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

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

Purpose: To update the 2004 USPSTF review on screening for HBV infection in adolescents and adults.

Data Sources: MEDLINE (through January 2014), the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and PsycINFO.

Study Selection: Randomized trials of screening and treatment and observational studies of screening or the association between intermediate and clinical outcomes after antiviral therapy.

Data Extraction: One investigator abstracted data, and a second investigator checked them; 2 investigators independently assessed study quality.

Data Synthesis: No study directly evaluated the effects of screening for HBV infection versus no screening on clinical outcomes. Vaccination against HBV infection was associated with decreased risk in high-risk populations. On the basis of 11 primarily fair-quality trials, antiviral therapy may be more effective than placebo for reducing the risk for clinical outcomes associated with HBV infection. However, differences were not statistically significant. On the basis of 22 primarily fair-quality trials, antiviral therapy was more effective than placebo for various intermediate outcomes, with limited evidence that first-line antiviral agents are superior to lamivudine. Antiviral therapy was associated with a higher risk for withdrawal due to adverse events than placebo, but risk for serious adverse events did not differ.

Limitation: Only English-language articles were included; clinical outcome data for antiviral therapies were limited, and several studies were done in countries where the prevalence and natural history of HBV infection differ from those of the United States.

Conclusion: Antiviral treatment for chronic HBV infection is associated with improved intermediate outcomes, but more research is needed to understand the effects of screening and subsequent interventions on clinical outcomes and to identify optimal screening strategies.

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In 2008, an estimated 704,000 persons in the United States were chronically infected with hepatitis B virus (HBV) (1). Potential long-term sequelae of chronic HBV infection include cirrhosis, hepatic decompensation, and hepatocellular carcinoma (2). In 2010, deaths associated with HBV infection were estimated at 0.5 per 100,000 persons (3).

In the United States, persons born in countries with a prevalence of HBV infection of 2% or greater account for 47% to 95% of chronically infected persons (4–7). Persons at high risk for HBV infection include household contacts or sexual partners of persons with HBV infection, men who have sex with men, injection drug users, and HIV-positive persons. The number of reported acute cases of HBV infection in the United States decreased from more than 20,000 annually in the mid-1980s to 2,890 in 2011 (the actual number of new cases is estimated at 6.5 times the number of reported cases) (3). Globally, incidence of HBV infection has markedly decreased, particularly among younger persons, after the implementation of universal vaccination programs (1, 8).

Screening for HBV infection could identify chronically infected persons who might benefit from antiviral therapies, surveillance to diagnose hepatocellular carcinoma, or interventions to reduce behaviors associated with progression of liver disease (for example, alcohol use) or transmission and to identify persons without HBV immunity who could benefit from vaccination (9). However, in 2004, the U.S. Preventive Services Task Force (USPSTF) recommended against screening asymptomatic persons for HBV infection (D recommendation) on the basis of a lack of evidence that screening improves clinical outcomes and the low prevalence of HBV infection in the general population (10). Other groups recommend screening high-risk persons (7, 9).

The purpose of this report is to review the current evidence on screening for HBV infection in asymptomatic adolescents and adults, excluding pregnant women. This report differs from the previous USPSTF review (11) by including additional key questions on the benefits and harms of antiviral treatment and the association between

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improvements in intermediate outcomes after antiviral therapy and subsequent clinical outcomes.

**Methods**

**Scope of the Review**

We developed a review protocol and analytic framework (Appendix Figure 1, available at www.annals.org) that included the following key questions.

1. What are the benefits of screening for HBV infection versus no screening in asymptomatic adolescents and adults on morbidity, mortality, and disease transmission?
2. What are the harms of screening for HBV infection?
3. How well do different screening strategies identify persons with HBV infection?
4. In persons without evidence of HBV immunity, how effective is HBV vaccination at improving clinical outcomes?
5. How effective is antiviral treatment at improving intermediate outcomes?
6. How effective is antiviral treatment at improving health outcomes?
7. What are the harms associated with antiviral treatment for HBV infection?
8. Are improvements in intermediate outcomes after antiviral therapy associated with improvements in health outcomes?

The full report (12) contains detailed methods and data, including search strategies, inclusion criteria, abstraction and quality rating tables, an additional key question on the effects of behavior change counseling and education, and results related to biochemical and composite intermediate outcomes. The protocol was developed by using a standardized process with input from experts and the public. The analytic framework focuses on direct evidence that screening for HBV infection improves important health outcomes versus not screening and the chain of indirect evidence linking screening to improved health outcomes. Links in the chain of indirect evidence include the yield and performance of testing strategies for identifying persons with HBV infection and benefits and harms from subsequent treatments.

We did not re-review the accuracy of HBV serologic testing, which the USPSTF previously determined to be accurate (sensitivity and specificity >98%) (13). We also did not evaluate prenatal screening, which the USPSTF is not currently addressing.

**Data Sources and Searches**

A research librarian searched MEDLINE (1946 through January 2014), the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and PsycINFO. We supplemented electronic searches by reviewing reference lists of retrieved articles.

**Study Selection**

At least 2 reviewers independently evaluated each study to determine inclusion eligibility. For screening, we included randomized trials and observational studies that compared different screening strategies in asymptomatic adults without known abnormal liver enzyme levels. We also reported clinical outcomes or the sensitivity and number needed to screen (NNS) to identify 1 HBV-infected person or provided the data to calculate these variables.

For treatment, we included placebo-controlled trials of vaccination of adolescents and adults without known immunity to HBV and relevant systematic reviews. For antiviral therapy, we included trials of monotherapy with a medication approved by the U.S. Food and Drug Administration versus placebo or no treatment or first-line antiviral therapies (entecavir, tenofovir, or pegylated interferon-α2a) (9) versus other approved therapies (adefovir, nonpegylated interferon, lamivudine, or telbivudine) that reported clinical outcomes (mortality, cirrhosis, hepatic decompensation, hepatocellular carcinoma, need for transplantation, or disease transmission), intermediate outcomes (histologic, virologic, or serologic), or harms (withdrawals due to adverse events, serious adverse events, or overall adverse events). We included trials of interferon-α2a (not approved for HBV infection) that reported clinical outcomes because evidence for interferon-α2b and pegylated interferon was limited. For the association between achieving an intermediate outcome after antiviral treatment and subsequent clinical outcomes, we included cohort studies that reported adjusted risk estimates.

We included only English-language articles and excluded studies published only as abstracts. We excluded trials of persons who did not respond to prior antiviral therapy or those who had virologic relapse and did not evaluate drug resistance as an outcome. We excluded studies of patients co-infected with HIV or hepatitis C virus, transplant recipients, and patients receiving hemodialysis. We excluded systematic reviews of antiviral therapies unless we were unable to abstract the primary studies because they were in a foreign language. Appendix Figure 2 (available at www.annals.org) shows the summary of evidence search and selection.

**Data Abstraction and Quality Rating**

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, analysis, follow-up, and results. A second investigator reviewed data for accuracy. Two investigators independently applied criteria developed by the USPSTF (14, 15) to rate the quality of each study as good, fair, or poor. Discrepancies were resolved through consensus.

**Data Synthesis and Analysis**

We assessed the aggregate internal validity (quality) of the body of evidence for each key question (good, fair, or poor) on the basis of the number, quality, and size of...
studies; consistency of results; and directness of evidence (14, 15).

For antiviral therapy and vaccination, we conducted meta-analyses to calculate relative risks using the DerSimonian–Laird random-effects model (Review Manager, version 5.2, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Primary analyses for antiviral therapy were based on total follow-up (including events after discontinuation of treatment), although we conducted sensitivity analyses of events during antiviral therapy. For harms, we analyzed events that occurred during antiviral therapy.

For all analyses, we stratified results by antiviral drug. Statistical heterogeneity was assessed by using the $I^2$ statistic (16). We did additional analyses in which trials were stratified by study quality, duration of follow-up (shorter or longer than 1 year), hepatitis B e antigen (HBeAg) status, and inclusion of patients with cirrhosis.

Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions. The AHRQ had no role in study selection, quality assessment, or synthesis. Staff from the AHRQ provided project oversight; reviewed the report to ensure that the analysis met methodological standards; and distributed the draft for peer review, including to representatives of professional societies and federal agencies. The investigators are solely responsible for the content and the decision to submit the manuscript for publication.

Results

No study compared clinical outcomes or harms in persons screened for HBV infection versus those not screened (the first 2 key questions).

Yield of Risk-Based Screening Methods

One fair-quality cross-sectional study ($n = 6194$) done in a French clinic for sexually transmitted infections found that targeted screening of persons born in countries with a prevalence of chronic HBV infection of 2% or greater, men, and unemployed persons identified 98% (48 of 49) of infections while testing approximately two thirds of patients, for an NNS of 82 to identify 1 case of HBV infection (17). Screening based on behavioral risk factors, such as injection drug use and high-risk sexual behaviors, resulted in a higher NNS and did not improve sensitivity. Screening only persons born in countries with a higher prevalence for HBV infection missed two thirds of infections (sensitivity, 31%), with an NNS of 16.

