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Antiviral Therapy for Chronic Hepatitis B Viral Infection in Adults: A Systematic Review and Meta-Analysis

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Chronic hepatitis B viral (HBV) infection remains a significant global health problem. Evidence-based guidelines are needed to help providers determine when treatment should be initiated, which medication is most appropriate, and when treatment can safely be stopped. The American Association for the Study of Liver Diseases HBV guideline methodology and writing committees developed a protocol *a priori* for this systematic review. We searched multiple databases for randomized controlled trials and controlled observational studies that enrolled adults ≥18 years old diagnosed with chronic HBV infection who received antiviral therapy. Data extraction was done by pairs of independent reviewers. We included 73 studies, of which 59 (15 randomized controlled trials and 44 observational studies) reported clinical outcomes. Moderate-quality evidence supported the effectiveness of antiviral therapy in patients with immune active chronic HBV infection in reducing the risk of cirrhosis, decompensated liver disease, and hepatocellular carcinoma. In immune tolerant patients, moderate-quality evidence supports improved intermediate outcomes with antiviral therapy. Only very low-quality evidence informed the questions about discontinuing versus continuing antiviral therapy in hepatitis B e antigen-positive patients who seroconverted from hepatitis B e antigen to hepatitis B e antibody and about the safety of entecavir versus tenofovir. Noncomparative and indirect evidence was available for questions about stopping versus continuing antiviral therapy in hepatitis B e antigen-negative patients, monotherapy versus adding a second agent in patients with persistent viremia during treatment, and the effectiveness of antivirals in compensated cirrhosis with low-level viremia. *Conclusion:* Most of the current literature focuses on the immune active phases of chronic HBV infection; decision-making in other commonly encountered and challenging clinical settings depends on indirect evidence. (HEPATOLOGY 2015; 00:000–000)

Chronic hepatitis B viral (HBV) infection remains a significant global health problem. Despite the availability of HBV vaccines for three decades, the global prevalence of chronic HBV infection has only declined slightly, from 4.2% in 1990 to 3.7% in 2005.[1] Worldwide, however, the absolute number of persons chronically infected has increased from 223 million in 1990 to 240 million in 2005. In the United States, based on 1999-2006 data from the National Health and Nutrition Examination Survey, the prevalence of chronic HBV infection was estimated to be 0.27%.[2] However, the National Health and

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; RCT, randomized controlled trial; RR, risk ratio.

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Nutrition Examination Survey undersampled high-prevalence groups, so when accounting for immigration from endemic countries, as many as 2.2 million US residents (instead of 730,000) may have chronic HBV infection.[3]

The natural course of chronic HBV infection consists of four characteristic phases: immune tolerant, hepatitis B e antigen (HBeAg)-positive immune active, inactive, and HBeAg-negative immune active phases.[4] The immune tolerant phase is characterized by the presence of HBeAg, normal alanine aminotransferase (ALT) levels, and high levels of HBV DNA, usually well over 20,000 IU/mL. The immune active phases, also called HBeAg-positive or HBeAg-negative chronic hepatitis, are characterized by intermittently or persistently elevated ALT with active hepatic inflammation and HBV DNA generally above 2000 IU/mL. The inactive phase is characterized by absence of HBeAg and presence of hepatitis B e antibody, normal ALT in the absence of other concomitant liver diseases, and undetectable or low levels of HBV DNA, generally below 2000 IU/mL. Although not all patients go through each phase and immune responses to HBV during each phase have not been fully characterized, this classification schema provides a useful framework when developing a management approach for chronic HBV infection.

Currently, seven medications are approved for treatment of chronic HBV infection: two formulations of interferon (IFN), standard and pegylated, and five nucleos(t)ide analogues: lamivudine, telbivudine, entecavir, adefovir, and tenofovir. These medications suppress HBV replication and ameliorate hepatic inflammation but do not eradicate HBV. While IFN is given for a finite duration, nucleos(t)ide analogues are administered for many years and often for life. Long durations of treatment are associated with risks of adverse reactions, drug resistance, nonadherence, and increased cost. Therefore, there is a need to have evidence-based guidelines to help providers determine when treatment should be initiated, which medication is most appropriate, and when treatment can safely be stopped.

Materials and Methods

The American Association for the Study of Liver Diseases (AASLD) HBV guideline methodology and writing committees developed a protocol *a priori* for this systematic review. The reporting of this review follows the standards set in the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.[5] The committee identified and developed a protocol for seven key Population Intervention Comparison Outcome questions (Supporting Table S1). The outcomes of interest were clinical outcomes (cirrhosis, liver decompensation, hepatocellular carcinoma [HCC], and all-cause mortality); however, when such outcome data were unavailable, surrogate (intermediate) outcomes were sought, specifically durability of HBeAg seroconversion, loss of hepatitis B surface (HBsAg), long-term suppression of HBV DNA, and normalization of ALT.

Eligibility Criteria. We included randomized controlled trials (RCTs) and controlled observational studies that enrolled adults $\geq$18 years old diagnosed with chronic HBV infection who received antiviral therapy. We excluded studies that included patients with acute HBV infection; patients who were pregnant; patients coinfected with hepatitis C or D or human immunodeficiency virus; patients receiving corticosteroids, chemotherapy, or immunosuppressive therapy; transplant recipients; and hemodialysis patients, as well as studies without control or comparison groups. Supporting Table S1 summarizes the inclusion and exclusion criteria for each key question.

Search Strategy. An experienced Mayo Clinic librarian conducted a comprehensive search of Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus from early 1988 to September 16, 2014. Controlled vocabulary supplemented with keywords was used to search for comparative studies of antivirals for chronic hepatitis B. No language restrictions were used. Members from the AASLD HBV guideline methodology and writing committees helped identify

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additional studies. Supporting Table S2 specifies the detailed search strategy.

Study Selections. Two reviewers independently screened titles and abstracts for potential eligibility using an online reference management system (DistillerSR; Evidence Partners, Inc.). Full texts of the included abstracts were retrieved and screened in duplicate. Disagreements were resolved by seeking consensus or arbitration by a third reviewer. Interreviewer agreement (kappa) was calculated during each screening level to assess agreement between reviewers. For Population Intervention Comparison Outcome questions where no studies meeting the predefined criteria were found, the AASLD HBV guideline methodology committee performed manual searches for uncontrolled observational studies. Data from these studies were summarized narratively and in general consistent with low-quality evidence.

Data Extraction. Data extraction was done using a standardized, piloted form. We extracted data on study characteristics, patient characteristics, intervention details, and outcomes of interest.

Methodological Quality and Risk of Bias Assessment. We used the Cochrane Risk of Bias assessment tool and modified Newcastle-Ottawa Scale to assess the risk of bias in RCTs and observational studies, respectively. Quality of evidence (i.e., certainty in the estimates) was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation approach. Criteria used to evaluate quality of evidence were risk of bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity), and publication bias.[6]

Statistical Analysis. For dichotomized outcomes, we calculated risk ratios (RRs) and 95% confidence intervals (95% CI) using binomial distribution. We then pooled the log-transformed RRs using the DerSimonian and Laird random-effects models and estimated heterogeneity using the Mantel-Haenszel model. To measure the overall heterogeneity across the included studies, we calculated the I^2 statistic, where $I^2 > 50\%$ suggests a high degree of heterogeneity. All statistical analyses were conducted using STATA, version 13 (StataCorp LP, College Station, TX). To explore heterogeneity, we conducted subgroup analysis for studies enrolling patients with more advanced liver disease; we performed stratified analysis for the following groups: compensated cirrhosis, decompensated cirrhosis, acute on chronic liver failure, and severe acute exacerbations of chronic hepatitis B. We explored the impact of publication bias using the Egger regression asymmetry test and constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low.[7]

Results

A total of 73 studies were included. Figure 1 describes the details of the selection process. The average weighted kappa for study selection was 0.78. Controlled studies that reported the outcomes of interest were only available for questions 1, 2, 3, and 5. Uncontrolled studies that are relevant to questions 4, 6, and 7 are summarized in Supporting Information. Supporting Table S4 provides the Grading of Recommendations Assessment, Development, and Evaluation summary of the evidence.

Question 1: Effectiveness of Antiviral Therapy in Patients With Immune Active Chronic HBV Infection

We included 59 studies (15 RCTs and 44 observational studies) that evaluated antiviral therapy and reported clinical outcomes. Forty-two studies compared antiviral therapy versus control, and 18 studies compared one antiviral agent versus another.

Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic Hepatitis B Infection. Among 42 studies comparing antiviral therapy versus control in 62,731 patients, 16 studies[8-23] compared IFN versus no treatment, 16 studies[24-39] compared lamivudine versus no treatment, seven studies[28,40-45] compared entecavir versus no treatment, one study each compared telbivudine[44] and tenofovir[46] versus placebo, and three studies[47-49] compared a variety of oral antiviral versus no treatment. Eleven studies enrolled only patients with compensated cirrhosis, five studies enrolled only patients with acute on chronic liver failure, two studies enrolled only patients with decompensated liver disease, three studies enrolled only patients with severe acute exacerbations of chronic hepatitis B, and 21 studies enrolled patients with stable chronic hepatitis B. Study characteristics are illustrated in Table 1. Risk of bias assessment for RCTs was low to moderate as two of the included RCTs reported the randomization method, two reported use of allocation concealment, and six reported the blinding method used. Most of the observational studies were at high risk of bias due to lack of clear description of the selection process of the population and inadequate exposure and outcome ascertainment. Risk of bias is described in Tables 2 and 3.

