Antiviral Therapy for Adults with Chronic Hepatitis B: A Systematic Review for a National Institutes of Health Consensus Development Conference

Tatyana A. Shamliyan, MD, MS; Roderick MacDonald, MS; Aasma Shaukat, MD, MPH; Brent C. Taylor, PhD, MPH; Jian-Min Yuan, MD, PhD; James R. Johnson, MD; James Tacklind, BS; Indulis Rutks, BS; Robert L. Kane, MD; and Timothy J. Wilt, MD, MPH

**Background:** Chronic hepatitis B infection can lead to liver failure, hepatocellular carcinoma, and death.

**Purpose:** To evaluate the effectiveness of antiviral therapy for adults with chronic hepatitis B infection.

**Data Sources:** Randomized, controlled trials (RCTs) of interferon-α2b and pegylated interferon-α2a, lamivudine, adefovir, entecavir, and telbivudine published from 1990 to 2008.

**Study Selection:** Randomized, controlled clinical trials of adults with chronic hepatitis B published in English after 1989 that reported death; incidence of hepatocellular carcinoma or liver failure; prevalence and incidence of cirrhosis; presence or seroconversion of hepatitis B e antigen (HBeAg) or surface antigen (HBsAg), viral load of hepatitis B virus DNA; aspartate aminotransferase and alanine aminotransferase (ALT) levels; or fibrosis scores after therapy with interferon-α2b, pegylated interferon-α2a, lamivudine, adefovir, entecavir, and telbivudine.

**Data Extraction:** Data extracted with standard protocols to calculate risk difference for clinical outcomes, viral load, HBeAg and HBsAg, ALT, histologic scores, and adverse events.

**Data Synthesis:** In 16 RCTs (4431 patients), drug treatment did not improve clinical outcomes of chronic hepatitis B infection, but the studies were underpowered. In 60 RCTs that examined intermediate outcomes, no single treatment improved all intermediate outcomes. Low-quality evidence suggested HBsAg clearance after interferon-α2b (2 RCTs; 211 patients). Moderate-quality evidence suggested ALT normalization at follow-up after treatment with adefovir (2 RCTs; 600 patients) and HBeAg loss with lamivudine (2 RCTs; 318 patients). With interferon-α2b, moderate-quality evidence suggested HBeAg loss (3 RCTs; 351 patients), seroconversion (2 RCTs; 304 patients), and ALT normalization (2 RCTs; 131 patients). Pegylated interferon-α2a versus lamivudine improved HBeAg seroconversion (1 RCT; 814 patients) and ALT normalization (2 RCTs; 905 patients) off treatment. Pegylated interferon-α2a combined with lamivudine versus lamivudine improved HBeAg loss (1 RCT; 543 patients) and ALT normalization (2 RCTs; 905 patients). Adverse events during antiretroviral therapy occurred in more than 50% of patients but were not associated with increased treatment discontinuation. However, most studies excluded patients with hepatic or renal insufficiency or other serious comorbid conditions.

**Limitation:** Marked heterogeneity in study samples, interventions, and measured outcomes preclude definitive conclusions.

**Conclusion:** Evidence was insufficient to assess treatment effect on clinical outcomes or determine whether inconsistent improvements in selected intermediate measures are reliable surrogates. Future research is needed to provide evidence-based recommendations about optimal antiviral therapy in adults with chronic hepatitis B infection.


For author affiliations, see end of text.

This article was published at www.annals.org on 6 January 2009.

---

Hepatitis B is highly prevalent, with 350 million chronic cases worldwide (1). Despite immunization efforts, 4713 incident cases of hepatitis B were diagnosed in the United States in 2006 (2). An estimated 2000 to 4000 deaths per year in the United States are related to chronic hepatitis B liver diseases (3), including liver cirrhosis and hepatocellular carcinoma (4).

Because most patients are asymptomatic, treatment goals of antiviral therapy include long-term prevention of progression, development of cirrhosis and liver failure, and hepatocellular carcinoma. Short-term intermediate laboratory responses have been proposed as potential surrogate measures of treatment effects on clinical outcomes (1). Normalization of liver enzyme levels, viral suppression and clearance, reduction in histologic scores of liver inflammation or fibrosis, and combinations of these outcomes have been used to measure response to antiviral drugs or development of antiviral resistance (1, 5).

Seven antiviral agents are approved to treat hepatitis B in the United States, including oral medications (lamivudine, telbivudine, adefovir, tenofovir, and entecavir) and injected interferons (standard interferon-α2b and pegylated interferon-α2a). Other agents are under investigation. The U.S. Food and Drug Administration approved tenofovir for adults in August 2008 on the basis of ongoing, unpublished trials that compared tenofovir with adefovir on intermediate outcomes, the results of which were not available for our review (6).

This review was commissioned as background material for the National Institutes of Health Consensus Development Conference on Management of Chronic Hepatitis B...
in Adults to synthesize the published evidence about the effectiveness of interferon therapy, oral therapy, and various combinations with defined or continuous courses of treatment. The full report, including a detailed description of our methods, is available at www.ahrq.gov/downloads/pub/evidence/pdf/hepb/hepb.pdf (7).

METHODS

Data Sources and Study Selection

We searched MEDLINE, PubMed, the Cochrane Library (8), and other databases (9–11). We included randomized, controlled clinical trials (RCTs) of adults with chronic hepatitis B published in English after 1989 that reported death, incidence of hepatocellular carcinoma or liver failure; prevalence and incidence of cirrhosis; presence or seroconversion of hepatitis B e antigen (HBeAg) or surface antigen (HBsAg); viral load of hepatitis B virus (HBV) DNA; aspartate aminotransferase and alanine aminotransferase (ALT) levels; and histologic necroinflammatory or fibrosis scores after therapy with interferon-α2a, lamivudine, adefovir, entecavir, and telbivudine (12). Studies that enrolled at least 50 adults and provided treatment for 24 weeks or more were eligible for this review. Interferon studies of any size were eligible if participants were given treatment for at least 12 weeks. We excluded studies evaluating pregnant women, patients with hepatocellular carcinoma or HIV infection at baseline, patients undergoing chemotherapy or liver transplantation, or patients with several causes of hepatitis, unless outcomes for participants meeting our eligibility criteria were reported separately. The full report describes the search strategies (7). We included publications from the multinational HBV 99-01 Study Group assessing pegylated interferon-α2b, a treatment that has been intensively examined in patients with chronic hepatitis B but is not yet approved in the United States (13). Three investigators independently measured study eligibility (14).