Effectiveness of HBV Vaccination

One systematic review found that HBV vaccination was associated with decreased risk for HBV infection in health care workers (4 trials; risk ratio [RR], 0.5 [95% CI, 0.4 to 0.7]; $I^2 = 18\%$) on the basis of the presence of hepatitis B surface antigen (HBsAg) or antibodies to hepatitis B core antigen (18). In men who have sex with men, pooled results from 1 good-quality trial (19) and 2 fair-quality trials (20, 21) found that vaccination was associated with decreased risk for HBV infection versus placebo on the basis of HBsAg seroconversion (RR, 0.2 [CI, 0.1 to 0.4]; $I^2 = 45\%$) or elevated alanine aminotransferase levels (RR, 0.2 [CI, 0.2 to 0.3]; $I^2 = 2\%$). Studies did not evaluate the effects of HBV vaccination on long-term clinical outcomes.

Effectiveness of Antiviral Treatment on Intermediate Outcomes

Twenty-two placebo-controlled trials ($n = 35$ to 515; duration, 8 weeks to 3 years) of antiviral therapy reported intermediate outcomes (Table). Four evaluated adefovir (22–25), 8 evaluated interferon-α2b (26–33), 9 evaluated lamivudine (37–42, 44–46), and 1 evaluated tenofovir (47). Fifteen enrolled exclusively or primarily HBeAg-positive patients (23–26, 29–33, 40–42, 45–47). When reported, baseline rates of cirrhosis ranged from 5% to 44% (22, 26–28, 30, 32, 33, 39, 40, 42, 44). Two were rated as good-quality (31, 47); methodological shortcomings in the other trials included unclear or inadequate methods of randomization, allocation concealment, and blinding.

In pooled estimates, antiviral therapy was more effective than placebo or no treatment at achieving histologic improvement (7 trials; RR, 2.1 [CI, 1.8 to 2.6]; $I^2 = 0\%$) (Figure 1), HBeAg loss or seroconversion (10 trials; RR, 2.1 [CI, 1.6 to 2.9]; $I^2 = 49\%$) (Figure 2), virologic response (9 trials; RR, 7.2 [CI, 3.2 to 16]; $I^2 = 58\%$) (Figure 3), and HBsAg loss or seroconversion (11 trials; RR, 2.4 [CI, 1.2 to 4.9]; $I^2 = 0\%$) (Figure 4). Results were generally consistent across individual drugs and in sensitivity and subgroup analyses based on study quality, duration of treatment, HBeAg-positive status, or outcomes during antiviral therapy.

Eight trials ($n = 42$ to 638; duration, 48 to 96 weeks) compared first-line antiviral agents with lamivudine or adefovir (Table) (48–56). Four were rated as good-quality (48, 52, 54, 55); the others were rated as fair-quality, primarily because of inadequate or unclear blinding. Entecavir (4 trials) (48, 51–53) and pegylated interferon (2 trials) (54, 55) were each associated with increased likelihood of achieving some intermediate outcomes versus lamivudine (Appendix Table 1, available at www.annals.org), but the small number of trials limited the analyses. Trials of entecavir versus lamivudine on the outcome of virologic response were markedly heterogeneous (4 trials; RR, 1.6 [CI, 1.1 to 2.5]; $I^2 = 94\%$) (Appendix Figure 3, available at www.annals.org) (48, 51–53). Estimates from all trials favored entecavir (RR, 1.3 to 2.1), including the 2 largest good-quality trials (RR, 2.1 [CI, 1.8 to 2.4] [48] and 1.3.
## Table. Characteristics of Studies of Antiviral Therapy

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Design</th>
<th>Duration</th>
<th>Country/Region</th>
<th>Sample Size, n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adefovir vs. placebo</strong></td>
<td></td>
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</tr>
<tr>
<td>Hadziyannis et al, 2003 (22)</td>
<td>RCT</td>
<td>48 wk</td>
<td>Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore</td>
<td>185</td>
</tr>
<tr>
<td>Jonas et al, 2008 (23)</td>
<td>RCT</td>
<td>48 wk</td>
<td>Germany, Poland, Spain, United Kingdom, United States</td>
<td>83</td>
</tr>
<tr>
<td>Marcellin et al, 2003 (24)</td>
<td>RCT</td>
<td>48 wk</td>
<td>Australia, Canada, France, Germany, Italy, Malaysia, the Philippines, Singapore, Spain, Taiwan, Thailand, United Kingdom, United States‡</td>
<td>515</td>
</tr>
<tr>
<td>Zeng et al, 2006 (25)</td>
<td>RCT</td>
<td>12 wk</td>
<td>China</td>
<td>480</td>
</tr>
<tr>
<td><strong>Interferon-α2b vs. no treatment</strong></td>
<td></td>
<td></td>
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<tr>
<td>Bayraktar et al, 1993 (26)</td>
<td>Controlled trial</td>
<td>6 mo</td>
<td>Turkey</td>
<td>35</td>
</tr>
<tr>
<td>Hadziyannis et al, 1990 (27)</td>
<td>RCT</td>
<td>14–16 wk of treatment plus 2-y follow-up</td>
<td>Greece</td>
<td>50</td>
</tr>
<tr>
<td>Lampertico et al, 1997 (28)</td>
<td>Open-label RCT</td>
<td>3 y</td>
<td>Italy</td>
<td>42</td>
</tr>
<tr>
<td>Müller et al, 1990 (29)</td>
<td>RCT</td>
<td>10 mo</td>
<td>Germany</td>
<td>58</td>
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<tr>
<td>Perez et al, 1990 (30)</td>
<td>RCT</td>
<td>24 wk (control phase)</td>
<td>Argentina</td>
<td>35</td>
</tr>
<tr>
<td>Perrillo et al, 1990 (31)</td>
<td>RCT</td>
<td>10 mo</td>
<td>United States</td>
<td>169</td>
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<tr>
<td>Sarin et al, 1996 (32)</td>
<td>RCT</td>
<td>16 mo</td>
<td>India</td>
<td>41</td>
</tr>
<tr>
<td>Waked et al, 1990 (33)</td>
<td>RCT</td>
<td>16 mo</td>
<td>Egypt</td>
<td>40</td>
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<tr>
<td><strong>Interferon-α2a vs. placebo</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al, 1999 (34); methods: Liaw et al, 1994 (35)</td>
<td>RCT</td>
<td>18 wk plus 7-y follow-up</td>
<td>Taiwan</td>
<td>101</td>
</tr>
<tr>
<td>Mazella et al, 1999 (36)</td>
<td>RCT</td>
<td>6 mo plus 7-y follow-up</td>
<td>Italy</td>
<td>64</td>
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<tr>
<td><strong>Lamivudine vs. placebo</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ali, 2003 (37)</td>
<td>RCT</td>
<td>12 mo</td>
<td>Iraq</td>
<td>74</td>
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<tr>
<td>Bozkaya et al, 2005 (38)</td>
<td>Controlled trial</td>
<td>12 mo (control phase)</td>
<td>Turkey</td>
<td>55</td>
</tr>
<tr>
<td>Chan et al, 2007 (39)</td>
<td>RCT</td>
<td>30 mo</td>
<td>China</td>
<td>139</td>
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<tr>
<td>Dienstag et al, 1999 (40)</td>
<td>RCT</td>
<td>16 mo</td>
<td>United States</td>
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<tr>
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<td>RCT</td>
<td>8 wk</td>
<td>Hong Kong</td>
<td>42</td>
</tr>
<tr>
<td>Lai et al, 1998 (42)</td>
<td>RCT</td>
<td>1 y</td>
<td>Hong Kong, Taiwan, Singapore</td>
<td>358</td>
</tr>
<tr>
<td>Liaw et al, 2004 (43)</td>
<td>RCT</td>
<td>Median, 2.7 y</td>
<td>Australia, Hong Kong, New Zealand, Singapore, Taiwan, Thailand</td>
<td>651</td>
</tr>
<tr>
<td>Tassopoulos et al, 1999 (44)</td>
<td>RCT</td>
<td>24 wk</td>
<td>Greece</td>
<td>125</td>
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<tr>
<td>Yalçın et al, 2004 (45)</td>
<td>RCT</td>
<td>1 y</td>
<td>Turkey</td>
<td>46</td>
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<tr>
<td>Yao et al, 1999 (46)</td>
<td>RCT</td>
<td>12 wk</td>
<td>China</td>
<td>429</td>
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<tr>
<td><strong>Tenofovir vs. placebo</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray et al, 2012 (47)</td>
<td>RCT</td>
<td>72 wk</td>
<td>United States, Bulgaria, France, Poland, Romania, Spain, Turkey</td>
<td>106</td>
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<tr>
<td><strong>Entecavir vs. lamivudine</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chang et al, 2006 (48); Gish et al, 2007 (49); Chang et al, 2009 (50)</td>
<td>RCT</td>
<td>96 wk</td>
<td>North America, Asia, Australia, South America</td>
<td>709</td>
</tr>
<tr>
<td>Lai et al, 2002 (51)</td>
<td>RCT</td>
<td>24 wk</td>
<td>Australia, Belgium, Canada, France, Germany, Hong Kong, Israel, Italy, Malaysia, the Netherlands, the Philippines, Poland, Russia, Singapore, Thailand</td>
<td>87††</td>
</tr>
<tr>
<td>Lai et al, 2006 (52)</td>
<td>RCT</td>
<td>52 wk</td>
<td>Europe, Middle East, Asia, Australia, North America, South America</td>
<td>638</td>
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<tr>
<td>Ren et al, 2007 (53)</td>
<td>RCT</td>
<td>48 wk</td>
<td>China</td>
<td>42††</td>
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</table>
### Table—Continued