In seven RCTs[8,23-25,29,33,46] involving 3463 subjects with a mean follow-up of 28 months, antiviral therapy versus control (Fig. 2) significantly decreased the overall

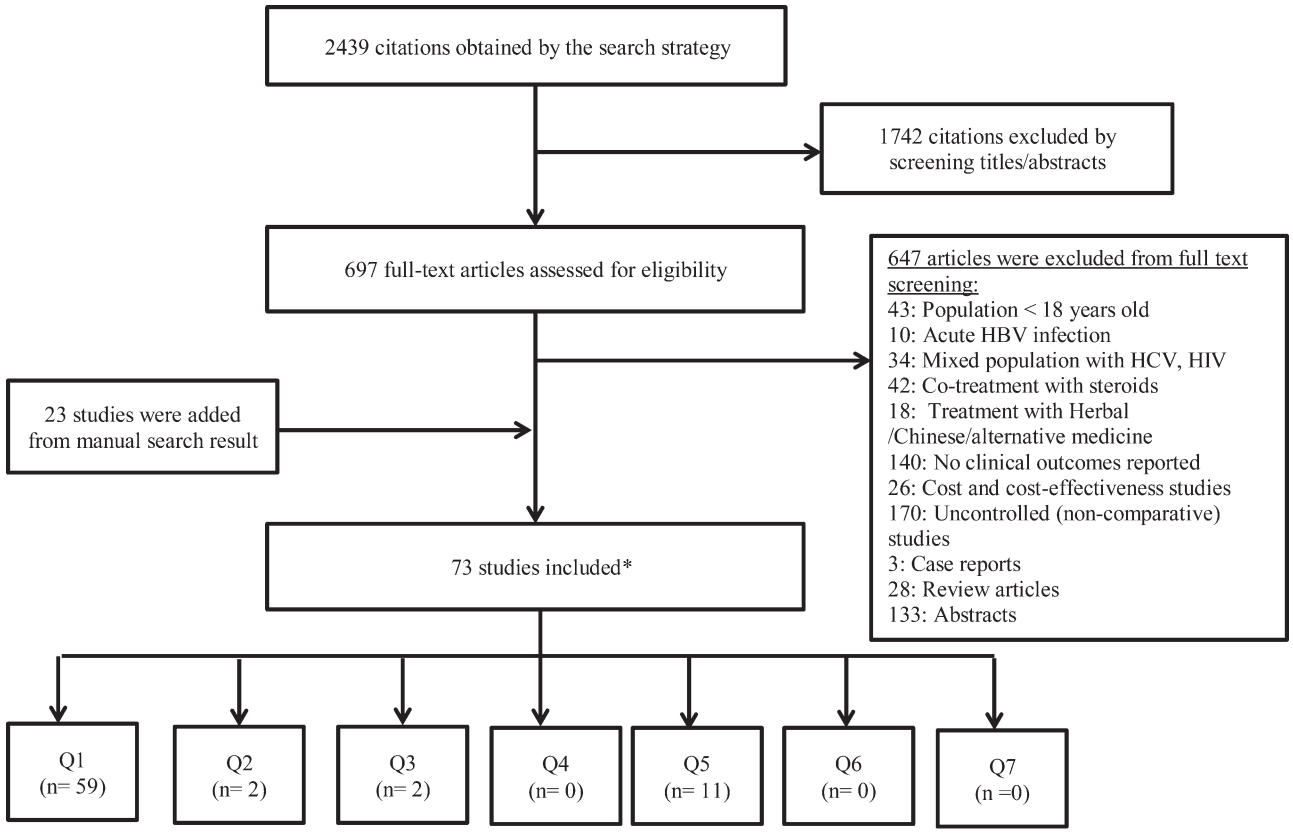

Fig. 1. Flow diagram showing selection process for studies to include. Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

risk of decompensated liver disease (one RCT, RR = 0.4, 95% CI 0.3-0.7) and cirrhosis (one RCT, RR = 0.4, 95% CI 0.2-0.8). No significant differences were found in all-cause mortality (four RCTs, RR = 0.5, 95% CI 0.2-1.3, I^2 = 72.9%) or HCC incidence (three RCTs, RR = 0.6, 95% CI 0.3-1.1, I^2 = 0%). The quality of the evidence was low to moderate. One RCT[29] examined adverse events including death and decompensation as outcomes, but no events were observed in either the intervention or the control group.

In 35 observational studies involving 59,201 patients with a mean follow-up of 60 months, meta-analysis showed that antiviral therapy versus control decreased the risk of HCC (23 studies, RR = 0.5, 95% CI 0.4-0.7, I^2 = 87.4%), all-cause mortality (23 studies, RR = 0.6, 95% CI 0.5-0.8, I^2 = 92.3%), and cirrhosis (four studies, RR = 0.6, 95% CI 0.4-0.8, I^2 = 0%) but did not significantly reduce the risk of decompensated liver disease (six studies, RR = 0.7, 95% CI 0.3-1.9, I^2 = 96.5%) when compared to untreated controls (Figs. 3–5). The quality of this evidence overall was low; however, these studies included large numbers of patients with long duration of follow-up, yielding precise and narrow 95% CIs.

Effectiveness of antiviral therapy compared to control in the subgroup with stable chronic hepatitis B. Of the 21 studies that enrolled patients with stable chronic hepatitis B, 0%-91% of the 54,719 patients included had compensated cirrhosis. Reduction in risk of decompensated cirrhosis was shown in only one RCT and reduction in HCC in 11 observational studies. No studies demonstrated reduction in all-cause mortality.

Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic HBV Infection and Compensated Cirrhosis. In one RCT[25] enrolling 222 patients with cirrhosis and a follow-up of 53 months, lamivudine versus control reduced all-cause mortality (RR = 0.1, 95% CI 0.1-0.3, moderate-quality evidence).

In 10 observational studies (Fig. 3) involving patients with compensated cirrhosis (mean follow-up 60 months), antiviral therapy decreased the risk of HCC (10 studies, RR = 0.6, 95% CI 0.4-0.8, I^2 = 36.3%), decompensated liver disease (two studies, RR = 0.5, 95% CI 0.2-0.9, I^2 = 67.2%), and all-cause mortality (three studies, RR = 0.5, 95% CI 0.4-0.6, I^2 = 0%).

Table 1. Characteristics of the Included Studies

Authors, Year	Country	Patients (N)	Interventions	Age (Years)	HBeAg Positive (N)	Baseline ALT (U/L)	Baseline HBV DNA (log10 IU/mL)*	Follow-up duration (months)	Baseline cirrhosis (%)	Study design
Question 1: Effectiveness of antiviral therapy in patients with immune active chronic HBV infection (antiviral versus control)										
Anderson et al., 1987[8]	England	14	IFN-α	36	14	77% elevated ALT	NR	12	20	RCT
		16	Control	35	16	77% elevated ALT	NR	12	20	
IIHCSG, 1998[9]	Italy and Argentina	49	IFN-α	54	NR	NR	NR	69.6	100	Case-control
		97	Control	54	NR	NR	NR	82.2	100	
Lin et al., 2007[10]	Taiwan	233	IFN-α	32 ± 7	233	175 ± 112	40% >7.7	81.6 ± 38.4	8.1	Cohort
		233	Control	31 ± 8	233	187 ± 109	40% >7.7	73.2 ± 36	10.7	
Truong et al., 2005[11]	Japan	27	IFN-α	33.2 ± 10.4	17	238.6 ± 250.1	NR	84 ± 30	3	Case-control
		35	Control	36.6 ± 10.9	20	142.3 ± 152.1	NR	74.4 ± 34.8	14.3	
Tangkijvanich et al., 2001[12]	Thailand	67	IFN-α	36.9 ± 10.5	67	180.7 ± 137.9	NR	59.4 ± 30.9	17.9	Case-control
		72	Control	39.9 ± 13.7	72	93.3 ± 114.4	NR	60.1 ± 35.3	22.2	
Papatheodoridis et al., 2001[13]	Greece	209	IFN-α	46.8 ± 11.3	0	112 (13-1905)	5.4	72 ± 32.4	27.3	Cohort
		195	Control	48.8 ± 13.7	0	68 (20-1335)	5.4	73.2 ± 46.8	34.9	
Niederau et al., 1996[14]	Germany	103	IFN-α	NR	103	NR	NR	50.0 ± 19.8	27	Cohort
		53	Control	NR	53	NR	NR	38.5 ± 18.2	16	
Lin et al., 2004[15]	Taiwan	109	IFN-α	31 ± 9	NR	132 ± 86	NR	84.5	90	Cohort
		34	Control	32 ± 6	NR	256 ± 232	NR	92	85	
Benvegnu et al., 1998[16]	Italy	13	IFN-α	57	NR	NR	NR	72	100	Cohort
		24	Control	60	NR	NR	NR	72	100	
Tong et al., 2006[17]	USA	22	IFN-α	48	49%	NR	NR	84	35	Cohort
		378	Control	48	NR	NR	NR	84	35	
Di Marco et al., 1999[18]	Italy	109	IFN-α	33	NR	NR	NR	93.6	29	Cohort
		193	Control	35	NR	NR	NR	93.6	29	
Brunetto et al., 2002[19]	Italy	103	IFN-α	40	0	NR	NR	72	38	Cohort
		61	Control	40	0	NR	NR	72	38	
Mahmood et al., 2005[20]	Japan	23	IFN-α	49	NR	NR	NR	84	100	Case-control
		68	Control	49	NR	NR	NR	84	100	
Ikeda et al., 1998[21]	Japan	94	IFN-α	41	NR	NR	NR	81.6	100	Case-control
		219	Control	44	NR	NR	NR	84	100	
Fattovich et al., 1997[22]	Italy	40	IFN-α	47 ± 1.8	40	5.3 (0.61 × ULN)	NR	74.4	100	Cohort
		50	Control	45 ± 2.2	50	5.3 (0.61 × ULN)	NR	74.4	100	
Krogsgaard et al., 1998[23]	Europe	210	IFN-α	36	210	100% elevated ALT	NR	15.6	19	RCT
		98	Control	36	98		NR	15.6	19	
Chan et al., 2007[24]	China	89	Lamivudine	39 ± 11	6	2.1 ± 1.7 (×ULN)	5 ± 0.0.9	120	31	RCT
		47	Placebo	39 ± 11	4	2.6 ± 2.3 (×ULN)	4.9 ± 0.8	120	21	
Eun et al., 2007[25]	Korea	111	Lamivudine	NR	NR	NR	NR	52.8	100	RCT
		111	Placebo	NR	NR	NR	NR	52.8	100	
Tong et al., 2009[26]	USA	27	Lamivudine	40	NR	NR	NR	63.6	100	Cohort

