Tenofovir and Entecavir Are the Most Effective Antiviral Agents for Chronic Hepatitis B: A Systematic Review and Bayesian Meta-Analyses

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BACKGROUND & AIMS: The relative efficacies of licensed antiviral therapies for treatment-naive chronic hepatitis B (CHB) infection in randomized controlled trials have not been determined. We evaluated the relative efficacies of the first 12 months of CHB treatments. **METHODS:** Drugs evaluated were lamivudine, pegylated interferon, adefovir, entecavir, telbivudine, and tenofovir, as monotherapies and combination therapies, in treatment-naive individuals. Databases were searched for randomized controlled trials of the first 12 months of therapy in hepatitis B e antigen (HBeAg)-positive and/or HBeAg-negative patients with CHB published in English before October 31, 2009. Bayesian mixed treatment comparisons were used to calculate the odds ratios, including 95% credible intervals and predicted probabilities of surrogate outcomes to determine the relative effects of each treatment. **RESULTS:** In HBeAg-positive patients, tenofovir was most effective in inducing undetectable levels of HBV DNA (predicted probability, 88%), normalization of alanine aminotransferase (ALT) levels (66%), HBeAg seroconversion (20%), and hepatitis B surface antigen loss (5%); it ranked third in histologic improvement of the liver (53%). Entecavir was most effective in improving liver histology (56%), second for inducing undetectable levels of HBV DNA (61%) and normalization of ALT levels (70%), and third in loss of hepatitis B surface antigen (1%). In HBeAg-negative patients, tenofovir was the most effective in inducing undetectable levels of HBV DNA (94%) and improving liver histology (65%); it ranked second for normalization of ALT levels (73%). **CONCLUSIONS: In the first year of treatment for CHB, tenofovir and entecavir are the most potent oral antiviral agents for HBeAg-positive patients; tenofovir is most effective for HBeAg-negative patients.**

Keywords: Bayesian Direct and Indirect Comparison; Mixed Treatment Comparison (MTC); Meta-Analysis; Hepatitis B Virus (HBV).

An estimated 400 million people worldwide are chronically infected with the hepatitis B virus (HBV).[1] Approximately 25% eventually will die of the liver-related complications of liver failure and hepatocellular carcinoma (HCC) if left untreated. Many chronically infected individuals, however, achieve spontaneous immune control of their HBV infection and do not require treatment. Loss of the viral protein marker, hepatitis B e antigen (HBeAg), frequently is associated with spontaneous immune control of HBV infection. Currently available antiviral therapies can suppress viral replication, whereas sustained immune suppression of HBV DNA is required to clear virus (loss of hepatitis B surface antigen [HBsAg]). For those who do not achieve spontaneous immune control, the goal is long-term suppression of HBV-DNA replication, which in some patients is followed by loss of HBsAg; the latter is associated with a lower risk of HCC and improved survival.[2,3]

Currently available treatments include individualized single-agent therapy with interferon-alfa, nucleos(t)ide analogue polymerase inhibitors, and, potentially, combinations of these 2 forms of treatment. The specific drugs available worldwide for chronic hepatitis B (CHB) include standard and pegylated interferon alfa, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Interferon is used as a short-term treatment that, when successful, may lead to long-term immune control without the need for further antiviral therapy.[4] Nucleos(t)ide analogues that directly inhibit the HBV reverse-transcriptase polymerase have no immune effect. Thus, once started, lifelong treatment may be required. Initiating therapy with each of these medications involves consideration of drug-specific trade-offs such as high and potentially lifelong medication costs, potential side effects including risks during pregnancy, and, perhaps most importantly, the risk of drug resistance over time.[5] The risk of cross-drug resistance to polymerase inhibitors is a very serious problem because new HBV variants respond less well to new treatments with other polymerase inhibitors and often higher doses are required.[6]

Abbreviations used in this paper: CHB, chronic hepatitis B; CrI, credible interval; RCTs, randomized controlled trials; MCT, mixed treatment comparisons; OR, odds ratio; PP, predicted probability.

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Published studies evaluate the ability of drugs in treatment-naive CHB to achieve the following: (1) suppress HBV-DNA levels to clinically relevant levels (<1000 copies/mL, a level associated with inactive disease and a decreased risk of subsequent drug resistance)[7,8]; (2) normalize ALT levels because normalization usually indicates cessation of ongoing liver injury; (3) induce HBeAg loss with seroconversion to anti-HBe because those who achieve this outcome may no longer require ongoing antiviral therapy; (4) decrease serum HBsAg titer because subsequent loss of HBsAg is a marker of sustained viral suppression; (5) improve liver histology; and (6) not to cause serious adverse events either while on or shortly after stopping therapy. Except for the trials of pegylated interferon, results are reported only for as long as the patients remain on treatment. Hence, few studies address the question of whether HBV-DNA suppression can be sustained long term once any of the oral therapies are discontinued.

The purpose of our study was to systematically review all published randomized controlled trials (RCTs) of drugs used to treat CHB as monotherapies or combination therapies to estimate their relative treatment efficacies at the end of 1 year of treatment and to rank the treatments according to the success rates for each outcome.

Materials and Methods

Eligibility Criteria

To be included, studies must have examined adults with HBeAg-positive and/or HBeAg-negative CHB in randomized, phase 3, controlled trials comparing new drug treatments with either placebo or already licensed drugs. The drugs evaluated included pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, or tenofovir as monotherapy or combination therapy administered for a 1-year period (48–52 wk). Trials that used standard interferon therapy were not included in the analysis. The trials that used pegylated interferon were conducted for 48 weeks only. Thus, measurements of treatment efficacy were taken at 48 weeks, after which pegylated interferon therapy was discontinued. Discontinuations of both interferons and oral antivirals may be associated with a short-lived or sustained flare-up of hepatitis. Those studies using oral antiviral therapy may have continued on therapy beyond 48 weeks but some trial designs stopped treatment in some patients[9,10] at 48 weeks. Because an intention-to-treat approach was not used for all drug trials past the first year of treatment, direct comparisons could be made only at 48 weeks of treatment.

Excluded were the following studies: (1) studies of patients who were co-infected with human immunodeficiency virus, hepatitis C, or hepatitis D, (2) studies not reporting any efficacy measures, and (3) studies of patients with lamivudine resistance owing to mutations in the YMDD motif of the reverse-transcription polymerase gene. When several publications pertaining to one study were identified, the primary publication was used.

Literature Search

MEDLINE, EMBASE, Cochrane Systematic Reviews, and Web of Science Databases were searched using MeSH terms and keywords describing CHB, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, tenofovir, RCTs, and surrogate treatment outcome. The search was limited to the English language and started from the date of inception of each database until October 30, 2009. The search strategy is described in greater detail in Supplementary Appendix A. Initial screening of abstracts was performed for each article by 2 reviewers (G.W. and Y.N.); a third-party arbiter addressed disagreements. We obtained full articles for all potentially relevant trials, and the reference list of each article was searched for other potential studies. Clinical experts were consulted to determine if any published studies were missing. Meeting abstracts, unpublished data, and theses were not reviewed.

Study Quality

Methodologic quality was assessed independently by 2 reviewers (G.W. and Y.N.) using the Cochrane risk of bias tool, an established tool based on assessing sequence generation for the randomization of subjects, allocation concealment of treatment, blinding, reporting of data, and other sources of bias. When discrepancies arose, a third party (M.K.) was consulted.

Efficacy Measures and Definitions

All outcome measurements were intermediate end points taken at 12 months. It is appreciated that some patients would be continued on oral therapy beyond this time period, whereas patients on pegylated interferon therapy would be at the end of their treatment. However, because of the variability in study design of the trials after the first year of treatment, it was most appropriate to analyze the data at 12 months. Data extracted included rates of virologic and biochemical response, HBeAg loss, HBeAg seroconversion, HBsAg loss, histologic improvement, and serious adverse events. Virologic response was defined as attainment of undetectable levels of HBV DNA as determined by the polymerase chain reaction test for the particular study. Threshold values for undetectable DNA levels according to the technique used for measurement were documented because they could be a source of heterogeneity. Only studies in which the threshold of detection was 1000 copies/mL or less were used in the analysis of undetectable HBV-DNA levels.[11] Variability in baseline viral load between studies was not adjusted for because mixed treatment comparison (MTC) assesses relative and not absolute treatment

effects. Biochemical responses were defined as normalization of ALT levels to below the upper limit of normal for that study. In HBeAg-positive patients, seroconversion was defined as undetectable HBeAg and the presence of anti-HBeAg. HBeAg loss and HBsAg loss were defined as undetectable, using the threshold of detection used in each corresponding study. Histologic improvement of the liver was defined as a 2- point improvement on the Knodell inflammation score without an increase in fibrosis. Treatment safety was assessed using the occurrence of serious adverse events requiring withdrawal from treatment or reduction in treatment dosage. For studies that did not include a complete list of all surrogate outcomes, only the outcomes that were available were included in the statistical analysis.

Data Extraction

Two authors (G.W. and Y.N.) independently extracted the data using a standard form. Discrepancies were resolved between the reviewers with the assistance of an arbiter when necessary. The following data were recorded: (1) number of patients in the study, (2) details of the study design, (3) treatment doses and duration, (4) patient characteristics, and (5) outcome measures performed as described earlier.

