JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE A 2014 review for the US Preventive Services Task Force (USPSTF) found antiviral therapy for hepatitis B virus (HBV) infection associated with improved intermediate outcomes, although evidence on clinical outcomes was limited.

OBJECTIVE To update the 2014 HBV screening review in nonpregnant adolescents and adults to inform the USPSTF.

DATA SOURCES Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE (2014 to August 2019); with surveillance through July 24, 2020.

STUDY SELECTION Randomized clinical trials (RCTs) on screening and antiviral therapy; cohort studies on screening, antiviral therapy clinical outcomes, and the association between achieving intermediate outcomes after antiviral therapy and clinical outcomes.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data; a second investigator checked accuracy. Two investigators independently assessed study quality. Random-effects profile likelihood meta-analysis was performed.

RESULTS Thirty trials and 20 cohort studies, with a total of 94 168 participants, were included. No study directly evaluated the effects of screening for HBV infection vs no screening on clinical outcomes such as mortality, hepatocellular carcinoma, or cirrhosis. Screening strategies that focused on risk factors such as ever having immigrated from high-prevalence countries and demographic and behavioral risk factors would identify nearly all HBV infection cases. In 1 study (n = 21 008), only screening immigrants from high-prevalence countries would miss approximately two-thirds of infected persons. Based on 18 trials (n = 2972), antiviral therapy compared with placebo or no treatment was associated with greater likelihood of achieving intermediate outcomes, such as virologic suppression and hepatitis B e-antigen (HBeAg) or hepatitis B surface antigen loss or seroconversion; the numbers needed to treat ranged from 2.6 for virologic suppression to 17 for HBeAg seroconversion. Based on 12 trials (n = 4127), first-line antiviral therapies were at least as likely as nonpreferred therapies to achieve intermediate outcomes. Based on 16 trials (n = 4809), antiviral therapy might be associated with improved clinical outcomes, but data were sparse and imprecise. Nine cohort studies (n = 3893) indicated an association between achieving an intermediate outcome following antiviral therapy and improved clinical outcomes but were heterogeneous (hazard ratios ranged from 0.07 to 0.87). Antiviral therapy was associated with higher risk of withdrawal due to adverse events vs placebo or no antiviral therapy.

CONCLUSIONS AND RELEVANCE There was no direct evidence for the clinical benefits and harms of HBV screening vs no screening. Antiviral therapy for HBV infection was associated with improved intermediate outcomes and may improve clinical outcomes.

Editorial page 2380

Author Audio Interview

Related article page 2415 and JAMA Patient Page page 2452

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The overall prevalence of chronic hepatitis B virus (HBV) infection in the US has been estimated at about 0.3% in 2007 to 2012, or approximately 847 000 persons.[1,2] People born in countries with a 2% or greater HBV prevalence accounted for 47% of chronic infections in the US, based on survey data published through 2010, and for 95% of chronic infections in the US, based on an analysis of cases during 1974 to 2008.[3,4] Since 2010, an increase in acute and chronic HBV infection related to drug use in younger adults has been reported in several states.[5-7]

In 2014, the US Preventive Services Task Force (USPSTF) recommended screening for HBV infection in persons at high risk for infection (B recommendation); an HBV prevalence of 2% or greater was noted as a reasonable threshold for deciding to screen.[8] This evidence report was conducted to update the 2014 review on HBV screening[9,10] to inform the USPSTF for an updated recommendation statement.

Methods

Scope of the Review

Detailed methods and additional study details are available in the full evidence report.[11] **Figure 1** shows the analytic framework and key questions (KQs) that guided the review; the contextual questions that were not reviewed systematically are addressed in the full report.

Data Sources and Searches

Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched from 2014 to August 2019 (eMethods 1 the Supplement). Searches were supplemented by reference list review of relevant systematic reviews; studies from the prior USPSTF review[9,13] that met inclusion criteria were carried forward. Ongoing surveillance was conducted to identify major studies published since August 2019 that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on July 24, 2020, and identified no studies affecting review conclusions.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria. The population for screening was asymptomatic adults and adolescents without prior HBV infection. For treatment, to evaluate patients more likely to be asymptomatic and identified by screening, inclusion was restricted to studies in which less than 20% of patients had cirrhosis at baseline (less than 30% for cohort studies that also controlled for fibrosis stage). Randomized clinical trials of screening, antiviral therapy vs placebo, and preferred (first-line) antiviral therapy (entecavir, tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF], pegylated interferon [adults], and nonpegylated interferon [children]) vs nonpreferred (adefovir, lamivudine, and telbivudine) antiviral therapy (according to recent guidelines)[14] were included. Nonpegylated interferon in adults was included because there were few trials of pegylated interferon. Studies that compared the yield of alternative screening strategies, large (n >1000) cohort studies of antiviral treatment vs no treatment that controlled for potential confounders and evaluated clinical outcomes at 1 year or later, and cohort studies that reported adjusted risk estimates for the association between achieving intermediate outcomes following antiviral treatment and long-term clinical outcomes (mortality or morbidity) were also included.

Clinical outcomes were mortality or morbidity (cirrhosis, hepatocellular cancer, quality of life, HBV transmission, extrahepatic outcomes, or harms). Intermediate outcomes were virologic (HBV DNA [DNA]) suppression, histologic improvement, biochemical improvement (normalization of alanine aminotransferase [ALT] or aspartate aminotransferase levels, hepatitis B e-antigen [HBeAg] clearance [loss of HBeAg or seroconversion, defined as acquisition of antibody to HBeAg], and hepatitis B surface antigen [HBsAg] clearance [HBsAg loss or or seroconversion, defined as acquisition of antibody to HBsAg]). Studies that focused on patients previously treated, co-infected with HIV or with hepatitis C virus co-infection, transplant patients, and persons with advanced kidney disease were excluded.

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, interventions, analysis, follow-up, and results from each study. A second investigator reviewed abstracted data for accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement).[12] Discrepancies were resolved through a consensus process. In accordance with the USPSTF Procedure Manual,[12] studies rated poor-quality because of critical methodological limitations were excluded.