<table>
<thead>
<tr>
<th>Age, y*</th>
<th>Men, %</th>
<th>HBeAg Status at Baseline</th>
<th>Patients With Cirrhosis at Baseline, %</th>
<th>Outcomes Reported†</th>
<th>Quality</th>
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<tbody>
<tr>
<td>46</td>
<td>83</td>
<td>Negative</td>
<td>11</td>
<td>Biochemical and virologic response, histologic improvement</td>
<td>Fair</td>
</tr>
<tr>
<td>14</td>
<td>75</td>
<td>Positive</td>
<td>NR</td>
<td>Biochemical response, composite outcomes, mortality</td>
<td>Fair</td>
</tr>
<tr>
<td>35</td>
<td>74</td>
<td>Positive</td>
<td>NR</td>
<td>Biochemical response, HBeAg loss/seroconversion, histologic improvement</td>
<td>Fair</td>
</tr>
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<td>32</td>
<td>83</td>
<td>Positive</td>
<td>NR</td>
<td>Biochemical response, HBeAg loss/seroconversion, virologic response, mortality</td>
<td>Fair</td>
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<td>36</td>
<td>71</td>
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<td>29</td>
<td>Biochemical response, HBeAg and HBsAg loss/seroconversion</td>
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<td>49</td>
<td>94</td>
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<td>Composite outcomes</td>
<td>Poor</td>
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<td>46</td>
<td>86</td>
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<td>17</td>
<td>Composite outcomes, HBsAg loss/seroconversion, histologic improvement, hepatocellular carcinoma</td>
<td>Fair</td>
</tr>
<tr>
<td>NR§</td>
<td>79</td>
<td>Positive</td>
<td>5</td>
<td>Composite outcomes</td>
<td>Fair</td>
</tr>
<tr>
<td>39</td>
<td>77</td>
<td>Positive</td>
<td>14</td>
<td>Biochemical and virologic response, HBeAg and HBsAg loss/seroconversion</td>
<td>Fair</td>
</tr>
<tr>
<td>40</td>
<td>85</td>
<td>Positive</td>
<td>NR</td>
<td>HBeAg loss/seroconversion, composite outcomes, mortality</td>
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</tr>
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<td>35</td>
<td>94</td>
<td>Positive</td>
<td>44</td>
<td>HBeAg and HBsAg loss/seroconversion, virologic response, composite outcomes</td>
<td>Fair</td>
</tr>
<tr>
<td>36</td>
<td>78</td>
<td>Positive</td>
<td>40</td>
<td>HBeAg and HBsAg loss/seroconversion, histologic improvement, mortality, incident cirrhosis</td>
<td>Fair</td>
</tr>
<tr>
<td>32</td>
<td>100</td>
<td>Positive</td>
<td>12</td>
<td>Incident cirrhosis, hepatocellular carcinoma, mortality</td>
<td>Fair</td>
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<td>78</td>
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<td>36</td>
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<td>NR</td>
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<td>39</td>
<td>84</td>
<td>Negative</td>
<td>27</td>
<td>Biochemical and virologic response, HBsAg loss/seroconversion, histologic improvement, hepatocellular carcinoma, mortality</td>
<td>Fair</td>
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<tr>
<td>Median, 39</td>
<td>83</td>
<td>Positive</td>
<td>10</td>
<td>Biochemical and virologic response, HBeAg and HBsAg loss/seroconversion, histologic improvement, mortality</td>
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<td>32</td>
<td>64</td>
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<td>Median, 43</td>
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<td>Median, 43</td>
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<td>HBsAg loss/seroconversion, composite outcomes</td>
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<td>24</td>
<td>54</td>
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<td>NR</td>
<td>HBeAg and HBsAg loss/seroconversion, virologic response, composite outcomes</td>
<td>Fair</td>
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<tr>
<td>32</td>
<td>73</td>
<td>Positive</td>
<td>NR</td>
<td>Biochemical and virologic response, HBeAg loss/seroconversion</td>
<td>Fair</td>
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<td>15</td>
<td>73</td>
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<td>Biochemical and virologic response, HBeAg and HBsAg loss/seroconversion, composite outcomes</td>
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<td>35</td>
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<td>Good</td>
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<td>Biochemical and virologic response, HBeAg loss/seroconversion, composite outcomes</td>
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<td>Biochemical and virologic response, histologic improvement, hepatocellular carcinoma, mortality</td>
<td>Good</td>
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<td>32</td>
<td>55</td>
<td>Positive</td>
<td>NR</td>
<td>Biochemical and virologic response, HBeAg loss/seroconversion, hepatocellular carcinoma, mortality</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Intermediate outcomes did not clearly differ between tenofovir versus adefovir (2 trials), but estimates were imprecise (56).

**Effectiveness of Antiviral Treatment on Clinical Outcomes**

Eleven trials (n = 40 to 651; duration, 10 months to 7.5 years) of antiviral therapy versus placebo or no treatment reported clinical outcomes (Table). Three evaluated interferon-α2b (28, 31, 33), 2 evaluated interferon-α2a (34, 36), 2 evaluated adefovir (23, 25), and 4 evaluated lamivudine (39, 40, 42, 43). Two enrolled primarily HBeAg-negative patients (28, 39). When reported, rates of baseline cirrhosis ranged from 5% to 40% (28, 33, 34, 39, 40, 42, 43). One was rated as good-quality (31), and the remainder was rated as fair-quality; methodological shortcomings included inadequate details about method of randomization, allocation concealment, and blinding.

Pooled estimates for incident cirrhosis (3 trials; RR, 0.70 [CI, 0.33 to 1.46]; I² = 0%) (Appendix Figure 4, available at www.annals.org), hepatocellular carcinoma (5 trials; RR, 0.57 [CI, 0.32 to 1.04]; I² = 2%) (Figure 5), and mortality (5 trials; RR, 0.55 [CI, 0.18 to 1.71]; I² = 43%) (Appendix Figure 5, available at www.annals.org) favored antiviral therapy over placebo. However, differences were not statistically significant and estimates were imprecise because of the small number of events. Excluding trials with less than 2 years of follow-up (28, 34, 36, 39, 43) resulted in similar but less precise estimates.

The largest trial (n = 658), which enrolled Asian patients with more advanced liver disease, heavily influenced the pooled estimate for hepatocellular carcinoma and accounted for 70% (33 of 47) of cases in the analysis (43). The trial was discontinued early (median follow-up, 2.7 years) after reaching a prespecified stopping threshold on a composite outcome (hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or liver-related mortality). The risk estimate for hepatocellular carcinoma from this trial was similar to the pooled estimate and became statistically significant after adjustment for country, sex, baseline alanine aminotransferase levels, Child–Pugh score, and Ishak fibrosis score (adjusted hazard ratio, 0.49 [CI, 0.25 to 0.99]). Lamivudine was also associated with decreased risk for disease progression (adjusted hazard ratio, 0.45 [CI, 0.28 to 0.73]) and worsening liver disease (adjusted hazard ratio, 0.45 [CI, 0.22 to 0.90]) versus placebo (43). The number of clinical events in head-to-head trials of entecavir or pegylated interferon-α2a versus lamivudine (48–50, 52, 54, 55) or pegylated versus nonpegylated interferon (57) was too low to determine the effects on clinical outcomes.

**Harms of Antiviral Treatment for HBV Infection**

Pooled estimates showed no difference between antiviral therapy versus placebo or no treatment in risk for serious adverse events (12 trials; RR, 0.8 [CI, 0.6 to 1.1]; I² = 0%) (22, 24, 39–47, 58) or any adverse event (7 trials; RR, 0.96 [CI, 0.9 to 1.0]; I² = 0%) (22, 42–44, 46, 47, 58) but increased risk for withdrawal due to adverse events (9 trials; RR, 4.0 [CI, 1.4 to 11]; I² = 0%) (22–24, 28, 30, 31, 37, 44, 46). Rates of withdrawal due to adverse events ranged from 0% to 24% with antiviral therapy, with only 1 event reported with placebo or no treatment.

