; detectable serum HBV DNA in year preceding study	HCV, HDV or HIV positive; pregnant or lactating; drug abuse' alcoholism; antiviral or immunosuppressive therapy in 12 months preceding study; platelet counts <100,000/mL; white blood cell counts <3,000/mL; serum markers of autoimmunity; renal failure; history of hepatic decompensation; other serious medical illness	Screened: NR Eligible: NR Enrolled: 42 Analyzed: unclear	Withdrawals: 6/42 (14%) Loss to followup: 3/42 (7%)	N/A
Liaw 2004 <sup>6</sup>	Patients >16 years of age who were positive for HBsAg for at least 6 months, positive for HBeAg or negative for HBeAg with detectable HBV DNA at screening, and had liver biopsy showing Ishak fibrosis score at least 4 at screening or in previous 2 years	Evidence of hepatocellular carcinoma, serum ALT > 10 times ULM, hepatic decompensation, autoimmune hepatitis, coinfection with HCV, HDV, or HIV, serious concurrent illness, amylase or lipase >2 times ULN, elevated creatinine level, hemoglobin < 8 g per cubic deciliter, white cell count <15000 per cubic millimeter, platelet count <50,000 per cubic mm, treatment with immunomodulatory or chronic antiviral therapy within 6 months of screening, treatment with any investigational drug within 30 days of study start, or any previous treatment with lamivudine. Pregnant women excluded.	Screened: NR Eligible: NR Enrolled: 651 Analyzed: 651	Per-protocol withdrawals: 21% (135/651) Withdrawals for other reasons: 8% (52/651)	HR adjusted for country, sex, baseline alanine aminotrasferase level, Child-Pugh score, and Ishak fibrosis score; CI unadjusted for interim analyses
Lin 1999 <sup>3</sup>	Age 16-65 years; heterosexual male; HBsAg and HBeAg positive; elevated ALT (<40 U/l); liver biopsy within 3 months of study entry showing chronic active hepatitis or chronic lobular hepatitis; presence of serum HBV-DNA	Immunosuppressive or antiviral therapy use; HDV infection; IV drug abuse; decompensated liver disease; other serious medical illness; AFP >100 ng/ml	Screened: NR Eligible: NR Enrolled: 120 Analyzed: 101	NR	Age, baseline ALT, baseline HBV-DNA, preexisting cirrhosis AFP level, duration of hepatitis, treatment regimen

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Eligibility criteria</b>	<b>Exclusion criteria</b>	<b>Number screened, eligible, enrolled, analyzed</b>	<b>Withdrawals (Number, %) Loss to followup (Number, %)</b>	<b>Adjusted variables for statistical analysis</b>
Marcellin 2003 <sup>42</sup>	Age 16-65 years with HBeAg positive chronic HBV and compensated liver disease. Chronic HBV defined as presence of serum HBsAg for at least 6 months, serum HBV DNA of at least 1 million copies per mL, and serum ALT 1.2-10 xULN. Prothrombin time no more than 1 second above normal range, serum albumin greater than 3 g/dL, total bilirubin level no more than 2.5 mg/dL, serum creatinine level of no more than 1.5 mg/dL, adequate blood count. Negative pregnancy test and contraception use for women.	Coexisting serious medical or psychiatric illness; immune globulin, interferon, or other immune or cytokine based therapies with possible activity against HBV disease within 6 months before screening, organ or bone marrow transplantation, recent treatment with systemic corticosteroids, immunosuppressants, or chemotherapeutic agents; serum alpha-fetoprotein level of at least 50ng/mL, evidence of hepatic mass, liver disease not due to HBV, prior therapy for more than 12 weeks with a nucleoside or nucleotide analogue with activity against HBV, seropositivity for HIV or HCV or HDV.	Screened: NR Eligible: NR Enrolled: 515 Analyzed: 494 for histologic outcomes Note: 4 patients (1 in group A, 3 in group C) took no study medications and were excluded after randomization, baseline n=171 in group A, 173 in group B, 167 in group C	A vs. B vs. C Withdrawals: 7% (12/171) vs. 8% (14/173) vs. 8% (13/167) Loss to followup for baseline biopsies: 1.8% (3/171) vs. 4.6% (8/173) vs. 3.6% (6/167) Loss to followup for total group: Unclear	Adjustments made for 7 geographic regions
Mazzella 1999 <sup>75</sup>	HBsAg, HBeAg and HBV-DNA positive; elevated ALT; histologic evidence of chronic active or persistent hepatitis	Age <18 or >65 years; pregnancy; histologically proven cirrhosis; HDV or HIV antibodies; history of drug abuse	Screened: NR Eligible: NR Enrolled: 64 Analyzed: 64	NR	N/A
Muller 1990 <sup>47</sup>	Age 18-65 years; HBsAg and HBV DNA positive for ≥6 months	HDV or HIV positive; decompensated cirrhosis; chronic renal insufficiency; use of hemodialysis or immunosuppressive agents; previous organ transplantation; poor physical condition	Screened: NR Eligible: NR Enrolled: 58 Analyzed: 55	Withdrawals: 3/58 (5%) Loss to followup: none reported	N/A

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Eligibility criteria</b>	<b>Exclusion criteria</b>	<b>Number screened, eligible, enrolled, analyzed</b>	<b>Withdrawals (Number, %) Loss to followup (Number, %)</b>	<b>Adjusted variables for statistical analysis</b>
Murray 2012 <sup>61</sup>	Age 12 to <18 years; chronic HBV defined as documented positive serum HBsAg for at least 6 months; positive or negative for HBeAg; HBV DNA $\geq 10^5$ copies/mL and either ALT $\geq 2x$ upper limit of normal or any history of ALT $\geq 2x$ 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 $\geq 16$ weeks prior to screening and any interferon therapy $\geq 6$ months prior to screening. Poland sites only required patients to have had a history of treatment for HBV or a contraindication for treatment with existing drugs	Previous tenofovir use; HCV, HDV or HIV coinfection; history of significant bone disease, decompensated liver disease, or renal disease; evidence of hepatocellular carcinoma	Screened: 149 Eligible: NR Enrolled: 106 Analyzed: 101	Withdrawals: 5/106 (5%) Loss to followup: none reported	N/A
Perez 1990 <sup>48</sup>	Age $\geq 18$ years; HBsAg, HBeAg and HBV DNA for at least 6 months; ALT $> 1.3$ ULN; compensated liver disease with prolonged prothrombin $< 3$ seconds; normal serum albumin and bilirubin; no history of hepatic encephalopathy, bleeding esophageal varices or ascites	HDV or HIV positive; low hematocrit ( $< 30\%$ ), platelets ( $< 100,000/mm^3$ ), white blood cells ( $< 4,000/mm^3$ ), granulocytes ( $< 1,500/mm^3$ )	Screened: NR Eligible: NR Enrolled: 35 Analyzed: 35	Withdrawals: none reported Loss to followup: none reported	N/A
Perrillo 1990 <sup>49</sup>	Age $\geq 18$ years; HBsAg positive for at least 6 months; HBeAg and HBV DNA positive in 6 months prior to study entry; serum ALT $\geq 1.3$ ULN; compensated liver disease; chronic hepatitis B (per liver biopsy)	Corticosteroid or antiviral therapy during previous 12 months; pregnancy; serious medical illness; low hematocrit ( $< 0.3$ ), platelet ( $< 70 \times 10^9$ ), white-cell ( $< 3 \times 10^9$ ) and granulocyte ( $< 1.5 \times 10^9$ ) counts; elevated serum creatinine; alcoholism; drug abuse; other potential causes of liver disease; HDV or HIV positive	Screened: 545 Eligible: 169 Enrolled: 169 Analyzed: 169	Withdrawals: 4/169 (2%) Loss to followup 2/169 (1%)	N/A
Sarin 1996 <sup>50</sup>	Age $< 70$ years; HBsAg positive for at least 6 months; HBeAg and HBV DNA positive on at least 2 occasions 1 month apart; compensated liver disease; chronic hepatitis with or	Antiviral therapy within 12 months; pregnancy; platelet count $< 70,000/cmm$ ; white cell count $< 3,000/cmm$ ; elevated serum creatinine	Screened: NR Eligible: NR Enrolled: 41 Analyzed: 41	Withdrawals: none reported Loss to followup: none reported	N/A