Data Extraction and Quality Assessment

Three researchers independently evaluated the studies and extracted data to detect errors and discrepancies (14). We abstracted the number of events among treatment groups to calculate rates, relative risks (RRs), and absolute risk differences (15). We abstracted the number of patients randomly assigned to each treatment group as the denominator to calculate estimates, applying the intention-to-treat principle. We recorded intervals for outcome assessments in weeks from randomization for the active-treatment period and from the end of treatment for follow-up assessments. We prioritized clinical outcomes in the assessment of treatment benefits and harms. Sustained HBsAg loss or seroconversion was considered the criterion for resolution of hepatitis B viral infection and a major goal of antiviral therapy (1). Liver histologic outcomes included improved necroinflammatory and fibrosis scores. Sustained ALT normalization as diagnostic criteria of hepatocyte injury and sustained clearance of HBV DNA were assigned as secondary outcomes. Although positive associations with better clinical outcomes exist in observational studies, both outcomes may reverse after treatment. Because low levels of evidence from observational studies suggested that HBeAg-negative status was associated with worse clinical outcomes, we defined sustained HBeAg seroconversion as a desirable intermediate outcome.

We analyzed RCTs for participant selection, duration of and loss to follow-up, intention-to-treat principle, masking of treatment status, randomization scheme and its adequacy, allocation concealment, and justification of sample sizes (16). We assessed the level of evidence on the basis of the Grading of Recommendations Assessment, Development and Evaluation Working Group criteria (17, 18). We assigned a low level of evidence when data were from small RCTs or RCTs with flaws in design or analysis or were from post hoc subgroup analysis. We assigned a moderate level of evidence when a single, large multinational study or several small RCTs reported consistent associations between antiviral agents and outcomes and a high level of evidence when several high-quality studies in applicable patients reported consistent sustained effects at least 6 months after therapy.

Data Synthesis and Analysis

The full report includes evidence tables that summarize results of individual studies (7). We compared baseline data across the studies to test for differences in the target sample and to detect unusual patterns in the data (19–21). Analyses were conducted separately for clinical, biochemical, virologic, and histologic outcomes and for RRs and absolute risk differences. The protocol for meta-analyses was created according to recommendations (22, 23) to assess the consistency of the association between treatments and outcomes with random-effects models (24). Pooling criteria included the same operational definitions of outcomes and drug interventions (23). We used chi-square tests to assess heterogeneity (25, 26). Calculations used Stata statistical software, version 9.2 (StataCorp, College Station, Texas) (27). We assumed the presence of publication bias and did not use statistical tests for bias caused by sparse and heterogeneous data (14, 28–30).

Role of the Funding Source

The Agency for Healthcare Research and Quality suggested the initial questions and provided copyright release for this manuscript. The funding source had no role in the literature search, data analysis, conduct of the study, preparation of the review, or interpretation of the results. The funding source reviewed and approved the submitted manuscript without revisions.

RESULTS

Ninety-three articles represented 60 unique RCTs (31–102). The full report contains the study flow diagram and the appendix with excluded studies (7). Studies en-
rolled 20 to 1367 patients who were predominately HBeAg-positive. Men constituted 78% of enrollees. Most enrollees were Asian (64%) or white (30%). The estimated duration of infection, reported in 8 studies, ranged from approximately 2 to 6 years. However, individual patient duration of infection ranged from 6 months to 20 years (31–40).

Clinical Outcomes

Studies that reported death, liver-related death, hepatocellular carcinoma, hepatic decompensation, or cirrhosis (Table) were not designed nor had sufficient power to reliably assess drug effects on these clinical outcomes.

Death was assessed in 13 studies, with very few deaths reported (36, 39–50). Low-level evidence suggested that interferon-α2b, pegylated interferon-α2a, pegylated interferon-α2b with corticosteroids, or interferon-a with no treatment after lamivudine (41) demonstrated a statistically significant difference compared with placebo, drugs did not increase HBsAg clearance at the end of the treatments. Only 1 RCT of 169 HBeAg-positive patients found a significant increase in HBsAg loss at the end of 24 weeks of interferon-α2b therapy (38) and interferon-α2b with corticosteroid therapy. Two RCTs (38, 48) found that steroid pretreatment followed by interferon-α2b compared with no antiviral drugs significantly increased HBsAg loss by 11% at the end of the treatments.

Eight RCTs (34, 38, 44, 47, 54, 58–60) investigated combined virologic and biochemical outcomes, including HBV DNA loss, HBeAg clearance and seroconversion, and ALT normalization (Appendix Table 1, available at www.annals.org) at the end of treatment, and 13 RCTs (33–35, 44, 46, 50, 51, 54–57, 59, 60) examined the same outcomes at follow-up off interferon treatments. Interferon-α2b increased sustained rates of undetectable HBV DNA and HBeAg (33, 35, 54, 55), negative HBV DNA and HBeAg combined with normal ALT (57), and rates of undetectable HBV DNA combined with normalization of ALT (34, 54). Interferon-α2b combined with lamivudine compared with lamivudine alone increased HBV DNA loss and HBeAg clearance and seroconversion in 75 treatment-naïve patients (59).

Histologic Outcomes

Histologic outcomes (Appendix Table 1, available at www.annals.org) included improvement in total, fibrosis, or necroinflammatory scores as proposed surrogates to assess preventive effects of treatments on development of cirrhosis in individual patients (61, 62).

Effects of Drugs on Histologic Outcomes at the End of Treatment

Adefovir for 48 to 96 weeks improved necroinflammatory and fibrosis scores compared with placebo with no dose–response association (Appendix Table 1, available at www.annals.org) (63–65). Lamivudine administration for 48 to 96 weeks improved necroinflammatory scores in all RCTs (60, 66–68). Entecavir compared with lamivudine improved necroinflammatory scores but without a dose–response association (44–46).