Data Synthesis

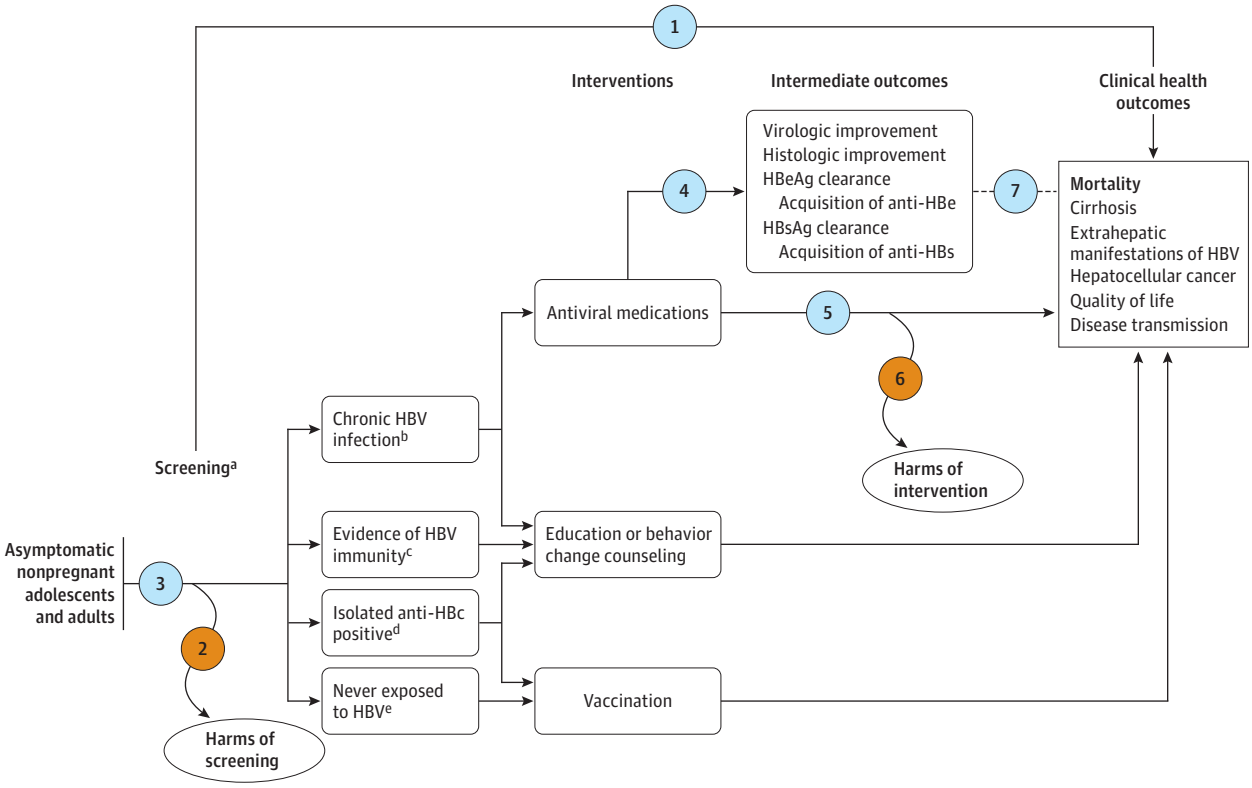
Random-effects meta-analysis, stratified by antiviral drug or comparison (for head-to-head trials), was performed to summarize the proportion of patients experiencing intermediate outcomes, clinical outcomes, and harms using a profile likelihood model in Stata/IC 14.2 (StataCorp). When the profile likelihood model did not converge, the Dersimonian-Laird model was used instead. Statistical heterogeneity was assessed using the I^2 statistic. Subgroup analyses were conducted on study quality, geographic setting, duration of follow-up, HBeAg status, immune tolerant or immune active phase of HBV infection,[14] prior antiviral treatment status, and cirrhosis (excluded or included some [up to 20% of sample] with baseline cirrhosis) and interactions were assessed using a test for heterogeneity across subgroups. Meta-analysis was not performed for the association between achieving an intermediate outcome after antiviral therapy and clinical outcomes because of small numbers of studies. Graphical and statistical tests for small sample effects were not conducted because of fewer than 10 trials for most analyses and clinical heterogeneity (due to differences in the drugs evaluated and populations [eg, HBeAg status]) in analyses with more than 10 trials.[15]

All significance testing was 2-tailed; $P \leq .05$ or less was considered statistically significant.

Results

Across all KQs, 30 randomized clinical trials[16-44] (n = 7099), 17 cohort studies[45-61] (n = 56 029), and 3 retrospective studies

Figure 1. Analytic Framework: Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults



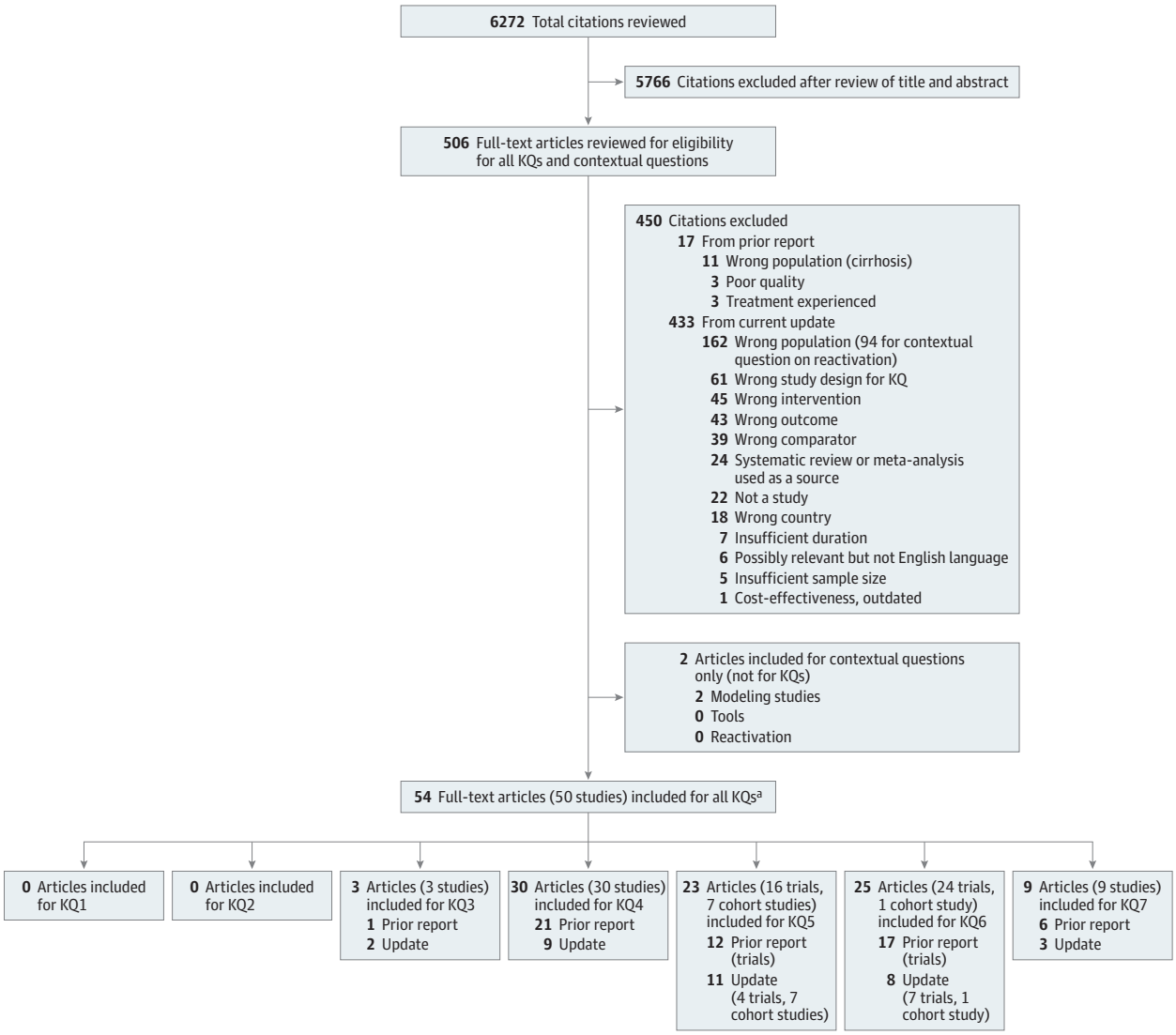
Key questions

1. What are the benefits of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?
2. What are the harms of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults (eg, labeling or anxiety)?
3. What is the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV screening strategies (eg, universal vs targeted screening or screening strategies based on alternative risk factors)?
4. How effective is antiviral treatment in improving intermediate outcomes among nonpregnant adolescents and adults with chronic HBV infection, including virologic or histologic improvement, clearance of HBeAg (as indicated by loss of HBeAg or acquisition of the antibody to HBeAg), or clearance of HBsAg (as indicated by loss of HBsAg or acquisition of anti-HBs)?[f]
5. How effective is antiviral treatment in improving health outcomes among nonpregnant adolescents and adults with chronic HBV infection?[f]
6. What are the harms associated with antiviral treatment in nonpregnant adolescents and adults with chronic HBV infection?[f]
7. What is the association between improvements in intermediate outcomes as a result of antiviral treatment of chronic HBV infection and reduction in risk of HBV-related adverse health outcomes?