Statistical Analysis

There were 10 different treatment combinations, and data were available for only 13 of the 45 possible pairs of comparisons. Standard methods of meta-analysis would give an incomplete picture of the relative benefits of the treatment regimens because they only evaluate 2 treatments at a time. Therefore, our primary analysis used Bayesian MTC. This method can be used to perform direct (head-to-head) comparisons, as well as indirect comparisons of treatments not compared directly within any of the individual trials. The indirect comparison of 2 treatments requires a common comparator or a link between them by a chain of comparisons. For example, an indirect comparison of treatments A and C can be made if head-to-head data for the comparisons A versus B and B versus C are available (Figure 1). MTC analysis preserves the within-trial randomized treatment comparisons (eg, A vs B and B vs C); it does not directly compare the single arms A and C, but rather combines all chains of evidence to provide unbiased treatment effect estimates.[12,13]

Lamivudine was used as the common comparator because it is the most commonly used treatment for CHB and the first antiviral oral therapy to be licensed. We ran the MTC model to calculate the odds ratio (OR) comparing each of the treatments. Using the same data, we ran a Bayesian random effects meta-analysis of pairs compared directly in trials. We reported the median of the posterior probability distribution and 95% credible interval (CrI) for each OR. When the OR 95% CrI did not include 1, the OR was considered statistically significantly different from the comparator.

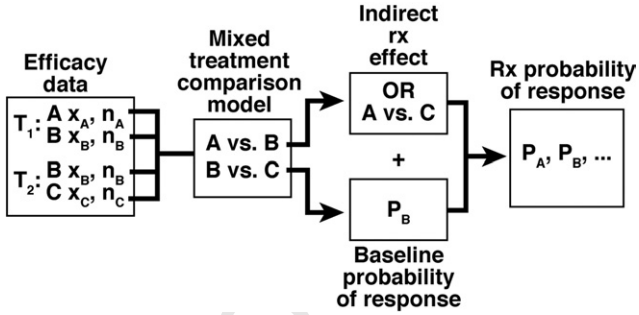

Figure 1. Bayesian MTC method. Binary efficacy data of pair-wise comparisons are entered into a Bayesian MTC model that calculates indirect treatment effects and the probability of a response from the common comparator treatment (P_B). The indirect treatment effects (OR of A vs C) and probability of response of the common comparator (P_B) are used to calculate the probability of response for each of the treatments (P_A and P_C). T_1, trial 1; T_2, trial 2; x_A, number of responders on treatment A; n_A, number of patients on treatment A; x_B, number of responders on treatment B; n_B, number of patients on treatment B; x_C, number of responders on treatment C; n_C, number of patients on treatment C; P_A, probability of a response from treatment A; P_B, probability of response from treatment B; RX, treatment effect.

Because the predicted probabilities of an outcome with a given treatment are more readily understood than the OR comparing treatments, we used the MTC model to estimate these probabilities. This required that we run in parallel a separate meta-analysis to estimate the probability of an outcome for lamivudine, the baseline comparator. The estimate of the response probability for lamivudine then was combined with the results of the MTC model to obtain the probability of a therapeutic effect for each treatment. The analysis was performed using a Bayesian random effects model using WinBUGS software version Cambridge, UK 1.4.3[14] (Supplementary Appendix B). For example, if the probability of a virologic response for lamivudine is P_{lam} and the OR for successful treatment comparing pegylated interferon with lamivudine is $OR_{peg\text{-}lam}$, the estimated probability of a virologic response under treatment with pegylated interferon would be as follows: $P_{peg} = OR_{peg\text{-}lam} \times P_{lam}/[1 + P_{lam}(OR_{peg\text{-}lam} - 1)]$.

To fit the model, we used 3 sets of starting values sampled from uniform and normal prior distributions and 5000 burn-in iterations. Convergence was assessed using the Gelman–Rubin–Brooke statistic.[15] A further 20,000 Markov Chain Monte Carlo iterations were run, and the sampled values were used to estimate posterior means, medians, and credible intervals for response probabilities and ORs.

The treatments then were ranked for each of the surrogate outcomes on the basis of their predicted probabilities. Because there was some uncertainty in the rankings owing to uncertainty in the estimation of the treatment OR, we also present the probability that each

treatment was ranked first among the 10 treatments. For each surrogate outcome, heterogeneity was assessed through calculation of the between-study standard deviation in log-ORs, and guidance on interpreting the sizes of the standard deviation is provided. In addition, the range of ORs at extremes of the random effects distribution and the median ORs for a randomly selected pair of studies estimating the same treatment effect are presented.[16]

Results

Search Results and Study Characteristics

We initially identified 3338 potentially eligible citations. After evaluating these citations and their bibliographies, we included 20 trials[9,10,17–33] (Figure 2); 15 in HBeAg-positive patients, 8 in HBeAg-negative patients. Three of these studies evaluated both HBeAg-positive and HBeAg-negative patients.

Table 1 provides a summary of the characteristics of the 20 studies that met our inclusion criteria. Double-blinding was described fully in 12 studies, partially in 2 studies, 4 studies were open-label studies, and 2 studies did not report blinding. As assessed by the Cochrane Risk of Bias tool, inadequate sequence generation provided the largest risk of bias followed by inadequate allocation concealment (Figure 3).

The doses of pegylated interferon varied (100 or 180 μg/wk or 1.5 μg/kg/wk) whereas standard doses of lamivudine, adefovir, entecavir, and tenofovir were 100 mg, 10 mg, 0.5 mg, and 300 mg, respectively. Findings from studies with doses of telbivudine of 400 and 600 mg were pooled together because these doses have been found to be pharmacodynamically equivalent.[23]

HBeAg-Positive Patients

Lamivudine. For the treatment of CHB, there were 10 trials with 1540 individuals treated with lamivudine, the common comparator used for our analysis (Table 1). When outcomes are beneficial, an OR greater than 1 reflects a treatment that is more effective in comparison with the common comparator (lamivudine) whereas an OR less than 1 reflects a less effective treat-

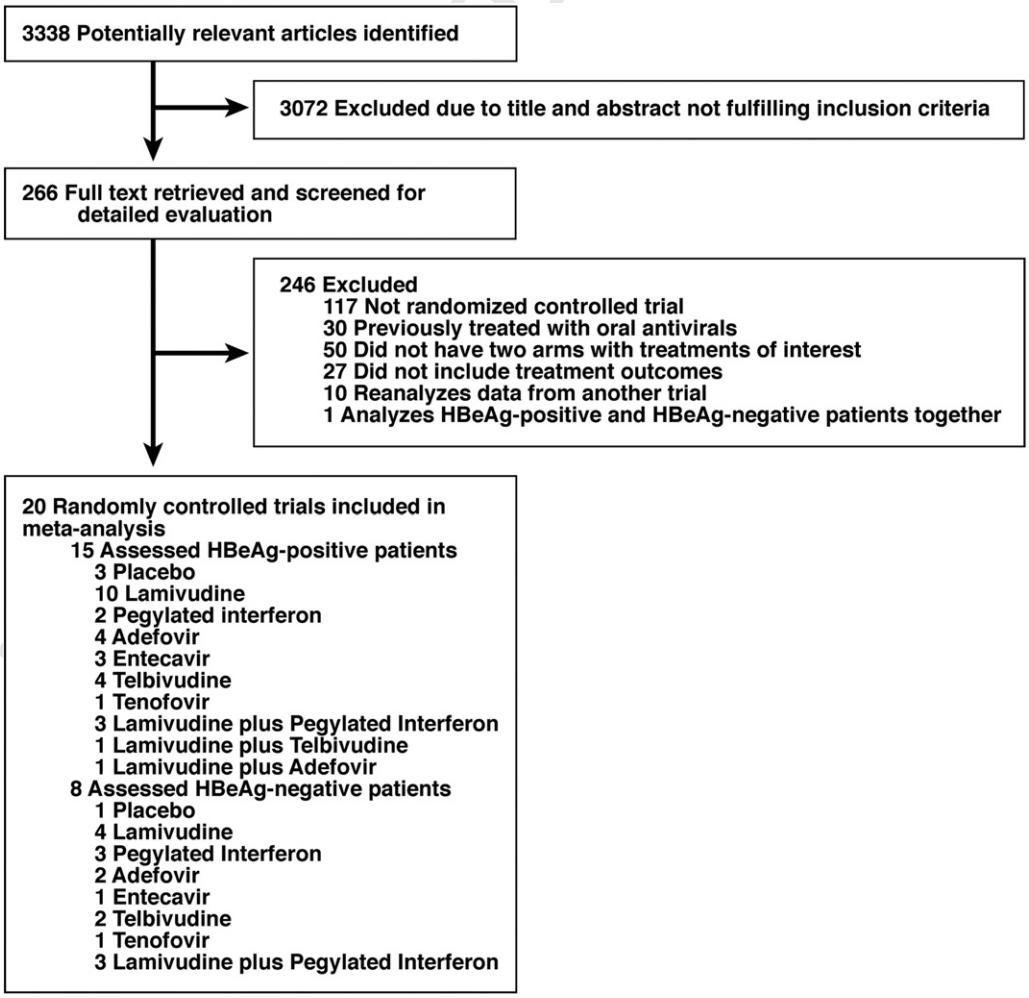

Figure 2. Study selection and disposition.