Effects of Drugs on Histologic Outcomes at Follow-up After Treatment

Only 1 RCT (69) reported histologic improvement in necroinflammatory scores at 24-week follow-up after com-
**Table. Effects of Drug Therapies for Chronic Hepatitis B on Clinical Outcomes**

<table>
<thead>
<tr>
<th>Active vs. Control Treatment (Reference)</th>
<th>Treatment Duration, wk</th>
<th>Follow-up After Therapy, wk</th>
<th>Studies, n</th>
<th>Participants Enrolled, n</th>
<th>Absolute Risk Difference Estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver-related death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine vs. placebo (41)</td>
<td>130</td>
<td>0</td>
<td>1</td>
<td>651</td>
<td>0.00 (−0.01 to 0.01)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine vs. placebo (41)</td>
<td>130</td>
<td>0</td>
<td>1</td>
<td>651</td>
<td>0.00 (−0.01 to 0.01)</td>
</tr>
<tr>
<td>Interferon-α2b vs. placebo (40)</td>
<td>16</td>
<td>48–64</td>
<td>1</td>
<td>40</td>
<td>No statistically significant difference at end of treatment and after follow-up</td>
</tr>
<tr>
<td>Adefovir (42)</td>
<td>114 vs. 240</td>
<td>0</td>
<td>1</td>
<td>125</td>
<td>−0.01 (−0.03 to 0.01)</td>
</tr>
<tr>
<td>Entecavir (43)</td>
<td>48</td>
<td>0</td>
<td>1</td>
<td>89</td>
<td>No statistically significant difference between all compared doses</td>
</tr>
<tr>
<td>Entecavir vs. lamivudine (43–47)</td>
<td>48–96</td>
<td>0–28</td>
<td>5</td>
<td>2476</td>
<td>No statistically significant difference among all studies</td>
</tr>
<tr>
<td>Interferon-α2b plus corticosteroid vs. interferon-α2b (39)</td>
<td>24</td>
<td>0</td>
<td>1</td>
<td>37</td>
<td>−0.11 (−0.27 to 0.06)</td>
</tr>
<tr>
<td>Interferon-α2b plus corticosteroid vs. symptomatic treatment (48)</td>
<td>24</td>
<td>48</td>
<td>1</td>
<td>20</td>
<td>−0.10 (−0.34 to 0.14)</td>
</tr>
<tr>
<td>Interferon-α2b (36, 39)</td>
<td>24–48</td>
<td>0–24</td>
<td>2</td>
<td>76</td>
<td>No statistically significant difference between all compared doses</td>
</tr>
<tr>
<td>Pegylated interferon-α2a plus placebo vs. lamivudine (49)</td>
<td>48</td>
<td>8</td>
<td>1</td>
<td>543</td>
<td>0.00 (−0.01 to 0.01)</td>
</tr>
<tr>
<td>Pegylated interferon-α2a plus lamivudine vs. lamivudine (49)</td>
<td>48</td>
<td>8</td>
<td>1</td>
<td>543</td>
<td>0.01 (0.00 to 0.03)</td>
</tr>
<tr>
<td>Pegylated interferon-α2a plus lamivudine vs. pegylated interferon-α2a (49)</td>
<td>48</td>
<td>8</td>
<td>1</td>
<td>543</td>
<td>0.01 (0.00 to 0.03)</td>
</tr>
<tr>
<td>Pegylated interferon-α2b plus lamivudine vs. lamivudine (49)</td>
<td>50–60</td>
<td>56–64</td>
<td>1</td>
<td>100</td>
<td>0.02 (−0.03 to 0.07)</td>
</tr>
<tr>
<td><strong>Incident cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2b vs. no treatment (40)</td>
<td>16</td>
<td>48–64</td>
<td>1</td>
<td>40</td>
<td>−0.05 (−0.21 to 0.11)</td>
</tr>
<tr>
<td>Interferon-α2b plus corticosteroid vs. interferon-α2b (51)</td>
<td>24</td>
<td>24</td>
<td>1</td>
<td>56</td>
<td>−0.06 (−0.24 to 0.11)</td>
</tr>
<tr>
<td><strong>Hepatic decompensation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine vs. placebo (53)</td>
<td>80</td>
<td>0</td>
<td>1</td>
<td>74</td>
<td>0.05 (−0.11 to 0.22)</td>
</tr>
<tr>
<td>Lamivudine vs. no treatment (53)</td>
<td>80</td>
<td>0</td>
<td>1</td>
<td>74</td>
<td>0.00 (−0.12 to 0.12)</td>
</tr>
<tr>
<td>Pegylated interferon-α2b plus lamivudine vs. lamivudine (50)</td>
<td>52–60</td>
<td>57–72</td>
<td>1</td>
<td>100</td>
<td>0.00 (−0.04 to 0.04)</td>
</tr>
<tr>
<td>Entecavir vs. lamivudine (44, 46)</td>
<td>52–96</td>
<td>0–24</td>
<td>2</td>
<td>709</td>
<td>No statistically significant difference after different treatment duration</td>
</tr>
<tr>
<td><strong>Hepatocellular carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine vs. placebo (41)</td>
<td>130</td>
<td>0</td>
<td>1</td>
<td>651</td>
<td>−0.04 (−0.07 to 0.00)</td>
</tr>
<tr>
<td>Interferon-α2b vs. placebo (54)</td>
<td>96</td>
<td>0</td>
<td>1</td>
<td>42</td>
<td>0.05 (−0.07 to 0.17)</td>
</tr>
<tr>
<td>Adefovir (42)</td>
<td>114 vs. 240</td>
<td>0</td>
<td>1</td>
<td>250</td>
<td>0.03 (−0.01 to 0.07)</td>
</tr>
<tr>
<td>Interferon-α2b plus corticosteroid vs. interferon-α2b (51)</td>
<td>24</td>
<td>24</td>
<td>1</td>
<td>56</td>
<td>−0.02 (−0.28 to 0.24)</td>
</tr>
<tr>
<td>Dose–Response Heterogeneity (95% CI)*</td>
<td>Level of Evidence</td>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (0 events in both groups)</td>
<td>No effect of lamivudine on liver-related death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peto OR, 4.46 (0.23 to 85.16)</td>
<td>Low; sparse data (0 events in control group)</td>
<td>No effect of lamivudine on death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (minimal events)</td>
<td>No effect of interferon-α2b on death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peto OR, 0.14 (0.00 to 6.82)</td>
<td>Low; sparse data (0 events at second interval and no formal control)</td>
<td>Length of adefovir therapy did not affect death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dose–response</td>
<td>Low; sparse data (minimal events)</td>
<td>No effect of entecavir on death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– 0.003 (−0.008 to 0.002)‡</td>
<td>Low; sparse data (minimal events)</td>
<td>No differences between entecavir and lamivudine on death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (0 events in active group)</td>
<td>No differences of pretreatment with steroid and interferon-α2b on death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (0 events in active group)</td>
<td>No differences of pretreatment with steroid and interferon-α2b on death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dose–response</td>
<td>Low; sparse data (0 events in active group)</td>
<td>No dose–response effect on death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (0 events in both groups)</td>
<td>No differences between pegylated interferon-α2a and lamivudine on death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peto OR, 7.47 (0.77 to 72.13)</td>
<td>Low; sparse data (0 events in control group)</td>
<td>No differences between pegylated interferon-α2a plus lamivudine and lamivudine alone on death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peto OR, 7.44 (0.77 to 71.86)</td>
<td>Low; sparse data (0 events in control group)</td>
<td>No differences between pegylated interferon-α2a plus lamivudine and pegylated interferon-α2a alone on death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peto OR, 7.39 (0.15 to 372.38)</td>
<td>Low; sparse data (0 events in control group)</td>
<td>No differences between pegylated interferon-α2b plus lamivudine and lamivudine alone on death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (minimal events)</td>
<td>No effect of interferon-α2b on cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (minimal events)</td>
<td>No differences of pretreatment with steroid and interferon-α2b on incidence of cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (minimal events)</td>
<td>No effect of lamivudine on liver decompensation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peto OR, 1.00 (0.19 to 5.25)</td>
<td>Low; sparse data (minimal events)</td>
<td>No effect of lamivudine on severe liver decompensation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (0 events in both groups)</td>
<td>No differences between combined pegylated-α2b with lamivudine vs. lamivudine alone on liver decompensation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (0 events in active group)</td>
<td>No differences between entecavir vs. lamivudine on liver decompensation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; significant protective effects of active drug after adjustment for country, sex, baseline ALT level, Child–Pugh score, and Ishak fibrosis score§</td>
<td>No effect of lamivudine on hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (0 events in control group)</td>
<td>No effect of interferon-α2b on hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low; sparse data (minimal events at first interval and no formal control)</td>
<td>Length of adefovir therapy did not affect hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Low</td>
<td>No difference on active hepatitis between interferon-α2b with pretreatment using corticosteroid vs. interferon-α2b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table—Continued