Evidence reviews for the USPSTF use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a service. The questions are depicted by linkages that relate interventions and outcomes. For additional information see the USPSTF Procedure Manual.[12] Anti-HBc indicates antibody to the hepatitis B core antigen; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

[a] Defined as testing for anti-HBs and HBsAg, with or without testing for anti-HBc. [b]Defined by a positive HBsAg result. Chronic HBV infection should be staged by assessment for hepatitis fibrosis/inflammation, HBV viral load, HBeAg status, antibody to HBeAg (anti-HBe) status, and liver function test results. Appropriate interventions depend on disease stage. [c]Defined as positive anti-HBs, negative HBsAg, and positive (cleared infection) or negative (seroprotection due to vaccination) anti-HBc test results. Patients who have positive anti-HBc results may benefit from education regarding risk of reactivation. [d]Defined as positive anti-HBc test results but negative anti-HBs and HBsAg test results and indicates prior HBV exposure or false-positive result. Patients who have positive isolated anti-HBc test results may benefit from education regarding risk of reactivation and, if immunocompromised, HBV DNA testing. HBV vaccination is recommended for patients with positive isolated anti-HBc test results who are from countries with low prevalence of HBV infection (eg, US) or who are immunocompromised. [e]Defined as negative anti-HBs, anti-HBc, and HBsAg test results. [f]Subpopulations of interest for key questions 4, 5, and 6 include those defined by age, race/ethnicity, sex, injection drug use status, HBV genotype, HBeAg status, fibrosis stage, ALT level, presence of nonalcoholic steatohepatitis, HBV DNA, and hepatitis D virus status.

Figure 2. Literature Search Flow Diagram: Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults



HCV indicates hepatitis C virus; KQ, key question.

[a] Some included studies overlap among the KQs.

(n = 31 040)[62-64] addressing the yield of alternative strategies were included (**Figure 2**). Twenty-two studies[30-33,40-52,59-61,63,64] were new for this update, and 28 studies[16-29,34-39,53-58,62] were carried forward from the previous review. Seventeen studies included in the prior USPSTF review were excluded for this update because the proportion of patients with cirrhosis at baseline was above the 20% threshold[65-71] or the 30% threshold (for association studies),[72-75] patients were antiviral therapy–experienced,[76-78] or the studies were rated poor-quality.[79-81]

Benefits and Harms of Screening

Key Question 1. What are the benefits of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?

No study met inclusion criteria for this KQ.

Key Question 2. What are the harms of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults (eg, labeling or anxiety)?

No study met inclusion criteria for this KQ.

Key Question 3. What is the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV screening strategies (eg, universal vs targeted screening or screening strategies based on alternative risk factors)?

Three fair-quality European studies (n = 30 040)[62-64] retrospectively compared the yield of alternative screening strategies (eTables 1-3 in the Supplement). They found that screening based on the presence of any of multiple risk factors (ever having immigrated from high-prevalence countries, other demographic risk factors, and behavioral risk factors) would result in screening about two-thirds of the population and identify nearly all cases of

HBV infection; the numbers needed to screen to identify 1 HBV infection ranged from 32 to 148. Screening only immigrants from high-prevalence (≥2%) countries was more efficient (number needed to screen, 19-71) and identified 85% to 99% of patients with HBV infection in higher-prevalence clinical settings but missed about two-thirds of HBV infections in a study[64] conducted in primary care practices.

Benefits and Harms of Treatment

Key Question 4. How effective is antiviral treatment in improving intermediate outcomes among nonpregnant adolescents and adults with chronic HBV infection, including virologic suppression, histologic improvement, biochemical improvement, clearance of HBeAg (as indicated by loss of HBeAg or acquisition of the antibody to HBeAg), or clearance of HBsAg (as indicated by loss of HBsAg or acquisition of hepatitis B surface antibody)?

Antiviral Therapy vs Placebo or No Treatment

Eighteen trials (n = 2972) reported effects of antiviral therapy (entecavir, nonpegylated interferon alfa-2a or alfa-2b, adefovir, or lamivudine) vs placebo or no treatment on intermediate outcomes (eTables 4-5 in the Supplement).[16-33] No trial evaluated pegylated interferon, tenofovir (TDF or TAF), or telbivudine. All trials included only adults. The duration of follow-up ranged from 1.8 to 86 months. All trials were rated fair-quality; methodological limitations included unclear reporting of randomization, allocation concealment, and blinding methods (eTable 6 in the Supplement).

Antiviral therapy, vs placebo or no antiviral therapy, was associated with increased likelihood of HBeAg loss (6 trials, n = 1121; risk ratio [RR], 1.91 [95% CI, 1.46 to 2.81]; I^2 = 15%; absolute risk difference [ARD], 14% [95% CI, 5.8% to 23%]) (**Figure 3**A),[18,24,25,29-31] HBeAg seroconversion (4 trials, n = 1104; RR, 2.11 [95% CI, 1.30 to 3.55]; I^2 = 0%; ARD, 6.2% [95% CI, 2.4% to 10%]) (eFigure 1 in the Supplement),[18,24,28,29] HBsAg loss (3 trials, n = 714; RR, 4.63 [95% CI, 1.10 to 19.55]; I^2 = 70%; ARD, 8.2% [95% CI, −2.6% to 19%]) (eFigure 2 in the Supplement),[25,27,33] HBV DNA suppression vs placebo (13 trials, n = 2522; RR, 4.39 [95% CI, 2.61 to 7.39]; I^2 = 86%; ARD, 39% [95% CI, 24% to 53%]) (Figure 3B),[17-20,24,25,27-33] normalization of ALT levels (11 trials, n = 2044; RR, 2.62 [95% CI, 2.22 to 3.10]; I^2 = 0%; ARD, 24% [95% CI, 7.8% to 39%] (**Figure 4**A),[16-20,23-25,29,30,33] and histologic improvement (6 trials, n = 1057; RR, 2.00 [95% CI, 1.63 to 2.41]; I^2 = 0%; ARD, 28% [95% CI, 22% to 34%]; (Figure 4B).[17-20,24,32]

Antiviral therapy was also associated with increased likelihood of the composite outcomes HBV DNA suppression plus normalization of ALT levels (3 trials, n = 286; RR, 6.30 [95% CI, 3.06 to 13.11]; I^2 = 0%; ARD, 48% [95% CI, 29% to 61%]) (eFigure 3 in the Supplement)[17,22,27] and HBeAg loss or seroconversion plus HBV DNA suppression (4 trials, n = 623; RR, 2.36 [95% CI, 1.44 to 4.28]; I^2 = 0%; ARD, 12% [95% CI, 4.8% to 24%]) (eFigure 4 in the Supplement).[20,23,28,31] The estimates stratified by each individual drug consistently favored antiviral therapy, except when there was marked imprecision. For HBV DNA suppression, there were statistically significant interactions between geographic region, duration of follow-up, and HBeAg status and antiviral therapy effects, but results favored antiviral therapy in each of these subgroups (eTable 7 in the Supplement). For normalization of ALT levels, there was a statistically significant interaction between HBeAg status and antiviral therapy effects, but only 1 trial excluded HBeAg-positive patients. Otherwise, there were no significant interactions between geographic region, prior antiviral treatment status, follow-up duration, HBeAg status, or immune tolerant phase and effects on intermediate outcomes.

Preferred vs Nonpreferred Regimens

Twelve trials (reported in 11 publications) (n = 4127) compared preferred (entecavir, TDF, or pegylated interferon alfa-2a) vs nonpreferred (lamivudine, telbivudine, or adefovir) antiviral regimens on intermediate outcomes (eTables 8-9 in the Supplement).[34-44] Duration of follow-up ranged from 3.7 to 22 months. Five trials were rated good-quality,[34,35,37,40,43] and the others were rated fair-quality because of unclear or no blinding of outcome assessors, care providers, or patients (eTable 6 in the Supplement).