Table 1. RCTs Reporting the Use of Antiviral Agents

Source	Treatment duration, wk	Study design	No.	Medication	Outcomes					
					HBV DNA	ALT norm	HBeAg sero	HBeAg loss	HBsAg loss	Histo improv
Chronic HBeAg-positive patients										
Lai et al,[17] 1998	52	Double-blind; follow-up and withdrawal described	358	PLA: daily		12/50	3/70		0/72	18/72
				LAM: 100 mg/day		68/95	22/140		0/143	80/143
Dienstag et al,[35] 1999	52	Double-blind; follow-up and withdrawal described	143	PLA: daily		5/68	4/69	8/71	0/71	24/71
				LAM: 100 mg/day		27/66	11/63	21/66	1/66	42/66
Marcellin et al,[20] 2003	48	Double-blind; follow-up and withdrawal described	515	PLA: daily	0/167	26/164	9/161	17/161		41/161
				ADV: 10 mg/day	36/171	81/168	20/171	41/171		89/168
Chan et al,[21] 2005	52	Open-label; follow-up and withdrawal described	100	LAM: 100 mg/day	2/50	39/50			0/50	4/50
				LAM + PEG: 100 mg/day + 1.5 μg/kg/wk	5/50	45/50			1/50	4/50
Janssen et al,[22] 2005	52	Double-blind; follow-up and withdrawal described	307	PEG: 100 μg/wk	13/136	46/136	30/136	40/130	7/136	31/58
				LAM + PEG: 100 mg/day + 100 μg/wk	43/130	66/130	33/130	57/130	9/130	25/52
Lai et al,[23] 2005	52	Double-blind; follow-up and withdrawal described	107	LAM: 100 mg/day	6/19	12/19	4/19	5/19	0/19	
				LdT: 400/600 mg/day	27/44	38/44	14/44	15/44	0/44	
				LAM + LdT: 100 mg + 400/600 mg/day	20/41	32/41	6/41	7/41	0/41	
Lau et al,[24] 2005	48	Partially double-blind[a]; follow-up and withdrawal described	814	LAM: 100 mg/day	108/272	168/272	55/272	59/272		
				PEG: 180 μg/wk	68/271	105/271	72/271	81/271		
				LAM + PEG: 180 μg × wk + 100 mg/day	186/271	126/271	64/271	73/271		
Chang et al,[9] 2006	52	Double-blind; follow-up and withdrawal described	715	LAM: 100 mg/day	129/355	213/355	64/355	70/355	4/355	195/314
				ETV: 0.5 mg/day	236/354	242/354	74/354	78/354	6/354	226/314
Chan et al,[25] 2007	52	Open-label; follow-up and withdrawal described	89	ADV: 10 mg/day	17/44	37/44	8/44	9/44	0/44	
				LdT: 600 mg/day	26/45	35/45	12/45	13/45	0/45	
Lai et al,[26] 2007	52	Double-blind; follow-up and withdrawal described	1370	LAM: 100 mg/day	187/463	347/463	100/463	108/463		261/463
				LdT: 600 mg/day	275/458	354/458	103/458	118/458		296/458
Ren et al,[27] 2007	48	Blinding not known; follow-up and withdrawal described	42	LAM: 100 mg/day	8/21	16/21	4/21			
				ETV: 0.5 mg/day	15/21	18/21	3/21			
Hou et al,[28] 2008	52	Double-blind; follow-up and withdrawal described	290	LAM: 100 mg	38/143	75/143	18/143	20/143	0/143	
				LdT: 600 mg	67/147	87/147	25/147	31/147	0/147	
Marcellin et al,[34] 2008	48	Double-blind; follow-up and withdrawal described	266	ADV: 10 mg/day	12/90	49/90	14/80		0/82	61/90
				TDF: 300 mg/day	134/176	115/169	32/153		5/158	131/176
Sung et al,[30] 2008	52	Double-blind; follow-up and withdrawal described	111	LAM: 100 mg	23/56	39/56	9/54	12/54		
				LAM + ADV: 100 mg + 10 mg/day	21/53	24/51	5/52	6/52		
Leung et al,[41] 2009	52	Open-label; follow-up and withdrawal described	69	ADV: 10 mg/day	6/32	20/32	7/32	7/32		
				ETV: 0.5 mg/day	19/33	25/33	5/33	6/33		

Table 1. Continued

					HBV DNA	ALT norm	HBsAg loss	Histo improv
Chronic HBeAg-negative patients								
Hadziyannis et al,[31] 2003	48	Double-blind; follow-up and withdrawal described	185	PLA: daily	0/61	17/59		19/57
				ADV: 10 mg/day	63/123	84/116		77/121
Marcellin et al,[32] 2004	48	Partially double-blind[a]; follow-up and withdrawal described	537	LAM: 100 mg/day	133/181	132/181		
				PEG: 180 μg/wk	112/177	67/177		
				PEG + LAM: 180 μg/wk + 100 mg/day	156/179	87/179		
Lai et al,[10] 2006	52	Double-blind; follow-up and withdrawal described	648	LAM: 100 mg/day	225/313	222/313	1/313	174/287
				ETV: 0.5 mg/day	293/325	253/325	1/325	208/296
Kaymakoglu et al,[33] 2007	48	Open-label; follow-up and withdrawal described	48	PEG: 1.5 μg/kg/wk	5/19	10/19		
				PEG + LAM: 1.5 μg/kg/wk + 100 mg/day	7/29	19/29		
Lai et al,[26] 2007	52	Double-blind; follow-up and withdrawal described	1370	LAM: 100 mg/day	160/224	177/224		148/224
				LdT: 600 mg/day	196/222	165/222		148/222
Hou et al,[28] 2008	52	Double-blind; follow-up and withdrawal described	42	LAM: 100 mg	17/22	17/22	0/22	
				LdT: 600 mg	17/20	20/20	0/20	
Marcellin et al,[34] 2008	48	Double-blind; follow-up and withdrawal described	375	ADV: 10 mg/day	79/125	91/118	0/125	86/125
				TDF: 300 mg/day	233/250	180/236	0/250	181/250
Papadopoulos et al,[42] 2009	48	Blinding unknown; follow-up, withdrawal described	123	PEG: 1.5 μg/kg/wk	24/35			
				PEG + LAM: 1.5 μg/kg/wk + 100 mg/day	73/88			

HBV DNA, undetectable HBV-DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBeAg sero, hepatitis B e antigen seroconversion; HBeAg loss, hepatitis B e antigen loss; HBsAg loss, hepatitis B surface antigen loss; Histo improv, histologic improvement of the liver; PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir.

[a]In studies with pegylated interferon, partial blinding was used because placebo injections were not administered.

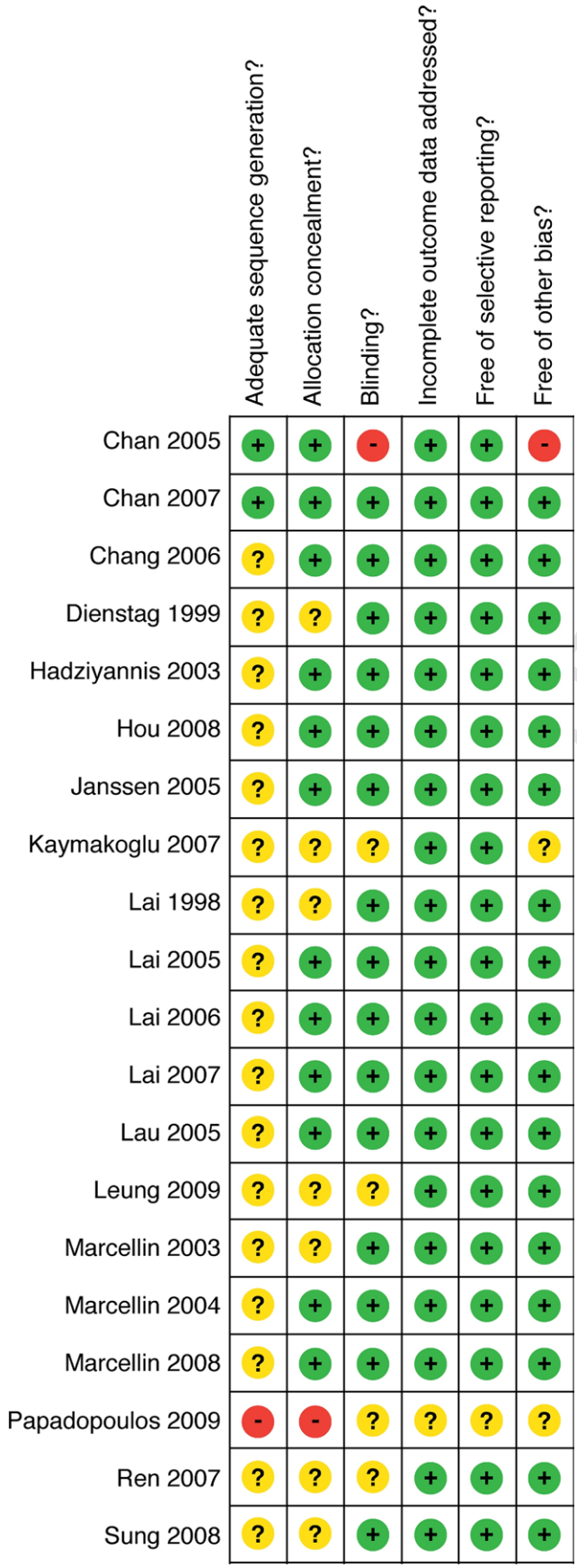

Figure 3. Cochrane risk of bias tool results.

ment. In direct comparisons, placebo was significantly less effective in inducing ALT normalization (OR, 0.11; 95% CrI, 0.03–0.38) and improving liver histology (OR, 0.27; 95% CrI, 0.09–0.84) compared with lamivudine.

In indirect comparisons, lamivudine was superior to placebo for all surrogate outcomes except inducing HBsAg loss (Supplementary Table 1).

Pegylated interferon. Pegylated interferon (n = 407) was evaluated as monotherapy in 2 trials. Studies of standard interferon were omitted because this short-acting form of interferon is no longer considered by most as the standard of care. Direct comparisons suggested that it is significantly more effective than lamivudine monotherapy in inducing decreases in HBeAg loss and HBsAg loss. Pegylated interferon ranked among the top 4 treatments for HBeAg seroconversion (predicted probability [PP], 0.23; 95% CrI, 0.14–0.35), HBeAg loss (PP, 0.33; 95% CrI, 0.15–0.54), HBsAg loss (PP, 0.01; 95% CrI, 0–0.07), and histologic improvement of the liver (PP, 0.52; 95% CrI, 0.06–0.95) (Table 2).

Adefovir. Adefovir (n = 337) was evaluated in 4 trials and was not significantly better than lamivudine. Adefovir did not rank above fourth place for any outcome.