Table 1. *Continued*

Authors, Year	Country	Patients (N)	Interventions	Age (Years)	HBeAg Positive (N)	Baseline ALT (U/L)	Baseline HBV DNA (log10 IU/mL)*	Follow-up duration (months)	Baseline cirrhosis (%)	Study design
		101	Control	46	NR	NR	NR	63.6	100	
Das et al., 2010[27]	India	151	Lamivudine and adefovir	42	45%	NR	NR	48	100	Case-control
		102	Control	46	NR	NR	NR	45.6	100	
Cui et al., 2010[28]	China	33	Entecavir	38.4 ± 10.8	10	364 (47-2861)	5.2 ± 0.8	0.2-41.5	NR	Cohort
		34	Lamivudine	39.4 ± 10.6	13	226.5 (22-2314)	5.1 ± 0.6	0.2-41.5	NR	
		37	Control	41.0 ± 11.5	11	287 (17-2535)	5 ± 0.9	0.2-41.5	NR	
Dienstag et al., 1999[29]	USA	66	Lamivudine	40 (18-73)	66	125 (46-401)	6.7 (4.6-7.9)	12	6	RCT
		71	Placebo	38 (20-67)	71	135 (33-592)	6.5 (4.6-7.6)	12	14	
Chan et al., 2002[30]	Hong Kong	28	Lamivudine	42.7 ± 13.5	16	1416.6 ± 577.7	NR	12	NR	Cohort
		18	Control	47.2 ± 14	2	1659.5 ± 1928.4	NR	12	NR	
Lok et al., 2003[31]	Multinational	998	Lamivudine	32.0 (15-73)	998	1.6 (0.2-23.4) (/ULN)	6.7 (4.7-8.1)	48	10	Cohort
		200	Placebo	34.5 (15-67)	200	2.3 (0.4-4.14) (/ULN)	6.6 (4.7-7.8)	12	13	
Manolakopoulos et al., 2004[32]	UK	30	Lamivudine	63.1 ± 1.7	30	77 (26-280)	4.9 (3.2-7)	18 (3-36)	100	Case-control
		30	Control	62.8 ± 1.4	30	80 (30-199)	NR	22 (2-55)	100	
Liaw et al., 2004[33]	Multinational	436	Lamivudine	43 (17-74)	252	70 (14-959)	6.4 (<5.1-10.3)	32 (0-42)	31	RCT
		215	Placebo	44 (22-71)	124	68 (7-821)	6.6 (<5.1-8.9)	32 (0-42)	39	
Matsumoto et al., 2005[34]	Japan	657	Lamivudine	40.9 ± 11.0	355	183.4 ± 211.1	NR	58.8 ± 52.8	14.9	Case-control
		2138	Control	37.3 ± 12.4	1272	163.5 ± 234.3	NR	74.4 ± 66	15.5	
Ma et al., 2007[35]	China	51	Lamivudine	NR	12	NR	NR	35	100	Cohort
		166	Control	NR	39	NR	NR	35	100	
Yuen et al., 2007[36]	Hong Kong	142	Lamivudine	33.9 (20.2-54.4)	142	125 (47-514)	8 (3.5-11)	89.9 (26.5-128.3)	0	Cohort
		124	Control	33.4 (20.8-59)	124	125 (47-514)	6.1 (0.8-8.9)	107.8 (30.9-127.3)	0	
Sun et al., 2009[37]	China	130	Lamivudine	44.3 ± 3.5	90	474.1 ± 83.4	>4.3	3	10	Cohort
		130	Control	45.2 ± 3.6	95	492.3 ± 82.6	>4.3	3	10	
Kim et al., 2012[38]	Korea	240	Lamivudine	49.6 ± 10.9	145	159 ± 265.4	6.2 ± 0.6	46.4 (1-124)	100	Cohort
		481	Control	46.4 ± 10.3	280	90.2 ± 136.3	NR	51.4 (2-94)	100	
Eun et al., 2010[39]	Korea	872	Lamivudine	40.1 ± 12.2	694	161 ± 183.8	7.1 ± 0.4	56.4 ± 28.8	47.4	Cohort
		699	Control	35.5 ± 12.9	637	141.3 ± 199.1	6.7 ± 0.3	68.4 ± 50.4	37.2	
Wong et al., 2013[40]	Hong Kong	1466	Entecavir	51 ± 12	443	145 ± 319	5	36 ± 13	100	Cohort
		424	Control	41 ± 13	155	84 ± 113	5	114 ± 31	100	
Hosaka et al., 2013[41]	Japan	472	Entecavir	42 ± 12.4	219	70 (42-163)	6 (4.6-7.3)	38.4 (25.2-51.6)	25	Cohort
		1143	Control	39 ± 13.1	398	33 (20-68)	5.1 (3.3-6.8)	114 (52.8-193.2)	17	
Lin et al., 2013[42]	China	53	Entecavir	38 (32-49)	16	360 (181-704)	5.8 ± 0.8	12	32.1	Cohort
		55	Control	40 (34-47)	20	467 (107-1192)	5.3 ± 0.7	12	27.3	
Xiao et al., 2009[43]	China	39	Entecavir	NR	NR	NR	NR	NR	NR	Cohort
		39	Control	NR	NR	NR	NR	NR	NR	

Table 1. *Continued*

Authors, Year	Country	Patients (N)	Interventions	Age (Years)	HBeAg Positive (N)	Baseline ALT (U/L)	Baseline HBV DNA (log10 IU/mL)*	Follow-up duration (months)	Baseline cirrhosis (%)	Study design
Xu et al., 2009[44]	China	133	Telbivudine, entecavir, or lamivudine	40.6 ± 11.4	NR	534 ± 712.8	4.3	NR	NR	Cohort
		215	Control	40.6 ± 10.5	NR	526.1 ± 688.5	3.8	NR	NR	
Chen et al., 2009[45]	China	55	Entecavir	43.6 ± 10.9	14	357 ± 405.2	5 ± 0.65	3	NR	Cohort
		74	Control	40.3 ± 11. 7	25	451.9 ± 464.6	4.4 ± 0.1.1	3	NR	
Garg et al., 2011[46]	India	14	Tenofovir	47.5 (16-62)	13	226 (188-1185)	5.2	3	NR	RCT
		13	Placebo	45 (16-67)	12	206 (186-2000)	5.5	3	NR	
Wu et al., 2014[47]	Taiwan	21595	Variety of oral antivirals	43.5 ± 13.4	26	179	5.3 ± 0.3	40 (16.8-66)	13.2	Cohort
		21595	Control	43.6 ± 13.6	12	185	5.3 ± 1.3	78. (42.5-84)	14	
Gordon et al., 2014[48]	USA	820	IFN and variety of oral antiviral	NR	820	NR	NR	62.4 (36-108)	32.9	Cohort
		1851	Control	NR	1851	NR	NR	62.4 (36-108)	14.6	
Kumada et al., 2013[49]	Japan	148	Variety of oral antiviral	53 (26-81)	76	65 (7-1088)	6.3 (1.9-8.9)	153.6 (37.2-235.2)	62	Cohort
		637	Control	48 (4-85)	151	26 (5-3410)	3.1 (1.6-9.2)	164.4 (37.2-240)	91	
Question 1. Head-to-head studies comparing individual antiviral agents										
Cui et al., 2010[28]	China	33	Entecavir	38.4 ± 10.8	10	364 (47-2861)	5.2 ± 0.8	0.2-41.5	NR	Cohort
		34	Lamivudine	39.4 ± 10.6	13	226.5 (22-2314)	5.1 ± 0.6	0.2-41.5	NR	
		37	Control	41.03 ± 11.5	11	287 (17-2535)	5 ± 0.9	0.2-41.5	NR	
Chan et al., 2012[50]	China	114	Telbivudine	49.6 ± 10.9	61	75.1 ± 54.4	6.9 ± 1.2	24	100	RCT
		114	Lamivudine	51.9 ± 10	55	84 ± 87.8	6.9 ± 1.2	24	100	
Chang et al., 2006[51]	Multinational	354	Entecavir	35 ± 13	348	140.5 ± 114.3	8.9 ± 1.3	12	8	RCT
		355	Lamivudine	35 ± 13	351	146.3 ± 132.3	9 ± 1.3	12	8	
Lai et al., 2006[52]	Multinational	325	Entecavir	44 ± 11	3	141 ± 114.7	6.9 ± 1.1	12	5	RCT
		313	Lamivudine	44 ± 11	4	143 ± 119.4	6.9 ± 1	12	10	
Lau et al., 2005[53]	Multinational	271	Peg-IFN plus placebo	32.5 ± 9.6	271	114.6 ± 114.3	9.2 ± 1.4	18	18	RCT
		271	Peg-IFN plus lamivudine	31.7 ± 10.3	271	114.9 ± 94.1	9.4 ± 1.2	18	15	
		272	Lamivudine	31.6 ± 9.7	272	102.3 ± 78.4	9.4 ± 1.3	18	17	
Marcellin et al., 2004[54]	Multinational	177	Peg-IFN plus placebo	40 ± 11.7	0	94.4 ± 85.9	6.4 ± 1.1	18	31	RCT
		179	Peg-IFN plus lamivudine	41 ± 10.8	0	90.8 ± 76.2	6.5 ± 1.1	18	22	
		181	Lamivudine	40 ± 11.1	0	105.7 ± 128.2	6.5 ± 1.1	18	29	
Wang et al., 2013[55]	China	102	Adefovir	44 ± 9.5	NR	72.76 ± 61.8	6.2 ± 1.2	24	100	RCT
		104	Lamivudine	44.9 ± 10.03	NR	72.6 ± 46.4	6.1 ± 1.1	24	100	
Yang et al., 2009[56]	China	32	Adefovir	31-62	NR	NR	NR	NR	100	RCT
		30	Lamivudine	25-69	NR	NR	NR	NR	100	
Liaw et al., 2011[57]	Taiwan	100	Entecavir	51 ± 1.2	54	99.2 ± 11.1	6.8 ± 0.01	24	100	RCT
		91	Adefovir	53 ± 1.1	50	100 ± 8.6	7.5 ± 0.01	24	100	
Lim et al., 2014[58]	Korea	2000	Entecavir	47 ± 11	1168	101 (53-190)	7.1 ± 1.6	37.2 (26.4-51.6)	53.6	Cohort
		3374	Lamivudine	43 ± 11	2421	128 (68-244)	7.5 ± 1.2	104.4 (78-138)	48	
Hsu et al., 2012[59]	Taiwan	53	Entecavir	48 (40-56)	18	467 (78-879)	6.1	12	45.3	Cohort
		73	Lamivudine	46 (37-58)	17	391 (68-1530)	6.3	12	48	
Wong et al., 2011[60]	Hong Kong	36	Entecavir	51 ± 13	13	1151 ± 724	6.6 ± 1.4	18. ± 12	14	Cohort