Preferred antiviral therapy, vs nonpreferred antiviral therapy, was associated with similar or increased likelihood of HBeAg loss (3 trials, n = 813),[36,37,40] HBeAg seroconversion (7 trials, n = 2173) (eFigure 5 in the Supplement),[36-39,43,44,82] HBsAg loss or seroconversion (3 trials, n = 1492),[34,37,38] virologic suppression (12 trials, n = 3983) (eFigure 6 in the Supplement),[35-44,82] normalization of ALT levels (11 trials, n = 3875) (eFigure 7 in the Supplement),[35-41,43,44,82] and histologic improvement (2 trials, n = 1211) (eFigure 8 in the Supplement).[35,82] However, estimates for some head-to-head comparisons were based on few trials and were imprecise. Subgroup analyses found no statistically significant interactions between HBeAg status or duration of follow-up and effects of entecavir vs lamivudine on normalization of ALT levels or virologic suppression (eTable 10 in the Supplement). Otherwise, subgroup analyses were not performed because of small numbers of trials.

Key Question 5. How effective is antiviral treatment in improving health outcomes among nonpregnant adolescents and adults with chronic HBV infection?

Antiviral Therapy vs Placebo or No Treatment

Seven randomized trials of antiviral therapy vs placebo or no treatment (n = 1042) reported effects on clinical outcomes (eTables 4-5 in the Supplement).[17,18,20,22,23,25,31] None of the trials reported effects on quality of life, risk of HBV disease transmission, or extrahepatic outcomes. The trials were not designed to evaluate effects on clinical outcomes and there were a total of 23 cases of incident cirrhosis in 2 trials,[23,25]13 cases of hepatocellular carcinoma in 4 trials,[17,22,23,25] and 8 deaths in 3 trials[23,25,31] (2 other trials that reported mortality recorded no deaths).[18,20] The duration of follow-up ranged from 11 to 86 months.

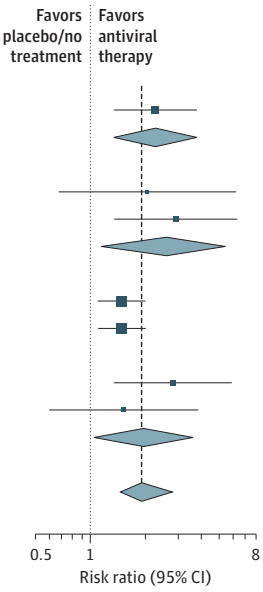
Antiviral therapy was associated with decreased risk of mortality vs placebo or no therapy (3 trials, n = 349; RR, 0.15 [95% CI, 0.03 to 0.69]; I^2 = 0%; ARD, −0.3% [95% CI, −1.7% to 0.8%]) (**Figure 5**A); all of the trials reporting mortality evaluated nonpegylated interferon.[23,25,31] Pooled estimates for incident cirrhosis (2 trials, n = 165; RR, 0.72 [95% CI, 0.29 to 1.77]; I^2 = 0%) (Figure 5B)[23,25] and hepatocellular carcinoma (4 trials, n = 343; RR, 0.60 [95% CI, 0.16 to 2.33]; I^2 = 20%) (Figure 5C)[17,22,23,25] favored antiviral therapy over placebo or no therapy, but differences were not statistically significant.

Seven fair-quality cohort studies (n ≈ 50 912) evaluated effects of antiviral therapy vs no therapy on mortality or hepatocellular carcinoma after controlling for potential confounders

Figure 3. Antiviral Treatment vs Placebo or No Treatment on Intermediate Outcomes (HBeAg Loss; HBV DNA Loss or Virologic Suppression)

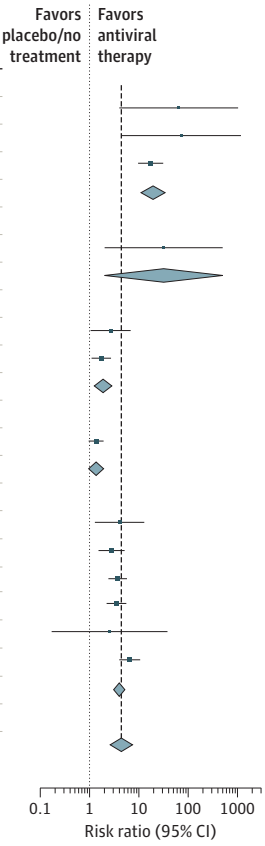
A HBeAg loss

Study	Drug and dose	Follow-up, wk	No./total Treatment	No./total Control	Risk ratio (95% CI)
Adefovir dipivoxil					
Marcellin et al,[24] 2003	Adefovir dipivoxil 10 mg daily	48	41/171	17/161	2.27 (1.35-3.83)
Subgroup (Heterogeneity: I^2 = 0%)			41/171	17/161	2.27 (1.35-3.83)
Interferon alpha-2a					
Realdi et al,[30] 1990	Interferon alfa-2a	64	8/39	4/40	2.05 (0.67-6.26)
Thomas et al,[31] 1994	Interferon-alfa-2a 5 or 10 MIU m2	74	40/91	6/40	2.93 (1.35-6.35)
Subgroup (Heterogeneity: I^2 = 0%)			48/130	10/80	2.61 (1.15-5.47)
Interferon alpha-2b					
Mazzella et al,[25] 1999	Interferon alfa 5 MU/m2 ×3/w	360	30/33	19/31	1.48 (1.10-2.00)
Subgroup (Heterogeneity: I^2 = 0%; P = .61)			30/33	19/31	1.48 (1.10-2.00)
Lamivudine					
Dienstag et al,[18] 1999	Lamivudine 100 mg daily	52	21/66	8/71	2.82 (1.34-5.93)
Yao et al,[29] 1999	Lamivudine 100 mg daily	12	23/284	5/94	1.52 (0.60-3.89)
Subgroup (Heterogeneity: I^2 = 0%)			44/350	13/165	2.06 (0.94-4.93)
Heterogeneity between groups: P = .44					
Overall (Heterogeneity: I^2 = 15.0%; P = .23)			163/684	59/437	1.91 (1.46-2.81)



B HBV DNA loss or virologic suppression

Study	Drug and dose	Follow-up, wk	Outcome definition	No./total Treatment	No./total Control	Risk ratio (95% CI)
Adefovir dipivoxil						
Hadziyannis et al,[19] 2003	Adefovir dipivoxil 10 mg daily	48	<400 copies/mL	63/123	0/61	63.50 (4.00-1009.28)
Marcellin et al,[24] 2003	Adefovir dipivoxil 10 mg daily	48	<400 copies/mL	36/171	0/167	71.30 (4.41-1152.34)
Wen et al,[33] 2014	Adefovir dipivoxil 10 mg	100	<500 IU/mL	174/252	11/274	17.20 (9.58-30.87)
Subgroup (Heterogeneity: I^2 = 0%; P = .38)				273/546	11/502	19.22 (10.98-33.67)
Entecavir						
Tseng et al,[32] 2014	Entecavir 0.5 mg daily	52	NR	16/21	0/20	31.50 (2.02-492.36)
Subgroup (Heterogeneity: I^2 = 0%)				16/21	0/20	31.50 (2.02-492.36)
Interferon alpha-2a						
Realdi et al,[30] 1990	Interferon alfa-2a	64	NR	13/39	5/40	2.67 (1.05-6.77)
Thomas et al,[31] 1994	Interferon-alfa-2a 5 or 10 MIU	74	NR	55/91	14/40	1.73 (1.10-2.72)
Subgroup (Heterogeneity: I^2 = 0%; P = .41)				68/130	19/80	1.88 (1.25-2.82)
Interferon alpha-2b						
Mazzella et al,[25] 1999	Interferon alfa 5 MU/m	360	NR	26/33	18/31	1.36 (0.96-1.92)
Subgroup (Heterogeneity: I^2 = 0%)				26/33	18/31	1.36 (0.96-1.92)
Lamivudine						
Chan et al,[17] 2007	Lamivudine 100 mg daily	96	<100 copies/mL	23/89	3/47	4.05 (1.28-12.79)
Dienstag et al,[18] 1999	Lamivudine 100 mg daily	52	<1.6 pg/mL	28/63	11/69	2.79 (1.52-5.12)
Lai et al,[20] 1998	Lamivudine 25 or 100 mg daily	52	<1.6 pg/mL	233/275	16/70	3.71 (2.40-5.72)
Tassopoulos et al,[27] 1999	Lamivudine 100 mg daily	26	<2.5 pg/mL	49/54	14/54	3.50 (2.21-5.54)
Yalçin et al,[28] 2004	Lamivudine 100 mg daily	52	<1 pg/mL	1/13	1/33	2.54 (0.17-37.64)
Yao et al,[29] 1999	Lamivudine 100 mg daily	12	<1.6 pg/mL	269/293	14/99	6.49 (3.99-10.56)
Subgroup (Heterogeneity: I^2 = 12.5%; P = .29)				603/787	59/372	3.98 (3.07-5.17)
Heterogeneity between groups: P <.001						
Overall (Heterogeneity: I^2 = 86.5%; P <.001)				986/1517	107/1005	4.39 (2.61-7.39)