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (Number, %) Loss to followup (Number, %)	Adjusted variables for statistical analysis
Tassopoulos 1999 <sup>58</sup>	without cirrhosis Men and women 16 to 70 years of age with detectable HBsAg, detectable HBeAg antibody, and undetectable HBeAg at screening and for 6 months prior to screening; serum HBV DNA > 2.5 pg/mL at screening, presence of HBV DNA in serum for 3 months before screening; ALT 1.5 to 10 times ULN at screening and at least once >3 months before screening with no value falling in reference range during intervening period	HCV, HDV, HIV positive; presence of decompensated liver disease; evidence of autoimmune hepatitis; interferon treatment within previous 6 months	Screened: 260 Eligible: 125 Enrolled: 125 Analyzed: 124	A vs. B. Withdrawals: 12% (7/60) vs. 6.3% (4/64) Per-protocol withdrawals at week 26 (HBV DNA >2.5 pg/mL): 8.3% (5/60) vs. 43/64 (67%) Withdrawals for other reasons (protocol violation/adverse event): 3.3% (2/60) in treated group	N/A
Waked 1990 <sup>51</sup>	HBsAg positive for >6 months; elevated aminotransferase; histologically active liver disease; normal blood count; normal renal function; compensated liver disease	Normal aminotransferase; chronic persistent hepatitis; inactive cirrhosis or normal histology; serum albumin <3 gm/dL; serum bilirubin >4 mg/dL; serum creatinine >1/5 mg/dL; history of encephalopathy, ascites 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	Screened: NR Eligible: NR Enrolled: 40 Analyzed: 35	Withdrawals: 5/40 (13%) Loss to followup: 1/40 (3%)	N/A

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Eligibility criteria</b>	<b>Exclusion criteria</b>	<b>Number screened, eligible, enrolled, analyzed</b>	<b>Withdrawals (Number, %) Loss to followup (Number, %)</b>	<b>Adjusted variables for statistical analysis</b>
Yalcin 2004 <sup>59</sup>	Adult patients with no previous antiretroviral treatment; HBsAg positive for >6 months; positive HBeAg; serum HBV DNA >1 pg/ml; persistently normal ALT vlaues on at least 3 occasions in the previous 6 months; histological evidence of absent or minimal changes in liver biospy; 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 suring study and 6 months after treatment completion	Previously treated with interferon or antiviral or immunosuppressive medications; positive for antibody to HDV, HCV, HIV and pregnancy; with decompensated liver disease; with medical condition associated with chronic liver disease other than viral hepatitis; alcohol and/or drug abuse within one year of study entry	Screened: 53 Eligible: 46 Enrolled: 46 Analyzed: 46	Withdrawals: 0 vs. 3% (1/33) Loss to followup: None	N/A
Yao 1999 <sup>60</sup>	Aged 16 to 65 years; HBeAg and HBsAg positive in the 6 months prior to screening; detectable HBV DNA at screening; ALT levels <10 times the upper limit of normal at screening	HCV, HDV, or HIV infection; decompensated liver disease; evidence of autoimmune or hereditary liver disease; bone marrow depression; serious concurrent illness; alcoholism; drug abuse; elevated creatinine concentration >1.5 times the upper limit of normal; had received antiviral or cytotoxic agents, corticosteroids, or immunomodulators in the previous 6 months; history of hypersensitivity to nucleoside analogs; pregnancy or lactation; females of childbearing age not using contraceptives	Screened: 440 Eligible: 429 Enrolled: 429 Analyzed: 429	A vs. B Withdrawals: 2.8% (9/322) vs. 1.8% (2/110)	N/A

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Eligibility criteria</b>	<b>Exclusion criteria</b>	<b>Number screened, eligible, enrolled, analyzed</b>	<b>Withdrawals (Number, %) Loss to followup (Number, %)</b>	<b>Adjusted variables for statistical analysis</b>
Zeng, 2006 <sup>43</sup>	At least 18 years old with detectable HBsAg for previous 6 months, detectable HBeAg, HBV DNA >10 <sup>6</sup> copies/mL, ALT level more than 1 xULN, and ALT more than 2 xULN sometime in previous 6 months	Evidence of hepatocellular carcinoma, clinical signs of liver decompensation, creatinine greater than 1.5 mg/dL, ALT more than 10 xULN, seropositivity for HCV or HDV or HIV; lamivudine therapy in previous 3 months, ADV therapy or other anti-HBV therapy in previous 6 months Note: systemic antiviral therapy, immunomodulators, immunosuppressive therapies, Chinese traditional medicines, or agents known to lower ALT not permitted during study	Screened: NR Eligible: NR Enrolled: 480 Analyzed: 480	A vs. B vs. C Withdrawals: NR for first 12 weeks, 1.2% (6/480) after 52 weeks Loss to followup: NR for first 52 weeks, 6% (14/240) vs. 5% (6/120) vs. 11% (13/120) after 5 years	N/A
<b>Head-to-head</b>					
Chang 2006 <sup>64</sup> , Gish 2007 <sup>65</sup> , Chang 2009 <sup>66</sup>	Age ≥16 years, HBeAg positive, compensated liver function, serum HBsAg present for at least 24 weeks prior to screening, evidence of chronic HBV per liver biopsy, evidence of HBV DNA at least 4 weeks prior to screening, ALT 1.3-10x ULN	HCV, HDV or HIV coinfection, other liver disease, use of antiviral agents within 24 weeks of randomization, prior lamivudine use lasting >12 weeks, AFP >100mg/ml, history of ascites requiring diuretics or paracentesis, previous entecavir treatment	Screened: 1,056 Eligible: NR Enrolled: 715 Analyzed: 709	Withdrawals: unclear; 10/715 (1%) withdrew due to AEs Loss to follow up: 54/715 (8%)	N/A
Lai 2002 <sup>68</sup>	Age ≥16 years, HBsAg positive, HBeAg positive or HBeAg negative and anti-HBeAg positive, HBV DNA >40 Meq/mL, ALT <10x ULN, compensated liver disease	Pregnancy, previous use of immunosuppressive therapy or antiviral therapy within 24 weeks of randomization, HIV, HCV or HDV infection, serious medical illness, pancytopenia, alcohol or drug abuse	Screened: 431 Eligible: NR Enrolled: 185 Analyzed: 169 (87 A vs B)	Withdrawals: 8/185 (4%) Loss to followup: NR	N/A
Lai 2006 <sup>67</sup>	Age ≥16 years, HBeAg negative, compensated liver function, serum HBsAg present for at least 24 weeks prior to screening, evidence of chronic HBV per liver biopsy, evidence of HBV DNA at least 4 weeks prior to screening, ALT 1.3-10x ULN	HCV, HDV or HIV coinfection, other liver disease, use of antiviral agents within 24 weeks of randomization, prior lamivudine use lasting >12 weeks, AFP >100ng/ml, history of ascites requiring diuretics or paracentesis, previous entecavir treatment	Screened: 1,468 Eligible: 694 Enrolled: 648 Analyzed: 638	Withdrawals: 31/638 (5%) Loss to follow-up: NR	N/A