Entecavir. Entecavir (n = 408) was a comparator in 3 trials. In direct comparisons, it had increased efficacy in comparison with lamivudine in improving liver histology (OR, 1.56; 95% CrI, 1.12–2.19). Entecavir consistently ranked in the top 5 treatments for all surrogate outcomes and was ranked first with regard to improving liver histology (PP, 0.56; 95% CrI, 0.12–0.94).

Telbivudine. Telbivudine (n = 684) was a comparator in 4 trials. In direct comparisons, it had improved efficacy compared with lamivudine in inducing undetectable HBV DNA (OR, 2.34; 95% CrI, 1.31–5.36) and histologic improvement of the liver (OR, 1.41; 95% CrI, 1.09–1.84). Indirect comparisons confirmed the results of the direct comparison of HBV-DNA undetectability. Telbivudine's rankings ranged from second for HBeAg loss to last for HBsAg loss.

Tenofovir. Tenofovir (n = 176) was a comparator in one study. In indirect comparisons, tenofovir showed improved efficacy compared with lamivudine in inducing undetectable HBV-DNA levels (OR, 23.34; 95% CrI, 6.19–76.39). Tenofovir was consistently ranked in the top 3 treatments for all surrogate outcomes except HBeAg loss, for which no data were available. It was ranked first for inducing undetectable HBV DNA (PP, 0.88; 95% CrI, 0.69–0.97) normalization of ALT levels (PP, 0.66; 95% CrI, 0.41–0.91), HBeAg seroconversion (PP, 0.20; 95% CrI, 0.07–0.43), and HBsAg loss (PP, 0.05; 95% CrI, 0–0.54).

Combination therapy. Three combination strategies were assessed in this analysis, lamivudine plus pegylated interferon (n = 451), lamivudine plus telbivudine (n = 41), and lamivudine plus adefovir (n = 53). In

Table 2. Rank Order of Treatments for 6 Outcomes for Chronic HBeAg-Positive Patients

	Outcomes																					
	HBV DNA			ALT norm			HBeAg sero			HBeAg loss			HBsAg loss			Histo improv					
Rank	Treatment	Best[a]	*P*[b] (95% CrI)	Treatment	Best[a]	*P*[b] (95% CrI)	Treatment	Best[a]	*P*[b] (95% CrI)	Treatment	Best[a]	*P*[b] (95% CrI)	Treatment	Best[a]	*P*[b] (95% CrI)	Txt	Best[a]	*P*[b] (95% CrI)
1	TDF	98.9	.88 (0.69–0.97)	TDF	39.02	.66 (0.41–0.91)	TDF	25.65	.20 (0.07–0.43)	LAM + PEG	52.20	.39 (0.18–0.63)	TDF	47.90	.05 (0–0.54)	ETV	26.65	.56 (0.12–0.94)
2	ETV	0.79	.61 (0.36–0.80)	ETV	28.94	.70 (0.52–0.86)	PEG	24.75	.23 (0.14–0.35)	LdT	19.56	.34 (0.18–0.56)	LAM + PEG	13.87	.01 (0–0.09)	PEG	24.15	.52 (0.06–0.95)
3	LAM + PEG	0.20	.57 (0.34–0.77)	LAM + LdT	23.25	.64 (0.32–0.90)	LAM + PEG	23.15	.23 (0.13–0.34)	PEG	9.68	.33 (0.15–0.54)	ETV	12.87	.01 (0–0.05)	TDF	21.26	.53 (0.06–0.95)
4	LdT	0.00	.51 (0.30–0.70)	LdT	5.99	.65 (0.47–0.81)	LdT	12.28	.21 (0.14–0.32)	ADV	7.28	.28 (0.11–0.52)	PEG	10.38	.01 (0–0.07)	LdT	17.17	.54 (0.12–0.93)
5	LAM + LdT	0.00	.43 (0.17–0.73)	LAM + PEG	1.20	.54 (0.35–0.76)	ETV	6.29	.19 (0.10–0.27)	ETV	6.49	.28 (0.13–0.51)	LAM + LdT	5.69	.01 (0–0.04)	LAM + PEG	7.28	.48 (0.07–0.93)
6	ADV	0.00	.33 (0.11–0.64)	ADV	0.70	.58 (0.37–0.80)	LAM + ADV	3.09	.12 (0.03–0.30)	LAM + LdT	2.69	.19 (0.04–0.45)	ADV	5.09	.02 (0–0.18)	ADV	3.09	.46 (0.07–0.92)
7	LAM	0.00	.31 (0.16–0.48)	LAM + ADV	0.50	.39 (0.16–0.68)	LAM + LdT	2.70	.11 (0.03–0.28)	LAM + ADV	1.70	.17 (0.04–0.42)	LAM	2.70	.00 (0–0.02)	LAM	0.40	.48 (0.13–0.86)
8	LAM + ADV	0.00	.30 (0.10–0.56)	LAM	0.20	.61 (0.47–0.73)	ADV	1.90	.17 (0.08–0.30)	LAM	0.04	.28 (0.16–0.45)	PLA	0.90	.00 (0–0.01)	PLA	0.00	.23 (0.03–0.67)
9	PEG	0.00	.20 (0.08–0.36)	PEG	0.00	.39 (0.20–0.61)	LAM	0.00	.18 (0.15–0.21)	PLA	0.00	.11 (0.04–0.27)	LdT	0.60	.00 (0–0.01)			
10	PLA	0.00	.01 (0.00–0.04)	PLA	0.00	.20 (0.08–0.36)	PLA	0.00	.06 (0.03–0.12)									

PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV-DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBeAg sero, hepatitis B e antigen seroconversion; HBeAg loss, hepatitis B e antigen loss; HBsAg loss, hepatitis B surface antigen loss; Histo Improv, histologic improvement of the liver.

[a]Percentage of iterations for which the treatment is ranked first.

[b]Posterior probability of an outcome.

indirect comparisons, lamivudine plus pegylated interferon was more effective in inducing undetectable HBV DNA than lamivudine alone (OR, 3.08; 95% CrI, 1.88–4.91). In overall rankings, this combination was first in inducing HBeAg loss (PP, 0.39; 95% CrI, 0.18–0.63) and third for HBeAg seroconversion and second for HBsAg loss. In neither direct nor indirect comparisons were significant improvements found with combination therapy of 2 oral therapies (ie, lamivudine plus telbivudine or lamivudine plus adefovir) relative to lamivudine monotherapy.

The all-oral antiviral combinations of lamivudine plus telbivudine and lamivudine plus adefovir were ranked low in comparison with other therapies.

The between-study standard deviations of log-ORs for the surrogate outcomes, undetectable HBV DNA, ALT normalization, HBeAg seroconversion, HBeAg loss, HBsAg loss, and histologic improvement had posterior medians of 0.14, 0.29, 0.16, 0.27, 0.58, and 0.30, respectively (Table 3).

For all but HBsAg loss, the degree of heterogeneity of the estimates was considered reasonable.[16]

HBeAg-Negative Patients

Lamivudine. In indirect comparisons, lamivudine (n = 740) was more effective in comparison with placebo in inducing undetectable HBV DNA. In comparison with other treatments, lamivudine was ranked in the bottom 2 treatments for all outcomes measured (Table 4).

Monotherapies. In direct comparisons, pegylated interferon was less effective than lamivudine in inducing undetectable HBV-DNA levels and ALT normalization 1 year after the initiation of therapy. In direct pair-wise comparisons with lamivudine, neither adefovir, telbivudine, entecavir nor tenofovir were more efficacious. However, in indirect comparisons, treatment with entecavir was more efficacious for all outcomes. Entecavir was ranked among the top 4 treatments for all outcomes, HBV DNA (PP, 0.88; 95% CrI, 0.65–0.97), ALT normalization (PP, 0.76; 95% CrI, 0.25–0.98), and histologic improvement (PP, 0.64; 95% CrI, 0.01–1.00). Tenofovir ranked first for HBV-DNA suppression (PP, 0.94; 95% CrI, 0.56–1.00) and histologic improvement (PP, 0.65; 95% CrI, 0.01–1.00), and second for ALT normalization (PP, 0.73; 95% CrI, 0.07–1.00) (Supplementary Table 2).

Combination therapy. Lamivudine plus pegylated interferon (n = 296) was more effective than lamivudine alone in inducing undetectable HBV-DNA levels (OR, 2.40; 95% CrI, 1.41–4.19). However, it was less effective in inducing ALT normalization (OR, 0.35; 95% CrI, 0.23–0.55) at 1 year.

The standard deviation for the surrogate outcomes, undetectable HBV DNA, ALT normalization, and histologic improvement, were 0.48, 0.83, and 0.48, respectively (Table 3).

Table 3. Measures of Heterogeneity: Standard Deviation on the Log-Odds Scale, and Measures of Spread of the ORs for any Given Treatment Comparison for Chronic HBeAg-Positive and HBeAg-Negative Patients

	HBV DNA	ALT norm	HBeAg sero	HBeAg loss	HBsAg loss	Histo improv
HBeAg-positive patients						
SD (log OR)	0.1399	0.278	0.1647	0.2667	0.5827	0.2988
Median ratio of pairs of ORs[a]	1.16	1.35	1.20	1.34	1.89	1.38
Ratio of an extreme pair of ORs[b]	1.73	2.97	1.91	2.84	9.82	3.23
HBeAg-negative patients						
SD (log OR)	0.48	0.83				0.49
Median ratio of pairs of ORs[a]	1.68	2.46				1.70
Ratio of an extreme pair of ORs[b]	6.53	25.48				6.71

NOTE. Values of SD from 0.1 to 0.5 are reasonable, from 0.5 to 1.0 are considered fairly high, and greater than 1.0 represent extreme heterogeneity.[16]

HBV DNA, undetectable HBV DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; HBeAg sero, hepatitis B e antigen seroconversion; HBeAg loss, hepatitis B e antigen loss; HBsAg loss, hepatitis B surface antigen loss; Histo improv, histological improvement of the liver.