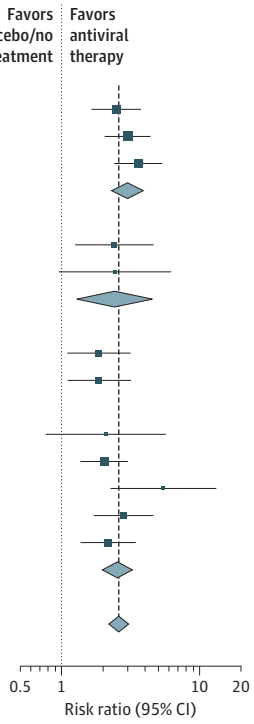
Dashed line indicates the overall effect. HBeAg indicates hepatitis B e-antigen; HBV, hepatitis B virus; NR, not reported.

(eTables 11-13 in the Supplement).[45-51] Follow-up ranged from 2.7 to 8.9 years. Three studies appeared to examine overlapping populations from a Taiwanese administrative database.[48,50,51] Studies typically adjusted for age, sex, and fibrosis stage; some studies also adjusted for HBV DNA level, ALT level, or medical comorbidities.

Figure 4. Antiviral Treatment vs Placebo or No Treatment on Intermediate Outcomes (ALT Level Normalization; Histologic Improvement)

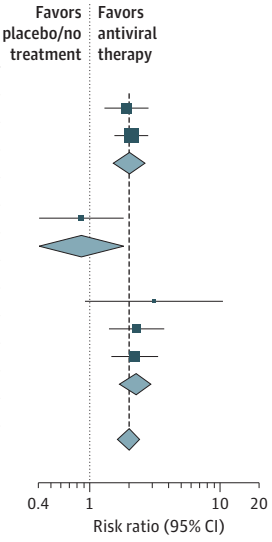
A ALT level normalization

Study	Drug and dose	Follow-up, wk	No./total Treatment	No./total Control	Risk ratio (95% CI)
Adefovir dipivoxil					
Hadziyannis et al,[19] 2003	Adefovir dipivoxil 10 mg daily	48	84/116	17/59	2.51 (1.66-3.81)
Marcellin et al,[24] 2003	Adefovir dipivoxil 10 mg daily	48	81/168	26/164	3.04 (2.07-4.47)
Wen et al,[33] 2014	Adefovir dipivoxil 10 mg	100	87/252	26/274	3.64 (2.43-5.45)
Subgroup (Heterogeneity: I^2 = 0%; P = .46)			252/536	69/497	3.04 (2.32-3.96)
Interferon alpha-2a					
Lin et al,[23] 1999	Interferon alfa 2a 4-5 MU/m2	364	37/76	8/40	2.43 (1.26-4.72)
Realdi et al,[30] 1990	Interferon alfa-2a	64	12/39	5/40	2.46 (0.96-6.34)
Subgroup (Heterogeneity: I^2 = 0%)			49/115	13/80	2.44 (1.29-4.62)
Interferon alpha-2b					
Mazzella et al,[25] 1999	Interferon alfa 5 MU/m2	360	22/33	11/31	1.88 (1.10-3.20)
Subgroup (Heterogeneity: I^2 = 0%; P = .99)			22/33	11/31	1.88 (1.10-3.20)
Lamivudine					
Bozkaya et al,[16] 2005	Lamivudine 100 mg daily	52	8/18	4/19	2.11 (0.77-5.81)
Chan et al,[17] 2007	Lamivudine 100 mg daily	96	66/89	17/47	2.05 (1.38-3.06)
Dienstag et al,[18] 1999	Lamivudine 100 mg daily	52	27/66	5/68	5.56 (2.28-13.58)
Lai et al,[20] 1998	Lamivudine 25 or 100 mg daily	52	132/193	12/50	2.85 (1.72-4.71)
Yao et al,[29] 1999	Lamivudine 100 mg daily	12	91/151	14/51	2.20 (1.38-3.49)
Subgroup (Heterogeneity: I^2 = 0%)			324/517	52/235	2.43 (1.90-3.39)
Heterogeneity between groups: P = .38					
Overall (Heterogeneity: I^2 = 0%; P = .44)			647/1201	145/843	2.62 (2.22-3.10)



B Histologic improvement

Study	Drug and dose	Follow-up, wk	Outcome definition	No./total Treatment	No./total Control	Risk ratio (95% CI)
Adefovir dipivoxil						
Hadziyannis et al,[19] 2003	Adefovir dipivoxil 10 mg daily	48	Knodell ≥2	77/121	19/57	1.91 (1.29-2.82)
Marcellin et al,[24] 2003	Adefovir dipivoxil 10 mg daily	48	Knodell ≥2	89/168	41/161	2.08 (1.54-2.81)
Subgroup (Heterogeneity: I^2 = 0%; P = .73)				166/289	60/218	2.02 (1.51-2.65)
Entecavir						
Tseng et al,[32] 2014	Entecavir 0.5 mg daily	52	Knodell ≥2	16/21	8/18	0.86 (0.40-1.82)
Subgroup (Heterogeneity: I^2 = 0%)				16/21	8/18	0.86 (0.40-1.82)
Lamivudine						
Chan et al,[17] 2007	Lamivudine 100 mg daily	96	Knodell ≥2	23/89	2/8	3.11 (0.91-10.59)
Dienstag et al,[18] 1999	Lamivudine 100 mg daily	52	HAI ≥2	28/63	16/71	2.29 (1.40-3.73)
Lai et al,[20] 1998	Lamivudine 25 or 100 mg daily	52	Knodell ≥2	49/54	18/73	2.21 (1.46-3.35)
Subgroup (Heterogeneity: I^2 = 0%; P = .88)				603/787	36/152	2.29 (1.66-3.26)
Heterogeneity between groups: P = .06						
Overall (Heterogeneity: I^2 = 0%; P = .30)				986/1517	104/388	2.00 (1.63-2.41)



ALT indicates alanine aminotransferase; HAI, histology activity index.