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Eligibility criteria</b>	<b>Exclusion criteria</b>	<b>Number screened, eligible, enrolled, analyzed</b>	<b>Withdrawals (Number, %) Loss to followup (Number, %)</b>	<b>Adjusted variables for statistical analysis</b>
Lau 2005 <sup>70</sup>	HBsAg positive for at least 6 months, anti-HBs negative, HBeAg positive, HBV DNA >500,000 copies/mL, ALT >1 and <10x ULN, chronic HBV confirmed by liver biopsy	Decompensated liver disease, coexisting serious medical or psychiatric illness, neutrophil count <1500/mL <sup>3</sup> , platelet count <90,000/mL <sup>3</sup> , creatinine >1.5x ULN, history of alcohol or drug abuse, HIV, HCV or HDV coinfection, HBV treatment within 6 months of study	Screened: NR Eligible: NR Enrolled: n=543 (excluding 271 patients randomized to peg interferon + lamivudine combination therapy Analyzed: 543	Withdrawals: 70/543 (13%) Loss to followup: NR	N/A
Marcellin 2004 <sup>71</sup>	Adults, HBeAg negative, anti-HBe antibody and HBsAg positive, HBV DNA >100,000 copies/mL, serum ALT >1 and <10x ULN, HBV positive confirmed by liver biopsy within previous 24 months, evidence of prominent necroinflammatory activity	Decompensated liver disease, coexisting serious medical or psychiatric illness, neutrophil count <1500/mL <sup>3</sup> , platelet count <90,000/mL <sup>3</sup> , creatinine >1.5x ULN, history of alcohol or drug abuse, HIV, HCV or HDV coinfection, HBV treatment within 6 months	Screened: Not reported Eligible: Not reported Enrolled: 552 Analyzed: 537	Withdrawals: 38/358 (11%) Loss to followup: not reported	N/A
Marcellin 2008 <sup>72</sup> Study 102 (HBeAg negative at baseline)	Age 18-69 years, compensated liver disease, Knodell necroinflammatory score ≥3 (scale 0-18, higher score= more severe hepatitis), HBsAg positive for at least 6 months before screening, ALT >1 to <10x ULN, HBV DNA > 10 <sup>5</sup> copies/mL, <12 weeks treatment with any nucleoside or nucleotide or use of lamivudine or emtricitabine for at least 12 weeks	HIV, HCV or HDV infection, evidence of HCC, creatinine clearance <70 ml/minute, hemoglobin <8 g/dL, neutrophil count <1000/mL <sup>3</sup> , liver decompensation or failure	Screened: 846 Eligible: 382 Enrolled: 375 Analyzed: 375	Withdrawals: 10/375 (3%) Loss to followup: 1/375 (0.3%)	
Study 103 (HBeAg positive at baseline)	Age 18-69 years, compensated liver disease, Knodell necroinflammatory score ≥3 (scale 0-18, higher score= more severe hepatitis), HBsAg positive for at least 6 months before screening, ALT >2 to <10x ULN, HBV DNA > 10 <sup>6</sup> copies/mL, <12 weeks treatment with any nucleoside or nucleotide		Screened: 603 Eligible: 272 Enrolled: 266 Analyzed: 266	Withdrawals: 15/266 (6%) Loss to followup: none reported	



**Appendix B5. Treatment Trials Evidence Table**

Author, year	Eligibility criteria	Exclusion criteria	Number screened, eligible, enrolled, analyzed	Withdrawals (Number, %) Loss to followup (Number, %)	Adjusted variables for statistical analysis
Ren 2007 <sup>69</sup>	Age 19-68 years, HBeAg positive chronic HBV, compensated liver function, serum bilirubin $\leq$ 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	HIV, HCV or HDV infection, other liver disease, use of interferon, thymosin or HBV antivirals within 24 weeks of randomization, prior lamivudine therapy lasting more than 12 weeks, AFP >100 ng/mL, history of ascites requiring diuretics or paracentesis, previous treatment with entecavir or adefovir	Screened: Not reported Eligible: Not reported Enrolled: 61 Analyzed: unclear of efficacy, 61 for harms	Withdrawals: 1/61 (2%) Loss to followup: None reported	N/A

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
<b>Placebo-controlled</b>					
Ali 2003 <sup>52</sup>	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	NR	A vs. B Withdrawal due to adverse events 9.4% (3/32) vs. 0% (0/30) RR 6.6 (95% CI 0.4 to 122)	Poor	NR
Bayraktar 1993 <sup>44</sup>	A vs. B ALT normalization: 17/25 (68%) vs 0/10 (0%); RR 15 (95% CI 0.97 to 225) HBeAg loss: 15/25 (60%) vs 0/10 (0%); RR 13 (95% CI 0.86 to 200) HBsAg loss: 1/25 (4%) vs 0/10 (0%); RR 1.27 (95% CI 0.06 to 29)	NR	Interferon alfa 2b (no results presented for untreated group) Withdrawals due to adverse events 0% (0/25)	Poor	NR
Bozkaya 2005 <sup>53</sup>	A vs. B vs. C Month 12 ALT normalization (group C had normal ALT at baseline): 44% (8/18) vs. 21% (4/19); RR 2.1 (95% CI 0.7 to 5.8)	NR	NR	Poor	NR

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
Chan 2007 <sup>54</sup>	<p>A vs. B</p> <p>Month 24</p> <p>Complete response: 56% (50/89) vs. (11%) 5/47; adjusted OR 10.8 (95% CI 3.8-30.2)</p> <p>HBV &lt;10,000 copies/ml: 58% (52/89) vs. 19% (9/47); RR 3.1 (95% CI 1.7 to 5.6)</p> <p>HBV undetectable: 26% (23/89) vs. 6% (3/47); RR 4.1 (95% CI 1.3 to 12.8)</p> <p>HBsAg loss: 0 vs. 0</p> <p>ALT normalization: 74% (66/89) vs. 36% (17/47); RR 2.1 (95% CI 1.4 to 3.1)</p> <p>Month 30</p> <p>Complete response: 26% (23/89) vs. 19% (9/47); RR 1.4 (95% CI 0.7 to 2.7)</p> <p>HBV &lt;10,000 copies/ml: 33% (29/89) vs. 26% (12/47); RR 1.3 (95% CI 0.7 to 2.3)</p> <p>HBV undetectable: 10% (9/89) vs. 2% (1/47); RR 4.8 (95% CI 0.6 to 36.4)</p> <p>HBsAg loss: 1% (1/89) vs. 0% (0/47); RR 1.6 (95% CI 0.07 to 38.5)</p> <p>ALT normalization: 60% (53/89) vs. 38% (18/47); RR 1.6 (95% CI 1.0 to 2.3)</p> <p>Necroinflammatory improvement: 78% (14/18) vs. 25% (2/8); RR 3.1 (95% CI 0.9 to 10.6)</p> <p>Fibrosis improvement: 33% (6/18) vs. 0% (0/8); RR 6.2 (95% CI 0.4 to 97.7)</p>	<p>A vs. B</p> <p>Mortality: NR</p> <p>Hepatocellular cancer: 3.4% (3/89) vs. 2.1% (1/47); RR 1.6 (95% CI 0.2 to 14.8)</p> <p>Note: Study not powered to detect effect of lamivudine on prevention of hepatocellular carcinoma</p>	<p>A vs. B</p> <p>Serious adverse events</p> <p>15% (13/89) vs. 13% (6/47) RR 1.1 (95% CI 0.5 to 2.8)</p>	Fair	Glaxo-Smith Kline
Dienstag 1999 <sup>55</sup>	<p>A vs. B</p> <p>One-year results (on treatment)</p> <p>Histologic improvement: 52% (34/66) vs. 23% (16/71); RR 2.29 (95% CI 1.40-3.73)</p> <p>ALT normalization: 41% (27/66) vs. 7% (5/68); RR 5.56 (95% CI 2.28-13.58)</p> <p>HBV DNA loss: 44% (28/63) vs. 16% (11/69); RR 2.79 (95% CI 1.52-5.12)</p> <p>HBeAg loss: 17% (11/63) vs. 6% (4/69); RR 3.01 (95% CI 1.01-8.98)</p> <p>16 month results (post-treatment)</p> <p>HBeAg seroconversion: 17% (11/63) vs. 9% (6/69); RR 2.01 (95% CI 0.79-5.11)</p> <p>HBeAg loss: 29% (19/66) vs. 15% (11/71); RR 1.86 (95% CI 0.96-3.60)</p> <p>HBsAg loss: 2% (1/66) vs. 0% (0/71); RR 3.22 (95% CI 0.13-77.78)</p> <p>HBV DNA undetectable at least once during treatment: 98%</p>	Mortality: None	<p>A vs. B</p> <p>Serious adverse events 0% (0/66) vs 0% (0/71)</p> <p>RR 1.1 (95% CI 0.0 to 53) (inferred)</p>	Fair	Glaxo Wellcome; Hepatitis Research Fund of Massachusetts General Hospital; National Institutes of Health Clinical Research Center