Table 1. *Continued*

Authors, Year	Country	Patients (N)	Interventions	Age (Years)	HBeAg Positive (N)	Baseline ALT (U/L)	Baseline HBV DNA (log10 IU/mL)*	Follow-up duration (months)	Baseline cirrhosis (%)	Study design
		117	Lamivudine	44 ± 14	55	1499 ± 841	6.8 ± 0.9	79 ± 6	21	
Liang et al., 2009[61]	China	40	Telbivudine	51.8 ± 10.7	20	NR	5.8 ± 0.6	12	100	Cohort
		40	Lamivudine	52.4 ± 8.5	18	NR	5.7 ± 0.6	12	100	
Chen et al., 2014[62]	Taiwan	215	Lamivudine	49.5 ± 14.4	60	1239.4 ± 941.7	5.8 ± 1	20 (6.5-71.3)	42.8	Cohort
		107	Entecavir	48.6 ± 14.1	35	1045.3 ± 782.8	5.8 ± 1.2	20 (6.5-71.3)	49.5	
Zhang et al., 2014[63]	China	65	Entecavir	42.8 ± 13.1	21	352.5 ± 77.2	6.3 ± 0.7	12	NR	Cohort
		54	Lamivudine	45.6 ± 11.4	23	345.2 ± 89.5	6.5 ± 0.9	12	NR	
Tsai et al., 2014[64]	Taiwan	53	Entecavir	49 ± 13	15	1287 ± 788	8.2 ± 6.8	4	NR	Cohort
		114	Lamivudine	43 ± 15	47	1629 ± 1011	7.5 ± 6.9	4	NR	
Tsai et al., 2014[65]	Taiwan	88	Telbivudine	55.7 ± 11.4	20	102.5 ± 137.5	5.1 ± 0.5	27.6	100	Cohort
		88	Entecavir	56.1 ± 9.8	17	125.8 ± 179	5.3 ± 0.4	53.1	100	
Koklu et al., 2013[66]	Turkey	72	Tenofovir	54.2 ± 10.5	9	115.2 ± 217.1	4.9 ± 1.2	12	100	Cohort
		76	Entecavir	54.2 ± 11.2	17	86.2 ± 115.6	5 ± 1.2	12	100	
		74	Lamivudine	56.8 ± 11.4	10	53.2 ± 44.5	4 ± 1.3	12	100	
Question 2. Effectiveness of antiviral therapy in patients with immune tolerant chronic HBV infection										
Chan et al., 2014[67]	Multinational	64	Tenofovir and placebo	33 ± 9.5	63	26.9 ± 14.05	8.4 ± 0.4	48	NR	RCT
		62	Tenofovir and emtricitabine	33 ± 11.2	62	26.2 ± 9.88	8.4 ± 0.4	48	NR	
Lu et al., 2015[68]	China	30	Peg-IFN and adefovir	26.8 ± 3.1	30	<40	>5	6	NR	Cohort
		38	Control	26.8 ± 3.1	30			6	NR	
Question 3: Discontinuing versus continuing antiviral therapy in HBeAg-positive patients who seroconverted from HBeAg to anti-HBe										
Chaung et al., 2012[69]	USA	49	Variety of oral antiviral alone or in combination	39 ± 12	NR	87 (16-1281)	7 ± 1.3	12	NR	Cohort
		39	Discontinued therapy	34 ± 10	NR	139 (37-576)	7 ± 1.2	12	NR	
Fung et al., 2009[70]	Hong Kong	79	Lamivudine, continued therapy	32 (21-55)	NR	158 (21-2069)	7.9 (3-10.3)	45	NR	Cohort
		22	Discontinued therapy			176 (46-1670)	8.7 (6.4-10.2)	45	NR	
Question 5. Safety of entecavir compared to tenofovir										
Koklu et al., 2013[66]	Turkey	54	Tenofovir	54.2 ± 10.2	9	115.2 ± 217.1	4.9 ± 1.2	21.4 ± 9.7	100	Cohort
		60	Entecavir	52.4 ± 11.2	17	86.2 ± 115.6	5 ± 1.2	24.0 ± 13.3	100	
Liaw et al., 2011[71]	Multinational	45	Tenofovir	52 (48-57)	14	48 (31-73)	5 (4.2-5.9)	12	NR	RCT
		45	Tenofovir and Emtricitabine	50 (42-58)	18	54 (34-98)	5.6 (3.8-6.6)	12	NR	
		22	Entecavir	54 (47-58)	7	52 (41-66)	5.2 (3.5-6.7)	12	NR	
Dogan et al., 2012[72]	Turkey	65	Tenofovir	NR	29	114 ± 181	7 ± 6.9	12	NR	Cohort
		29	Entecavir	NR	10	84 ± 69	7.2 ± 7.6	12	NR	
Batirel et al., 2014[73]	Turkey	90	Tenofovir	43.3 ± 12.9	29	116.7 ± 92.6	7.6 ± 4.6	30.2 ± 15.7	NR	Cohort

Table 1. *Continued*

Authors, Year	Country	Patients (N)	Interventions	Age (Years)	HBeAg Positive (N)	Baseline ALT (U/L)	Baseline HBV DNA (log10 IU/mL)*	Follow-up duration (months)	Baseline cirrhosis (%)	Study design
		105	Entecavir	42.0 ± 11.2	36	120 ± 96.6	7.6 ± 4.3	30.2 ± 15.7	NR	
Cholongitas et al., 2015[74]	Greece	31	Tenofovir	60 ± 10	NR	57 ± 40	3.8 (>0-5.6)	25 (6-66)	100	Cohort
		21	Entecavir	58 ± 9	NR	75 ± 34	4.6 (>0-7.4)	18 (7-68)	100	
Huang et al., 2015[75]	China	33	Tenofovir	35 (26-61)	NR	194.1 ± 128.5	6.50 ± 0.69	13.4 (6.2-28.0)	NR	Cohort
		65	Entecavir	39 (20-67)	NR	157.6 ± 216.8	6.15 ± 1.36	16 (6.0-27.0)	NR	
Hung et al., 2015[76]	Taiwan	41	Tenofovir	49.8 ± 13.1	NR	1104 ± 918	6.3 ± 1.2	6	20	Cohort
		148	Entecavir	50.6 ± 14.7	NR	1084 ± 830	5.8 ± 1.2	6	34	
Mallet et al., 2014[77]	France	70	Tenofovir	47 (37.8-56)	NR	52 (32-107)	4.4 (2.9-6.6)	22	NR	Cohort
		61	Entecavir	47 (37.8-56)	NR	52 (32-107)	4.4 (2.9-6.6)	22	NR	
Mauss et al., 2011[78]	Germany	37	Tenofovir	43 (19-75)	11	73 (21-528)	5.58 (2.41->8.04)	12 (6-36)	NR	Cohort
		32	Entecavir	43 (20-73)	16	72 (18-2230)	6.38 (3.49->8.04)	24 (6-48)	NR	
Tien et al., 2014[79]	USA	42	Tenofovir	49 ± 12	11	NR	NR	26 ± 13	20	Cohort
		44	Entecavir	51 ± 9	8	NR	NR	32 ± 24	10	
Gish et al., 2012[80]	USA	80	Tenofovir	54.5 ± 13	NR	NR	6.99 (0-8.8)	20 (2-45)	NR	Retrospective cohort
		80	Entecavir	55.1 ± 12	NR	NR	7.36 (0-8.7)	29 (1-55)	NR	

*Baseline HBV DNA in studies that used different units were converted using the formulas 1 copy = 0.2 IU and 1 pg = 283,000 copies or 56,000 IU.

Abbreviations: anti-HBe, hepatitis B e antibody; NR, not reported; Peg, pegylated; ULN, upper limit of normal.

Table 2. Risk of Bias Assessment in the Included RCTs

Author, Year	Sequence Generation	Allocation Concealment	Blinding			Baseline Imbalance	Attrition Bias or Lost to Follow-Up
			Participants	Providers	Outcome Assessors		
Question 1: Effectiveness of antiviral therapy compared to control in patients with immune active chronic HBV infection (antiviral versus control)							
Anderson et al., 1987[8]	NR	NR	Yes	Yes	Yes	NR	NR
Krogsgaard et al., 1998[23]	NR	NR	Yes	Yes	Yes	NR	NR
Chan et al., 2007[24]	Randomized; randomization was centralized and stratified according to geographical region	NR	Yes	Yes	Yes	No	>15%
Eun et al., 2007[25]	Randomized	NR	NR	NR	NR	NR	NR
Dienstag et al., 1999[29]	Randomized	Yes	Yes	Yes	NR	No	10%-15%
Liaw et al., 2004[33]	Randomized	NR	Yes	NR	Yes	NR	NR
Garg et al., 2011[46]	Randomized; randomization was done with a random number table	Yes	Yes	Yes	NR	No	<10%
Question 1. Head-to-head studies comparing individual antiviral agents							
Chan et al., 2012[50]	Randomized; centralized, stratifying based on screening CTP score and ALT level	Yes	Yes	Yes	Yes	No	<10%
Chang et al., 2006[51]	Randomized	NR	Yes	Yes	Yes	NR	NR
Lai et al., 2006[52]	Randomized	NR	Yes	NR	Yes	NR	NR
Lau et al., 2005[53]	Randomized; centralized and stratified according to geographic region and ALT levels	NR	NR	NR	NR	NR	NR
Marcellin et al., 2004[54]	Randomized; centralized and stratified according to geographic region and ALT levels	NR	Yes	Yes	Yes	NR	NR
Wang et al., 2013[55]	Randomized	NR	NR	NR	NR	No	NR
Yang et al., 2009[56]	Randomized	NR	NR	NR	NR	NR	<10%
Liaw et al., 2011[57]	Randomized; randomization was not blocked or stratified	NR	No	No	No	No	<10%
Question 2. Effectiveness of antiviral therapy in patients with immune tolerant chronic HBV infection							
Chan et al., 2014[67]	Randomization	NR	Yes	Yes	NR	None	<10%
Question 5. Safety of entecavir compared to tenofovir							
Liaw et al., 2011[71]	Randomization	NR	Yes	Yes	NR	None	<10%

Abbreviations: CTP, Child-Turcotte-Pugh; NR, not reported.