Antiviral therapy was consistently associated with decreased risk of hepatocellular carcinoma vs no antiviral therapy in 2 US studies (n = 2671; adjusted hazard ratio [HR], 0.39 [95% CI, 0.27 to 0.56] after 5.2 years,[45] and n=1302; adjusted HR, 0.24 [95% CI, to 0.10 to 0.58] after 8.9 years)[46] and in 5 studies conducted in Asian populations (n = ≈ 44 576 [excluding potentially overlapping populations], adjusted HRs ranged from 0.37 at 2.7 years' follow-up to 0.64 at 5.3 years' follow-up).[47-51] A study conducted in Taiwan found antiviral therapy associated with decreased risk of mortality (n = 3088; adjusted HR, 0.58 [95% CI, 0.43 to 0.79]).[50]

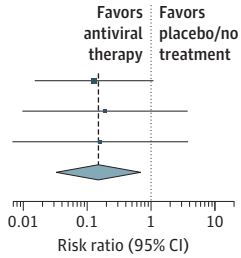
Preferred vs Nonpreferred Regimens

Nine trials (n = 3767, reported in 8 publications) evaluated effects of preferred vs nonpreferred antiviral therapy on clinical outcomes (mortality, cirrhosis, hepatocellular carcinoma) (eTables 8-9 in the Supplement).[34,35,37-41,43] The trials were not designed to evaluate

Figure 5. Antiviral Treatment vs Placebo or No Treatment on Health Outcomes

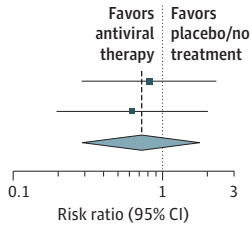
A Mortality

Study	Drug and dose	Follow-up, wk	No./total Treatment	No./total Control	Risk ratio (95% CI)
Lin et al,[23] 1999	Interferon alfa 2a 4-5 MU/m2	364	1/67	4/34	0.13 (0.01-1.09)
Mazzella et al,[25] 1999	Interferon alfa 5 MU/m2 ×3/wk	360	0/33	2/31	0.19 (0.01-3.77)
Thomas et al,[31] 1994	Interferon-alfa-2a 5/10 MIU/m2	74	0/125	1/59	0.16 (0.01-3.84)
Overall Heterogeneity: I^2 = 0%; P = .98			1/225	7/124	0.15 (0.03-0.69)



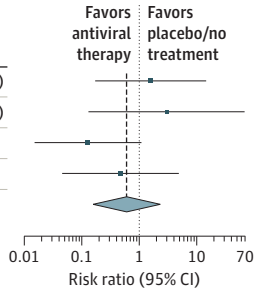
B Incident cirrhosis

Study	Drug and dose	Follow-up, wk	No./total Treatment	No./total Control	Risk ratio (95% CI)
Lin et al,[23] 1999	Interferon alfa 2a 4-5 MU/m2	364	8/67	5/34	0.81 (0.29-2.29)
Mazzella et al,[25] 1999	Interferon alfa 5 MU/m2 ×3/wk	360	4/33	6/31	0.63 (0.20-2.01)
Overall Heterogeneity: I^2 = 0%; P = .74			12/100	11/65	0.72 (0.29-1.77)



C Hepatocellular carcinoma

Study	Drug and dose	Follow-up, wk	No./total Treatment	No./total Control	Risk ratio (95% CI)
Chan et al,[17] 2007	Lamivudine 100 mg daily	96	3/89	1/47	1.58 (0.17-14.81)
Lampertico et al,[22] 1997	Interferon alfa 2b 6MU IM ×3/wk	156	1/21	0/21	3.00 (0.13-69.70)
Lin et al,[23] 1999	Interferon alfa 2a 4-5 MU/m2	364	1/67	4/34	0.13 (0.01-1.09)
Mazzella et al,[25] 1999	Interferon alfa 5 MU/m2 ×3/wk	360	1/33	2/31	0.47 (0.04- 4.92)
Overall Heterogeneity: I^2 = 20.5%; P = .29			6/210	7/133	0.60 (0.16-2.33)



Dashed line indicates the overall effect.

clinical outcomes and reported very small numbers of events, resulting in very imprecise estimates.

Key Question 6. What are the harms associated with antiviral treatment in nonpregnant adolescents and adults with chronic HBV infection?

Antiviral Therapy vs Placebo or No Treatment

There were no statistically significant differences between antiviral therapy vs placebo or no antiviral therapy in risk of serious adverse events (4 trials, n = 802; RR, 0.92 [95% CI, 0.45 to 1.85]; I^2 = 0%) (eFigure 9 in the Supplement),[17,19,20,27] any adverse event (5 trials, n = 1290; RR, 1.01 [95% CI, 0.90 to 1.11]; I^2 = 0%) (eFigure 10 in the Supplement),[19,20,27,29,31] nausea (3 trials; RR, 0.80 [95% CI, 0.48 to 2.10]; I^2 = 0%) (eFigure 11 in the Supplement),[24,27,29] or elevated creatinine levels (3 trials; RR, 1.27 [95% CI, 0.31 to 3.55]; I^2 = 0%) (eFigure 12 in the Supplement).[17,18,20] However, estimates were imprecise. The estimate for withdrawal due to adverse events suggested increased risk (3 trials, n = 505; RR, 4.44 [95% CI, 0.95 to 20.77]; I^2 = 0%) (eFigure 13 in the Supplement),[22,24,27] which was highest in a trial of interferon alfa-2a (n = 42; 23.8% vs 0%; RR, 11.00 [95% CI, 0.65 to 187.17]).[22] Another trial found interferon associated with markedly increased risk of any adverse event (89.6% vs 0%; RR, 107.14 [95% CI, 6.78 to 1694.36]).[31] A cohort study (n = 1224) of Asian patients in the US found neither TDF nor entecavir associated with increased risk of osteopenia or osteoporosis compared with no therapy, although estimates were imprecise (adjusted HR, 0.74 [95% CI, 0.34 to 1.59] and 0.98 [95% CI, 0.51 to 1.90], respectively); fracture risk was not assessed.

Preferred vs Nonpreferred Regimens

There were no statistically significant differences between entecavir vs lamivudine or tenofovir vs adefovir in risk of serious adverse events (7 trials, n = 3136) (eFigure 14 in the Supplement),[35,38,40,41,43,82] withdrawal due to adverse events (7 trials, n = 3223) (eFigure 15 in the Supplement),[35,36,38,40,41,43,82] or any adverse event (7 trials, n = 3223) (eFigure 16 in the Supplement).[35,36,38,40,41,43,82] However, estimates were imprecise. One trial (n = 543) found pegylated interferon alfa-2a associated with increased risk of serious adverse events (RR, 2.41 [95% CI, 0.86 to 6.74]), withdrawal due to adverse events (RR, 4.01 [95% CI, 0.86 to 18.73]), and any adverse event (RR, 1.58 [95% CI, 1.41 to 1.78]) vs lamivudine, though only the estimate for any adverse event was statistically significant.[37] One small trial (n = 44) found entecavir associated with increased risk of any adverse event vs telbivudine, but the estimate was imprecise (RR, 1.58 [95% CI, 0.86 to 2.91]).[42] Three head-to-head trials reported too few cases of elevated creatinine levels to determine effects of preferred vs

nonpreferred therapy.[38,41] No trial compared preferred vs nonpreferred antiviral therapy for bone adverse events.

Key Question 7. What is the association between improvements in intermediate outcomes as a result of antiviral treatment of chronic HBV infection and reduction in risk of HBV-related adverse health outcomes?

Nine fair-quality studies evaluated the association between improvement vs no improvement in intermediate outcomes following antiviral therapy for chronic HBV infection and clinical outcomes (eTables 14-16 in the Supplement). Sample sizes ranged from 63 to 1531 patients (total n = 3893), and the duration of follow-up ranged from 3.2 to 9.9 years.

Variability in patient populations (eg, HBeAg status and prevalence of cirrhosis at baseline), intermediate and clinical outcomes evaluated, and methodological limitations made it difficult to draw strong conclusions regarding the association between achieving intermediate outcomes after antiviral treatment and improvement in clinical outcomes (eTable 17 in the Supplement). However, across intermediate and clinical outcome comparisons, estimates of risk consistently favored achieving the intermediate outcomes and reduced risk of mortality (1 study, n = 103),[55] hepatocellular carcinoma (4 studies, n = 3326),[58-61] cirrhosis (1 study, n = 233),[60] and composite clinical outcomes (6 studies, n = 1311),[53-57,59] although some estimates were not statistically significant. The composite clinical outcomes consisted of various combinations of mortality, hepatocellular carcinoma, hepatic decompensation and associated complications, and liver transplant.