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
	(62/63) vs. 33% (23/69); RR 2.95 (95% CI 2.11-4.13) Likelihood of histologic response: OR 7.5, 95% CI 2.7-20.9 Likelihood of HBeAg seroconversion: OR 9.7, 95% CI 1.7-56.1				
Hadziyannis 1990 <sup>45</sup>	A vs. B 4-month outcomes (time on treatment) Complete treatment response: 10/25 (40%) vs 0/25 (0%); RR 21 (95% CI 1.30 to 340) Partial treatment response: 7/25 (28%) vs 4/25 (16%); RR 1.75 (95% CI 0.59 to 5.24) 12-month outcomes (post-treatment) Complete treatment response: 11/25 (44%) vs 2/25 (8%); RR 5.5 (95% CI 1.36 to 22) Partial treatment response: 3/25 (12%) vs 6/25 (24%); RR 0.5 (95% CI 0.14 to 1.78)	NR	Interferon alfa 2b (no results presented for untreated group) Serious adverse events 0/25 (0%)	Poor	NR
Hadziyannis 2003 <sup>40</sup>	A vs. B Histologic improvement: 64% (77/121) vs. 33% (19/57); RR 1.9 (95% CI 1.3 to 2.8) HBV DNA undetectable: 51% (63/123) vs. 0% (0/61); RR 64 (95% CI 4.0 to 1009) ALT normalization: 72% (84/116) vs. 29% (17/59); RR 2.5 (95% CI 1.7 to 3.8)	NR	A vs. B Serious adverse events 3% (4/123) vs. 7% (4/61) RR 0.5 (95% CI 0.1 to 1.9) Withdrawal due to adverse events 0% (0/123) vs. 0% (0/61) RR 0.5 (95% CI 0.0 to 25) Any adverse events 76% (94/123) vs. 74% (45/61) RR 1.0 (95% CI 0.9 to 1.2) Note: any adverse event refers to those reported by at least 5 percent of patients in group A	Fair	Gilead Sciences
Jonas 2008 <sup>41</sup>	A vs. B HBV DNA <1000 copies/mL and ALT normalization: 23% (13/56) vs. 0% (0/27); RR 13 (95% CI 0.8 to 215.1) Note: p-value in text is significant for above association ALT normalization: 64% (36/56) vs. 22% (6/27); RR 2.9 (95% CI 1.4 to 6.0) Note: n values calculated from proportions provided by study, based on the number of participants at baseline in target age group	Mortality: None	A vs. B Withdrawal due to adverse event 1.7% (1/56) vs. 0% (0/27) RR 1.5 (95% CI 0.1 to 35)	Fair	Gilead Sciences

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Intermediate outcomes</b>	<b>Clinical health outcomes</b>	<b>Adverse events</b>	<b>Quality</b>	<b>Funding source</b>
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% (56/73) 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% 0.65 to 187)	Fair	Istituto Superiore di Sanità (Italian National Health Service)

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
Liaw 2004 <sup>6</sup>	NR	<p>A vs. B</p> <p>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</p> <p>Mortality during double-blind phase: &lt;1% (2/436) vs. 0</p> <p>Hepatocellular carcinoma: 3.9% (17/436) vs. 7.4% (16/215); adjusted HR 0.49 (95% CI 0.25 to 0.99); excluding 5 cases diagnosed in first year; HR 0.47 (95% CI 0.22 to 1.00)</p> <p>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)</p> <p>Disease progression: 7.8% (34/436) vs. 18% (38/215); adjusted HR 0.45 (95% CI 0.58 to 0.73)</p>	<p>A vs. B</p> <p>Serious adverse event 12% (54/436) vs. 18% (38/215)</p> <p>RR 0.7 (95% CI 0.5 to 1.0)</p> <p>Any adverse event 77% (335/436) vs. 83% (178/215)</p> <p>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</p>	Fair	Glaxo-SmithKline; some authors received funding by industry
Lin 1999 <sup>3</sup>	Not relevant <sup>a</sup>	<p>A vs. B</p> <p>Mortality: 1/67 (1%) vs 4/34 (12%); RR 0.13 (95% CI 0.01 to 1.09)</p> <p>Hepatocellular cancer: 1/67 (1%) vs 4/34 (12%); RR 0.13 (95% CI 0.01 to 1.09)</p> <p>Incident cirrhosis: 8/67 (12%) vs 5/34 (15%); RR 0.81 (95% CI 0.29 to 2.29)</p>	Not relevant <sup>a</sup>	Fair	The Prosperous Foundation (Taipei, Taiwan)

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
Marcellin 2003 <sup>42</sup>	<p>A vs. B vs. C                      Histologic improvement (unassessable data: 1-2%, missing data: 9-10%): 53 (89/168) vs. 59% (98/165) vs. 25% (41/161); A vs. C adjusted RR 2.1 (95% CI 1.6 to 2.8); B vs. C adjusted RR 2.3 (95% CI 1.7 to 3.1)                      HBeAg loss: 24% (41/171) vs. 27% (44/165) vs. 11% (17/161); A vs. C RR 2.3 (95% CI 1.3 to 3.8); B vs. C RR 2.5 (95% CI 1.5 to 4.2)                      HBeAg seroconversion: 12% (20/171) vs. 14% (23/165) vs. 6% (9/161); A vs. C RR 2.1 (95% CI 1.0 to 4.5); B vs. C RR 2.5 (95% CI 1.2 to 5.2)                      ALT normalization: 48% (81/168) vs. 55% (93/169) vs. 16% (26/164); A vs. C RR 3.0 (95% CI 2.1 to 4.5); B vs. C RR 3.5 (95% CI 2.4 to 5.1)</p>	NR	<p>A + B vs. C                      Serious adverse events 10% (33/344) vs. 8% (13/167)                      RR 1.2 (95% CI 0.7 to 2.3) Withdrawal due to adverse events 2.3% (8/344) vs. &lt;1% (1/167)                      RR 3.9 (95% CI 0.5 to 31)                      Note: n values calculated from proportions provided by study, based on the number of participants at baseline                      Combined treatment arms</p>	Fair	Gilead Sciences
Mazzella 1999 <sup>75</sup>	Not relevant <sup>a</sup>	<p>A vs. B                      Mortality: 0/33 (0%) vs 2/31 (6%); RR 0.19 (95% CI 0.01 to 3.77)                      Hepatocellular cancer: 2/33 (3%) vs 2/31 (6%); RR 0.94 (95% CI 0.14 to 6.27)                      Incident cirrhosis: 4/33 (12%) vs 6/31 (19%); RR 0.63 (95% CI 0.2 to 2.01)</p>	Not relevant <sup>a</sup>	Fair	NR
Muller 1990 <sup>47</sup>	<p>A vs. B                      Complete response: 1/30 (3%) vs 0/28 (0%); RR 2.81 (95% CI 0.12 to 66)                      Partial response: 8/30 (27%) vs 3/28 (0%); RR 2.49 (95% CI 0.73 to 8.45)</p>	NR	<p>Interferon alfa 2b (no results presented for untreated group)                      Withdrawals due to adverse events 3.7% (1/27)</p>	Fair	NR