### Table—Continued

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Design</th>
<th>Duration</th>
<th>Country/Region</th>
<th>Sample Size, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon-α2a vs. lamivudine</td>
<td>RCT</td>
<td>72 wk</td>
<td>Asia, Australasia, Europe, North America, South America</td>
<td>543††</td>
</tr>
<tr>
<td>Lau et al, 2005 (54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>72 wk</td>
<td>Asia, Europe</td>
<td>358††</td>
</tr>
<tr>
<td>Marcellin et al, 2004 (55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir vs. adefovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marcellin et al, 2008 (56) (study 102)</td>
<td>RCT</td>
<td>48 wk</td>
<td>Europe, North America, Australia, New Zealand</td>
<td>375</td>
</tr>
<tr>
<td>Marcellin et al, 2008 (56) (study 103)</td>
<td>RCT</td>
<td>48 wk</td>
<td>Europe, North America, Australia, New Zealand</td>
<td>266</td>
</tr>
</tbody>
</table>

HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; NA = not applicable; NR = not reported; RCT = randomized, controlled trial.

* Mean age unless otherwise indicated.
† Definition of histologic improvement varied but most commonly was a reduction of ≥2 points in Histology Activity Index scores. The full report (12) addresses results for biochemical and composite outcomes.
‡ The U.S. sample was 69% Asian.
§ Range, 18 to 65 y.
¶ Excluded persons with cirrhosis.
** 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.
†† Subset of a larger study group.
Results for harms were largely consistent across individual drugs, but there were no placebo-controlled trials of pegylated interferon-α2a or entecavir and only 1 trial each of telbivudine (58) and tenofovir (47). In 2 head-to-head trials, pegylated interferon-α2a was associated with greater risk for serious adverse events (RR, 2.1 [CI, 1.0 to 4.5]; I² = 0%), withdrawals due to adverse events (RR, 7.6 [CI, 1.1 to 52]; I² = 38%), and any adverse event (RR, 1.7 [CI, 1.5 to 2.0]; I² = 55%) than lamivudine (54, 55). There were no differences between entecavir versus lamivudine (3 trials) (48, 51, 52) or between tenofovir versus adefovir (2 trials) (56).

Association Between Improvements in Intermediate Outcomes After Antiviral Therapy and Clinical Outcomes

Ten observational studies (n = 22 to 818; duration of follow-up, 4.0 to 9.9 years) evaluated the association between improvement in intermediate outcomes after antiviral therapy and subsequent clinical outcomes (Appendix Table 2, available at www.annals.org) (59–68). Three studies evaluated lamivudine (59, 61, 68), and the remainder evaluated interferon. Studies assessed various intermediate (virologic and biochemical response, histologic improvement, HBeAg loss, or a composite) and clinical (death, hepatocellular carcinoma, or a composite) outcomes. Four studies evaluated HBeAg-positive patients (62, 63, 65, 66), and the remainder evaluated HBeAg-negative patients (59–61, 64, 67, 68). Two studies were restricted to patients with cirrhosis (59, 62), 1 excluded patients with cirrhosis (60), and the proportion with cirrhosis at baseline ranged from 12% to 60% in the others.

Seven studies were rated as fair-quality (59–61, 64–66, 68), and 3 were rated as poor-quality (62, 63, 67). Methodological shortcomings included unclear blinding status of outcome assessors and failure to report loss to follow-up. Poor-quality studies did not address at least 4 of 5 key confounders (age, sex, fibrosis stage, HBV viral load, and HBeAg status) through adjustment or restriction.

Although the studies generally reported an association between achieving various intermediate outcomes and improved clinical outcomes (Appendix Table 3, available at www.annals.org), the methodological limitations, failure of some estimates to reach statistical significance, and variability in patient populations and intermediate and clinical outcomes evaluated preclude strong conclusions.

### Table—Continued

<table>
<thead>
<tr>
<th>Age, y*</th>
<th>Men, %</th>
<th>HBeAg Status at Baseline</th>
<th>Patients With Cirrhosis at Baseline, %</th>
<th>Outcomes Reported†</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>79</td>
<td>Positive</td>
<td>18</td>
<td>Biochemical and virologic response, HBeAg and HBsAg loss/seroconversion, histologic improvement, composite outcomes, hepatocellular carcinoma, mortality</td>
<td>Good</td>
</tr>
<tr>
<td>40</td>
<td>86</td>
<td>Negative</td>
<td>30</td>
<td>Biochemical and virologic response, HBeAg loss/seroconversion, histologic improvement, composite outcomes, hepatocellular carcinoma, mortality</td>
<td>Good</td>
</tr>
<tr>
<td>44</td>
<td>77</td>
<td>Negative</td>
<td>20</td>
<td>Biochemical and virologic response, HBeAg loss/seroconversion, histologic improvement, composite outcomes, mortality</td>
<td>Fair</td>
</tr>
<tr>
<td>34</td>
<td>69</td>
<td>Positive</td>
<td>20</td>
<td>Biochemical and virologic response, HBeAg and HBsAg loss/seroconversion, histologic improvement, composite outcomes, mortality</td>
<td>Fair</td>
</tr>
</tbody>
</table>

### DISCUSSION

Appendix Table 4 (available at www.annals.org) summarizes the evidence reviewed in this update. As in the 2004 review (11), we found no direct evidence on effects of screening for HBV infection versus no screening on clinical outcomes. The USPSTF previously determined that standard serologic markers are accurate for diagnosing HBV infection (13).

Evidence on the usefulness of different screening strategies for identifying persons with HBV infection was limited to a single fair-quality, cross-sectional study. It identified a relatively efficient screening strategy based on country of origin, sex, and employment status but was done in a French clinic for sexually transmitted infections and had limited applicability to primary care settings in the United States (17).

Randomized trials suggest that antiviral therapy may be more effective than placebo for reducing the risk for clinical outcomes associated with HBV infection, such as cirrhosis, hepatocellular carcinoma, and mortality. However, results were based on only a few underpowered trials and differences were not statistically significant. The duration of follow-up and the patient populations (for example, those with or without cirrhosis and HBeAg) varied among trials, and few trials evaluated recommended first-line antiviral agents (entecavir, tenofovir, and pegylated interferon). The pooled estimate for hepatocellular carcinoma nearly reached statistical significance; however, it was heavily influenced by results from 1 Asian trial that primarily...
enrolled patients with more advanced liver disease, potentially reducing applicability to screen-detected U.S. populations (43).

Our findings are similar to those of a recent systematic review that focused on results from randomized trials (69). Although other reviews found an association between use of antiviral therapy and improved clinical outcomes, results were primarily based on observational studies, including those that did not adjust well for confounders (70–75).

Evidence is stronger for beneficial effects of antiviral therapy versus placebo on intermediate histologic, serologic, and virologic outcomes. Results were generally consistent across individual drugs, although some estimates were imprecise and not statistically significant. Like other recent systematic reviews, we found limited evidence that the currently recommended first-line drugs tenofovir and entecavir are more effective than lamivudine at achieving some intermediate outcomes (69, 76–79).

The degree to which improvements in intermediate outcomes after antiviral therapy are associated with improved clinical outcomes is less clear. Although observational studies generally found an association between an improved intermediate outcome after antiviral therapy and reduced risk for clinical outcomes, results were not statistically significant in some studies; the populations and intermediate and clinical outcomes evaluated varied; and studies had important methodological limitations, including failure to adequately address confounders.

Antiviral therapy was associated with greater risk for withdrawal due to adverse events versus placebo but not with increased risk for serious adverse events. Head-to-head trials found that pegylated interferon-α2a was associated with increased risk for adverse events compared with lamivudine (54, 55), consistent with the high prevalence of adverse events with interferon-based therapies (80). In general, adverse events associated with antiviral therapy, in-

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**Figure 1. Antiviral therapy versus placebo or no treatment for histologic improvement.**

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiviral Therapy</strong></td>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadziyannis et al, 2003 (22)</td>
<td>77/121</td>
<td>19/57</td>
<td>22.8</td>
<td>1.91 (1.29–2.82)</td>
</tr>
<tr>
<td>Marcellin et al, 2003 (24)</td>
<td>89/168</td>
<td>41/161</td>
<td>38.7</td>
<td>2.08 (1.54–2.81)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>289</td>
<td>218</td>
<td>61.5</td>
<td>2.02 (1.59–2.56)</td>
</tr>
<tr>
<td>Total events</td>
<td>166</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.12 (P = 0.73); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.77 (P &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interferon-α2b</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lampertico et al, 1997 (28)</td>
<td>7/21</td>
<td>2/21</td>
<td>1.7</td>
<td>3.50 (0.82–14.93)</td>
</tr>
<tr>
<td>Waked et al, 1990 (33)</td>
<td>4/20</td>
<td>1/20</td>
<td>0.8</td>
<td>4.00 (0.49–32.72)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>41</td>
<td>41</td>
<td>2.4</td>
<td>3.65 (1.11–12.06)</td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.01 (P = 0.92); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.13 (P &lt; 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al, 2007 (39)</td>
<td>14/18</td>
<td>2/8</td>
<td>2.3</td>
<td>3.11 (0.91–10.59)</td>
</tr>
<tr>
<td>Dienstag et al, 1999 (40)</td>
<td>34/66</td>
<td>16/71</td>
<td>14.5</td>
<td>2.29 (1.40–3.73)</td>
</tr>
<tr>
<td>Lai et al, 1998 (42)</td>
<td>80/143</td>
<td>18/73</td>
<td>19.2</td>
<td>2.27 (1.48–3.48)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>227</td>
<td>152</td>
<td>36.0</td>
<td>2.32 (1.70–3.17)</td>
</tr>
<tr>
<td>Total events</td>
<td>128</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.23 (P = 0.89); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.30 (P &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>557</td>
<td>411</td>
<td>100.0</td>
<td>2.15 (1.79–2.59)</td>
<td></td>
</tr>
<tr>
<td>305</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 1.65 (P = 0.95); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 8.04 (P &lt; 0.001)</td>
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<tr>
<td>Test for subgroup differences: chi-square = 1.28 (P = 0.53); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M–H = Mantel–Haenszel.
including interferon, were self-limited and resolved after

drug discontinuation.