Discussion

The findings in this evidence report are summarized in the **Table**. The USPSTF previously determined that HBV screening tests are highly accurate.[83] Studies in this review found that screening strategies that focused on patients with a variety of risk factors (immigration from high-prevalence country, other demographic risk factors, and/or behavioral risk factors) would identify nearly all cases of HBV infection while screening about two-thirds of the population.[62-64] The number needed to screen to identify 1 HBV infection ranged from 32 to 148. A more focused strategy of only screening immigrants from high-prevalence countries would be more efficient (number needed to screen, 16-71), but missed about two-thirds of infected persons in 1 study[64] conducted in primary care practices. The studies applied screening strategies retrospectively and were conducted in Europe, including some studies of high–HBV prevalence populations, which might limit applicability to primary care settings in the US.

As in the previous USPSTF review, randomized trials found antiviral therapy to be associated with increased likelihood of achieving various intermediate outcomes vs placebo or no treatment for achieving various intermediate outcomes. The numbers needed to treat to achieve 1 intermediate outcome ranged from 2.6 for HBV DNA suppression to 17 for HBeAg seroconversion. Results were generally consistent when analyses were stratified by individual drug, although some estimates were imprecise and not statistically significant. Although this update focused on US Food and Drug Administration–approved antiviral therapies, almost all of the placebo-controlled trials evaluated therapies classified as nonpreferred in current guidelines.[14] However, the effectiveness of preferred therapies is supported by head-to-head trials, which found entecavir, TDF, and pegylated interferon associated with greater or similar likelihood of achieving various intermediate outcomes vs nonpreferred therapies. Effects of antiviral therapies were generally consistent when trials were stratified according to HBeAg status or whether some patients with cirrhosis were included.

As in the prior USPSTF review, antiviral therapy was not associated with an increased risk of serious adverse events or experiencing any adverse event vs placebo. Interferon therapy was associated with an increased risk of withdrawal due to adverse events, and pegylated interferon alfa-2a was associated with increased risk of serious adverse events and withdrawal due to adverse events vs lamivudine, consistent with known adverse effects of interferon-based therapies. Data on risks of kidney and bone adverse events were limited but did not indicate increased risk; this included the antiviral TDF, which has been associated with bone and kidney toxicities in some conditions.[84] In general, adverse events associated with antiviral therapy, including interferon-based therapies, are self-limited and resolve following discontinuation of the drug.

Data from randomized trials on effects of antiviral therapy vs placebo or no therapy on clinical outcomes remains sparse. The trials were not designed to assess these outcomes because of small sample sizes and insufficient duration of follow-up. Although antiviral therapy was associated with decreased risk of mortality, the estimate was based on 3 trials of nonpegylated interferon with a total of 8 deaths. Antiviral therapy might be associated with decreased risk of cirrhosis and hepatocellular carcinoma, but estimates were imprecise and not statistically significant. Cohort studies found a consistent association between receipt of antiviral therapy and decreased risk of hepatocellular carcinoma. Most of the cohort studies were conducted in Asia, although studies conducted in the US reported findings consistent with those from the Asian studies. No trial evaluated effects of antiviral therapy on quality of life, risk of HBV transmission, or extrahepatic manifestations of HBV infection.

As in the prior USPSTF review, observational studies generally found an association between achieving an intermediate outcome and reduced risk of mortality, hepatocellular carcinoma, cirrhosis, or a composite clinical outcome. However, results were not statistically significant in all studies. In addition, differences across studies in the intermediate and clinical outcomes evaluated, variability in patient populations (eg, with regard to HBeAg status, ALT levels, or HBV DNA levels) and methodological limitations precluded strong conclusions.

Research is needed to clarify effects of screening and subsequent interventions on clinical outcomes and to identify optimal screening strategies. In addition, no study meeting inclusion criteria evaluated adolescents and the trials focused on treatment of patients with immune active HBV infection, with very little data for immune tolerant phase infection. No trial evaluated the preferred antiviral TAF, which was FDA-approved for chronic HBV infection in 2016 and may have fewer kidney and bone toxicities compared with TDF.[85]

Limitations

This review has several limitations. First, evidence from placebo-controlled trials of preferred antiviral therapy was limited; therefore, head-to-head trials of preferred vs nonpreferred antiviral

Table. Summary of Evidence

Studies observations (No.); study designs	Summary of findings	Consistency and precision	Other limitations	EPC assessment of strength of evidence	Applicability
KQ1: What are the benefits of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?					
No studies	No evidence	NA	No studies	No evidence	NA
KQ2: What are the harms of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults (eg, labeling or anxiety)?					
No studies	No evidence	NA	No studies	No evidence	NA
KQ3: What is the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV screening strategies (eg, universal vs targeted screening or screening strategies based on alternative risk factors)?					
Prior report: 1 retrospective study[62] (n = 6194) Update: 2 retrospective studies[63,64] (n = 24 846)	Three European studies found that screening strategies that targeted persons with a variety of risk factors (immigration from areas with high HBV infection prevalence, other demographic risk factors, and behavioral risk factors) would identify nearly all cases of HBV infection, while screening about two-thirds of the population; numbers needed to screen to identify 1 HBV infection ranged from 32 to 148 Screening only immigrants from high-prevalence (≥2%) countries was more efficient (number needed to screen, 19-71) and identified 85% to 99% of patients with HBV infection in higher-prevalence clinical settings but missed about two-thirds of HBV infections in a study conducted in primary care practices	Consistent; precise	Studies applied screening strategies retrospectively	Moderate	Some studies included patients in high-prevalence settings; all studies were conducted in Europe
KQ4: How effective is antiviral treatment in improving intermediate outcomes among nonpregnant adolescents and adults with chronic HBV infection, including virologic or histologic improvement, clearance of HBeAg (as indicated by loss of HBeAg or acquisition of the anti-HBe), or clearance of HBsAg (as indicated by loss of HBsAg or acquisition of anti-HBs)?					
Treatment vs placebo/no treatment: Prior report: 14 RCTs[16-29] (n = 2148) Update: 4 RCTs[30-33] (n = 824) Preferred vs nonpreferred: Prior report: 7 RCTs[34-39] (n = 2793) Update: 5 RCTs[40-44] (n = 1334)	Antiviral treatment vs placebo or no treatment: HBeAg loss: 6 trials, n = 1121; RR, 1.91 (95% CI, 1.46-2.81); I^2 = 15% HBeAg seroconversion: 4 trials, n = 1104; RR, 2.11 (95% CI, 1.30-3.55); I^2 = 0% HBsAg loss: 3 trials, n = 714; RR, 4.63 (95% CI, 1.10-19.55); I^2 = 70% Virologic suppression: 13 trials, n = 2522; RR, 4.39 (95% CI, 2.61-7.39); I^2 = 86% ALT normalization: 11 trials, n = 2044; RR, 2.62 (95% CI, 2.22-3.10); I^2 = 0% Histologic improvement: 6 trials, n = 1057; RR, 2.00 (95% CI, 1.63-2.41); I^2 = 0% Entecavir was associated with increased likelihood of achieving intermediate outcomes vs lamivudine (6 trials) and pegylated interferon was associated with increased likelihood of intermediate outcomes vs lamivudine (1 trial); TDF was associated with increased likelihood of virologic suppression vs adefovir (3 trials)	Consistency: high for antiviral therapies and for entecavir vs lamivudine and TDF vs adefovir; consistency could not be assessed for pegylated interferon vs lamivudine (1 trial) Precision: high for antiviral therapy vs placebo and entecavir vs lamivudine; some imprecision for TDF vs adefovir and pegylated interferon vs lamivudine	Study duration and patient characteristics varied widely; few good-quality studies; almost all placebo-controlled trials evaluated nonpreferred antiviral therapies; no trials of tenofovir alafenamide	Moderate for antiviral therapy vs placebo, entecavir vs lamivudine, and pegylated interferon vs adefovir; low for TDF vs adefovir	About one-half of the studies were conducted outside of the US or other low-prevalence settings; about one-third enrolled HBeAg-negative patients; no trial enrolled adolescents; inclusion restricted to studies in which <20% of patients had cirrhosis at baseline or were treatment-experienced
KQ5: How effective is antiviral treatment in improving health outcomes among nonpregnant adolescents and adults with chronic HBV infection?					