In five observational studies[25,26,35,38,41] (Fig. 4) with a mean follow-up of 84 months, IFN-α compared to no treatment significantly decreased the risk of HCC (five studies, RR = 0.6, 95% CI 0.4-0.9, I^2 = 0%) but not of all-cause mortality (one study, RR = 0.7, 95% CI 0.5-2.4, I^2 = 56.9%) or decompensated liver disease (one study, RR = 0.7, 95% CI 0.3-1.5).

In four observational studies[26,35,38,41] (Fig. 5) with a mean follow-up of 45 months, lamivudine versus no treatment significantly reduced the risk of HCC (four studies, RR = 0.6, 95% CI 0.4-0.96, I^2 = 49.9%), all-cause mortality (one study, RR = 0.4, 95% CI 0.3-0.6), and decompensated liver disease (one study, RR = 0.3, 95% CI 0.3-0.5). In one cohort study[40] of 1980 patients with cirrhosis followed for a mean of 52 months, entecavir versus control reduced the risk of HCC (RR = 0.3, 95% CI 0.1-0.5) and death (RR = 0.6, 95% CI 0.3-0.98).

Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic HBV Infection and Decompensated Cirrhosis. In two observational studies with follow-up of 29 months,[27,32] lamivudine versus control reduced all-cause mortality (two studies, RR = 0.5, 95% CI 0.3-0.8, I^2 = 0%).

Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic HBV Infection Experiencing Acute on Chronic Liver Failure. In one RCT[46] involving 26 patients followed for 1 year, tenofovir reduced all-cause mortality (RR = 0.5, 95% CI 0.3-0.99, moderate-quality evidence). In four observational studies[28,37,42,44] with a mean follow-up of 26 months, antiviral therapy versus no therapy reduced all-cause mortality (RR = 0.7, 95% CI 0.6-0.8, I^2 = 5.4%). Similarly, reduced mortality was also found in studies evaluating individual therapies including lamivudine (RR = 0.8, 95% CI 0.7-0.9, I^2 = 50.2%),[28,37,44]

Table 3. Risk of Bias Assessment for the Included Nonrandomized Studies

Author, Year	Selection of Cohort/Patients: Exposed Cohort	Selection of Cohort/Patients: Nonexposed Cohort/Control	Ascertainment of Exposure	Assessment and Clear Ascertainment of Outcome	Adequacy of Follow-Up	Funding Sources
Question 1: Effectiveness of antiviral therapy compared to control in patients with immune active chronic HBV infection (antiviral versus control)						
IIHCSG, 1998[9]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Lin et al., 2007[10]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Truong et al., 2005[11]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NA	NR
Tangkijvanich et al., 2001[12]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Papatheodoridis et al., 2001[13]	No description	No description of the derivation of the nonexposed cohort	Secure records	Record linkage	Complete follow-up	NR
Niederau et al., 1996[14]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Lin et al., 2004[15]	Somewhat representative of the community or population	Drawn from a different community or population from the exposed cohort	Secure records	Record linkage	Complete follow-up	Reported
Benvegnu et al., 1998[16]	No description	No description	No description	No description	NR	NR
Tong et al., 2006[17]	No description	No description	No description	No description	NR	NR
Di Marco et al., 1999[18]	No description	No description	No description	No description	NR	NR
Brunetto et al., 2002[19]	No description	No description	No description	No description	NR	NR
Mahmood et al., 2005[20]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Ikeda et al., 1998[21]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Fattovich et al., 1997[22]	Selected group of users	No description of the derivation of the nonexposed cohort	Secure records	Record linkage	NR	NR
Tong et al., 2009[26]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Das et al., 2010[27]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Cui et al., 2010[28]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Chan et al., 2002[30]	Selected group of users	Drawn from a different community or population from the exposed cohort	Secure record	Record linkage	NR	NR
Lok et al., 2003[31]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Follow-up rate <90% and no description of the reasons for loss to follow-up	NR
Manolakopoulos et al., 2004[32]	Selected group of users	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Matsumoto et al., 2005[34]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NA	Reported

Table 3. *Continued*

Author, Year	Selection of Cohort/Patients: Exposed Cohort	Selection of Cohort/Patients: Nonexposed Cohort/Control	Ascertainment of Exposure	Assessment and Clear Ascertainment of Outcome	Adequacy of Follow-Up	Funding Sources
Ma et al., 2007[35]	No description	Drawn from the same community as the exposed cohort	No description	No description	NR	NR
Yuen et al., 2007[36]	Truly representative of the community or population	Drawn from a different community or population from the exposed cohort	Secure records	Record linkage	Follow-up rate <90% and no description of the reasons for loss to follow-up	Reported
Sun et al., 2010[37]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Kim et al., 2012[38]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	Reported
Eun et al., 2010[39]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	Reported
Wong et al., 2013[40]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	No description	No description	NR	NR
Hosaka et al., 2013[41]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	No description	No description	NR	NR
Lin et al., 2013[42]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Subjects lost to follow-up unlikely to introduce bias, small number lost to follow-up	Reported
Xiao et al., 2009[43]	No description of the derivation of the cohort	Drawn from the same community as the exposed cohort	No description	No description	NR	NR
Xu et al., 2009[44]	Truly representative of the community or population	No description of the derivation of the nonexposed cohort	No description	No description	NR	NR
Chen et al., 2009[45]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	No description	Record linkage	Complete follow-up, all subjects accounted for	Reported
Wu et al., 2014[47]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Gordon et al., 2014[48]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	Reported
Kumada et al., 2013[49]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	Reported
Question 1. Head-to-head studies comparing individual antiviral agents						
Cui et al., 2010[28]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Lim et al., 2014[58]	Selected group of users	Drawn from a different community or population from the exposed cohort	Secure records	Record linkage	Complete follow-up	Reported
Hsu et al., 2012[59]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	No description	NR	Reported
Wong et al., 2011[60]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Independent blind assessment	Follow-up rate <90% and no description	Reported

Table 3. *Continued*

Author, Year	Selection of Cohort/Patients: Exposed Cohort	Selection of Cohort/Patients: Nonexposed Cohort/Control	Ascertainment of Exposure	Assessment and Clear Ascertainment of Outcome	Adequacy of Follow-Up	Funding Sources
					of the reasons for loss to follow-up	
Liang et al., 2009[61]	No description	Drawn from the same community as the exposed cohort	Secure records	No description	Not reported	NR
Chen et al., 2014[62]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	Reported
Zhang et al., 2014[63]	No description of the derivation of the cohort	No description of the derivation of the non-exposed cohort	Secure records	Record linkage	Follow-up rate <90% and no description of the reasons for loss to follow-up	NR
Tsai et al., 2014[64]	Selected group of users	Drawn from a different community or population from the exposed cohort	Secure records	Independent blind assessment	NR	NR
Tsai et al., 2014[65]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Follow-up rate <90% and no description of the reasons for loss to follow-up	Reported
Koklu et al., 2013[66]	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Question 2. Effectiveness of antiviral therapy in patients with immune tolerant chronic HBV infection						
Lu et al., 2015[68]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Question 3: Discontinuing versus continuing antiviral therapy in HBeAg-positive patients who seroconverted from HBeAg to anti-HBe						
Chaung et al., 2012[69]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Fung et al., 2009[70]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Question 5. Safety of entecavir compared to tenofovir						
Koklu et al., 2013[66]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Dogan et al., 2012[72]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Batirel et al., 2014[73]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Cholongitas et al., 2015[74]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Huang et al., 2015[75]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Hung et al., 2015[76]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Mallet et al., 2014[77]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Mauss et al., 2011[78]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR

Table 3. *Continued*

Author, Year	Selection of Cohort/Patients: Exposed Cohort	Selection of Cohort/Patients: Nonexposed Cohort/Control	Ascertainment of Exposure	Assessment and Clear Ascertainment of Outcome	Adequacy of Follow-Up	Funding Sources
Tien et al., 2014[79]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Gish et al., 2012[80]	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR

Abbreviations: anti-HBe, hepatitis B e antibody; NR, not reported.

entecavir (RR = 0.7, 95% CI 0.6-0.8, I^2 = 0%),[28,42,44] and telbivudine (RR = 0.4, 95% CI 0.2-0.9).[44]

Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic HBV Infection With Severe Acute Exacerbations. In three observational studies[30,43,45] with more than 12-month mean follow-up, meta-analysis of antiviral therapy versus control showed no statistically significant reduction in all-cause mortality (RR = 0.9, 95% CI 0.5-1.5, I^2 = 54.5%), which was consistent with studies evaluating the effect of individual agents: lamivudine (RR = 0.5, 95% CI 0.2-1.7)[30] and entecavir (RR = 0.9, 95% CI 0.5-1.9, I^2 = 71.3%).[43,45]

Head-to-Head Studies Comparing Individual Antiviral Agents. We included eight RCTs[50-57] enrolling 2318 patients and 10 observational studies[28,58-66] enrolling 6737 patients that compared one antiviral agent with another. We considered most of these RCTs[52,55-57] to have high risk of bias due to unclear randomization methods, allocation concealment, blinding, and loss to follow-up. The observational studies were also limited by the unclear description of the characteristics for cohort selection, ascertainment of the outcomes, and inadequate follow-up. Tables 1 and 2 describe the details of the included studies and risk of bias.

Among five studies enrolling 3300 patients with chronic HBV infection and compensated cirrhosis (mean follow-up 22 months), one RCT[55] compared adefovir versus lamivudine and four observational studies compared entecavir versus lamivudine,[58] entecavir versus telbivudine,[65] lamivudine versus tenofovir,[66] and telbivudine versus lamivudine, respectively.[61] Only 1 study[58] showed a significant difference in outcome with reduction in all-cause mortality in patients who received entecavir versus lamivudine (one study, RR = 0.4, 95% CI 0.3-0.6, very low-quality evidence).

Four studies enrolled 607 patients with chronic HBV infection and decompensated cirrhosis (mean follow-up 28 months). Three RCTs compared entecavir versus adefovir,[57] adefovir versus lamivudine,[56] and telbivudine versus lamivudine, respectively[50]; and one cohort study[59] compared entecavir versus lamivudine. Reduction in risk of HCC was observed in the RCT[57] comparing entecavir versus adefovir (RR = 0.4, 95% CI 0.2-0.8), and reduction in all-cause mortality was observed in the cohort study comparing entecavir versus lamivudine (RR = 0.4, 95% CI 0.3-0.7) in patients who received entecavir.