<table>
<thead>
<tr>
<th>Active vs. Control Treatment (Reference)</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver-related death</strong></td>
<td></td>
</tr>
<tr>
<td>Lamivudine vs. placebo (41)</td>
<td>Allocation concealment: unclear; double-blinded: yes; intention-to-treat analysis: yes; attrition bias: no; funding: pharmaceutical</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
</tr>
<tr>
<td>Lamivudine vs. placebo (41)</td>
<td>Allocation concealment: unclear; double-blinded: yes; intention-to-treat analysis: yes; attrition bias: no; funding: pharmaceutical</td>
</tr>
<tr>
<td>Interferon-2b vs. placebo (40)</td>
<td>Allocation concealment: adequate; double-blinded: yes; intention-to-treat analysis: no; attrition bias: yes; funding: several authors received support from pharmaceutical companies</td>
</tr>
<tr>
<td>Adefovir (42)</td>
<td>Allocation concealment: unclear; double-blinded: yes; pathologist-blinded (biopsy): yes; intention-to-treat analysis: yes (1 dose required); attrition bias: not reported; funding: pharmaceutical</td>
</tr>
<tr>
<td>Entecavir (43)</td>
<td>Allocation concealment: adequate; double-blinded: yes; intention-to-treat analysis: yes; attrition bias: yes; funding: pharmaceutical</td>
</tr>
<tr>
<td>Entecavir vs. lamivudine (43–47)</td>
<td>Allocation concealment: adequate (43, 46); unclear (44, 45, 47); double-blinded (43–47); yes; pathologist-blinded (44, 46, 47); yes; intention-to-treat analysis: yes (43–47); attrition bias: yes (43–47); funding: pharmaceutical (44, 45); unclear 46, 47</td>
</tr>
<tr>
<td>Interferon-α2b plus corticosteroid vs. interferon-α2b (39)</td>
<td>Allocation concealment: adequate; blinding: unclear, although study was a placebo-controlled; pathologist-blinded: yes; intention-to-treat analysis: no; attrition bias: no; funding: not reported</td>
</tr>
<tr>
<td>Interferon-α2b plus corticosteroid vs. symptomatic treatment (48)</td>
<td>Allocation concealment: unclear; open-label: yes; intention-to-treat analysis: no; attrition bias: no; funding: pharmaceutical</td>
</tr>
<tr>
<td>Interferon-α2b (36, 39)</td>
<td>Allocation concealment: adequate; blinding: unclear, although studies were placebo-controlled; pathologist-blinded: yes; intention-to-treat analysis: no; attrition bias: no; funding: not reported</td>
</tr>
<tr>
<td>Pegylated interferon-α2a plus placebo vs. lamivudine (49)</td>
<td>Allocation concealment: unclear; partially double-blinded: yes; intention-to-treat analysis: yes (1 dose required); attrition bias: yes; funding: pharmaceutical</td>
</tr>
<tr>
<td>Pegylated interferon-α2a plus lamivudine vs. lamivudine (49)</td>
<td>Allocation concealment: unclear; partially double-blinded: yes; intention-to-treat analysis: yes (1 dose required); attrition bias: yes; funding: pharmaceutical</td>
</tr>
<tr>
<td>Pegylated interferon-α2a plus lamivudine vs. pegylated interferon-α2a (49)</td>
<td>Allocation concealment: unclear; partially double-blinded: yes; intention-to-treat analysis: yes (1 dose required); attrition bias: yes; funding: pharmaceutical</td>
</tr>
<tr>
<td>Pegylated interferon-α2b plus lamivudine vs. lamivudine (49)</td>
<td>Allocation concealment: adequate; open-label: yes; pathologist-blinded: yes; intention-to-treat analysis: yes (1 dose required); attrition bias: yes; funding: pharmaceutical</td>
</tr>
<tr>
<td><strong>Incident cirrhosis</strong></td>
<td></td>
</tr>
<tr>
<td>Interferon-α2b vs. no treatment (40)</td>
<td>Allocation concealment: unclear; open-label: yes; intention-to-treat analysis: no; attrition bias: yes; funding: not reported</td>
</tr>
<tr>
<td>Interferon-α2b plus corticosteroid vs. interferon-α2b (51)</td>
<td>Allocation concealment: unclear; pathologist-blinded: yes; intention-to-treat analysis: yes; attrition bias: no withdrawals reported; funding: pharmaceutical</td>
</tr>
<tr>
<td><strong>Hepatic decompensation</strong></td>
<td></td>
</tr>
<tr>
<td>Lamivudine vs. placebo (53)</td>
<td>Allocation concealment: adequate; intention-to-treat analysis: yes; attrition bias: yes; funding: institution</td>
</tr>
<tr>
<td>Lamivudine vs. no treatment (53)</td>
<td>Allocation concealment: adequate; intention-to-treat analysis: yes; attrition bias: yes; funding: institution</td>
</tr>
<tr>
<td>Pegylated interferon-α2b plus lamivudine vs. lamivudine (50)</td>
<td>Allocation concealment: adequate; open-label: yes; pathologist-blinded: yes; intention-to-treat analysis: yes; (1 dose required); attrition bias: yes; funding: pharmaceutical</td>
</tr>
<tr>
<td>Entecavir vs. lamivudine (44, 46)</td>
<td>Allocation concealment: unclear; double-blinded: yes; pathologist-blinded: yes; intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical</td>
</tr>
<tr>
<td><strong>Hepatocellular carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td>Lamivudine vs. placebo (41)</td>
<td>Allocation concealment: unclear; double-blinded: yes; intention-to-treat analysis: yes; attrition bias: no; funding: pharmaceutical</td>
</tr>
<tr>
<td>Interferon-α2b vs. placebo (54)</td>
<td>Allocation concealment: unclear; open-label: yes; intention-to-treat analysis: yes; attrition bias: yes; funding: private</td>
</tr>
<tr>
<td>Adefovir (42)</td>
<td>Allocation concealment: unclear; double-blinded: yes; pathologist-blinded: yes; intention-to-treat analysis: yes (1 dose); attrition bias: yes; funding: pharmaceutical</td>
</tr>
<tr>
<td>Interferon-α2b plus corticosteroid vs. interferon-α2b (51)</td>
<td>Allocation concealment: unclear; pathologist-blinded: yes; intention-to-treat analysis: yes; attrition bias: no withdrawals reported; funding: pharmaceutical</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; OR = odds ratio.