(continued)

Table. Summary of Evidence (continued)

Studies observations (No.); study designs	Summary of findings	Consistency and precision	Other limitations	EPC assessment of strength of evidence	Applicability
Treatment vs placebo/no treatment: Prior report: 6 trials[17,18,20,22,23,25] (n = 866) Update: 1 RCT[31] (n = 176) and 7 cohort studies[45-51] (n = ≈ 50 912; 3 studies likely examined overlapping populations) Preferred vs nonpreferred: Prior report: 6 trials[34,35,37-39] (n = 2608) Update: 3 trials[40,41,43] (n = 1159)	Antiviral therapy vs placebo or no treatment: Incident cirrhosis: 2 trials; RR, 0.72 (95% CI, 0.29-1.77); I^2 = 0% Hepatocellular carcinoma: 4 trials; RR, 0.60 (95% CI, 0.16-2.33); I^2 = 20% Mortality: 3 trials; RR, 0.15 (95% CI, 0.03-0.69; I^2 = 0% Seven cohort studies with longer-term (2.7 to 8.9 y) follow-up found antiviral therapy consistently associated with decreased risk of hepatocellular carcinoma vs no antiviral therapy (adjusted HRs ranged from 0.24 to 0.64) Data from head-to-head trials of preferred vs nonpreferred antiviral therapy were insufficient to evaluate effects on clinical outcomes	Consistent Some imprecision (RCTs)	RCTs were not designed to assess clinical outcomes and reported few events; most studies rated fair-quality, heterogeneity in patient populations and settings; observational studies for long-term clinical outcomes susceptible to residual confounding	Low	About one-half of the studies were conducted outside of the US or other low-prevalence settings; about one-third of studies enrolled HBeAg-negative patients; inclusion restricted to studies in which <20% of patients had cirrhosis at baseline or were treatment-experienced; most studies evaluated nonpreferred outcomes
KQ6: What are the harms associated with antiviral treatment in nonpregnant adolescents and adults with chronic HBV infection?					
Treatment vs placebo/no treatment: Prior report: 10 RCTs[17-22,24,27-29] (n = 1851) Update: 2 RCTs[30,31] (n = 255) and 1 cohort study[52] (n = 1224) Preferred vs nonpreferred: Prior report: 7 RCTs[34-39] (n = 2774) Update: 5 RCTs[40-44] (n = 1334)	Antiviral therapy vs placebo or no therapy: Serious adverse events: 4 trials, n = 802; RR, 0.92 (95% CI, 0.45-1.85); I^2 = 0%[17,19,20,27] Withdrawal due to adverse events: 3 trials, n = 496; RR, 4.44 (95% CI, 0.95-20.77); I^2 = 0%[22,24,27] Any adverse event: 5 trials, n = 1290; RR, 1.01 (95% CI, 0.90-1.11); I^2 = 0% Nausea: 3 trials; RR, 0.80 (95% CI, 0.48-2.10); I^2 = 0% Diarrhea: 4 trials; RR, 1.50 (95% CI, 0.87-2.46); I^2 = 0% Kidney adverse events: 3 trials; RR, 1.27 (95% CI, 0.31-3.55); I^2 = 0%[17,18,20] One cohort study found no association between TDF or entecavir vs no antiviral therapy and risk of osteopenia or osteoporosis In head-to-head trials, pegylated interferon was associated with increased risk of any adverse event (1 trial, n = 543; RR, 1.58 (95% CI, 1.41-1.78) vs lamivudine and is probably associated with increased risk of withdrawal due to adverse events (1 trial, n = 543; RR, 4.01 (95% CI, 0.86-18.73)[37] TDF was associated with increased risk of nausea vs adefovir (RR, 3.36 [95% CI, 0.45-7.81])	Consistency: high Some imprecision present	See KQ4 In addition, no study evaluated tenofovir alafenamide, which may be associated with fewer kidney adverse effects	Moderate	See KQ4
KQ7: What is the association between improvements in intermediate outcomes as a result of antiviral treatment of chronic HBV infection and reduction in risk of HBV-related adverse health outcomes?					
Prior report: 6 observational studies[53-58] (n = 1385) Update: 3 observational studies[59-61] (n = 2508)	Nine cohort studies found consistent associations between achieving or not achieving various intermediate outcomes (virologic remission, biochemical remission, histologic improvement, HBeAg loss, or a composite intermediate outcome) and decreased adverse health outcomes (death, hepatocellular carcinoma, cirrhosis, or a composite clinical outcome) However, variability in patient populations, the intermediate and clinical outcomes evaluated, and presence of methodological limitations make it difficult to draw strong conclusions In some studies, estimates were imprecise and associations were not statistically significant	Consistency: high Some imprecision in individual study estimates	High variability in patient characteristics and outcomes evaluated; all studies were rated fair-quality; all studies were observational and susceptible to residual confounding	Moderate	Inclusion restricted to studies that adjusted for baseline fibrosis stage, and fewer than 30% of patients had cirrhosis at baseline; most studies conducted in Asia (although US studies reported consistent findings); few studies focused on use of current preferred antiviral therapies

Abbreviations: ALT, alanine aminotransferase; anti-HBe, antibody to HBeAg; anti-HBs, antibody to HBsAg; EPC, evidence-based practice center; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HR, hazard ratio; KQ, key question; NA, not applicable; RCT, randomized clinical trial; RR, relative risk; TDF, tenofovir disoproxil fumarate.

therapy were also included. Second, studies included in the prior USPSTF review were excluded if they were rated poor-quality or exceeded predefined thresholds for the proportion of patients with baseline cirrhosis or prior antiviral therapy, reducing the available evidence base. However, these exclusions strengthened the quality and applicability of the reviewed evidence to screening populations. Third, observational studies were included on the effects of antiviral therapy on long-term clinical outcomes and the association between achieving an intermediate outcome after antiviral therapy and clinical outcomes.[86] To reduce potential confounding, inclusion was restricted to studies that controlled for potential confounders. Fourth, studies conducted in countries where the prevalence, characteristics, and natural history of HBV infection may differ from those in the US were included. However, findings were similar for studies conducted in settings with low or high HBV prevalence and for studies conducted in Asia and the US. Fifth, the review did not include a search for studies published only as abstracts and could not formally assess for publication bias with graphical or statistical methods because of small numbers of studies.[15]

Conclusions

There was no direct evidence for the clinical benefits and harms of HBV screening vs no screening. Antiviral therapy for chronic HBV infection was associated with improved intermediate outcomes and may improve clinical outcomes.

ARTICLE INFORMATION

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Author Contributions: Dr Chou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Chou, Jou.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Chou, Bougatsos, Selph, Grusing.
Critical revision of the manuscript for important intellectual content: Chou, Blazina, Holmes, Jou.
Statistical analysis: Chou, Blazina.
Obtained funding: Chou.
Administrative, technical, or material support: Blazina, Bougatsos, Grusing.
Supervision: Chou, Bougatsos, Jou.

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Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to JAMA.

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