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Intermediate outcomes</b>	<b>Clinical health outcomes</b>	<b>Adverse events</b>	<b>Quality</b>	<b>Funding source</b>
Murray 2012 <sup>61</sup>	<p>A vs. B</p> <p>Viral load achieved: 46/52 (89%) vs 0/54 (0%); RR 97 (95% CI 6 to 1526)</p> <p>Viral load undetectable: 44/52 (85%) vs 0/54 (0%); RR 92 (95% CI 6 to 1462)</p> <p>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)</p> <p>ALT normalization, all patients: 40/52 (77%) vs 21/54 (39%); RR 1.98 (95% CI 1.37 to 2.85)</p> <p>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)</p> <p>HBsAg loss: 1/52 (2%) vs 0/54 (0%); RR 3.11 (95% CI 0.13 to 75)</p> <p>Composite outcomes</p> <p>Viral load achieved + ALT normalization: 37/52 (71%) vs 0/54 (0%); RR 77 (95% CI 5 to 1235)</p> <p>Viral load achieved + ALT normalization + HBeAg loss: 11/52 (21%) vs 0/54 (0%); RR 24 (95% CI 1.44 to 395)</p> <p>Viral load achieved + ALT normalization + HBsAg loss: 8/52 (15%) vs 0/54 (0%); RR 18 (95% CI 1.04 to 298)</p>	NR	<p>A vs. B</p> <p>Serious adverse events</p> <p>12% (6/52) vs 22% (12/54)</p> <p>RR 0.5 (95% CI 0.2 to 1.3)</p> <p>Any adverse event</p> <p>85% (44/52) vs 89% (48/54)</p> <p>RR 0.95 (95% CI 0.8 to 1.1)</p>	Good	Gilead Sciences
Perez 1990 <sup>48</sup>	<p>A vs. B</p> <p>HBeAG loss: 10/17 (59%) vs 1/18 (6%); RR 11 (95% CI 1.59 to 78)</p> <p>HBsAG loss: 1/17 (6%) vs 0/18 (0%); RR 3.17 (95% CI 0.14 to 73)</p> <p>HBV DNA loss: 1/17 (6%) vs 0/18 (0%); RR 3.17 (95% CI 0.14 to 73)</p> <p>ALT normalization: 2/17 (12%) vs 1/18 (6%); RR 2.12 (95% CI 0.21 to 21)</p>	NR	<p>A vs. B</p> <p>Withdrawals due to adverse events</p> <p>6% (1/18) vs. 0% (0/17)</p> <p>RR 2.7 (95% CI 0.1 to 62)</p>	Fair	NR
Perrillo 1990 <sup>49</sup>	<p>A vs B vs C vs D vs no treatment</p> <p>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)</p> <p>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)</p> <p>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)</p>	<p>A + B + C (all arms) vs C (no treatment)</p> <p>Mortality: 1/126 (0.8%) vs 2/43 (5%); RR 0.17 (95% CI 0.02 to 1.84)</p>	<p>A vs. B</p> <p>Withdrawals due to adverse events</p> <p>3% (4/126) vs 0% (0/43) RR 3.12 (95% CI 0.17 to 57)</p>	Good	University of California Public Health Service; National Institutes of Health

**Appendix B5. Treatment Trials Evidence Table**

<b>Author, year</b>	<b>Intermediate outcomes</b>	<b>Clinical health outcomes</b>	<b>Adverse events</b>	<b>Quality</b>	<b>Funding source</b>
Sarin 1996 <sup>50</sup>	A vs. B 4-month outcomes Complete response: 10/20 (50%) vs 1/21 (5%); RR 11 (95% CI 1.48 to 75) HBeAg loss: 10/20 (50%) vs 3/21 (14%); RR 3.5 (95% CI 1.12 to 11) HBV DNA loss: 10/20 (50%) vs 1/21 (5%); RR 11 (95% CI 1.48 to 75) HBsAg loss: 1/20 (5%) vs 1/21 (5%); RR 1.05 (95% CI 0.07 to 16) 16-month outcomes HBsAg loss: 3/20 (15%) vs 1/21 (5%); RR 3.15 (95% CI 0.36 to 28)	NR	Interferon alfa 2b (no results presented for untreated group) Serious adverse events 0% (0/20)	Fair	Schering-Plough
Tassopoulos 1999 <sup>58</sup>	A vs. B Week 24 Complete response: 63% (34/54) vs. 6% (3/54); RR 11 (95% CI 3.7 to 34.7) Partial response: 28% (15/54) vs. 20% (11/54); RR 1.4 (95% CI 0.7 to 2.7) HBsAg loss: 0% (0/60) vs. 2% (1/64); RR 0.4 (95% CI 0.02 to 8.55) HBsAg seroconversion: 0 vs. 0	NR	A vs. B Serious adverse events 5% (3/60) vs. 6% (4/65) RR 0.8 (95% CI 0.2 to 3.5) Withdrawal due to adverse events 2% (1/60) vs. 0% (0/65) RR 3.2 (95% CI 0.1 to 78) Any adverse events 47% (28/60) vs. 62% (40/65) RR 0.8 (95% CI 0.5 to 1.1)	Fair	Glaxo Wellcome Research and Development
Waked 1990 <sup>51</sup>	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)	A vs. B 16-week outcomes Mortality: 3/20 (15%) vs 1/20 (5%); RR 3 (95% CI 0.34 to 26) End of followup outcomes Mortality: 0/20 (0%) vs 1/20 (5%); RR 0.33 (95% CI 0.01 to 7.72) Cirrhosis: 1/20 (5%) vs 2/20 (10%); RR 0.5 (95% CI 0.05 to 5.08)	Interferon alfa 2b (no results presented for untreated group) Withdrawals due to adverse events 0% (0/20)	Fair	NR



**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
	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) HBeAg 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)				
Yalcin 2004 <sup>59</sup>	A vs. B Month 1 (on treatment) Loss of HBV DNA: 100% (13/13) vs. 0% (0/33); RR 66 (95% CI 4.2 to 1029) Month 12 (treatment plus post-treatment followup) HBeAg seroconversion: 8% (1/13) vs. 3% (1/33); RR 2.5 (95% CI 0.2 to 37.6) Loss of HBV DNA: 8% (1/13) vs. 3% (1/33); RR 2.5 (95% CI 0.2 to 37.6) Loss of HBsAg: 0/13 vs. 0/33 HBeAg seroconversion + HBV DNA loss: 1/13 (8%) vs 1/33 (3%); RR 2.5 (95% CI 0.2 to 37.6)	NR	A vs. B Serious adverse events 0% (0/13) vs. 0% (0/33) RR 2.4 (95% CI 0.1 to 116)	Fair	NR
Yao 1999 <sup>60</sup>	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

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
Zeng, 2006 <sup>43</sup>	<p>A + B vs. C                      Week 12                      HBV DNA undetectable: 5% (18/352) vs. 0% (0/119); RR 12.6 (95% CI 0.8 to 207.1)                      ALT normalization: 42% (140/330) vs. 14% (15/108); RR 3.1 (95% CI 1.9 to 5.0)                      HBeAg loss: 6% (20/354) vs. 5% (6/119); RR 1.1 (95% CI 0.5 to 2.7)                      HBeAg seroconversion: 6% (20/344) vs. 5% (6/119); 1.1 (95% CI 0.5 to 2.8)                      Note: no adjustment for missing data</p>	Mortality: None	<p>A vs. B vs. C                      Serious adverse event during 52 weeks (off treatment since week 12): 2% (4/240) vs. 7% (8/120) vs. 0.9% (1/120); A vs. C RR 2.0 (95% CI 0.2 to 17.7); B vs. C RR 8.0 (95% CI 1.0 to 63.0)                      Withdrawal due to adverse events during 52 weeks (off treatment since week 12): 0.6% (3/480); 0.8% (2/240) vs. 0.8% (1/120) vs. 0% (0/120); A vs. C: RR 2.5 (95% CI 0.1 to 51.9); B vs. C RR 3.0 (95% CI 0.1 to 72.9)</p>	Fair	Glaxo-SmithKline
<b>Head-to-head</b>					
Chang 2006 <sup>64</sup> , Gish 2007 <sup>65</sup> , Chang 2009 <sup>66</sup>	<p>A vs B                      HBeAg loss: 110/354 (31%) vs 92/355 (26%); RR 1.2 (95% CI 0.95 to 1.5)                      HBsAg loss: 18/354 (5%) vs 10/355 (3%); RR 1.8 (95% CI 0.9 to 3.9)                      HBV DNA &lt; 300 copies/ml: 284/354 (80%) vs 137/355 (39%); RR 2.1 (95% CI 1.8 to 2.4)                      ALT normalization (<math>\leq 1 \times</math> ULN): 307/354 (87%) vs 280/355 (79%); RR 1.1 (95% CI 1.03 to 1.2)                      Histologic improvement (Knodell necroinflammatory score improvement <math>\geq 2</math> 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)</p>	<p>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</p>	<p>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)</p>	Good	Bristol Myers Squibb