Three cohort studies[28,62,63] that enrolled 508 patients with acute on chronic liver failure and compared entecavir to lamivudine (mean follow-up 32 months) showed no significant effect on all-cause mortality.

Two cohort studies[60,64] that compared entecavir versus lamivudine in 320 patients with severe acute exacerbation of chronic hepatitis B (mean follow-up 32 months) showed no significant effect on mortality.

Question 2. Effectiveness of Antiviral Therapy in Patients With Immune-Tolerant Chronic HBV Infection

Two studies[67,68] evaluated antiviral therapy in HBeAg-positive patients with normal ALT levels. Detailed study characteristics and risk of bias are described in Tables 1 and 2.

One RCT[67] compared tenofovir (64 patients) to a combination of tenofovir and emtricitabine (62 patients) for 192 weeks. Although no long-term clinical outcomes were reported, tenofovir and emtricitabine versus tenofovir showed a statistically significant increase in viral suppression (RR = 1.4, 95% CI 1.1-1.8, moderate-quality evidence) but no statistically significant increase in HBeAg loss (RR = 0.3, 95% CI 0.03-2.2), HBeAg seroconversion (RR = 0.1, 95% CI 0.01-2.8), or HBsAg clearance (RR = 1.0, 95% CI 0.3-3.9). The quality of evidence was low due to indirectness and imprecision.

In a cohort study[68] of 68 HBeAg-positive postpartum women, pegylated IFN and adefovir versus untreated control significantly improved rates of HBeAg

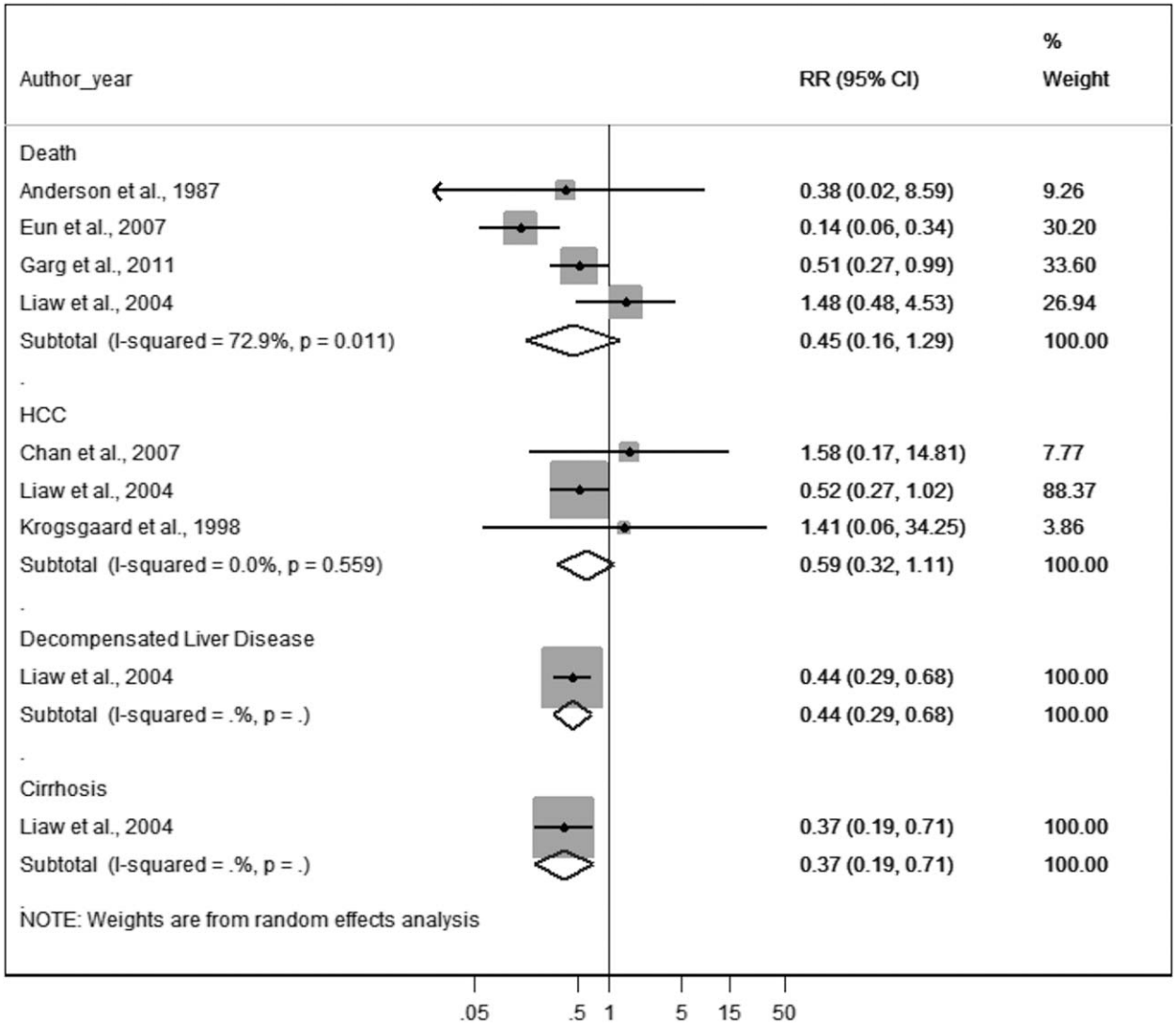

Fig. 2. Forest plot of clinical outcomes for randomized controlled trials comparing any antiviral vs. no treatment. I-square and *P* values for study heterogeneity cannot be computed for outcomes with only one study.

seroconversion (RR = 41.8, 95% CI 2.6-666.9) and HBeAg loss (RR = 20.3, 95% CI 1.2-337.7). The quality of evidence was very low, down-rated due to the observational nature of the study, risk of bias, and imprecision.

Question 3: Discontinuing Compared to Continuing Antiviral Therapy in HBeAg-Positive Patients Who Seroconverted From HBeAg to Hepatitis B e Antibody

Two observational studies[69,70] compared patients with chronic hepatitis B who stopped therapy (61 patients) after HBeAg seroconversion to those who continued (128 patients) to receive antiviral therapy. For both studies, the median (range) duration of therapy leading to HBeAg seroconversion was 21 (1-120) months, median follow-up after stopping therapy was 40 (range 2-120) months, and median duration of consolidation treatment after HBeAg seroconversion was 12 (range 1-55) months. Characteristics and risk of bias for both studies are illustrated in Tables 1 and 3.

Compared to continued antiviral therapy, very low-quality evidence suggests increased risk of relapse of viremia in patients who stopped antiviral therapy (RR = 94.4, 95% CI 13.3-670.7, I^2 = 0%) with no effect on ALT flares. The rate of HBeAg seroreversion was 8% after a median of 6 months in 1 study,[69] with a cumulative incidence of 9% at 5 years in another study.[70] No clinical outcomes were reported. The quality of evidence was very low due to increased risk of bias, indirectness, and imprecision. Additional noncomparative and indirect evidence is summarized in the Supporting Information.

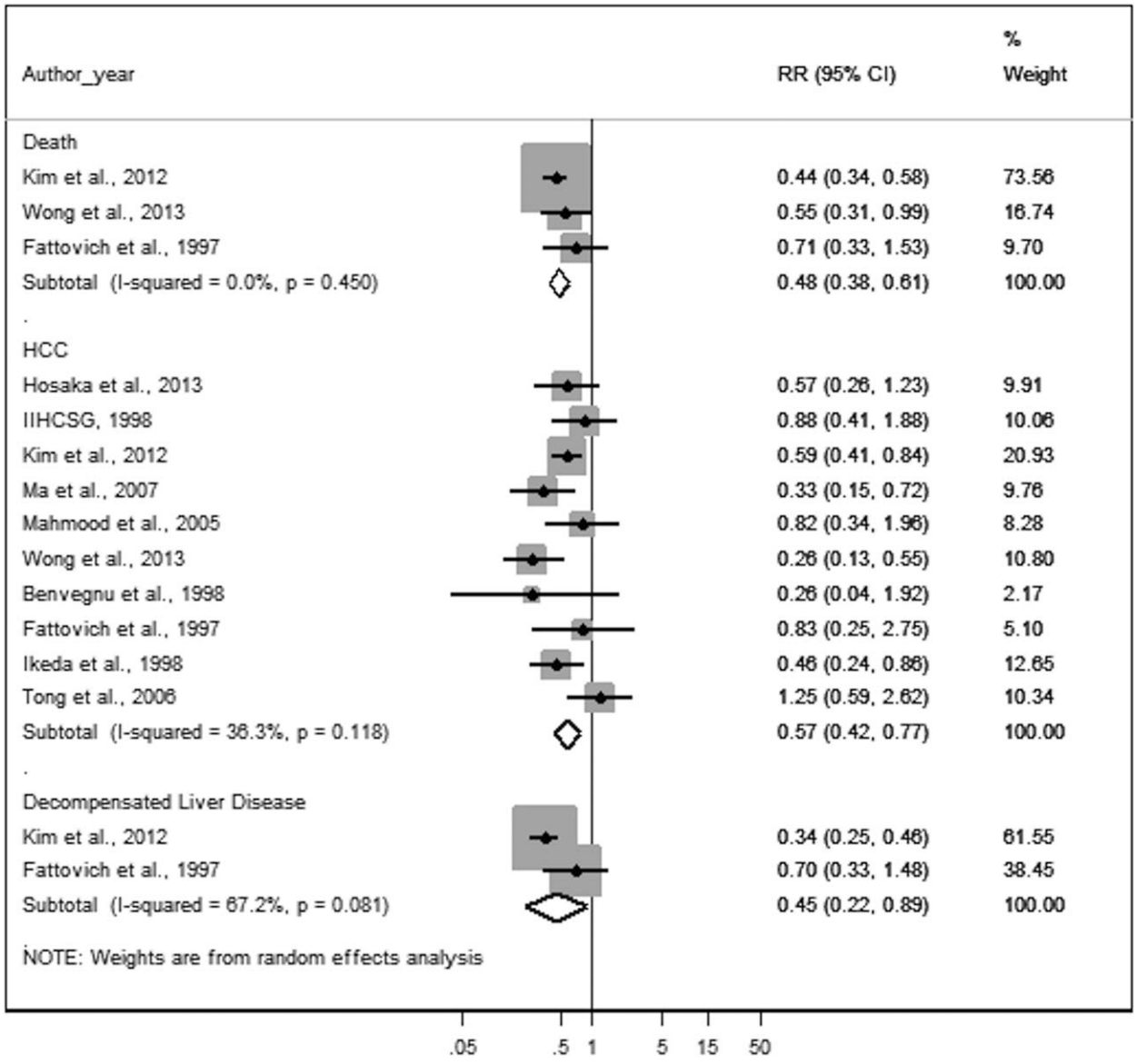

Fig. 3. Forest plot of clinical outcomes for observational studies comparing antiviral therapy vs. no treatment in patients with chronic HBV infection and compensated cirrhosis.