* Peto OR was calculated when 0 events occurred in 1 of the treatment groups.

† “Attrition bias” refers to the clear description of study withdrawals.

‡ $P = 0.7$, $P = 0.9%$.

§ Hazard ratio, 0.49 (CI, 0.25 to 0.99).
pletion of a 48-week administration of pegylated interferon-α2a compared with lamivudine in 552 HBeAg-negative patients (69) (Appendix Table 1, available at www.annals.org).

Viral (HBV DNA) Clearance

Viral (HBV DNA) clearance was associated with a favorable prognosis in observational longitudinal studies, although few data are available that are adjusted for baseline HBV DNA levels (1, 4) (Appendix Table 1, available at www.annals.org). The studies used assays with different sensitivity to detect HBV DNA, including polymerase chain reaction assay (31, 33, 36, 44, 45, 47, 58, 60, 63, 70–77), reverse transcription polymerase chain reaction assay (43, 78), or solution hybridization assay (32, 37–39, 51, 59, 67, 68, 79–84).

Effects of Drugs on Viral Clearance at Follow-up After Treatment

Limited low to moderate evidence suggested that antiviral drugs and their combinations resulted in HBV DNA clearance at follow-up after therapy, ranging from 18 to 24 weeks. Interferon-α2b at 8- to 24-week follow-up increased HBV DNA loss compared with placebo or no antiviral therapy (33, 37); however, the effects were attenuated at longer follow-up (33, 37, 38). Limited, low-level evidence from 1 RCT suggested effects of lamivudine on HBV DNA loss at 24-week follow-up after 46 weeks of drug administration (60). One large RCT reported a significant benefit from adefovir administration in HBeAg-negative patients that was maintained at 18 weeks after treatment (64). Entecavir provided similar HBV DNA loss compared with lamivudine at 24-week follow-up (44) (Appendix Table 1, available at www.annals.org).

Effects of Drugs on ALT Normalization at Follow-up Off Treatment

Alanine aminotransferase normalization at follow-up off treatment was greater after adefovir administration compared with placebo in HBeAg-negative (64) as well as positive patients (74). Lamivudine compared with placebo increased rates of ALT at 24-week follow-up off treatment in 139 HBeAg-negative patients (60). Interferon-α2b at doses of 35 million units per week but not 7 million units per week compared with no antiviral treatment increased rates of ALT normalization at 8- to 24-week follow-up (33, 38). In contrast with the superior effectiveness of lamivudine at the end of the treatment, ALT normalization at 24-week follow-up after treatment was greater after pegylated interferon-α2a compared with lamivudine and after combined therapy of pegylated interferon-α2a with lamivudine compared with lamivudine alone (49, 69).

Effects of Drugs on HBeAg Clearance or Seroconversion at Follow-up Off Treatment

Moderate evidence demonstrated a significant sustained HBeAg clearance at follow-up off treatment for interferon-α2b (33, 40, 85). In patients receiving 52 weeks of lamivudine, HBeAg loss was greater at 16 weeks after therapy than in patients receiving placebo (68, 80). Interferon-α2b (40, 85) increased rates of HBeAg seroconversion versus placebo at 28- to 64-week follow-up. Pooled analysis of individual patient data from 4 RCTs found a significant increase in HBeAg seroconversion after combined therapy with interferon-α2b and lamivudine (85). Telbivudine compared with adefovir for 24 to 52 weeks increased HBeAg seroconversion in relative terms without significant differences in absolute rates (76). Pegylated interferon-α2a increased HBeAg seroconversion at 24-week follow-up compared with lamivudine (49). Pegylated interferon-α2a combined with lamivudine resulted in greater HBeAg seroconversion compared with lamivudine alone but not pegylated interferon-α2a alone (49). Combined treatments of pegylated interferon-α2b with lamivudine for 60 weeks increased HBeAg seroconversion compared with lamivudine alone (48). All other comparisons demonstrated random differences between compared drugs.

