



## Effects of telbivudine and entecavir for HBeAg-positive chronic hepatitis B: A meta-analysis

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**Author contributions:** Su QM was responsible for data acquisition, analysis and interpretation and drafted the manuscript; Ye XG conceived and designed the study, and revised the article critically for important intellectual content, and both authors read and approved the final version to be published.

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### Abstract

**AIM:** To compare the effects of telbivudine (LDT) and entecavir (ETV) in treatment of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B by meta-analysis.

**METHODS:** We conducted a literature search using PubMed, MEDLINE, EMBASE, the China National Knowledge Infrastructure, the VIP database, the Wanfang database and the Cochrane Controlled Trial Register for all relevant articles published before April 1, 2012. Randomized controlled trials (RCTs) comparing LDT with ETV for treatment of HBeAg-positive chronic hepatitis B were included. The data was analyzed with Review Manager Software 5.0. We used relative risk (RR) as an effect measure, and reported its 95% CI. Meta-analysis was performed using either a fixed-effect or random-effect model, based on the absence or presence of significant heterogeneity. Two reviewers assessed the risk of bias and extracted data independently and in duplicate. The analysis was executed using the main outcome parameters including hepatitis

B virus (HBV) DNA undetectability, alanine aminotransferase (ALT) normalization, HBeAg loss, HBeAg seroconversion, drug-resistance, and adverse reactions. Meta-analysis of the included trials and subgroup analyses were conducted to examine the association between pre-specified characteristics with the therapeutic effects of the two agents.

**RESULTS:** Thirteen eligible trials (3925 patients in total) were included and evaluated for methodological quality and heterogeneity. In various treatment durations of 4 wk, 8 wk, 12 wk, 24 wk, 36 wk, 48 wk, 52 wk, 60 wk and 72 wk, the rates of HBV DNA undetectability and ALT normalization in the two groups were similar, without statistical significance. At 4 wk and 8 wk of the treatment, no statistical differences were found in the rate of HBeAg loss between the two groups, while the rate in the LDT group was higher than in the ETV group at 12 wk, 24 wk, 48 wk and 52 wk, respectively (RR 2.28, 95% CI 1.16, 7.03,  $P = 0.02$ ; RR 1.45, 95% CI 1.16, 1.82,  $P = 0.001$ ; RR 1.45, 95% CI 1.11, 1.89,  $P = 0.006$ ; and RR 1.86, 95% CI 1.04, 3.32,  $P = 0.04$ ). At 4 wk, 8 wk, 60 wk and 72 wk of the treatment, there were no significant differences in the rate of HBeAg seroconversion between the two groups, while at 12 wk, 24 wk, 48 wk and 52 wk, the rate in the LDT group was higher than in the ETV group (RR 2.10, 95% CI 1.36, 3.24,  $P = 0.0008$ ; RR 1.71, 95% CI 1.29, 2.28,  $P = 0.0002$ ; RR 1.86, 95% CI 1.36, 2.54,  $P < 0.0001$ ; and RR 1.87, 95% CI 1.21, 2.90,  $P = 0.005$ ). The rate of drug-resistance was higher in the LDT group than in the ETV group (RR 3.76, 95% CI 1.28, 11.01,  $P = 0.02$ ). In addition, no severe adverse drug reactions were observed in the two groups. And the rate of increased creatine kinase in the LDT group was higher than in the ETV group (RR 5.58, 95% CI 2.22, 13.98,  $P = 0.0002$ ).

**CONCLUSION:** LDT and ETV have similar virological and biomedical responses, and both are safe and well tolerated. However, LDT has better serological response and higher drug-resistance.

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**Key words:** Telbivudine; Entecavir; Hepatitis B e antigen-positive chronic hepatitis B; Randomized controlled trials; Meta-analysis