Question 4. Stopping Compared to Continuing Antiviral Therapy In HBeAg-Negative Adults With Immune Active Chronic HBV Infection

We were unable to find comparative studies for this question. The Supporting Information summarizes uncontrolled studies and indirect evidence that may address this question. Data from these studies indicate a high rate of viral relapse when treatment was stopped, but rates of clinical relapse were lower.

Question 5. Safety of Entecavir Compared to Tenofovir

Eleven studies (one RCT[71] and 10 observational studies[66,72-80]) compared entecavir versus tenofovir in 1300 patients with a mean follow-up of 18.6 months. Characteristics of the included studies and risk of bias are described in Tables 1 and 2.

Meta-analysis of the studies included showed no statistically significant difference between entecavir and tenofovir in renal safety profiles or hypophosphatemia, but duration of observation was short. No studies reported on bone density. Table 4 describes the detailed outcomes reported for each study.

Question 6. Adding a Second Antiviral Agent Compared to Continuing Monotherapy (Entecavir or Tenofovir) in Patients With Chronic HBV Infection and Persistent Viremia

We were unable to identify comparative studies for this question. Uncontrolled studies and indirect

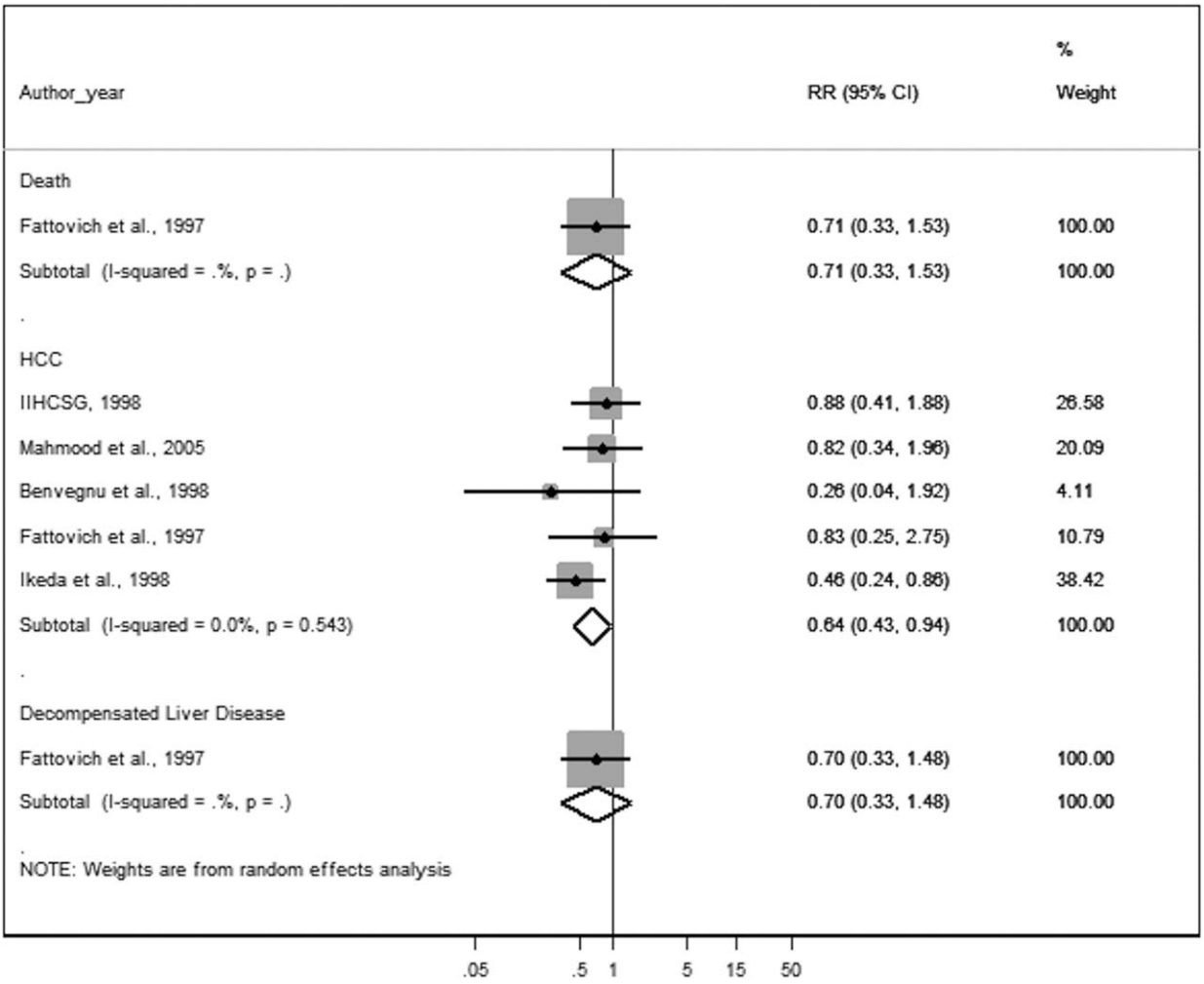

Fig. 4. Forest plot of clinical outcomes for observational studies comparing IFN-α vs. no treatment in patients with chronic HBV infection and compensated cirrhosis. I-square and *P* values for study heterogeneity cannot be computed for outcomes with only one study.

evidence (Supporting Information) showed little to no benefit in adding a second antiviral agent compared to continuing monotherapy with entecavir or tenofovir.

Question 7. Antiviral Therapy in Patients With Chronic HBV Infection and Compensated Cirrhosis and Low-Level Viremia (HBV DNA <2000 IU/mL)

We were unable to identify comparative studies on outcomes of these patients with or without antiviral therapy. The Supporting Information summarizes uncontrolled studies and indirect evidence that address this question. In patients with compensated cirrhosis and low-level viremia, one study specifically examined the benefit of antiviral therapy and found a decrease in incidence of HCC, but the results could be confounded by differences in the characteristics of treated versus untreated patients.[81]

Publication Bias. We were unable to evaluate publication bias due to high heterogeneity and the small number of studies for each outcome.

Discussion

The members of the AASLD methodology and writing committees for the HBV Practice Guideline developed seven key clinical questions that challenge clinicians and patients in daily practice. The methodologists performed an extensive literature search, selected studies that included a comparison group and data on clinical outcomes, and then rated the quality of the evidence. Sufficient comparative evidence was found for four of the key questions, but evidence was sparse or absent for the remaining three questions: when to stop therapy in persons with immune active chronic HBV infection who are HBeAg-negative, the benefit of adding

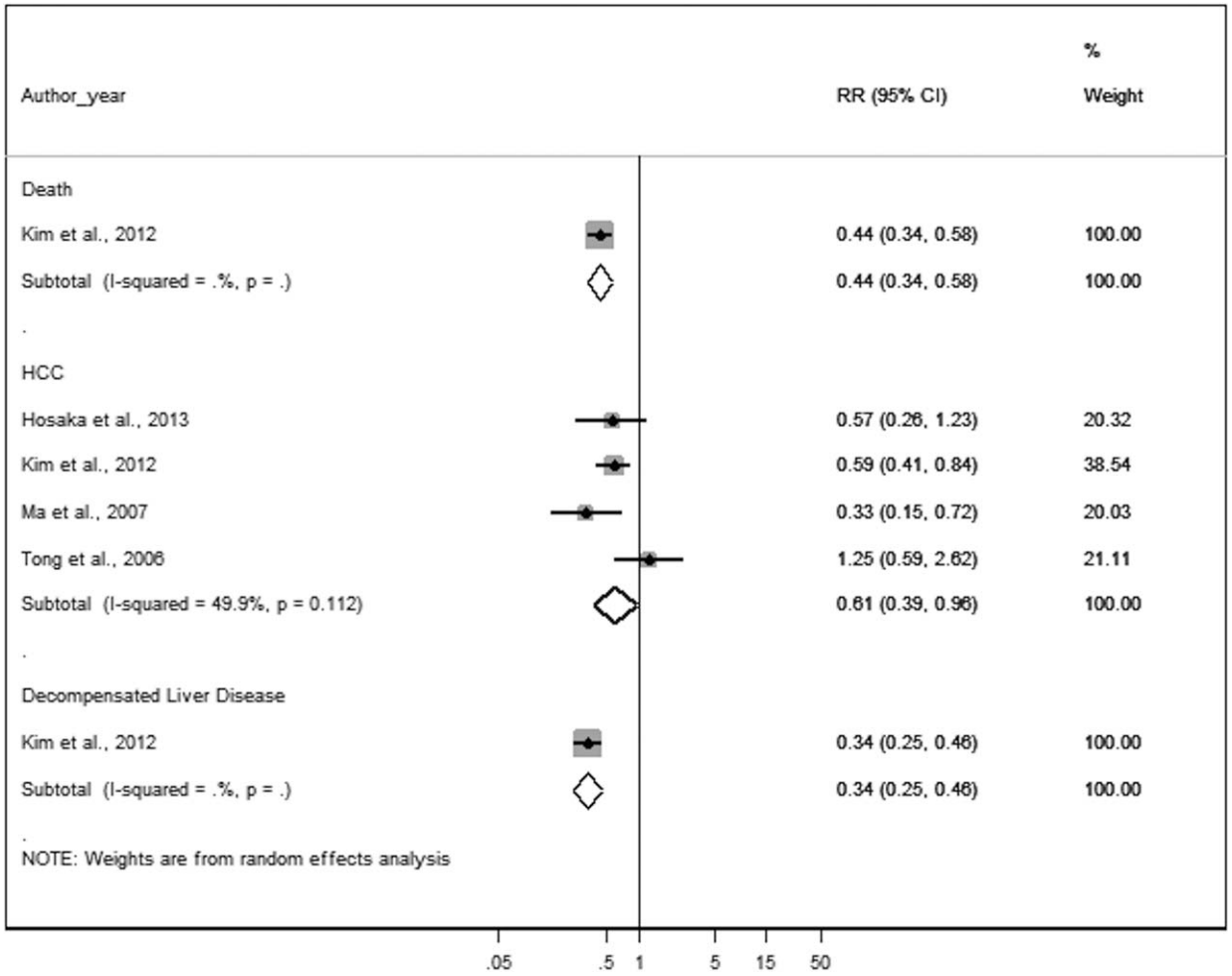

Fig. 5. Forest plot of clinical outcomes for observational studies comparing lamivudine vs. no treatment in patients with chronic HBV infection and compensated cirrhosis. I-square and *P* values for study heterogeneity cannot be computed for outcomes with only one study.

either entecavir or tenofovir in persons who fail to suppress HBV DNA to undetectable levels with either of these drugs alone, and whether antiviral therapy should be used in patients with compensated cirrhosis and HBV DNA levels below 2000 IU/mL. For these three questions, the committee identified indirect and noncomparative evidence (Supporting Information).