Relapse was reappearance of HBV DNA (31, 45, 47, 58, 73, 74, 82, 86–88) or increase in viral load and ALT levels (78) at the end of active treatments or at follow-up after therapies (34, 35, 38, 44, 50, 51, 54, 59, 83) (Appendix Table 1, available at www.annals.org). Lamivudine administration for 60 weeks compared with 48 weeks increased rates of virologic relapse in 1 RCT of HBeAg-positive patients (88). Entecavir administration for 52 weeks resulted in lower rates of viral relapse at 24-week follow-up after treatment compared with lamivudine in HBeAg-positive, treatment-naive patients (44).

Drug-Specific Mutations

Drug-specific mutation (Appendix Table 1, available at www.annals.org) was detected by the development of resistant HBV YMDD mutations (mutation in amino acid sequence tyrosine, methionine, aspartate, aspartate) at the end of lamivudine treatments (31, 41, 42, 49, 59, 63, 71, 73, 78, 80, 86–90) or at follow-up after the therapies (64, 79) (Appendix Table 1, available at www.annals.org). Lamivudine administration increased the rates of YMDD mutation compared with placebo by 43% (41, 80). Longer treatments for 60 weeks versus 48 weeks resulted in larger rates of mixed and pure YMDD mutations (88). Adefovir versus placebo increased rates of emerging amino acid substitutions in the HBV-RT domain and rates of rt221Y amino acid substitution but not rt134D, rt219A, rt91I, rt134N, rt54H, and rt145M substitutions (63, 86). Longer treatments for 240 versus 114 weeks increased rates of adefovir-resistant mutations (42). However, combined therapy with adefovir plus lamivudine reduced the rates of
YMDD compared with lamivudine monotherapy in patients with chronic hepatitis B and YMDD mutant HBV (71), with random differences in wild-type mutations. Interferon-α2b combined with lamivudine reduced rates of mutation compared with lamivudine alone, but with inconsistent effect sizes across 6 studies (31, 59, 73, 80, 87, 89). Pegylated interferon-α2a combined with lamivudine compared with pegylated interferon-α2a alone increased mutation in HBeAg-positive patients (49). The same study reported reduced rates of mutations with pegylated interferon-α2a or peginterferon-α2a combined with lamivudine than with lamivudine monotherapy (49). At follow-up after treatments, interferon-α2b alone or combined with lamivudine resulted in lower rates of mutations compared with lamivudine alone (79).

Baseline HBeAg status has been used for treatment decision making. However, the association between changes in HBeAg and clinical outcomes has not been tested in RCTs. Low-quality evidence indicates that treatment effects may vary by baseline HBeAg status.

Evidence From Trials That Combined Patients With HBeAg-Negative and -Positive Baseline Status

Lamivudine decreased disease progression (defined by hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease) compared with placebo among patients who were HBeAg-positive at baseline but did not decrease disease progression among those who were HBeAg-negative (41). Telbivudine compared with lamivudine reduced the rates of detectable HBV DNA and improved necroinflammatory scores, with no worsening in the Knodell fibrosis score among HBeAg-positive patients, and random differences occurred in HBeAg-negative patients (77). Telbivudine compared with lamivudine in patients with compensated hepatitis B resulted in better outcomes in HBeAg-positive patients with no difference in a small subsample of HBeAg-negative patients (91). In contrast, only entecavir compared with lamivudine resulted in higher rates of undetectable HBV DNA and normal ALT levels among patients with an HBeAg-negative baseline status, and random differences occurred in HBeAg-positive patients (43).

Evidence from trials that included only HBeAg-negative patients (11 studies) suggested no effects on clinical outcomes or resolved hepatitis and inconsistent effects on intermediate measures. Adefovir improved biochemical, virologic, and histologic outcomes at the end of treatment and at follow-up after the treatment without development of genetic mutations (63, 64). Interferon-α2b combined with lamivudine was not more effective than lamivudine alone on combined (virologic with biochemical) (82) or virologic (73, 82, 89) outcomes but lowered the rates of reappearance of detectable serum HBV DNA (71) and genetic viral mutations (89). Pegylated interferon-α2a compared with lamivudine improved off-treatment biochemical and virologic outcomes and necroinflammatory scores but did not improve fibrosis scores (69). Pegylated interferon-α2a combined with lamivudine compared with lamivudine improved biochemical and virologic outcomes, with no differences in liver histology, after treatment (69).

Applicability of the Results to Patient Subsamples

The results from published RCTs can be generalized to adults with chronic hepatitis B without hepatic decompensation and serious confounding illnesses, predominately Asian or white men. Low-level evidence from RCTs suggested moderate differences in treatment effects among patient subgroups with different baseline characteristics (www.ahrq.gov/clinic/epicpix.htm). Younger patient age was associated with enhanced HBV DNA clearance and ALT normalization in patients treated with pegylated interferon versus lamivudine (92, 93). Disease progression or treatment induced sustained ALT normalization, and HBV DNA clearance did not vary by sex (41, 53, 83, 92, 93) or baseline body weight (92). Patients with longer duration of hepatitis responded to therapy 2.5 times less frequently than those with shorter duration of the disease. Sustained virologic response (HBeAg and HBV DNA loss) at 48 weeks off therapy with interferon-α2b combined with lamivudine compared with lamivudine monotherapy was greater in patients with an estimated duration of hepatitis of 10 years or less after adjustment for sex and age (31).

Treatment-induced follow-up histology, HBeAg or DNA clearance, and ALT normalization did not clearly vary by baseline histology severity (31, 58, 85, 94). However, individual RCTs reported that HBeAg loss was higher per 1-unit increase in baseline histologic activity index score (85). Lamivudine improved histology more than placebo among patients with moderate or severe hepatitis but failed in those with mild hepatitis (67). Virologic response to interferon-α2b plus lamivudine after treatment increased in those with a baseline inflammation score of 7 or more, independent of sex and age (31). Presence of steatosis did not modify the effect of pegylated interferon-α2a combined with lamivudine on posttreatment response (HBV DNA disappearance and ALT normalization) in both HBeAg-positive and -negative patients (94). Adjusted rates of posttreatment response were greater per 1-unit increase in baseline Knodell histologic activity index (94).