Evidence on effects of other interventions was limited. Trials of health care workers and men who have sex with

men found that vaccination was associated with decreased risk for HBV infection on the basis of serologic and bio-

chemical markers but did not evaluate long-term clinical outcomes. Observational studies in countries with a high

Figure 2. Antiviral therapy versus placebo or no treatment for HBeAg loss.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marcellin et al, 2003 (24)*</td>
<td>44/165</td>
<td>28.6</td>
<td>2.53 (1.51–4.23)</td>
<td></td>
</tr>
<tr>
<td>Zeng et al, 2006 (25)</td>
<td>20/354</td>
<td>10.4</td>
<td>1.12 (0.46–2.72)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>519</td>
<td>39.0</td>
<td>1.83 (0.84–3.99)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>64</td>
<td>23</td>
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<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.19; chi-square = 2.40 (P = 0.12); P = 58%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 1.52 (P = 0.13)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Interferon-al</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bayraktar et al, 1993 (26)</td>
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<td>1.1</td>
<td>13.12 (0.86–200.39)</td>
<td></td>
</tr>
<tr>
<td>Perez et al, 1990 (30)</td>
<td>10/17</td>
<td>2.2</td>
<td>10.59 (1.51–74.11)</td>
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</tr>
<tr>
<td>Sarin et al, 1996 (32)</td>
<td>10/20</td>
<td>6.5</td>
<td>3.50 (1.12–10.90)</td>
<td></td>
</tr>
<tr>
<td>Waked et al, 1990 (33)</td>
<td>13/20</td>
<td>12.0</td>
<td>2.60 (1.14–5.93)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>82</td>
<td>21.8</td>
<td>3.62 (1.89–6.94)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>48</td>
<td>9</td>
<td></td>
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<tr>
<td>Heterogeneity: tau-square = 0.03; chi-square = 3.17 (P = 0.37); P = 5%</td>
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<td></td>
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<tr>
<td>Test for overall effect: Z = 3.89 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dienstag et al, 1999 (40)†</td>
<td>19/66</td>
<td>18.1</td>
<td>1.86 (0.96–3.60)</td>
<td></td>
</tr>
<tr>
<td>Lai et al, 1997 (41)</td>
<td>0/12</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yalçın et al, 2004 (45)</td>
<td>1/13</td>
<td>1.2</td>
<td>2.54 (0.17–37.64)</td>
<td></td>
</tr>
<tr>
<td>Yao et al, 1999 (46)</td>
<td>23/284</td>
<td>9.3</td>
<td>1.52 (0.60–3.89)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>375</td>
<td>28.6</td>
<td>1.76 (1.04–3.00)</td>
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</tr>
<tr>
<td>Total events</td>
<td>43</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.19 (P = 0.91); P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.10 (P = 0.04)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofivir</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray et al, 2012 (47)</td>
<td>10/48</td>
<td>10.6</td>
<td>1.43 (0.59–3.44)</td>
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</tr>
<tr>
<td>Subtotal</td>
<td>48</td>
<td>10.6</td>
<td>1.43 (0.59–3.44)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>10</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.80 (P = 0.43)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Total</td>
<td>1024</td>
<td>100.0</td>
<td>2.13 (1.59–2.85)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>165</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.01; chi-square = 9.34 (P = 0.41); P = 4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.06 (P &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: chi-square = 3.98 (P = 0.26); P = 24.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HBeAg = hepatitis B e antigen; M–H = Mantel–Haenszel.
* Adefovir, 30 mg, vs. placebo.
† 68-wk data.
prevalence of infection indicate that implementation of universal vaccination is associated with declining incidence of HBV infection and reduced rates of hepatocellular carcinoma and other adverse clinical outcomes but were outside the scope of this review (8, 81, 82). As detailed in our full report, we identified no trials on the effectiveness of education or behavior change counseling in HBV-infected patients for reducing transmission or improving health outcomes (12). We did not review evidence on the effectiveness of surveillance for hepatocellular carcinoma in patients with HBV infection, which is currently limited to 2 trials done in Asia with somewhat mixed results (83, 84).

Our review has limitations. We excluded non–English-language articles and did not search for studies published only as abstracts. We could not formally assess publication bias because of the small number of studies. Evidence on the effectiveness of current first-line antiviral therapies was limited, particularly for clinical outcomes.

**Figure 3. Antiviral therapy versus placebo or no treatment for HBV DNA loss.**

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adefovir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadziyannis et al, 2003 (22)</td>
<td>63/123</td>
<td>6.6</td>
<td>63.50 (4.00–1009.28)</td>
</tr>
<tr>
<td>Zeng et al, 2006 (25)</td>
<td>18/352</td>
<td>6.4</td>
<td>12.58 (0.76–207.12)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>475</td>
<td>13.0</td>
<td>28.55 (3.99–204.39)</td>
</tr>
<tr>
<td>Total events</td>
<td>81</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.71 (P = 0.40); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.34 (P &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interferon-α2b</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez et al, 1990 (30)</td>
<td>1/17</td>
<td>5.4</td>
<td>3.17 (0.14–72.80)</td>
</tr>
<tr>
<td>Sarin et al, 1996 (32)</td>
<td>10/20</td>
<td>10.5</td>
<td>10.50 (1.48–74.71)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>37</td>
<td>15.9</td>
<td>7.49 (1.42–39.54)</td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.41 (P = 0.52); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.37 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al, 2007 (39)</td>
<td>9/89</td>
<td>10.1</td>
<td>4.75 (0.62–36.39)</td>
</tr>
<tr>
<td>Dienstag et al, 1999 (40)</td>
<td>28/63</td>
<td>23.6</td>
<td>2.79 (1.52–5.12)</td>
</tr>
<tr>
<td>Yalçın et al, 2004 (45)</td>
<td>1/13</td>
<td>6.8</td>
<td>2.54 (0.17–37.64)</td>
</tr>
<tr>
<td>Yao et al, 1999 (46)</td>
<td>229/293</td>
<td>24.0</td>
<td>7.03 (4.02–12.32)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>458</td>
<td>64.5</td>
<td>4.36 (2.22–8.58)</td>
</tr>
<tr>
<td>Total events</td>
<td>267</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.19; chi-square = 5.56 (P = 0.14); I² = 46%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.27 (P &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tenofovir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray et al, 2012 (47)</td>
<td>46/52</td>
<td>6.6</td>
<td>96.51 (6.10–1526.38)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>52</td>
<td>6.6</td>
<td>96.51 (6.10–1526.38)</td>
</tr>
<tr>
<td>Total events</td>
<td>46</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.24 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1022</td>
<td>100.0</td>
<td>7.22 (3.20–16.31)</td>
</tr>
<tr>
<td>Total events</td>
<td>405</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.64; chi-square = 19.01 (P = 0.01); I² = 58%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.76 (P &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: chi-square = 7.19 (P = 0.07); I² = 58.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HBV = hepatitis B virus; M–H = Mantel–Haenszel.
differ from those of the United States, potentially limiting applicability to screening in the United States.

Additional research may clarify the benefits and harms of screening for HBV infection. Studies that compare clinical outcomes in persons screened and not screened for HBV infection would require large samples and long follow-up. In lieu of such direct evidence, prospective studies on the accuracy and yield of alternative screening strategies (such as those targeting immigrants from countries with a high prevalence of HBV infection) (85) could help identify optimal screening strategies.