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## INTRODUCTION

Chronic hepatitis B (CHB) infection is a major health problem affecting over 350 million people worldwide<sup>[1,2]</sup>. CHB can lead to various life-threatening conditions, such as liver failure, liver cirrhosis (LC) and hepatocellular carcinoma (HCC)<sup>[3]</sup>. Hepatitis B virus (HBV) covalent closed circular DNA (cccDNA) is the main cause of the sustainability of the hepatitis virus, and it is difficult to completely eliminate it<sup>[4]</sup>. So the primary therapeutic goal is to sustain viral suppression. Current anti-viral medication includes interferon [interferon-alpha (IFN- $\alpha$ ), and pegylated (PEG) IFN- $\alpha$ ] and nucleosides or nucleoside analogues [entecavir (ETV), adefovir dipivoxil, telbivudine (LDT), and lamivudine]<sup>[5]</sup>. Recent studies have shown that LDT and ETV are the strongest nucleoside analogues. LDT ( $\beta$ -L-2'-deoxythymidine) is an orally bioavailable L-nucleoside. It can effectively suppress HBV DNA replication, and has a higher rate of hepatitis B e antigen (HBeAg) seroconversion than other current oral antiviral agents<sup>[6]</sup>. However, its drug-resistance remains high<sup>[7]</sup>. ETV is a new generation nucleoside analogues. It has the advantage of higher rate of HBV DNA suppression, low drug-resistance and high safety, especially in lamivudine-resistant CHB patients<sup>[8]</sup>. But the rates of HBeAg loss and seroconversion are very low in ETV group, which is difficult to meet the withdrawal standards. There are few systematic reviews about the comparison of LDT and ETV. Therefore, we conducted a meta-analysis of the randomized controlled trials (RCTs) using the Cochrane methodology to explore the efficacy of LDT and ETV for clinical treatment of HBeAg-positive chronic hepatitis B.

## MATERIALS AND METHODS

### Literature search

We searched PubMed, MEDLINE, EMBASE, China

National Knowledge Infrastructure, the VIP database, the Wanfang database and the Cochrane Controlled Trial Register for articles published up to April 1, 2012, using the following keywords: "HBeAg-positive chronic hepatitis B", "telbivudine", "entecavir", and "RCTs". The reference lists of eligible studies were also searched.

### Inclusion criteria

The following inclusion criteria were used: (1) RCTs; (2) Articles studying HBeAg-positive chronic hepatitis B patients, according to diagnostic standards in "China guidelines for HBV management (2010)"<sup>[9]</sup>; (3) Studies comparing LDT (600 mg/d) with ETV (0.5 mg/d); and (4) The main outcome parameters included virological, biochemical, and serological responses [HBV DNA undetectability, alanine aminotransferase (ALT) normalization, HBeAg loss, HBeAg seroconversion, drug-resistance, and adverse reactions]. Virological response was defined as attainment of undetectable levels of HBV DNA. Determined by quantitative polymerase chain reaction, the threshold of detection was 1000 copies/mL or less in each corresponding study (Table 1). Biochemical response was defined as normalization of ALT levels to below the upper limit of normal ( $< 40$  IU/mL). HBeAg loss was defined as HBeAg levels  $< 1.0$  S/CO, HBeAg seroconversion was defined as HBeAg loss and the presence of anti-HBeAg, determined by microparticle enzyme immunoassay or enzyme-linked immunosorbent assay.