Antiviral therapy in patients with immune active chronic HBV infection had 59 published studies available for review and evaluation. Moderate-quality to low-quality evidence supported the benefit of therapy in reducing adverse outcomes of chronic HBV infection including progression to cirrhosis, liver decompensation, and all-cause mortality. Because the observational studies had more patients (59,201 versus 3463) and longer follow-up (60 versus 28 months), data on mortality and HCC from 35 observational studies were sufficiently precise, whereas data from seven RCTs were imprecise. These larger sample sizes and longer follow-up in the observational studies account for the significant benefit of antiviral treatment on HCC and mortality found in the observational studies but not in the RCTs.

Given the indolent nature of chronic HBV infection, it is not surprising that evidence supporting the benefit of antiviral treatment on clinical outcomes was found only when the analysis was limited to patients with more advanced disease: compensated cirrhosis, decompensated cirrhosis, or acute on chronic liver failure. Indeed, most RCTs of antiviral therapy in chronic HBV infection enrolled only or mostly patients with no cirrhosis, and very few trials that enrolled predominantly patients with no cirrhosis provided data on clinical outcomes. Provision of evidence to support that antiviral therapy improves clinical outcomes in patients with chronic HBV infection and no cirrhosis would require thousands of patients followed for many years and withholding treatment in the control group until the completion of the study. Such a study would be unethical

Table 4. Outcomes Reported for Tenofovir Versus Entecavir in Chronic HBV Infection

Author, Year	Outcomes Reported	Tenofovir	Entecavir	
		Events/Total	Events/Total	RR (95% CI)
Koklu et al., 2013[66]	Renal impairment	1/72	0/77	3.21 (0.13-77.44)
	Hypophosphatemia	1/72	0/77	3.21 (0.13-77.44)
	Increase of creatinine kinase	0/72	1/77	0.36 (0.01-8.60)
Liaw et al., 2011[71]	Increase in creatinine ≥0.5 mg/dL from baseline	4/45	1/22	1.96 (0.23-16.47)
	Phosphorus <2.0 mg/dL	1/45	0/22	1.50 (0.00-35.40)
Batirel et al., 2014[73]	Hypophosphatemia	2/90	0/105	5.82 (0.28-119.75)
Cholongitas et al., 2015[74]	eGFR <50 mL/minute	3/31	2/21	1.02 (0.19-5.57)
	Serum phosphate levels	NR	NR	NA
Hung et al., 2015[76]	Baseline serum creatinine 0.5 mg/dL	2/30	2/99	3.30 (0.49-22.44)
	Reduction of eGFR	108 to 87 189 mL/min/1.73 m^2	92 to 84 mL/ min/1.73 m^2	NA
Huang et al., 2015[75]	CK levels 2 times over the upper limit of normal	1/33	1/65	1.97 (0.13-30.50)
Mallet et al., 2014[77]	Mean eGFR variation	0.6 (-0.8 to 1.94)	-0.1 (-1.5 to 1.3)	NA
Mauss et al., 2011[78]	Changes in eGFR (CKD-EPI formula)	-0.92 mL/min	-1.00 mL/min	NA
	Decrease of eGFR >20 mL/min	1/37	2/32	0.43 (0.04-4.55)
Tien et al., 2015[79]	Phosphate threshold for renal tubular reabsorption < 2.8 mg/dL	18/42	10/44	1.89 (0.99-3.60)
	GFR by Cockcroft-Gault <60 mL/min	1/42	2/44	0.52 (0.05-5.56)
	GFR by MDRD <60 mL/min	1/42	2/44	0.52 (0.05-5.56)
	Serum phosphate (mg/dL) <2.8 mg/dL	6/42	2/44	3.14 (0.67-14.71)
	SCr (mg/dL) >1.5 mg/dL	0/42	0/44	NA
	Serum alkaline phosphatase >145 U/L	0/42	1/44	0.35 (0.01-8.33)
Gish et al., 2012[80]	Confirmed SCr increase 0.5 mg/dL	3/80	11/80	0.27 (0.08-0.94)
	New Cockcroft-Gault eGFR <60 mL/min	15/80	6/80	2.50 (1.02-6.12)
	Decrease in eGFR 20% (MDRD)	33/80	35/80	0.94 (0.66-1.35)

Abbreviations: CK, creatine kinase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NA, not available; NR, not reported; SCr, serum creatinine.

and likely infeasible. Thus, evidence supporting the benefit of antiviral therapy in patients without cirrhosis has to rely on intermediate outcomes such as HBV DNA suppression, ALT normalization, HBeAg seroconversion, HBsAg loss, and cirrhosis prevention or regression. These intermediate outcomes have been shown to correlate with improvement in clinical outcomes and represent a series of steps toward the ultimate goal of improving clinical outcome. For example, HBV DNA suppression precedes HBeAg seroconversion, which precedes HBsAg loss; and HBsAg loss has been associated with decreased risk of HCC, particularly if it occurs before the development of cirrhosis.

Recent studies showed that high levels of HBV viremia are associated with an increased risk of cirrhosis, HCC, and liver-related mortality.[82-84] Patients in the immune tolerant phase have the highest level of viremia. In the two studies exclusively enrolling patients in the immune tolerant phase, clinical outcomes were not reported but rates of intermediate outcomes were lower than those in patients in the HBeAg-positive immune active phase.

In the two observational studies comparing the risk of viral relapse and HBeAg seroreversion in HBeAg-positive patients who achieved HBeAg seroconversion during nucleos(t)ide analogue therapy and who stopped versus continued therapy, very low-quality evidence suggests an increased risk of relapse of viremia with stopping. Other observational studies (see Supporting Information) showed durable HBeAg seroconversion varying from 20% to 90% depending on the duration of consolidation therapy after achieving HBeAg seroconversion, the most consistent predictor of durable response. Studies directly comparing stopping versus continuing therapy in HBeAg-negative patients on nucleos(t)ide analogue therapy were not found; however, observational studies in the literature on the virologic, serologic, and biochemical outcomes of patients who stopped therapy showed that viral relapse is universal but that sustained clinical remission and even HBsAg loss are possible (see Supporting Information). Because hepatitis flares and hepatic decompensation may occur after stopping treatment, close monitoring after discontinuation of treatment is important, especially for those with cirrhosis at the start of therapy who have the highest risk for decompensation.

Entecavir and tenofovir have been used as first-line nucleos(t)ide analogues because of their potent antiviral activity and low risk of antiviral drug resistance. Tenofovir can cause impairment in renal function, renal tubular

dysfunction including Fanconi anemia, and decreased bone mineral density. Meta-analysis of studies comparing monotherapy with entecavir or tenofovir did not show a significant difference in serum creatinine level, estimated glomerular filtration rate, or serum phosphate level; however, the duration of treatment was short in these studies.

While entecavir and tenofovir have potent antiviral activity, some patients have persistent viremia despite being adherent to medication. This is more common among HBeAg-positive patients with high baseline serum HBV DNA. Studies comparing continuing entecavir or tenofovir monotherapy versus adding a second antiviral agent in patients with persistent viremia were not found. Observational studies of patients who continued entecavir or tenofovir monotherapy showed that most patients ultimately achieved undetectable HBV DNA.

Patients with compensated cirrhosis have a high risk of liver failure and HCC, particularly those with high levels of HBV DNA. The benefit of antiviral therapy in patients with compensated cirrhosis and low levels of HBV DNA has not been established. One retrospective study comparing outcomes of patients with compensated cirrhosis and low levels of HBV DNA (<2000 IU/mL) with or without antiviral therapy suggests a benefit of antiviral therapy in decreasing the incidence of HCC; but patients who received treatment differed substantially from those who did not receive treatment, and in most patients the HBV DNA was level was higher than 2000 IU/mL at the time treatment was started.[81]

Several questions that had been addressed in the previous AASLD HBV Guidelines were not included in this systematic review: who should be screened for HBV infection, who should be vaccinated against HBV, what clinical and laboratory criteria (levels of HBV DNA and ALT) should be used to initiate antiviral therapy, who should undergo surveillance for HCC, and how frequently patients with chronic HBV infection who are not receiving antiviral therapy should be monitored. Management of special populations, such as those with human immunodeficiency virus or hepatitis C or D viral coinfection and those requiring immunosuppressive therapy, was also not addressed in the current review because data from controlled studies for these patient populations were sparse. Additional recommendations can be found in the previous AASLD HBV Guideline and in the Centers for Disease Control and Prevention and the World Health Organization guidelines.[85-88]

In conclusion, most of the current literature focuses on the immune active phases of chronic HBV infection. Decision-making in other commonly encountered and challenging clinical settings depends on indirect evidence. In addition to evidence-based data, management of patients with chronic HBV infection should take into consideration individual patient preference and available resources. Recommendations for management of adults with chronic HBV infection based on this systematic review are provided in the updated AASLD guidelines.[89]

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