The effect of viral load on outcomes after therapy was difficult to interpret because of varying assays and cutoffs of baseline DNA. Inconsistent effects yielded no dose–response relationship. No studies reported subgroups with very low viral load. Combined administration of interferon-α2b with lamivudine resulted in greater HBV DNA clearance and HBeAg seroconversion after treatment in patients with baseline HBV DNA greater than 10^7 copies/mL (59). Pegylated interferon-α2a provided greater sustained response than lamivudine in patients with baseline HBV DNA in the 25th to 75th percentile range (49, 92), with random differences at other percentiles. Treatment-in-
duced ALT normalization and HBV DNA clearance or HBeAg seroconversion varied by HBV DNA genotype. Patients with genotypes B and C versus patients with genotype D had better responses at the end of treatments (92) and at follow-up after therapy (49, 90, 92, 93, 95–97). Patients with genotype A had lower adjusted odds of response than did patients with genotype C (92).

Baseline ALT Levels

Treatment-induced improvement in intermediate outcomes varied by baseline ALT levels, with inconsistent low-level evidence of a better response among patients with elevated baseline ALT levels (31, 49, 85, 94, 95). Hepatitis B virus DNA loss was more frequent among patients with elevated baseline ALT levels at follow-up after interferon-α2b administration with corticosteroid pretreatment than after interferon-α2b alone (95). Adjusted odds of sustained virologic response to interferon-α2b combined with lamivudine compared with lamivudine were higher in patients with baseline ALT levels of 150 U/L or more versus less than 150 U/L (RR, 3.12 [CI, 1.43 to 6.82]) (31). Sustained response to pegylated interferon-α2a combined with lamivudine compared with lamivudine alone was greater per 1-U/L increase in baseline ALT levels (RR, 10.32 [CI, 9.71 to 10.97]) (94). However, several studies reported no association between dose–response increase in baseline ALT levels and sustained response to pegylated interferon-α2a versus lamivudine (49) or pegylated interferon-α2b combined with lamivudine versus lamivudine (96).

Pretreatment Status

Seroconversion of HBeAg after pegylated interferon-α2a (alone or with lamivudine) was higher than that after lamivudine among lamivudine-naive patients (49), but not among previous lamivudine recipients. Five RCTs enrolled lamivudine-resistant patients (43, 46, 53, 72, 98). Among patients who did not respond to lamivudine, adefovir plus lamivudine versus lamivudine increased ALT normalization and HBV DNA clearance but not HBeAg clearance or seroconversion (72) without improving outcomes compared with adefovir monotherapy (72). Entecavir increased HBV DNA and HBeAg clearance and normalization of ALT in HBeAg-positive patients compared with lamivudine (43, 46) and improved necroinflammatory and fibrosis scores (46). Patients whose previous interferon therapy failed did not benefit from the addition of lamivudine (99).

Adverse Events

Investigators assessed adverse events to decide whether a change in dose or discontinuation of therapy was needed because of severity of events or laboratory abnormalities (Figure; Appendix Table 2, available at www.annals.org). Duration of the assessed events and treatment utilization for adverse events was not reported. Variability of the reported adverse events and the definitions of severity and seriousness preclude pooling of harms. We could not detect obvious reasons for such variability because no validated questionnaire exists to assess adverse events after antiviral drugs. Studies did not report run-in periods of drug therapy to identify and exclude patients with adverse events before randomization. Almost all studies excluded patients with hepatic decompensation or renal insufficiency. Many studies excluded patients with serious comorbid conditions (31, 41, 49, 51, 53, 58, 65, 68–70, 72, 78, 80, 90, 100, 101) or nonviral chronic liver diseases (31, 41, 43, 44, 46, 59, 67, 68, 75, 79–81, 89, 98, 102). Randomization still resulted in valid comparisons of adverse events in the active treatment group versus control group, and absolute rates of adverse events compared with the odds of positive effects on various outcomes permit an estimate of the balance between benefits and harms in clinical settings (Figure).

Adverse events during antiviral therapy were reported for more than 50% of patients. Forty-four publications reported withdrawal from treatment and adverse effects categorized as “serious” by the investigators. No study assessed treatment adherence. Withdrawal rates and frequency and severity of adverse events after oral antiviral drugs were similar to those with placebo. The general exceptions included increases in ALT levels with adefovir and lamivudine and an added black-box warning that participants with or at risk for impaired renal function may develop nephrotoxicity with long-term administration of adefovir. Other reported adverse events were usually mild, including fatigue, headache, abdominal pain, nausea, and diarrhea. Entecavir was better tolerated than lamivudine (44, 46, 47).

Interferon-based therapies were not as well tolerated as oral drugs. Dose modifications, primarily because of neutropenia and thrombocytopenia, were required for nearly 50% of individuals receiving interferon-based therapies. An initial influenza-like illness was commonly associated with pegylated interferon-α2a treatment, noted by pyrexia, fatigue, myalgia, and headache. Withdrawal rates were 24% higher after interferon-α2b than with no treatment (54). Pegylated interferon-α2a combined with lamivudine resulted in greater discontinuation versus placebo or lamivudine alone (69). Patients had serious adverse events more often after combined therapy of lamivudine with interferon-α2b (89) or pegylated interferon-α2a (49) than after lamivudine alone.

Discussion

We restricted our review to publications in English, but conducted an additional MEDLINE search for RCTs of eligible antiviral drugs that were published in other languages. We reviewed the abstracts of 10 publications published in Chinese that examined adefovir (103), entecavir (104, 105), interferon-α2b or pegylated interferon-α2b (106, 107), and lamivudine (108–112). We concluded that language bias, if present, would not change our overall
conclusions about the efficacy of the evaluated antiviral drugs in adults with chronic hepatitis B.

We did not evaluate antiviral drugs that have not been approved by the U.S. Food and Drug Administration for chronic hepatitis B, including emtricitabine, clevudine, pradefovir, valtorcitabine, and thymosin-α1 (113). These drugs did not prevent liver cancer or decompensation but resulted in viral loss and normalization of ALT levels (114–117), HBeAg seroconversion and improved histology (118), antiviral mutations, and immunologic biomarkers (119) in patients with chronic hepatitis B or co-infection with HIV (120, 121).