[a]Estimated median ratio of ORs for 2 randomly chosen studies examining the same treatment comparison and is equal to exp (1.09 × standard deviation).

[b]Ratio of the ORs at the 97.5% (upper end) and 2.5% (lower end) points of the random effects distribution and is equal to exp (3.92 × standard deviation).

Severe Adverse Events

Severe adverse events were documented inconsistently and had varied definitions for each study, which prevented quantitative analysis. The greatest number of events occurred with monotherapy and combination therapies involving pegylated interferon.[21,22] Most events resolved after a decrease in dosage of pegylated interferon, withholding of dosages for a short period of time, or termination of therapy.[21]

Depression was reported as the main concern in patients treated with pegylated interferon.[24,32] The rate of depression on pegylated interferon therapy was 5%; combination therapy of lamivudine plus pegylated interferon was associated with similar depression rates (6%–7%).[24,32] The reported average rates of discontinuation of therapy were as follows: pegylated interferon, less than 5%; lamivudine, 2.8%; adefovir, 1.0%; entecavir, 1.8%; and tenofovir 1.0%. The most common adverse events reported while on treatment with oral antivirals were headache, upper respiratory infection, nasopharyngitis, cough, fatigue, upper abdominal pain, back pain, and diarrhea, most of which were mild-to-moderate in severity as reported by each of the studies.[20,27,30,34,35] There was inconsistent documentation for adverse events after discontinuation of therapy. All treatments induced low rates of grade 3 or 4 changes in clinical laboratory values of liver tests (serum ALT, creatine kinase), and the rates were similar for each treatment.[28,34,35] The rates of hepatic flares on therapy were as follows: lamivudine (4%[30]), pegylated interferon (8%[32]), adefovir (2%[32]), entecavir (1%[10]), telbivudine (1%[34]), tenofovir (6%[34]), and combination therapy with lamivudine plus adefovir (7%[30]).

AQ: 21

Table 4. Rank Order of Treatments for 3 Outcomes for Chronic HBeAg-Negative Patients

	Outcomes								
	HBV DNA			ALT norm			Histo improv		
Rank	Treatment	Best[a]	P^b (95% CrI)	Treatment	Best[a]	P^b (95% CrI)	Treatment	Best[a]	P^b (95% CrI)
1	TDF	81.04	.94 (0.56–1.00)	LdT	27.25	.82 (0.47–0.99)	TDF	33.43	.65 (0.01–1.00)
2	ETV	11.08	.88 (0.65–0.97)	TDF	23.55	.73 (0.07–1.00)	ETV	23.15	.64 (0.01–1.00)
3	LdT	6.59	.86 (0.67–0.96)	ADV	22.55	.75 (0.11–1.00)	ADV	20.46	.63 (0.01–1.00)
4	LAM + PEG	0.70	.81 (0.56–0.93)	ETV	20.96	.76 (0.25–0.98)	LdT	14.77	.58 (0.00–1.00)
5	ADV	0.50	.81 (0.15–1.00)	LAM + PEG	1.99	.56 (0.15–0.93)	PLA	5.09	.47 (0.00–1.00)
6	PEG	0.00	.67 (0.41–0.89)	PLA	1.70	.50 (0.02–0.98)	LAM	3.09	.59 (0.01–1.00)
7	LAM	0.00	.73 (0.65–0.81)	LAM	1.40	.75 (0.54–0.89)			
8	PLA	0.00	.11 (0.00–0.71)	PEG	0.60	.46 (0.09–0.89)			

NOTE. No post-pegylated interferon liver biopsies were performed because the effect may continue to change after discontinuation because interferon is both an antiviral and an immune-stimulant.

PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV-DNA levels; ALT norm, normalization of serum alanine aminotransferase levels; Histo improv, histologic improvement of the liver.

[a]Percentage of iterations for which the treatment is ranked first.

[b]Posterior probability of an outcome.

Discussion

Many new antiviral treatments for CHB have become available within the past 2 decades. The first drug approved was interferon, an immune modulator and antiviral. After its inception, there has been a shift toward focusing on oral antiviral drugs, nucleos(t)ide analogues. RCTs comparing these treatments have been limited to comparing 2–3 drugs or drug combinations at a time whereas traditional meta-analytic techniques are limited to comparing 2 interventions. This has left clinicians to make their own judgments about the relative efficacy of treatments for which head-to-head trials are not available.

In our study, we used Bayesian MTC to evaluate the relative efficacy of all available treatments across 6 surrogate clinical outcomes. We consolidated the information of all RCTs that included the treatments of interest to provide the probability of an outcome at the end of 1 year of treatment as well as a rank for all treatments. The results of our analysis suggest that in treatment-naive individuals, entecavir and tenofovir are most effective at the end of the first year of therapy in HBeAg-positive patients whereas tenofovir is most effective in HBeAg-negative patients based on an overall assessment of all surrogates outcomes.

Our study focused on assessing surrogate clinical outcomes at the end of the first year of treatment. In recent years, there has been a shift toward evaluating outcomes that will reflect long-term improvements in the prognosis of those with CHB. Two authors (Fattovich et al[2] and Hui et al[3]) have suggested that loss of HBsAg is the optimal goal of treatment and is the only surrogate marker of successful immunologic control and is associated with a lower incidence of cirrhosis and HCC and improved survival rates. Loss of HBsAg was not seen in those patients on oral antiviral treatment for 1 year but was seen in some patients who received pegylated interferon at 1 year after the initiation of treatment in the studies we reviewed. Although useful as an initial comparison of the various drugs, the utility of this review is limited to standard clinical practice in which the nucleos(t)ide analogue polymerase inhibitors are used and they are rarely prescribed for just 1 year. Rather, long-term, perhaps lifelong, suppressive therapy may be required. Important treatment issues such as long-term drug cost and drug toxicity, treatment failure owing to inadequate patient adherence, and/or drug resistance have not been addressed. In our study, few severe adverse events were reported in the first year of treatment. However, incidents of renal toxicity, lactic acidosis, neuropathy, as well as myositis have now been reported with long-term treatment using nucleos(t)ide analogues. Finally, the change in biomarker status examined in this review, such as loss of HBeAg or suppression of HBV DNA to undetectable levels, was determined while continuing antiviral therapy and the durability of this response on stopping therapy is not well known, particularly for the newer agents, tenofovir and entecavir.

Our study had limitations. First, the number of studies included for each pair-wise comparison was small. There was only one study evaluating the efficacy of tenofovir, one of the recommended treatments. The quality of reporting for this study was optimal; however, the power of the comparison was limited, hence the wide CrIs. In addition, there was a limited number of patients within each of the oral combination studies as well as a limited number of studies assessing oral combination therapy. Our analysis may suggest that oral combination therapy does not improve surrogate outcomes but studies of different combinations may provide different results. Our review also was limited to fully published studies in the English language. A number of clinical studies of CHB have been conducted in non-English speaking countries.

Other limitations include variation in definitions, measurements, patient characteristics, and protocols across studies and the quality of reported data. For example, the threshold values for undetectable HBV DNA varied significantly, thus earlier studies with higher thresholds tended to have higher proportions of subjects with undetectable HBV DNA. There were too few studies with any given threshold value to determine its effect on the OR for each pair-wise comparison; any variation in treatment effect owing to the threshold became part of the random between-study variance. We chose a threshold of less than 1000 copies/mL because studies have shown that for treatment with lamivudine, telbivudine, and adefovir, subsequent resistance is low for those whose viral load is maintained at less than 1000 copies/mL.[36] In addition, the error of the diagnostic test is approximately 0.5 log copies so that a viral load of 300–1000 copies/mL is within the error of the test, and a majority of studies that used polymerase chain reaction to detect HBV-DNA levels were below that of 1000 copies/mL.

This study offers some insight into the relative benefits of current drugs at 1 year of treatment. Because many of these treatments will be taken for much longer, perhaps for a lifetime, these data are not sufficient to definitively resolve the question of optimal treatment choice. Although hard outcomes such as HCC, liver failure, and death are the most important clinical end points, these are rare events when observation times are only 1–2 years. There is presently no consensus regarding the most appropriate surrogate markers of a long-term outcome or even the validity of on-treatment measurements.

The controversy about which drug to use is dwarfed by the controversy about who should be treated. Patients with cirrhosis and ongoing viral replication appear to benefit from treatment in terms of rate of progression of liver disease. The only randomized trial conducted in patients with advanced liver disease was stopped prematurely because of a dramatic reduction in rates of liver

failure and liver cancer.[37] Any potential long-term benefits of treatment are unclear among patients with earlier stage disease.

Chronic infection with hepatitis B occurs predominantly in those who acquired the infection as a neonate or young infant. Neonatal infection induces an early immune-tolerant phase of the disease. Only when the infected individual enters the phase of active HBeAg-positive hepatitis is loss of HBeAg and seroconversion to anti-HBe possibly reducing the risk of developing significant chronic liver disease.[3] This seroconversion when followed by sustained immune control has been shown, in recent publications of such individuals followed up for a 20- to 30-year period, to have a 50% chance of spontaneously losing HBsAg. Those who lose HBsAg before the age of 50 years have a reduced likelihood of HCC.[38] On the other hand, individuals with HBeAg-positive hepatitis who fail to seroconvert within 3–6 months or who subsequently develop HBeAg-negative hepatitis may warrant lifelong antiviral therapy because of the risk of progressive liver disease and HCC.