More research is needed on long-term clinical outcomes associated with current first-line antiviral therapies. In particular, entecavir and tenofovir have potent antiviral activity, seem to have low rates of drug resistance, and are better tolerated than pegylated interferon (86). Studies on the association between use of antiviral therapy and risk for transmission would be useful for identifying additional public health benefits from screening (87). Improved standardization of the intermediate and clinical outcomes evaluated would greatly strengthen evidence from observational studies on the association between achieving

---

**Figure 4. Antiviral therapy versus placebo or no treatment for HBsAg loss.**

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon–α2b</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayraktar et al, 1993 (26)</td>
<td>1/25</td>
<td>0/10</td>
<td>5.4</td>
</tr>
<tr>
<td>Lampertico et al, 1997 (28)</td>
<td>2/21</td>
<td>0/21</td>
<td>5.9</td>
</tr>
<tr>
<td>Perez et al, 1990 (30)</td>
<td>1/17</td>
<td>0/18</td>
<td>5.3</td>
</tr>
<tr>
<td>Perrillo et al, 1990 (31)</td>
<td>11/126</td>
<td>0/43</td>
<td>6.6</td>
</tr>
<tr>
<td>Sarin et al, 1996 (32)</td>
<td>3/20</td>
<td>1/21</td>
<td>11.1</td>
</tr>
<tr>
<td>Waked et al, 1990 (33)</td>
<td>6/20</td>
<td>3/20</td>
<td>34.2</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>229</td>
<td>133</td>
<td>68.5</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>24</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ali et al, 2003 (37)</td>
<td>3/32</td>
<td>1/30</td>
<td>10.8</td>
</tr>
<tr>
<td>Chan et al, 2007 (39)</td>
<td>1/89</td>
<td>0/47</td>
<td>5.2</td>
</tr>
<tr>
<td>Dienstag et al, 1999 (40)</td>
<td>1/66</td>
<td>0/71</td>
<td>5.2</td>
</tr>
<tr>
<td>Tassopoulos et al, 1999 (44)</td>
<td>0/60</td>
<td>1/64</td>
<td>5.2</td>
</tr>
<tr>
<td>Yalçın et al, 2004 (45)</td>
<td>0/13</td>
<td>0/33</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>260</td>
<td>245</td>
<td>26.3</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Tenofovir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray et al, 2012 (47)</td>
<td>1/52</td>
<td>0/54</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>52</td>
<td>54</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Tenofvir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>52</td>
<td>54</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Not applicable</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect: Z = 0.70 (P = 0.48)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HBsAg = hepatitis B surface antigen; M–H = Mantel–Haenszel.**

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intermediate outcomes and clinical outcomes, and these studies should be designed to account for important confounders (88).

In conclusion, screening can identify persons with chronic HBV infection, and antiviral treatment is associated with improved intermediate outcomes. However, research is needed to better define 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 will probably affect future assessments of screening.

From the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, Portland, Oregon.

Note: This review was conducted by the Pacific Northwest Evidence-based Practice Center under contract to AHRQ. AHRQ staff provided oversight for the project and assisted in the external review of the companion draft evidence synthesis.

Disclaimer: The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by AHRQ or the U.S. Department of Health and Human Services.

Acknowledgment: The authors thank Iris Mabry-Hernandez, MD, MPH, and USPSTF leads Kirsten Bibbins-Domingo, MD, PhD; Mark Ebell, MD, MS; Douglas K. Owens, MD, MS; and Albert L. Siu, MD, MSPH.

Financial Support: By contract HHSA-290-2007-10057-I-EPC3, task order 13, from the AHRQ.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-2837.

Requests for Single Reprints: Roger Chou, MD, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Code BICC, Portland, OR 97239-3098; e-mail, chour@ohsu.edu.

Current author addresses and author contributions are available at www.annals.org.


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**Ad Libitum**

### Why I Startled

During storms, I used to inch along the rafters in the barn to perch in a windowless dormer that overlooked the pond.

Curtains of rain would trawl across, bristling the surface before driving on. I’d crouch there eavesdropping, absorbing the chatter between sheet metal and falling water until my head was full of rain. Today, your voice sounds like this.

In December, the great room dim and full of embers, I’d drag a chair across the floorboards to press my cheek against a pane.

Facing sideways, squinting, frost would blossom and clear in time with my breathing, until Sarah came and shielding me from mother set me down on the floor again. A clouded glass that blurs the line of earth and sky belongs to her. Today, my eyes work like this.

The way you stole into my room this morning and, leaning over set your hand against my shoulder, I thought you were my mother.

I was just remembering the weight of her beside me, the shock of the mattress heaving, how I understood without her speaking.

Your hand inside my gown, the metal pressed against my skin I felt a shiver coming on and saw the leaves begin to turn, upwards pale faces towards the sky.

_Gaetan Sgro, MD_  
Pittsburgh, Pennsylvania  

_Current Author Address:_ Gaetan Sgro, MD; e-mail, gaetan.sgro@va.gov.

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Appendix Figure 1. Analytic framework.

Key Questions
1. What are the benefits of screening for HBV infection versus no screening in asymptomatic adolescents and adults on morbidity, mortality, and disease transmission?
2. What are the harms of screening for HBV infection?
3. How well do different screening strategies identify persons with HBV infection?
4. In persons without evidence of HBV immunity, how effective is HBV vaccination for improving clinical outcomes?
5. How effective is antiviral treatment at improving intermediate outcomes?
6. How effective is antiviral treatment at improving health outcomes?
7. What are the harms associated with antiviral treatment for HBV infection?
8. Are improvements in intermediate outcomes after antiviral therapy associated with improvements in health outcomes?

HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; KQ = key question.
* The full report (12) addresses this KQ.
Appendix Figure 2. Summary of evidence search and selection.

Abstracts of potentially relevant articles identified through MEDLINE, Cochrane*, PsychINFO, and other sources† (n = 4506)

Excluded abstracts and background articles (n = 3893)

Full-text articles reviewed for relevance to key questions (n = 613)

Excluded articles (n = 567)
- Wrong population: 94
- Wrong intervention: 196
- Wrong outcome: 83
- Wrong study design for key question: 81
- Wrong publication type: 41
- Wrong comparison: 59
- Duplicate data: 13

Included studies‡ (n = 45 [in 46 publications])

Key question 1 (n = 0)
Key question 2 (n = 0)
Key question 3 (n = 1)
Key question 4: No studies on long-term clinical outcomes
Key question 5 (n = 30 [in 31 publications])
Key question 6 (n = 16 [in 18 publications])
Key question 7 (n = 0)
Key question 8 (n = 29 [in 28 publications])
Key question 9 (n = 10)

* Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Reference lists of relevant articles.
‡ Some studies are included for >1 key question.
§ The full report (12) addresses this key question.

Appendix Table 1. Intermediate Outcomes From Head-to-Head Trials*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Entecavir vs. Lamivudine</th>
<th>Pegylated Interferon-α2a vs. Lamivudine</th>
<th>Tenofovir vs. Adefovir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P², %</td>
<td>Trials, n</td>
</tr>
<tr>
<td>HBeAg loss/seroconversion</td>
<td>1.2 (0.9–1.5)</td>
<td>0 3</td>
<td>48, 51, 53</td>
</tr>
<tr>
<td>HBSAg loss/seroconversion</td>
<td>1.8 (0.9–3.9)</td>
<td>– 1</td>
<td>48</td>
</tr>
<tr>
<td>Virologic improvement</td>
<td>1.6 (1.1–2.5)</td>
<td>94 4</td>
<td>48, 51–53</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>1.2 (1.1–1.3)</td>
<td>0 2</td>
<td>48, 52</td>
</tr>
</tbody>
</table>

HBeAg = hepatitis B e antigen; HBSAg = hepatitis B surface antigen; RR = risk ratio.
* Significant values are bolded.
**Appendix Figure 3.** Head-to-head studies of antiviral therapy for HBV DNA loss.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entecavir vs. lamivudine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al, 2006 (48)</td>
<td>284/354</td>
<td>137/355</td>
<td>16.5</td>
<td>2.08 (1.81–2.39)</td>
</tr>
<tr>
<td>Lai et al, 2002 (51)</td>
<td>11/46</td>
<td>7/41</td>
<td>7.6</td>
<td>1.40 (0.60–3.27)</td>
</tr>
<tr>
<td>Lai et al, 2006 (52)</td>
<td>293/325</td>
<td>225/313</td>
<td>16.8</td>
<td>1.25 (1.16–1.36)</td>
</tr>
<tr>
<td>Ren et al, 2007 (53)</td>
<td>15/21</td>
<td>8/21</td>
<td>10.4</td>
<td>1.88 (1.02–3.45)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>746</td>
<td>730</td>
<td>51.3</td>
<td>1.63 (1.07–2.48)</td>
</tr>
<tr>
<td>Total events</td>
<td>603</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.14; chi-square = 46.98 (P &lt; 0.001); I² = 94%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.26 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Pegylated interferon-α2a vs. lamivudine** |                  |           |                                |                                |
| Lau et al, 2005 (54)     | 39/271           | 14/272    | 10.7                           | 2.80 (1.55–5.03)               |
| Marcellin et al, 2004 (55)| 34/177          | 12/181    | 10.2                           | 2.90 (1.55–5.41)               |
| Subtotal                 | 448              | 453       | 20.8                           | 2.84 (1.85–4.36)               |
| Total events             | 73               |           |                                |                                |
| Heterogeneity: tau-square = 0.00; chi-square = 0.01 (P = 0.94); I² = 0% |
| Test for overall effect: Z = 4.79 (P < 0.001) |

| **Tenofovir vs. adefovir** |                  |           |                                |                                |
| Marcellin et al, 2008 (56) (study 102) | 233/250          | 79/125    | 16.5                           | 1.47 (1.28–1.69)               |
| Marcellin et al, 2008 (56) (study 103) | 134/176          | 12/90     | 11.4                           | 5.71 (3.35–9.73)               |
| Subtotal                 | 426              | 215       | 27.9                           | 2.85 (0.56–14.56)              |
| Total events             | 367              | 91        |                                |                                |
| Heterogeneity: tau-square = 1.34; chi-square = 35.07 (P < 0.001); I² = 97% |
| Test for overall effect: Z = 1.26 (P = 0.21) |