Data available from RCTs are insufficient to provide patients, clinicians, researchers, and policymakers with high-quality information needed for decision making about the long-term effects of chronic hepatitis B treatments on clinical outcomes. None of the RCTs demonstrated an effect on death, hepatocellular carcinoma, liver decompensation, cirrhosis, or resolved hepatitis. However, none were of sufficient size or duration or were designed to
assess clinical outcomes. Individual studies reported very few events and compared different drugs and patients, generally precluding pooling. Therefore, we cannot exclude the possibility that antiviral agents might improve clinical outcomes.

A single study found a significant reduction in hepatocellular carcinoma due to lamivudine in 651 adults (98% were Asian; 85% were men) with baseline cirrhosis or fibrosis after adjustment for baseline variables (hazard ratio, 0.49 [CI, 0.25 to 0.99]; absolute risk reduction, 4%). The results were not significant after exclusion of patients who developed hepatocellular carcinoma within 1 year of randomization, and the risk for death increased, although not significantly (RR, 2.47 [CI, 0.12 to 51.25]) (41). Disease progression, defined by a 2-point increase in Child–Pugh score comprised nearly half of the events. The Child–Pugh score assesses severity of liver disease on the basis of components that include biochemical measures (serum bilirubin and albumin levels and prothrombin) in addition to clinical measurements (ascites, encephalopathy, and sepsis).

For most outcomes, most conclusions about changes in intermediate outcomes were based on low levels of evidence from a single study or inconsistent results from several studies; therefore, our confidence in the effect size estimate is generally low. The role of intermediate markers or their combinations as surrogates for effects of treatment on clinical outcomes in chronic hepatitis B has never been adequately tested. Trial authors did not justify selection of intermediate markers by the clinical or prognostic importance of the expected changes. Anticipated odds of improved intermediate outcomes should be compared with odds of adverse effects.

Consensus among investigators and regulatory agencies is needed about whether currently used intermediate markers are true surrogates for treatment effects on mortality, morbidity, and quality of life in adults with chronic hepatitis B. Standardization of the measurements of viral load and hepatic aminotransferase in relation to patient age, race, and sex, and a uniform scoring system for liver biopsies with a single definition of what constitutes a clinically meaningful change in score, are essential for synthesis of the results from different studies. Future clinical trials should assess sustained benefits 6 months or more after the active treatments.

From the Minnesota Evidence-based Practice Center, University of Minnesota School of Public Health, Minneapolis Veterans Affairs Center for Chronic Disease Outcomes Research, and the University of Minnesota Medical School, Minneapolis, Minnesota.

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

**Acknowledgment:** The authors thank the technical expert panel members Dr. Miriam Alter, Dr. Gary Davis, Dr. Daryl Lau, Dr. Michael Sorrell, and Dr. Myron Tong for their scientific and clinical input throughout this project; Shilpa Amin, MD, MBSC, AHRQ Task Order Officer, for her guidance throughout the project; and Dr. John Ward for reviewing and commenting on the draft. They also thank the librarians, Judith Stanke and Dr. Del Reed, for their contributions to the literature search; Maureen Carlyle and Marilyn Eells for their excellent technical assistance in preparation of the full evidence report and this manuscript; and Rebecca Schultz and Nancy Russell for her assistance with formatting the tables.

**Grant Support:** By the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services contract number 290-02-0009.

**Potential Financial Conflicts of Interest:** None disclosed.

**Requests for Single Reprints:** Tatyana A. Shamlayan, MD, MS, Division of Health Policy and Management, University of Minnesota School of Public Health, D351 Mayo (MMC 197), 420 Delaware Street SE, Minneapolis, MN 55455; e-mail, shaml005@umn.edu.

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

**References**


95. Qiu 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;36:1425-30. [PMID: 12447868]


Current Author Addresses: Drs. Shamliyan and Kane: Division of Health Policy and Management, University of Minnesota School of Public Health, D351 Mayo (MMC 197), 420 Delaware Street SE, Minneapolis, MN.
Mr. MacDonald, Drs. Taylor and Wilt and Mr. Rutks: Center for Chronic Disease Outcomes Research, Minneapolis Veterans Affairs Medical Center, 1 Veterans Drive, Minneapolis, MN 55417.
Dr. Shaukat: Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota Medical School, 420 Delaware Street SE (MMC 36), Minneapolis, MN 55454.
Dr. Yuan: Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Room 300, West Bank Office Building, 1300 South Second Street, Minneapolis, MN 55454.
Dr. Johnson: Department of Infectious Diseases, Minneapolis Veterans Affairs Medical Center (111-F), 1 Veterans Drive, Minneapolis, MN 55417.
Mr. Tacklind: Agency for Healthcare Research and Quality Center for Chronic Disease Outcomes Research and the Cochrane Prostatic Diseases and Urologic Cancers Group, Minneapolis Veterans Affairs Medical Center, 1 Veterans Drive, Minneapolis, MN 55417.

Author Contributions: Conception and design: T.A. Shamliyan, R.L. Kane, T.J. Wilt.
Analysis and interpretation of the data: T.A. Shamliyan, R. MacDonald, A. Shaukat, B.C. Taylor, J.R. Johnson, T.J. Wilt.
Drafting of the article: T.A. Shamliyan, R. MacDonald, A. Shaukat.
Critical revision of the article for important intellectual content: T.A. Shamliyan, A. Shaukat, B.C. Taylor, J.-M. Yuan, J.R. Johnson, R.L. Kane, T.J. Wilt.
Final approval of the article: T.A. Shamliyan, A. Shaukat, B.C. Taylor, J.-M. Yuan, J.R. Johnson, R.L. Kane, T.J. Wilt.
Provision of study materials or patients: I. Rutks.
Statistical expertise: R. MacDonald.
Obtaining of funding: R.L. Kane, T.J. Wilt.

Administrative, technical, or logistic support: R. MacDonald, J. Tacklind, I. Rutks, R.L. Kane, T.J. Wilt.

Collection and assembly of data: T.A. Shamliyan, R. MacDonald, A. Shaukat, J. Tacklind, I. Rutks.