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
Lai 2002 <sup>68</sup>	<p>A vs B</p> <p>HBV DNA undetectable: 11/46 (24%) vs 7/41 (17%)</p> <p>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)</p> <p>HBeAg loss (among HBeAg positive patients): 0/36 (0%) vs 2/36 (6%); RR 0.2 (95% CI 0.01 to 4.0)</p> <p>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)</p>	None reported	<p>A vs B</p> <p>Serious adverse events: None reported</p> <p>Withdrawals due to adverse events: 2/46 (4%) vs 1/41 (2%); RR 1.8 (95% CI 0.2 to 19)</p> <p>Any adverse event: 30/46 (65%) vs 30/41 (73%); RR 0.9 (95% CI 0.7 to 1.2)</p>	Fair	Not reported
Lai 2006 <sup>67</sup>	<p>A vs B (time on treatment)</p> <p>Histologic improvement (among patients with adequate baseline biosy specimen and Knodell necro-inflammatory score <math>\geq 2</math>; 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)</p> <p>HBV DNA loss (&lt;300 copies/mL): 293/325 (90%) vs 225/313 (72%); RR 1.3 (95% CI 1.2 to 1.4)</p> <p>ALT normalization (&lt;1 x ULN): 253/325 (78%) vs 222/313 (71%); RR 1.1 (95% CI 1.0 to 1.2)</p>	<p>A vs B</p> <p>Hepatocellular cancer: 1/325 (0.3%) vs 0/313 (0%); RR 2.89, 95% CI 0.12 to 71</p> <p>Mortality: 2/325 (0.6%) vs 0/313 (0%); RR 4.82, 95% CI 0.23 to 100</p>	<p>A vs B</p> <p>Serious adverse events: 21/325 (6%) vs 24/313 (8%); RR 0.8 (95% CI 0.5 to 1.5)</p> <p>Withdrawals due to adverse events: 6/325 (2%) vs 9/313 (3%); RR 0.6 (95% CI 0.2 to 1.8)</p> <p>Any adverse event: 246/325 (76%) vs 248/313 (79%); RR 1.0 (95% CI 0.9 to 1.04)</p>	Good	Bristol Myers Squibb

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
Lau 2005 <sup>70</sup>	<p>A vs B</p> <p>HBeAg loss/seroconversion: Time on treatment, loss: 81/271 (30%) vs 59/272 (22%), RR 1.4 (95% CI 1.0 to 1.8); Time on treatment, seroconversion: 72/271 (27%) vs 55/272 (20%), RR 1.3 (95% CI 1.0 to 1.8); Time on treatment + follow-up, loss: 91/271 (34%) vs 57/272 (21%), RR 1.6 (95% CI 1.2 to 2.1); Time on treatment + follow-up, seroconversion: 87/271 (32%) vs 52/272 (19%), RR 1.7 (95% CI 1.2 to 2.3)</p> <p>HBsAg loss/seroconversion: Time on treatment + follow-up, seroconversion: 8/271 (3%) vs 0/272 (0%); RR 17 (95% CI 1.0 to 294)</p> <p>HBV DNA loss: Time on treatment: 68/271 (25%) vs 108/272 (40%), RR 0.6 (95% CI 0.5 to 0.8); Time on treatment + follow-up: 39/271 (14%) vs 14/272 (5%); RR 2.8 (95% CI 1.6 to 5.0)</p> <p>ALT normalization: Time on treatment: 105/271 (39%) vs 168/272 (62%), RR 0.6 (95% CI 0.5 to 0.7); Time on treatment + follow-up: 111/271 (41%) vs 76/272 (28%); RR 1.5 (95% CI 1.2 to 1.9)</p> <p>Histologic improvement (reduction of at least 2 points in the modified Histology Activity Index): Time on treatment + follow-up: 102/271 (38%) vs 93/272 (34%); RR 1.1 (95% CI 0.9 to 1.4)</p> <p>HBeAg seroconversion + ALT normalization + HBV DNA &lt;100,000 copies/ml: Time on treatment: 27/271 (10%) vs 50/272 (18%), RR 0.5 (95% CI 0.4 to 0.8); Time on treatment + follow-up: 62/271 (23%) vs 28/272 (10%), RR 2.2 (95% CI 1.5 to 3.4)</p>	<p>A vs B</p> <p>Mortality: 0/271 (0%) vs 1/272 (0.4%)</p>	<p>A vs B (through week 56)</p> <p>Serious adverse events: 12/271 (12%) vs 5/272 (2%); RR 2.4 (95% CI 0.9 to 6.7)</p> <p>Withdrawals due to adverse events: 8/271 (3%) vs 2/272 (1%); RR 4.0 (95% CI 0.9 to 19)</p> <p>Any adverse event: 240/271 (89%) vs 152/272 (56%); RR 1.6 (95% CI 1.4 to 1.8)</p>	Good	Roche Pharmaceuticals
Marcellin 2004 <sup>71</sup>	<p>A vs B</p> <p>HBsAg loss/seroconversion: Time on treatment + follow-up, loss: 7/177 (4%) vs 0/181 (0%); RR 15 (95% CI 0.9 to 267)</p> <p>HBV DNA loss: Time on treatment: 112/177 (63%) vs 133/181 (73%), RR 0.9 (95% CI 0.7 to 1.0)</p> <p>Time on treatment + follow-up: 34/177 (19%) vs 12/181 (7%), RR 2.9 (95% CI 1.6 to 5.4)</p> <p>ALT normalization: Time on treatment: 67/177 (38%) vs 132/181 (73%), RR 0.5 (95% CI 0.4 to 0.6); Time on treatment + follow-up: 105/177 (59%) vs 80/181 (44%), RR 1.3 (95% CI 1.1 to 1.7)</p> <p>Histologic improvement: Time on treatment + follow-up: 85/177 (48%) vs 72/181 (40%); RR 1.2 (95% CI 1.0 to 1.5)</p> <p>ALT normalization + HBV DNA &lt;400 copies/ml: Time on treatment: 47/177 (27%) vs 109/181 (60%), RR 0.4 (95% CI 0.3 to 0.6); Time on treatment + follow-up: 26/177 (15%) vs 11/181 (6%), RR 2.4 (95% CI 1.2 to 4.7)</p>	<p>A vs B</p> <p>Mortality: 1/177 (1%) vs 0/181 (0%); RR 3.1 (95% CI 0.1 to 75)</p>	<p>A vs B</p> <p>Serious adverse events: 9/177 (5%) vs 5/181 (3%); RR 1.8 (95% CI 0.6 to 5.4)</p> <p>Withdrawals due to adverse events: 13/177 (7%) vs 0/181 (0%); RR 28 (95% CI 0.7 to 461)</p> <p>Any adverse event: 155/177 (88%) vs 86/181 (48%); RR 1.8 (95% CI 1.6 to 2.2)</p>	Good	Roche Pharmaceuticals