The first impetus toward earlier treatment was provided by a study performed in men in Taiwan. This large, population-based study, which recruited men between the ages of 30–65 years, showed that HBeAg status was associated with a high 9-year risk of HCC.[39] This study in men also noted that the risk of HCC was greatest in those who were older and who remained HBeAg-positive. The REVEAL study, which also was performed in Taiwan of both men and women between the ages of 30 and 65, showed that HCC risk was increased significantly in individuals with a high serum HBV-DNA level (>10,000 copies/mL).[40] This study showed that high serum HBV-DNA level was a prominent risk factor independent of HBeAg status, serum ALT level, and the presence of cirrhosis. These studies suggest that induction of HBeAg seroconversion and effective control of viral replication after antiviral therapy would lower the risk of HCC.

Finally, we do not know when and if it is appropriate to stop oral antiviral therapy once started if the individual has not undergone HBeAg loss or seroconversion for HBeAg-positive hepatitis. We only know that individuals who spontaneously achieve sustained immune control and who lose HBsAg (particularly if this occurs when the patient is younger than age 50), do secure a better chance of survival. Because treatment may continue for many years, the potential benefits of antiviral therapy on liver-related morbidity and mortality must be carefully weighed against the possibility of future drug resistance, high lifetime costs, and adverse effects.

Conclusions

Our systematic review and Bayesian MTC analysis shows that for patients with HBeAg-positive CHB, entecavir and tenofovir are the most effective treatments, whereas for HBeAg-negative patients, tenofovir is the most effective treatment as measured by our defined surrogate clinical outcomes. (Supplementary Tables 1 and 2).

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2010.06.042.

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Conflicts of interest

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Appendix: A. Details of Search Method

Summary

Databases searches were run in OVID MEDLINE (1950–2009), EMBASE (1980–2009), and Web of Science (1945–2009). All of the searches used available subject headings and text words and were limited to human studies and randomized control trials.

MEDLINE Search

The MEDLINE search strategy used a combination of MeSH terms and text word combinations for pegylated interferons, antivirals, and hepatitis B. The base set was limited to RCTs and human beings. The complete strategy is listed: ((interferon alfa-2a/ or interferon-alpha/ or interferon alfa-2b/ or interferon alfa-2c/) and ((peg or pegylated).mp.)) or ((peg adj5 interferon adj5 alpha) or (peginterferon adj5 alpha) or (pegylated adj5 interferon adj5 alpha:) or (peg adj5 ifn) or (pegylated adj5 ifn)).mp. or (LAMivudine/ or LAMIVUDINE (nm) or ("gr 103665" or gr103665 or heptodin or hepivir or "nsc 6207533 nsc6207533" or zefix or 3tc or epivir or (bch189 or "bch 189") or (gr109714x or "gr 109714x") or (hepitec or heptovir or trizivir or zeffix or zidovudine or lamivudine)).mp. or (adefovir or hepsera or preveon or pmea or adv or phosphonylmethoxyethyl: or ("gs 0393" or gs0393 or gs840 or "gs 840" or gs0840 or "gs 0840")).mp. or (142217-69-4 or 209216-23-9).rn. or (entecavir or baraclude or etv or "bms 200475" or bms200475 or "sq 34676" or sq34676).mp. or (Telbivudine or Epavudine or "LdT 600" or LdT600 or "Nv 02b Nv02b" or Sebivo).mp. or 3424-98-4.rn. or tenofovir:.mp. or 147127-19-3.rn. or 147127-20-6.rn. or pmpa.ti,ab. **AND** Hepatitis B Antibodies/ or hepatitis b/ or hepatitis b, chronic/ or Hepatitis B Antibodies/ or hepatitis b antigens/ or hepatitis b core antigens/ or hepatitis b e antigens/ or hepatitis b surface antigens/ or Hepatitis B virus/ or ("hep b" or "hepatitis b" or "type b hepatitis" or "hbv" or (chronic adj2 homologous adj2 serum adj2 jaundice) or (chronic adj2 diffuse adj2 hepatocellular adj2 inflamm:)).mp. **AND** (randomized controlled trial.pt. or controlled clinical trial.pt. or randomized controlled trials/ or Controlled Clinical Trials/ or (((rct or rcts or random: or (singl: or doubl: or tripl: or trebl:)) and (blind: or mask:)) or control:adj5 trial:).mp.limit 11 to (humans and (randomized controlled trial or controlled clinical trial)) or randomized controlled trials/ or Controlled Clinical Trials/ or (((rct or rcts or random: or (singl: or doubl: or tripl: or trebl:)) and (blind: or mask:)) or control:adj5 trial:).mp. **AND** human.

EMBASE Search

The EMBASE search strategy used a combination of MeSH terms and text word combinations for pegylated interferons, antivirals, and hepatitis B. The base set was limited to RCTs and human beings. The complete strategy is listed: (198153-51-4 or 215647-85-1).rn. or peginterferon/ or peginterferon alpha2a/ or peginterferon alpha2b/ or ((peg adj5 interferon adj5 alpha) or (peginterferon adj5 alpha) or (pegylated adj5 interferon adj5 alpha:) or (peg adj5 ifn) or (pegylated adj5 ifn)).mp. or 134680-32-3.rn. or lamivudine/ or lamivudine plus nevirapine plus stavudine/ or lamivudine plus zidovudine/ or ("gr 103665" or gr103665 or heptodin or hepivir or "nsc 6207533 nsc6207533" or zefix or 3tc or epivir or (bch189 or "bch 189") or (gr109714x or "gr 109714x") or (hepitec or heptovir or trizivir or zeffix or zidovudine or lamivudine)).mp. or (106941-25-7 or 142340-99-6).rn. or adefovir/ or adefovir dipivoxil/ or (adefovir or hepsera or preveon or pmea or adv or phosphonylmethoxyethyl: or ("gs 0393" or gs0393 or gs840 or "gs 840" or gs0840 or "gs 0840")).mp. or (142217-69-4 or 209216-23-9).rn. or entecavir/ or (entecavir or baraclude or etv or "bms 200475" or bms200475 or "sq 34676" or sq34676).mp.or peginterferon/ct or peginterferon alpha2a/ct or peginterferon alpha2b/ct or lamivudine/ct or lamivudine plus nevirapine plus stavudine/ct or lamivudine plus zidovudine/ct or adefovir/ct or adefovir dipivoxil/ct or entecavir/ct **AND** hepatitis b antibody/ or hepatitis b core antibody/ or "hepatitis b(e) antibody"/ or hepatitis b surface antibody/ or hepatitis b antigen/ or hepatitis b core antigen/ or "hepatitis b(e) antigen"/ or hepatitis b surface antigen/ or hepatitis b virus/ or Hepatitis B/ or hepatitis gb virus b/. **AND** ct. fs.randomized controlled trial/ or Clinical Trial/ or (((rct or rcts or random: or (singl: or doubl: or tripl: or trebl:)) and (blind: or mask:)) or control:adj5 trial:).mp. **AND** human.

Web of Science Search

The Web of Science database is not indexed with subject headings, only textwords were used. The complete strategy is listed: ((TS=interferon alfa-2a OR TS=interferon-alpha OR TS=interferon alfa-2b OR TS=interferon alfa-2c) and = (TS=peg OR TS=pegylated)) OR TS=((peg NEAR interferon adj5 alpha) OR TS=(peginterferon NEAR alpha) OR TS=(pegylated NEAR interferon adj5 alpha:) OR TS=(peg NEAR ifn) OR TS=(pegylated NEAR ifn))) AND = (TS=peg OR TS=pegylated) OR =(TS=LAMivudine OR TS=hepivir OR TS=zefix OR TS=3tc OR TS=epivir OR TS=hepitec OR TS=heptovir OR TS=trizivir OR TS= zeffix OR TS=zidovudine OR TS=lamivudine) OR =(TS= adefovir OR TS=hepsera OR TS=preveon OR TS=pmea OR TS=adv OR TS=phosphonylmethoxyethyl*) OR = (TS=entecavir OR TS=baraclude OR TS=etv) **AND** TS=Hepatitis B Antibodies OR TS=hepatitis b OR TS=hepatitis b, chronic OR TS=Hepatitis B Antibodies OR TS=hepatitis b antigens OR TS=hepatitis b core antigens OR TS=hepatitis b e antigens OR TS=hepatitis b surface antigens OR TS=Hepatitis B virus OR TS=("hep b" OR TS="hepatitis b" OR TS="type b hepatitis" OR TS="hbv" OR TS=(chronic NEAR homologous NEAR serum NEAR jaundice) OR TS=(chronic NEAR diffuse

NEAR hepatocellular NEAR inflamm:))) **AND** (TS=(((rct or rcts or random* OR (singl* OR doubl* OR tripl* OR trebl*)) AND (blind* OR mask*)) OR (control*NEAR trial*)) OR TI=(((rct or rcts or random* OR (singl* OR doubl* OR tripl* OR trebl*)) AND (blind* OR mask*)) OR (control*NEAR trial*)) OR ((TS=random* trial*) AND (TI=random* trial*)).