HBV = hepatitis B virus; M–H = Mantel–Haenszel.
## Appendix Figure 4. Antiviral therapy versus placebo or no treatment for incident cirrhosis.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiviral Therapy</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al, 1999 (34)</td>
<td>8/67</td>
<td>5/34</td>
<td>50.2</td>
<td>0.81 (0.29–2.29)</td>
</tr>
<tr>
<td>Mazzella et al, 1999 (36)</td>
<td>4/33</td>
<td>6/31</td>
<td>39.8</td>
<td>0.63 (0.20–2.01)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>100</td>
<td>65</td>
<td>89.9</td>
<td>0.72 (0.33–1.57)</td>
</tr>
<tr>
<td>Total events</td>
<td>12</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.11 (P = 0.74); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.82 (P = 0.41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waked et al, 1990 (33)</td>
<td>1/20</td>
<td>2/20</td>
<td>10.1</td>
<td>0.50 (0.05–5.08)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>20</td>
<td>20</td>
<td>10.1</td>
<td>0.50 (0.05–5.08)</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.59 (P = 0.56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>85</td>
<td>100.0</td>
<td>0.70 (0.33–1.46)</td>
</tr>
<tr>
<td>Total events</td>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.19 (P = 0.91); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.96 (P = 0.34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: chi-square = 0.09 (P = 0.77); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M–H = Mantel–Haenszel.
Appendix Figure 5. Antiviral treatment versus placebo or no treatment for mortality.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
<th>Risk Ratio M–H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiviral Therapy</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonas et al, 2008 (23)</td>
<td>0/56</td>
<td>0/27</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Zeng et al, 2006 (25)</td>
<td>0/360</td>
<td>0/120</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>416</td>
<td>147</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al, 1999 (34)</td>
<td>1/67</td>
<td>4/34</td>
<td>17.5</td>
<td>0.13 (0.01–1.09)</td>
</tr>
<tr>
<td>Mazzella et al, 1999 (36)</td>
<td>0/33</td>
<td>2/31</td>
<td>11.0</td>
<td>0.19 (0.01–3.77)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>100</td>
<td>65</td>
<td>28.5</td>
<td>0.15 (0.03–0.83)</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.00; chi-square = 0.04 (P = 0.83); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.16 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perrillo et al, 1990 (31)</td>
<td>1/126</td>
<td>2/43</td>
<td>15.4</td>
<td>0.17 (0.02–1.84)</td>
</tr>
<tr>
<td>Waked et al, 1990 (33)</td>
<td>3/20</td>
<td>2/20</td>
<td>23.4</td>
<td>1.50 (0.28–8.04)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>146</td>
<td>63</td>
<td>38.8</td>
<td>0.60 (0.07–4.92)</td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 1.26; chi-square = 2.15 (P = 0.14); I² = 53%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.48 (P = 0.63)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dienstag et al, 1999 (40)</td>
<td>0/66</td>
<td>0/71</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Lai et al, 1998 (42)</td>
<td>0/285</td>
<td>0/73</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Liaw et al, 2004 (43)</td>
<td>12/436</td>
<td>4/215</td>
<td>32.7</td>
<td>1.48 (0.48–4.53)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>787</td>
<td>359</td>
<td>32.7</td>
<td>1.48 (0.48–4.53)</td>
</tr>
<tr>
<td>Total events</td>
<td>12</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.69 (P = 0.49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1449</td>
<td>634</td>
<td>100.0</td>
<td>0.55 (0.18–1.71)</td>
</tr>
<tr>
<td>Total events</td>
<td>17</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: tau-square = 0.69; chi-square = 7.03 (P = 0.13); I² = 43%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.03 (P = 0.30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: chi-square = 4.84 (P = 0.09); I² = 58.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M–H = Mantel–Haenszel.
### Appendix Table 2. Studies of the Association Between Intermediate and Final Health Outcomes

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Country/Region</th>
<th>Design</th>
<th>Intermediate Outcome Evaluated; Patients With Intermediate Outcome, %</th>
<th>Treatment; Duration of Follow-up</th>
<th>Characteristics of HBV Infection</th>
<th>Mean Age, y</th>
<th>Sex, %</th>
<th>Race, %</th>
<th>Receiving Antiviral Treatment, n (%</th>
<th>Lost to Follow-up, %</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreone et al, 2004 (59)</td>
<td>Italy</td>
<td>Cohort (unclear whether prospective or retrospective)</td>
<td>No virologic breakthrough (HBV DNA became undetectable during receipt of treatment and remained undetectable); 41</td>
<td>Lamivudine; median, 42 mo</td>
<td>HBeAg-positive: None Mean ALT level: 192 U/L Mean HBV DNA level: 16 pg/ml Cirrhosis: 100%</td>
<td>53</td>
<td>Male: 82</td>
<td>NR</td>
<td>22</td>
<td>Unclear</td>
<td>Fair</td>
</tr>
<tr>
<td>Baltayiannis et al, 2006 (60)</td>
<td>Greece</td>
<td>Cohort (unclear whether prospective or retrospective)</td>
<td>Virologic response (HBV DNA &lt;10,000 copies/ml at 6 mo of treatment); 35</td>
<td>Interferon-α 6 y</td>
<td>HBeAg-positive: None Mean ALT level: 117 U/L Median HBV DNA level: 1.2 × 10^6 copies/ml Cirrhosis: Excluded</td>
<td>51</td>
<td>Male: 63</td>
<td>NR</td>
<td>63</td>
<td>1 (1.6)</td>
<td>Fair</td>
</tr>
<tr>
<td>Di Marco et al, 2004 (61)</td>
<td>Italy</td>
<td>Retrospective cohort</td>
<td>No virologic breakthrough (HBV DNA level &lt;1 × 10^5 copies/mL throughout follow-up after achieving undetectability); 39</td>
<td>Lamivudine; 4 y</td>
<td>HBeAg-positive: Excluded ALT level &gt;2 times ULN: 65% HBV DNA level: NR Cirrhosis on histologic evaluation: 25%</td>
<td>49</td>
<td>Male: 83</td>
<td>NR</td>
<td>656</td>
<td>NR*</td>
<td>Fair</td>
</tr>
<tr>
<td>Fattovich et al, 1997 (62)</td>
<td>Italy</td>
<td>Cohort (unclear whether prospective or retrospective)</td>
<td>Biochemical remission (normalization of ALT levels); 28</td>
<td>Interferon-α; mean, 7 y</td>
<td>HBeAg-positive: All Mean ALT level: 5.3 times ULN HBV DNA level: NR Cirrhosis: 100%</td>
<td>47</td>
<td>Male: 85</td>
<td>White: 100</td>
<td>40</td>
<td>NR for treated subgroup</td>
<td>Poor</td>
</tr>
<tr>
<td>Hui et al, 2008 (63)</td>
<td>China (Hong Kong)</td>
<td>Cohort (unclear whether prospective or retrospective)</td>
<td>Histologic response (improvement of ≥2 points on HAI score after end of treatment); 40</td>
<td>Interferon-α2a/b; median, 9.9 y</td>
<td>HBeAg-positive: All Mean ALT level: 113 U/L HBV DNA level: ≥1 × 10^5 copies/ml; 100% Cirrhosis: 12%</td>
<td>30</td>
<td>Male: 78</td>
<td>NR</td>
<td>89</td>
<td>NR</td>
<td>Poor</td>
</tr>
<tr>
<td>Lampertico et al, 2003 (64)</td>
<td>Italy</td>
<td>Cohort (unclear whether prospective or retrospective)</td>
<td>Sustained virologic and biochemical response (normalization of serum ALT levels and clearance of HBV DNA); 30</td>
<td>Interferon-α2b; 68 mo</td>
<td>HBeAg-positive: None Mean ALT level: 204 U/L Detectable HBV DNA level: 61% Ishak fibrosis score of 4–6: 60%</td>
<td>46</td>
<td>Female: 13</td>
<td>NR</td>
<td>101</td>
<td>4 (4.0)</td>
<td>Fair</td>
</tr>
<tr>
<td>Lau et al, 1997 (65)</td>
<td>United States</td>
<td>Cohort (originally enrolled in RCTs)</td>
<td>Response (sustained HBV DNA loss and HBeAg clearance within 1 y of starting treatment); 30</td>
<td>Interferon-α; mean, 6.2 y</td>
<td>HBeAg-positive: All Median ALT level: 154 U/L HBV DNA level: ≥4843 copies/mL Cirrhosis: 17%</td>
<td>41</td>
<td>Male: 83</td>
<td>White: 94; Black: 6</td>
<td>103</td>
<td>8 (7.8)†</td>
<td>Fair</td>
</tr>
<tr>
<td>Niederau et al, 1996 (66)</td>
<td>Europe</td>
<td>Prospective cohort</td>
<td>HBeAg loss after therapy; 51</td>
<td>Interferon-α2b; mean, 50 mo</td>
<td>HBeAg-positive: All HBeAg clearance: 9.7% ALT level: NR AST level: NR HBV DNA level: NR Cirrhosis stage: NR Child-Pugh class B or C excluded</td>
<td>NR</td>
<td>Female: NR</td>
<td>NR</td>
<td>103</td>
<td>0 (0.0)</td>
<td>Fair</td>
</tr>
<tr>
<td>Papatheodoridis et al, 2001 (67)</td>
<td>Greece</td>
<td>Cohort (unclear whether prospective or retrospective)</td>
<td>Sustained biochemical response (normalization of ALT levels at the end of interferon therapy and persistently normal ALT levels throughout the posttreatment follow-up period); 27</td>
<td>Interferon-α; mean, 6.0 y</td>
<td>HBeAg-positive: Excluded Median ALT level: 112 U/L Median HBV DNA level: 4.4 pg/mL Cirrhosis: 27%</td>
<td>47</td>
<td>Male: 83</td>
<td>NR</td>
<td>209</td>
<td>9 (4.3)</td>
<td>Poor</td>
</tr>
<tr>
<td>Papatheodoridis et al, 2011 (68)</td>
<td>Greece</td>
<td>Retrospective cohort</td>
<td>Virologic remission (HBV DNA level &lt;200 IU/mL throughout therapy); 28</td>
<td>Lamivudine; median, 4.7 y</td>
<td>HBeAg-positive: Excluded Median ALT level: 98 U/L HBV DNA level: ≤400 IU/mL (median, 1 × 10^3 IU/mL) Cirrhosis: 26%</td>
<td>54</td>
<td>Male: 72</td>
<td>NR</td>
<td>818</td>
<td>180 (22)</td>
<td>Fair</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HAI = Histology Activity Index; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NR = not reported; RCT = randomized, controlled trial; ULN = upper limit of normal.