**Appendix B5. Treatment Trials Evidence Table**

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
<p>Marcellin 2008<sup>72</sup> Study 102 (HBeAg negative at baseline)</p>	<p>A vs B HBsAg loss: 0/250 (0%) vs 0/125 (0%); RR not estimable 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) Histologic improvement**: 181/250 (72%) vs 86/125 (69%); ARD 5.2 (95% CI -4.5 to 15); RR 1.1 (95% CI 0.9 to 1.2) ALT normalization (among patients with elevated ALT as baseline): 180/236 (76%) vs 91/118 (77%); ARD -0.8 (95% CI -10 to 8.5); RR 1.0 (95% CI 0.9 to 1.1) HBV DNA loss + histologic improvement: 177/250 (71%) vs 61/125 (49%); RR 1.5 (95% CI 1.2 to 1.8) <i>*ARD=adjusted relative difference between groups</i> <i>**Histologic improvement defined as ≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis score</i></p>	<p>No deaths in either group; 3 cases of HCC but results not reported according to study group</p>	<p>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)</p>	<p>Fair</p>	<p>Gilead Sciences</p>
<p>Study 103 (HBeAg positive at baseline)</p>	<p>A vs B HBeAg seroconversion: 32/153 (21%) vs 14/80 (18%); ARD* 4.7 (95% CI -5.5 to 15); RR 1.2 (95% CI 0.7 to 2.1) HBsAg loss: 5/158 (3%) vs 0/82 (0%); ARD 11 (95% CI 1.9 to 20); RR 5.7 (95% CI 0.3 to 103) HBV DNA loss: 134/176 (76%) vs 12/90 (13%); ARD 63 (95% CI 54 to 72); RR 5.7 (95% CI 3.4 to 9.7) Histologic improvement: 131/176 (74%) vs 61/90 (68%); ARD 5.8 (95% CI -5.6 vs 17); RR 1.1 (95% CI 0.9 to 1.3) ALT normalization: 115/169 (68%) vs 49/90 (54%); ARD 14 (95% CI 1.1 to 26); RR 1.3 (95% CI 1.0 to 1.6) HBV DNA loss + histologic improvement: 117/176 (66%) vs 11/90 (12%); ARD 54 (95% CI 45 to 64); RR 5.4 (95% CI 3.1 to 9.6) <i>Histologic improvement defined as ≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis score</i></p>	<p>No deaths in either group</p>			

## Appendix B5. Treatment Trials Evidence Table

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality	Funding source
Ren 2007 <sup>69</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, immunoglobulin M; IM, intramuscular; MU, million units; N/A, not applicable; NR, not reported; PCR, polymerase chain reaction; RCT, randomized controlled trial; RR, relative risk; SC, subcutaneous; SD, standard deviation; qd, once per day; ULN, upper limit of normal.

**Appendix B6. Treatment Trials Quality Assessment**

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to follow-up: differential/high?	Analyze people in the groups in which they were randomized?	Quality
Ali 2003 <sup>52</sup>	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Yes	Poor
Bayraktar 1993 <sup>44</sup>	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	No	Unclear	Yes	Poor
Bozkaya 2005 <sup>53</sup>	No	No	Yes	Yes	No	No	No	No	Unclear	Unclear	Poor
Chan 2007 <sup>52</sup>	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/No	Yes	Fair
Chang 2006 <sup>64</sup> ; Gish 2007 <sup>65</sup> ; Chang 2009 <sup>66</sup>	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Dienstag 1999 <sup>55</sup>	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Fair
Hadziyannis 1990 <sup>45</sup>	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	No	Unclear	Yes	Poor
Hadziyannis 2003 <sup>40</sup>	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Jonas 2008 <sup>41</sup>	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Lai 1997 <sup>55</sup>	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Fair
Lai 1998 <sup>57</sup>	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Fair
Lai, 2002 <sup>68</sup>	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Lai 2006 <sup>67</sup>	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Lampertico 1997 <sup>46</sup>	Yes	Yes	Yes	Yes	No	No	No	Yes	Unclear	Yes	Fair
Lau 2005 <sup>70</sup>	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Liaw 2004 <sup>76</sup>	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Fair
Lin 1999 <sup>73</sup>	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Marcellin 2003 <sup>42</sup>	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Unclear	Fair
Marcellin 2004 <sup>71</sup>	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Marcellin 2008 <sup>72</sup>	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No/No	Yes	Fair
Mazzella 1999 <sup>75</sup>	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Muller 1990 <sup>47</sup>	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Murray 2012 <sup>61</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Perez 1990 <sup>48</sup>	Unclear	Unclear	No	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Perrillo 1990 <sup>49</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Ren 2007 <sup>69</sup>	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	Fair
Sarin 1996 <sup>50</sup>	Yes	Unclear	Yes	Yes	Unclear	Unclear	No	Yes	No	Yes	Fair
Tassopoulos 1999 <sup>58</sup>	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
Waked 1990 <sup>51</sup>	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Yalcin 2004 <sup>59</sup>	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Yao 1999 <sup>60</sup>	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Fair
Zeng, 2006 <sup>43</sup>	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	Fair

**Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table**

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



**Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table**

<b>Author, year Country</b>	<b>Study design</b>	<b>Comparison</b>	<b>Treatment Duration of followup</b>	<b>Inclusion criteria</b>	<b>Number receiving antiviral treatment Lost to followup</b>	<b>Age Sex Race</b>
Lau 1997 <sup>89</sup> United States	Cohort (originally enrolled in RCT's)	Response vs. non-response Response=Sustained loss of HBV DNA and clearance of HBeAg within 1 year of starting treatment	Interferon alfa Mean 6.2 years	HBeAg-positive chronic HBV infection with elevated AST and/or ALT Excluded: HDV, HIV after 1988	n=103 Lost to followup: 8 (7.8%); assumed to be alive and without liver-related complications	Mean age: 41 years Male: 83% Race: 94% white, 6% black
Niederau 1996 <sup>86</sup> Europe	Prospective cohort	Loss of HBeAg after therapy vs. no loss	Interferon alfa 2b Mean 4.2 years	HBeAg-positive chronic HBV infection, ALT >2 times upper limit of normal and histologic evidence of active hepatitis Excluded: HDV, HIV, advanced cirrhosis	n=103 Lost to followup: None	Mean age: NR Female: NR Race: NR
Papatheodoridis 2001 <sup>87</sup> Greece	Cohort (unclear if prospective or retrospective)	Sustained biochemical response vs. no sustained biochemical response Sustained biochemical response =normalization of ALT at the end of interferon therapy and persistently normal ALT levels throughout the posttreatment followup period	Interferon alfa Mean 6 years	HBeAg-negative chronic HBV infection with elevated ALT and histologic evidence of chronic hepatitis Excluded: decompensated liver disease, HCC, HCV, HDV, HIV	n=209 Lost to followup: 9 (4.3%)	Mean age: 47 years Male: 83% Race: NR
Papatheodoridis 2011 <sup>88</sup> Greece	Retrospective cohort	Virological remission vs. no virological remission Virological remission=HBV DNA <200 IU/ml throughout therapy	Lamivudine Median 4.7 years	HBeAg-negative chronic HBV infection with at least two of the following: elevated ALT, HBV DNA >2000 IU/ml, or histologic evidence of chronic hepatitis Excluded: HDV, HCV, HIV, HCC diagnosed before or within first 6 months of treatment	n=818 Lost to followup: 180 (22%)	Mean age: 54 years Male: 72% Race: NR

**Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table**

Author, year Country	Characteristics of HBV infection	Proportion of patients with intermediate outcome	Confounders adjusted for in analysis	Results (by clinical outcome)	Quality	Funding source
Baltayiannis 2006 <sup>81</sup> Greece	HBeAg positive: None HBsAg clearance: NR ALT (median): 177 AST (median): 130 Serum HBV-DNA (median, copies/mL): 1.2 x 10 <sup>6</sup> Fibrosis stage (mean, Desmet): 2.2 Cirrhosis: Excluded	Virological response at 6 months: 35% (22/63)	Age Gender Alcohol use ALT >200 IU/L at baseline HBV-DNA >10,000 copies/mL at baseline Histologic grade >9 Histologic stage >2 All patients HBeAg negative	Death or disease complication (not defined) Virological response at 6 months vs. no virological response: adjusted HR 0.24 (95% CI 0.06 to 0.96)	Fair	NR
Di Marco 2004 <sup>82</sup> Italy	HBeAg positive: Excluded HBsAg clearance: NR ALT >2 times ULN: 65% AST: NR Serum HBV-DNA: NR Fibrosis stage: NR Cirrhosis on histology: 25%	No virological breakthrough: 39% (240/616)	Age Sex HBV DNA level ALT Hepatic flare after virological breakthrough Previous interferon therapy Cirrhosis All patients HBeAg negative	Death No virological breakthrough vs. breakthrough: adjusted HR 0.34 (95% CI 0.15 to 0.80)	Fair	NR
Fattovich 1997 <sup>83</sup> Italy	HBeAg positive: All HBsAg clearance: ~40% ALT (mean): 5.3 times upper limit of normal AST (mean): 3.7 times upper limit of normal Serum HBV-DNA: NR Fibrosis stage: All cirrhosis Cirrhosis: 100%	Biochemical remission: 28% (11/40)	Age Sex Symptoms Hepatic stigmata Splenomegaly AST ALT AST/ALT ratio Bilirubin Albumin Gamma-globulins Platelets HBeAg clearance ALT normalization All patients HBeAg positive	Death Biochemical remission vs. no remission: adjusted HR 0.09 (95% CI 0.01 to 0.71)	Poor	NR
Hui 2008 <sup>84</sup> China (Hong Kong)	HBeAg positive: All HBsAg clearance: NR ALT (mean): 113 AST: NR Serum HBV-DNA >10 <sup>5</sup> copies/mL: 100% Fibrosis stage (mean, Ishak): 2 Cirrhosis: 12%	Histological response in HAI score: 40% (36/89) Histological response in fibrosis stage: 18% (16/89)	Fibrosis HBV DNA level All patients HBeAg positive	Liver complications (HBV- related decompensated liver cirrhosis or HCC) Histological response on HAI score vs. no response: adjusted HR 0.62 (95% CI 0.06 to 6.9)	Poor	Reports no funding received

**Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table**

<b>Author, year Country</b>	<b>Characteristics of HBV infection</b>	<b>Proportion of patients with intermediate outcome</b>	<b>Confounders adjusted for in analysis</b>	<b>Results (by clinical outcome)</b>	<b>Quality</b>	<b>Funding source</b>
Lampertico 2003 <sup>85</sup> Italy	HBeAg positive: None HBsAg clearance: 15% ALT (mean): 204 AST: NR HBV DNA detectable: 61% Fibrosis stage (median, Ishak): 4 Ishak F4-F6 fibrosis: 60%	Sustained virological and biochemical response: 30% (30/101)	Age Sex ALT HBV viral load IgM anti-HBc level Necroinflammatory grade Fibrosis stage All patients HBeAg negative	Liver complications (cirrhosis, ascites, jaundice, hepatic encephalopathy, gastroesophageal bleeding due to portal hypertension, or HCC) Sustained virological and biochemical response vs. no sustained response: adjusted HR 0.13 (95% CI 0.03 to 0.55)	Fair	Fondazione Italiana Ricerca Cancro and the consorzio Inter- universitario Trapianti d'Organo (Rome)
Lau 1997 <sup>89</sup> United States	HBeAg positive: All HBsAg clearance: 86% (responder) vs. 11% (nonresponder) ALT (median): 154 AST (median): 94 Serum HBV-DNA (meq/mL): 4843 Fibrosis stage (mean, HAI): 2.1 Cirrhosis: 17% HCV infection: 6.8% HIV infection: 14%	Response: 30% (31/103)	Cirrhosis Age Sex ALT AST All patients HBeAg positive	Death (results only adjusted for age and sex) Responder vs. non- responder: adjusted HR 0.59 (95% CI 0.20 to 1.67) Death or liver-related complication (variceal hemorrhage, ascites, encephalopathy) Responder vs. non- responder: adjusted HR 0.07 (95% CI 0.02 to 0.33)	Fair	NR
Niederrau 1996 <sup>86</sup> Europe	HBeAg positive: All HBsAg clearance: 9.7% ALT: NR AST: NR HBV DNA: NR Fibrosis stage: NR Cirrhosis: NR (Child-Pugh class B or C excluded)	HBeAg loss: 51% (53/103)	Age Sex Baseline HBV DNA Baseline ALT Duration of hepatitis Preexisting cirrhosis All patients HBeAg positive	Liver complications (death; need for liver transplantation; development of ascites, jaundice, or hepatic encephalopathy; occurrence of, or bleeding from, esophageal varices) HBeAg loss vs. no loss: adjusted HR 0.06 (95% CI 0.01 to 0.61)	Fair	Van Meeteren Foundation

**Appendix B5. Studies of Association Between Intermediate and Final Health Outcomes Evidence Table**

Author, year Country	Characteristics of HBV infection	Proportion of patients with intermediate outcome	Confounders adjusted for in analysis	Results (by clinical outcome)	Quality	Funding source
Papatheodoridis 2001 <sup>87</sup> Greece	HBeAg positive: Excluded HBsAg clearance: 13% mean 2.9 years after end of treatment) ALT (median): 112 AST (median): 67 Serum HBV DNA (median, pg/ml): 4.4 Fibrosis stage (mean, Ishak): 3.3 Cirrhosis: 27%	Sustained biochemical response: 27% (57/209)	Cirrhosis Age All patients HBeAg negative	Death or liver transplantation Sustained biochemical response vs. no sustained biochemical response: adjusted HR 0.48 (95% CI 0.23 to 1.0) Severe clinical complications (death, liver transplantation, liver decompensation [ascites, variceal bleeding, hepatic encephalopathy], and hepatocellular carcinoma]) Sustained biochemical response vs. no sustained biochemical response: adjusted HR 0.53 (95% CI 0.29 to 0.91)	Poor	NR
Papatheodoridis 2011 <sup>88</sup> Greece	HBeAg positive: Excluded HBsAg clearance: NR ALT (median): 98 AST (median): 68 Serum HBV DNA (median, x103 IU/ml): 400 Fibrosis stage: NR Cirrhosis: 26%	Virological remission: 28% (228/818)	Age Sex Liver disease severity ALT AST Bilirubin Albumin Hemoglobin Platelet count HBV DNA Interferon alfa in the past All patients HBeAg negative	Hepatocellular carcinoma Virological remission under therapy vs. no virological remission: adjusted HR 0.77 (95% CI 0.35 to 1.69)	Fair	Hellenic Center for Disease Control and Prevention

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, immunoglobulin M; NR, not reported; ULN, upper limit of normal.

**Appendix B8. Studies of Association Between Intermediate and Final Health Outcomes Quality Assessment**

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

<b>Author, year</b>	<b>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)?</b>	<b>Is there important (overall or differential) exclusion of patients due to missing data or loss to followup?</b>	<b>Were outcomes prespecified and defined, and ascertained using accurate methods?</b>	<b>Quality</b>
Andreone 2004 <sup>80</sup>	Yes	Unclear	Yes	Fair
Baltayiannis 2006 <sup>81</sup>	Yes	No	Yes	Fair
Di Marco 2004 <sup>82</sup>	Yes	Unclear	Yes	Fair
Fattovich 1997 <sup>83</sup>	No	No	Yes	Poor
Hui 2008 <sup>84</sup>	No	Unclear	Yes	Poor
Lampertico 2003 <sup>85</sup>	Yes	No	Yes	Fair
Lau 1997 <sup>89</sup>	No	No	Yes	Fair
Niederrau 1996 <sup>86</sup>	Yes	No	Yes	Fair
Papatheodoridis 2001 <sup>87</sup>	No	No	Yes	Poor
Papatheodoridis 2011 <sup>88</sup>	Yes	Yes	Yes	Fair