Appendix: B. Models and Computations Used for Meta-Analytic Estimates

Winbugs Code for Direct Comparisons

For one study

AQ: 30

```
model {
rA ~ dbin (pA, nA) # like for Lam
rcom ~ dbin (pcom,ncom) # like for comparator
pA ~ dunif(0,1)
pcom ~ dunif(0,1)
OR <- (pcom/(1-pcom))/(pA/(1-pA)) }
```

For more than one study

```
model {
for(i in 1: NS){
rA[i] ~ dbin (pA[i], nA[i])
rcom[i] ~ dbin (pcom[i],ncom[i])
logit(pA[i]) <- mu[i]
logit(pcom[i]) <-mu[i] + delta[i]
mu[i] ~ dnorm(0.0,0.000001)
delta [i] ~dnorm(d, prec) }

#priors for odds ratios
d ~ dnorm (0.0, 0.000001)
tau~ dt(0,1,2)I(0,) # half (positive half) t prior for random effect standard deviation
prec <-1/pow(tau,2) # precision is 1/sd^2
OR <-exp(d) }
```

WinBUGS Code for Indirect Comparisons

```
model{
for(i in 1:N) {
r[i] ~ dbin(p[i], n[i])
logit(p[i]) <- mu[s[i]] + delta[i]*(1-equals(t[i], b[i]))
delta[i] ~ dnorm(md[i], tau)
md[i] <- d[t[i]] - d[b[i]]

# measuring the goodness of fit
# expected value of the numerators
rhat[i] <- p[i] * n[i]
dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i])) +
(n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
}

# Priors for study-specific baselines
for(j in 1:NS) {
mu[j] ~ dnorm(0, 0.1)
}

# reference group has logOR=0 compared with itself
d[1] <- 0
#priors for other log-odds ratios
for(k in 2:NT) {
d[k] ~ dnorm(0, 0.1)
}

# Total deviance should be approximately N if the model fits well
# look at individual values dev[i] to see which observations do
# not fit well if resdev >> N
resdev<-sum(dev[])

#code for calculation of rate in LAM (baseline) group
for (k in 1:NB) {
rlam[k] ~ dbin(plam[k], nlam[k])
logit(plam[k]) <- mulam[k]
mulam[k] ~ dnorm(mu0lam, taulam)
}

sd ~ dt(0,1, 2)I(0, )
tau <- 1/pow(sd,2)

# these are the priors and calculations for
# the baseline probability model

mu0lam ~dnorm (0, 0.00001)
taulam <- 1/pow(sigmalam, 2)
sigmalam ~ dunif(0,10)
logit(plam0) <- mu0lam
prob[1] <-cut(plam0)
b1ODDS <-prob[1] / (1-prob[1])

# Calculate the probability of the treatment being a success
for (q in 2:NT) {
logit(prob[q]) <- mu0lam+d[q]
}

# Calculate the rank for each treatment
for(g in 1:NT) {
rk[g] <-NT+1-rank(prob[],g)
best[g] <-equals(rk[g],1)
}
```

Note: The model was run with a 5000-iteration burn-in followed by 20,000 monitored iterations. Convergence was assessed through the Brooks–Gelman–Rubin statistic.

Supplementary Table 1. ORs Outcome Results of Direct and Indirect Comparisons for Chronic HBeAg-Positive patients

		LAM		PEG		ADV		ETV		LdT		TDF		Placebo		LAM + PEG		LAM + LdT		LAM + ADV	
	Outcome	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)
LAM	HBV DNA			**0.51**	**(0.35–0.74)**			3.64	(0.91–17.33)	**2.34**	**(1.31–5.36)**					3.27	(0.70–14.48)	1.95	(0.67–6.15)	0.94	(0.43–2.04)
	ALT norm			**0.39**	**(0.28–0.55)**			1.51	(0.33–7.90)	1.35	(0.62–4.16)			**0.11**	**(0.03–0.38)**	0.96	(0.12–10.69)	2.05	(0.65–6.54)	0.40	(0.18–0.87)
	HBeAg Sero			1.43	(0.96–2.11)			1.09	(0.17–4.91)	1.20	(0.58–2.89)			0.25	(0.05–1.02)	1.22	(0.81–1.83)	0.62	(0.17–2.46)	0.56	(0.17–1.62)
	HBeAg loss			**1.54**	**(1.05–2.26)**			1.15	(0.81–1.66)	1.30	(0.64–3.10)			0.28	(0.11–0.67)	1.33	(0.90–1.97)	0.57	(0.16–2.02)	0.48	(0.16–1.28)
	HBsAg loss			**7.53**	**(1.58–87)**			1.44	(0.45–4.96)	0.71	(0.01–56.73)			0.52	(0.01–8.94)	6.96	(0.53–36.90)	0.48	(0.01–21)		
	Histo improv							**1.56**	**(1.12–2.19)**	**1.41**	**(1.09–1.84)**			**0.27**	**(0.09–0.84)**	1.12	(0.28–4.42)				
PEG	HBV DNA	**0.53**	**(0.34–0.95)**													**5.90**	**(1.36–24.24)**				
	ALT norm	**0.41**	**(0.21–0.94)**													1.62	(0.43–6.69)				
	HBeAg Sero	1.34	(0.76–2.30)													0.98	(0.28–3.72)				
	HBeAg loss	1.26	(0.62–2.36)													1.18	(0.22–6.57)				
	HBsAg loss	1.15	(0.03–35.79)													1.01	(0.39–2.60)				
	Histo improv	1.30	(0.12–8.98)													0.81	(0.40–1.72)				
ADV	HBV DNA	1.12	(0.39–2.96)	2.07	(0.61–6.11)			**5.40**	**(1.96–16.92)**	2.13	(0.93–5.03)	**19.66**	**(10.1–41)**	**0.01**	**(0.00–0.09)**						
	ALT norm	0.89	(0.45–2.09)	2.24	(0.80–6.36)			1.83	(0.65–5.26)	0.68	(0.24–1.87)	1.35	(0.78–2.34)	**0.21**	**(0.12–0.34)**						
	HBeAg Sero	0.87	(0.40–1.83)	0.65	(0.24–1.63)			0.65	(0.19–2.16)	1.58	(0.60–4.37)	1.22	(0.63–2.47)	0.47	(0.20–1.00)						
	HBeAg loss	0.95	(0.40–2.14)	0.75	(0.27–2.39)			0.80	(0.24–2.53)	1.55	(0.61–4.11)			0.38	(0.20–0.69)						
	HBsAg loss	0.67	(0.01–76.8)	0.63	(0–233)					0.96	(0.02–45)	4.43	(0.64–125)								
	Histo improv	0.93	(0.17–4.16)	0.73	(0.04–14.91)							1.39	(0.80–2.40)	**0.31**	**(0.19–0.49)**						
ETV	HBV DNA	**3.59**	**(2.28–5.93)**	**6.77**	**(3.16–12.73)**	**3.26**	**(1.07–9.89)**														
	ALT norm	1.53	(0.84–3.16)	**3.75**	**(1.4–10.46)**	1.72	(0.69–4.02)														
	HBeAg Sero	1.05	(0.53–1.63)	0.78	(0.31–1.66)	1.18	(0.48–2.72)														
	HBeAg loss	1.07	(0.53–2.02)	0.85	(0.35–2.15)	1.13	(0.42–2.85)														
	HBsAg loss	1.33	(0.12–13.95)	1.21	(0.02–77.26)	1.79	(0.01–190)														
	Histo improv	1.53	(0.34–5.81)	1.21	(0.09–14.91)	1.62	(0.15–15.91)														
LdT	HBV DNA	**2.31**	**(1.56–3.47)**	**4.33**	**(2.22–8.01)**	2.04	(0.84–5.46)	0.65	(0.35–1.28)									0.61	(0.25–1.43)		
	ALT norm	1.25	(0.77–2.21)	3.05	(1.21–8.07)	1.40	(0.65–3.15)	0.81	(0.35–1.71)									0.58	(0.19–1.67)		
	HBeAg Sero	1.20	(0.84–1.98)	0.90	(0.45–1.95)	1.75	(0.74–4.48)	1.04	(0.52–2.54)									0.39	(0.13–1.06)		
	HBeAg loss	1.31	(0.86–2.18)	1.04	(0.51–2.64)	1.40	(0.59–3.38)	1.21	(0.58–2.93)									0.42	(0.15–1.08)		
	HBsAg loss	0.07	(0–2.13)	0.06	(0–7.39)	0.10	(0–9.50)	0.05	(0–2.80)									1.06	(0.03–50)		
	Histo improv	1.41	(0.26–4.50)	1.10	(0.08–18.48)	1.53	(0.18–9.77)	0.93	(0.13–5.73)												
TDF	HBV DNA	**23.34**	**(6.19–76.39)**	**43.00**	**(8.99–157)**	**20.72**	**(8.67–45.81)**	**6.42**	**(1.47–25.20)**	**10.00**	**(2.66–31.19)**										
	ALT norm	1.58	(0.53–5.01)	3.77	(0.97–16.47)	1.25	(0.51–3.09)	1.01	(0.31–3.60)	1.28	(0.36–4.41)										
	HBeAg Sero	1.07	(0.34–3.31)	0.82	(0.24–2.89)	1.28	(0.54–3.06)	1.06	(0.33–3.74)	0.90	(0.28–2.68)										
	HBeAg loss																				
	HBsAg loss	3.94	(0.05–532)	3.35	(0.01–1113)	4.81	(0.27–162)	2.81	(0.02–478)	62.47	(0.39–27,092)										
	Histo improv	1.29	(0.15–10.25)	0.99	(0.05–19.12)	1.38	(0.26–6.14)	0.85	(0.06–10.71)	0.90	(0.07–10.55)										
Placebo	HBV DNA	**0.01**	**(0.00–0.08)**	**0.01**	**(0–0.15)**	**0.01**	**(0–0.07)**	**0**	**(0–0.02)**	**0**	**(0–0.03)**	**0**	**(0–0)**								
	ALT norm	**0.15**	**(0.07–0.30)**	0.36	(0.12–1.01)	**0.16**	**(0.07–0.34)**	**0.09**	**(0.04–0.23)**	**0.12**	**(0.05–0.26)**	**0.09**	**(0.02–0.37)**								
	HBeAg Sero	**0.31**	**(0.14–0.63)**	**0.23**	**(0.09–0.61)**	**0.36**	**(0.17–0.79)**	**0.30**	**(0.13–0.76)**	**0.25**	**(0.11–0.56)**	**0.28**	**(0.09–0.91)**								
	HBeAg loss	**0.31**	**(0.13–0.71)**	**0.24**	**(0.09–0.71)**	0.33	**(0.14–0.68)**	**0.29**	**(0.10–0.78)**	**0.23**	**(0.10–0.55)**										
	HBsAg loss	0.08	(0–2.66)	0.06	(0–8.18)	0.01	(0–22.73)	0.05	(0–3.85)	1.19	(0–405)	0.02	(0–4.75)								
	Histo improv	**0.28**	**(0.10–0.82)**	0.22	(0.02–2.93)	0.30	(0.07–1.09)	0.18	(0.03–1.12)	0.19	(0.04–1.68)	0.22	(0.04–1.47)								
LAM + PEG	HBV DNA	**3.08**	**(1.88–4.91)**	**5.75**	**(3.24–9.33)**	2.73	(0.94–8.86)	0.86	(0.42–1.62)	1.35	(0.69–2.32)	**0.13**	**(0.04–0.54)**	**405**	**(41.02–22,922)**						
	ALT norm	0.75	(0.45–1.72)	1.83	(1.00–4.17)	0.82	(0.35–2.55)	0.48	(0.23–1.37)	0.60	(0.30–1.56)	0.48	(0.13–2.08)	**5.11**	**(2.17–17.05)**						
	HBeAg Sero	1.323	(0.76–2.31)	0.99	(0.55–1.83)	1.54	(0.63–3.90)	1.29	(0.61–3.28)	1.11	(0.53–2.19)	1.22	(0.37–4.48)	**4.29**	(1.79–11.80)						
	HBeAg loss	1.59	(0.80–3.27)	1.26	(0.68–2.82)	1.69	(0.57–4.91)	1.48	(0.62–4.07)	1.21	(0.53–2.64)			5.20	(1.91–16.36)						
	HBsAg loss	1.68	(0.06–41.96)	1.40	(0.15–16.59)	2.36	(0.01–323)	1.20	(0.02–61.43)	24.72	(0.22–6707)	0.41	(0–106)	21.58	(0.18–6386)						
	Histo improv	0.99	(0.15–6.33)	0.82	(0.18–3.46)	1.04	(0.09–12.67)	0.66	(0.06–7.94)	0.70	(0.06–7.69)	0.75	(0.06–13.54)	3.58	(0.39–31.17)						
LAM + LdT	HBV DNA	1.60	(0.64–4.78)	**2.95**	**(1.05–9.69)**	1.43	(0.34–5.57)	0.45	(0.16–1.44)	0.69	(0.29–2.05)	**0.07**	**(0.02–0.38)**	**2419**	**(18.28–11,215)**	0.52	(0.19–1.73)				
	ALT norm	1.25	(0.37–5.01)	2.96	(0.67–14.82)	1.36	(0.30–6.24)	0.78	(0.19–3.42)	0.98	(0.27–3.87)	0.77	(0.14–4.71)	**8.40**	**(2.04–35.37)**	1.64	(0.35–6.29)				
	HBeAg Sero	0.51	(0.17–1.65)	0.38	(0.11–1.49)	0.59	(0.16–2.28)	0.49	(0.14–2.07)	0.42	(0.13–1.26)	0.48	(0.09–2.41)	1.67	(0.44–7.02)	0.39	(0.11–1.47)				
	HBeAg loss	0.52	(0.13–1.79)	0.41	(0.09–1.79)	0.55	(0.11–2.40)	0.48	(0.10–2.06)	0.39	(0.01–1.25)			1.70	(0.39–7.80)	**0.31**	**(0.07–0.52)**				
	HBsAg loss	0.17	(0–13.77)	0.14	(0–29.59)	0.20	(0–78.31)	0.11	(0–21.23)	2.54	(0–846)	0.04	(0–20.67)	2.32	(0–1602)	0.09	(0–18.02)				
	Histo improv																				