* 40 patients had no virologic response and were excluded from the analysis.
† Assumed to be alive and without liver-related complications.
### Appendix Table 3. Associations Between Intermediate and Clinical Outcomes

<table>
<thead>
<tr>
<th>Intermediate Outcome</th>
<th>Death</th>
<th>Hepatocellular Carcinoma</th>
<th>Composite Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies, n</td>
<td>Reference</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Virologic response</td>
<td>1</td>
<td>61</td>
<td>0.34 (0.15–0.80)*</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Histologic response</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Composite intermediate outcome</td>
<td>1</td>
<td>65</td>
<td>0.59 (0.20–1.67)</td>
</tr>
<tr>
<td>Normalization of ALT levels</td>
<td>1</td>
<td>62</td>
<td>0.09 (0.01–0.71)</td>
</tr>
</tbody>
</table>

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

* Study done in HBeAg-negative patients.
### Appendix Table 4. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Studies Identified for Update</th>
<th>Limitation</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of Findings</th>
<th>Overall Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the benefits of screening for HBV infection vs. no screening in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?</td>
<td>None</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>What are the harms of screening for HBV infection?</td>
<td>None</td>
<td>No studies</td>
<td>NA</td>
<td>NA</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>How well do different screening strategies identify persons with HBV infection?</td>
<td>1 cross-sectional study</td>
<td>Evidence available only from 1 study with methodologic limitations</td>
<td>NA</td>
<td>Moderate</td>
<td>1 study found that screening targeted at persons born in countries with a higher prevalence of chronic HBV infection, men, and unemployed persons identified 98% (48 of 49) of infections. Number needed to screen to identify 1 case of HBV infection, 82. Poor</td>
<td></td>
</tr>
<tr>
<td>In persons without evidence of HBV immunity, how effective is HBV vaccination for improving clinical outcomes?</td>
<td>No studies with evidence on long-term clinical outcomes</td>
<td>No evidence on long-term clinical outcomes</td>
<td>Moderate</td>
<td>Study done in high-risk populations (health care workers or MSM) and/or children</td>
<td>Vaccination is associated with decreased risk for HBV acquisition in health care workers (4 trials; RR, 0.51 [95% CI, 0.35 to 0.73]) and MSM (4 trials; RR, 0.21 [CI, 0.11 to 0.39]) on the basis of serologic markers. Studies did not evaluate the effectiveness of HBV vaccination on long-term clinical outcomes. Fair</td>
<td></td>
</tr>
<tr>
<td>How effective is antiviral treatment at improving intermediate outcomes?</td>
<td>30 RCTs</td>
<td>Study duration and patient characteristics varied widely; few good-quality studies</td>
<td>High</td>
<td>Study duration and patient characteristics varied widely; few good-quality studies</td>
<td>Approximately half of the studies were done outside of the United States/Europe, and approximately one third enrolled HBsAg-negative patients</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Antiviral treatment was more effective than placebo or no treatment for HBsAg loss/seroconversion (10 trials; RR, 2.1 [CI, 1.6 to 2.9]; \( \hat{p} = 4\% \)), HBsAg loss/seroconversion (12 trials; RR, 2.4 [CI, 1.2 to 4.9]; \( \hat{p} = 0\% \)), normalization of ALT levels (12 trials; RR, 2.5 [CI, 2.1 to 3.0]; \( \hat{p} = 27\% \)), HBV DNA loss (9 trials; RR, 7.2 [CI, 3.2 to 16]; \( \hat{p} = 58\% \)), and histologic improvement (7 trials; RR, 2.1 [CI, 1.8 to 2.6]; \( \hat{p} = 0\% \)). Results were generally consistent across specific antiviral drugs. Entecavir and pegylated interferon-α2a were each associated with greater likelihood of achieving some intermediate virologic and other outcomes than lamivudine on the basis of a few trials (1-4).
### Appendix Table 4—Continued

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Studies Identified for Update</th>
<th>Limitation</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of Findings</th>
<th>Overall Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How effective is antiviral treatment at improving health outcomes?</strong></td>
<td>16 RCTs</td>
<td>Many studies were small with few events; only 1 good-quality study</td>
<td>Moderate</td>
<td>Approximately half of the studies were done outside of the United States/Europe, and approximately one third enrolled HBeAg-negative patients</td>
<td>Estimates for incident cirrhosis (3 trials; RR, 0.70 [CI, 0.33 to 1.46]; P = 0%), hepatocellular carcinoma (5 trials; RR, 0.57 [CI, 0.32 to 1.04]; P = 2%), and mortality (5 trials; RR, 0.55 [CI, 0.18 to 1.71]; P = 0.43%) all favored antiviral therapy over placebo, although differences were not statistically significant. Clinical events in head-to-head trials of entecavir or pegylated interferon-α2a vs. lamivudine or pegylated interferon vs. nonpegylated interferon were too few to determine effects on clinical outcomes.</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>How effective is education or behavior change counseling in reducing transmission and improving health outcomes?</strong></td>
<td>None</td>
<td>No evidence</td>
<td>NA</td>
<td>NA</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td><strong>What are the harms associated with antiviral treatment for HBV infection?</strong></td>
<td>29 RCTs</td>
<td>Many studies were small with few events</td>
<td>High</td>
<td>Many studies were done outside of the United States/Europe</td>
<td>Treatment and control groups did not differ in serious adverse effects (12 trials; RR, 0.8 [CI, 0.6 to 1.1]; P = 0%) or any adverse events (7 trials; RR, 0.96 [CI, 0.90 to 1.00]; P = 0%). Antiviral therapy was associated with more withdrawals due to adverse effects, but estimates were imprecise because of the small number of events (9 trials; RR, 3.97 [CI, 1.40 to 11.00]; P = 0%). Results were generally consistent across specific antiviral drugs. In 2 head-to-head trials, pegylated interferon-α2a was associated with greater risk for serious adverse events (RR, 2.1 [CI, 1.0 to 4.5]; P = 0%) and withdrawal due to adverse events (RR, 7.6 [CI, 1.1 to 52.0]; P = 38%) vs. lamivudine.</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Are improvements in intermediate outcomes after antiviral therapy associated with improvements in health outcomes?</strong></td>
<td>10 observational studies</td>
<td>Patient characteristics and outcomes evaluated varied greatly; no studies were good-quality; 3 were poor-quality and did not address important confounders</td>
<td>Moderate</td>
<td>1 study excluded patients with cirrhosis, 2 included only patients with cirrhosis, and the proportion of patients with cirrhosis ranged from 12% to 60% in the remainder</td>
<td>10 observational studies found an association between various intermediate and clinical outcomes (death, hepatocellular carcinoma, or a composite clinical outcome), but variability in patient populations, intermediate and clinical outcomes evaluated, and methodological limitations make it difficult to draw strong conclusions. In some studies, results were not statistically significant.</td>
<td>Poor</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; MSM = men who have sex with men; NA = not applicable; RCT = randomized, controlled trial; RR = risk ratio.

* The full report (12) does not address this key question.