Supplementary Table 1. Continued

		LAM		PEG		ADV		ETV		LdT		TDF		Placebo		LAM + PEG		LAM + LdT		LAM + ADV	
	Outcome	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)
LAM + ADF	HBV DNA	0.95	(0.37–2.19)	1.76	(0.59–4.60)	0.83	(0.24–3.27)	**0.26**	**(0.09–0.71)**	0.40	(0.15–1.04)	**0.04**	**(0.01–0.20)**	**125**	**(9.83–8998)**	**0.31**	**(0.11–0.82)**	0.60	(0.13–2.12)		
	ALT norm	0.39	(0.15–1.26)	0.99	(0.26–3.93)	0.43	(0.12–1.60)	**0.26**	**(0.08–0.96)**	0.32	(0.10–1.06)	0.26	(0.05–1.31)	2.71	(0.83–9.38)	0.53	(0.13–1.65)	0.33	(0.06–1.58)		
	HBeAg Sero	0.52	(0.16–1.95)	0.39	(0.10–1.51)	0.61	(0.14–2.62)	0.51	(0.13–2.11)	0.44	(0.11–1.62)	0.47	(0.09–2.71)	1.69	(0.40–7.56)	0.40	(0.1–1.61)	0.99	(0.18–5.13)		
	HBeAg loss	0.46	(0.12–1.51)	0.36	(0.09–1.44)	0.47	(0.11–2.09)	0.43	(0.10–0.78)	0.35	(0.09–1.25)			0.89	(0.13–10.00)	0.27	(0.06–1.13)	0.87	(0.13–5.56)		
	HBsAg loss																				
	Histo improv																				

NOTE. Direct comparisons values are above the diagonal whereas indirect comparison values are below the diagonal. For values above the diagonal, values greater than 1 reflect increased efficacy by the treatment specified in the top row. For values below the diagonal, values less than 1 reflect an increased efficacy by the treatment specified in the first column. Bold numbers denote a statistically significant difference in efficacy of one treatment.
OR, median odds ratio; PLA, placebo; LAM, lamivudine; PEG, pegylated interferon; LdT, telbivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; HBV DNA, undetectable HBV-DNA levels; ALT norm, normalization of serum ALT levels; HBeAg sero, HBeAg seroconversion; Histo improv, histologic improvement of the liver.

Supplementary Table 2. ORs Outcome Results of Direct and Indirect Comparisons for Chronic HBeAg-Negative Patients

		LAM		PEG		ADV		ETV		LdT		TDF		Placebo		LAM + PEG	
	Outcome	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)	OR	(95% CrI)
LAM	HBV DNA			**0.62**	**(0.40–0.98)**			**3.53**	**(2.30–5.55)**	2.75	(0.65–9.60)					**2.40**	**(1.41–4.19)**
	ALT norm			**0.23**	**(0.15–0.35)**			**1.44**	**(1.00–2.06)**	2.14	(0.30–51)					**0.35**	**(0.23–0.55)**
	Histo improv							**1.53**	**(1.09–2.16)**	1.03	(0.70–1.52)						
PEG	HBV DNA	0.77	(0.33–2.74)													2.54	(0.66–7.40)
	ALT norm	0.25	(0.04–2.28)													1.60	(0.47–5.65)
	Histo improv																
ADV	HBV DNA	4.38	(0.10–171)	5.42	(0.11–231)							**7.75**	**(4.31–14.52)**	**0.01**	**(0–0.06)**		
	ALT norm	1.84	(0.04–94.89)	7.63	(0.10–507)							0.96	(0.56–1.61)	**0.16**	**(0.08–0.31)**		
	Histo improv	1.63	(0.07–26.42)									**1.19**	**(0.74–1.90)**				
ETV	HBV DNA	3.37	(0.74–12.90)	4.45	(0.52–20.03)	0.76	(0.01–39.51)										
	ALT norm	1.47	(0.16–12.76)	5.74	(0.28–101)	0.78	(0.01–64.25)										
	Histo improv	1.44	(0.23–7.63)			0.9	(0.05–20.51)										
LdT	HBV DNA	2.68	(0.83–7.75)	3.51	(0.64–14.2)	0.60	(0.01–26.82)	0.81	(0.12–4.82)								
	ALT norm	1.64	(0.32–19.63)	6.18	(0.42–174)	0.95	(0.01–89.91)	1.13	(0.09–36.02)								
	Histo improv	1.04	(0.18–6.83)			0.63	(0.03–23.55)	0.70	(0.05–11.67)								
TDF	HBV DNA	29.40	(0.69–1407)	36.38	(0.73–1859)	7.52	(1.11–26.36)	8.97	(0.15–475)	10.97	(0.23–686)						
	ALT norm	1.55	(0.03–94.68)	6.30	(0.05–515)	0.88	(0.08–9.07)	1.08	(0.01–88.49)	0.83	(0.01–70.59)						
	Histo improv	1.93	(0.06–47.38)			1.19	(0.09–19.27)	1.28	(0.04–28.45)	1.84	(0.03–63.09)						
Placebo	HBV DNA	**0.01**	**(0–0.89)**	**0.02**	**(0–0.92)**	**0**	**(0–0.06)**	**0**	**(0–0.33)**	**0.01**	**(0–0.36)**	**0**	**(0–0.01)**				
	ALT norm	0.35	(0.01–18.45)	1.23	(0.02–102)	0.17	(0.02–2.20)	0.22	(0–26.64)	0.18	(0–12.30)	0.20	(0.01–7.13)				
	Histo improv	0.47	(0.02–11.88)			0.29	(0.02–4.85)	0.36	(0.01–7.37)	0.46	(0.01–23.19)	0.25	(0.01–8.14)				
LAM + PEG	HBV DNA	1.81	(0.61–5.18)	2.38	(0.70–5.28)	0.42	(0.01–17.98)	0.53	(0.09–3.28)	0.68	(0.13–3.19)	0.06	(0–3.00)	**127**	**(1.84–11,320)**		
	ALT norm	0.38	(0.06–2.85)	1.50	(0.19–12.58)	0.22	(0–15.12)	0.27	(0.01–4.67)	0.24	(0.01–2.46)	0.28	(0–22.54)	1.24	(0.01–107)		
	Histo improv																

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