### Exclusion criteria

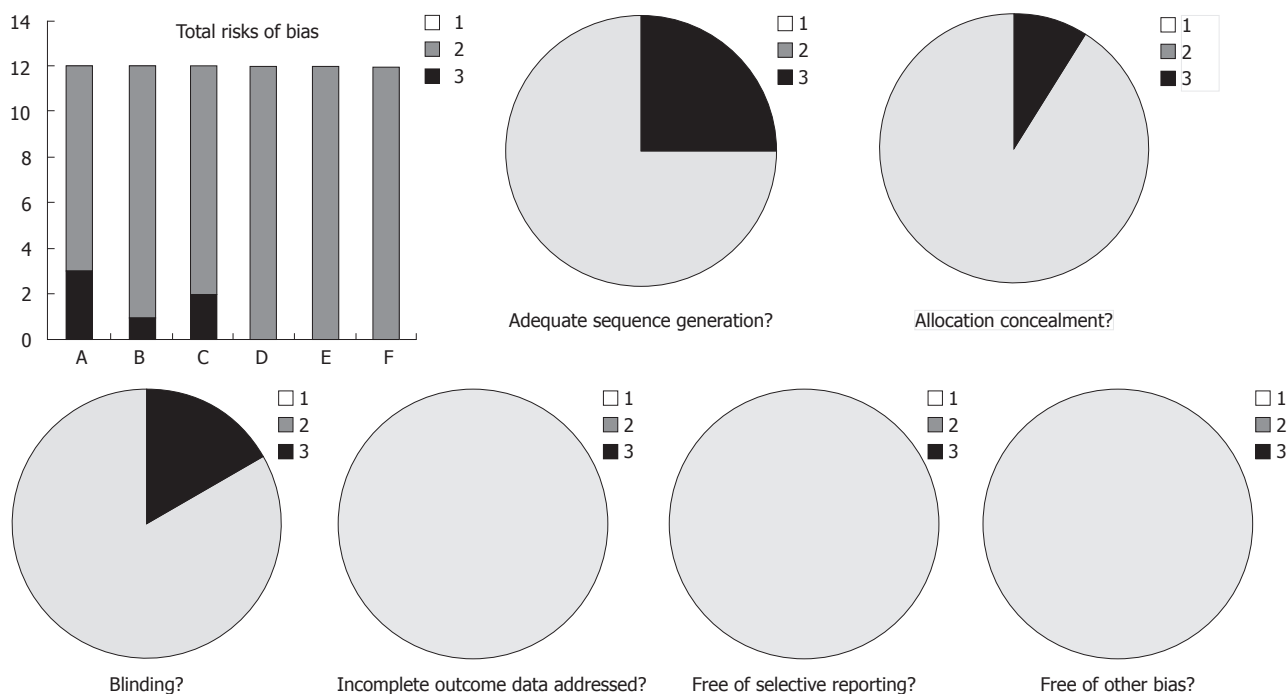
The following exclusion criteria were used: (1) Nonrandomized controlled trials (NRCTs); (2) Insufficient analytical information regarding treatment schedule, follow-up, and outcomes; (3) Patients receiving interferon, nucleosides or nucleotides for CHB within 6 mo; (4) Patients coinfecting with hepatitis A, C, D and E virus, cytomegalovirus, or human immunodeficiency virus; (5) Patients with liver failure, HCC, and liver-related complications caused by alcoholism, autoimmune disease, and cholestasis; and (6) Pregnant and breastfeeding patients.

### Data extraction

Data extraction was assessed independently by two reviewers (Song LY and Zhang SR). Discrepancies were solved through discussions between the reviewers or by a third person. Systematic Reviews of Interventions Version 5.0.2 (Cochrane Collaboration, Oxford, United Kingdom) was used to assess risk of bias (adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting and free of other bias)<sup>[10]</sup>. Basic information obtained from each eligible trial included study design, patient characteristics, number of two groups, treatment duration and related study results. Data were reviewed to eliminate duplicate reports of the same trial.

### Statistical analysis

We used Review Manager Software 5.0 (Cochrane Collab-



**Figure 1** Risk of bias in included trials. A: Adequate sequence generation; B: Allocation concealment; C: Blinding; D: Incomplete outcome data addressed; E: Free of selective reporting; F: Free of other bias. 1: No (high risk of bias); 2: Unclear; 3: Yes (low risk of bias).

oration, Oxford, United Kingdom) for the data analysis. For dichotomous data, we used relative risk (RR) as an effect measure, and reported its 95% CI. Meta-analysis was performed using either a fixed-effect or random-effect model, based on the absence or presence of significant heterogeneity.

Statistical heterogeneity between trials was evaluated by  $\chi^2$  and  $I^2$  analysis. The fixed-effect method was used in the absence of statistically significant heterogeneity ( $P \geq 0.1$ ), and the random-effect method was used when the heterogeneity test was statistically significant ( $P < 0.1$ ).  $P < 0.05$  was regarded as statistically significant. Subgroup analysis was performed to examine the association between pre-specified characteristics (treatment duration) and the therapeutic effect, sensitivity analysis was made to estimate result stability, and funnel plots were used to assess publication bias if more than five trials were included<sup>[11]</sup>.

## RESULTS

### Characteristics and quality of studies

We initially identified 1165 abstracts, and after evaluating the full texts, we included 13 trials (12 in Chinese and one in English)<sup>[12-24]</sup> based on the pre-specified criteria. A total of 3925 patients were included: 1987 treated with LDT and 1938 treated with ETV. Table 1 shows the characteristics of the 13 trials. All these studies showed baseline comparability, 9 of them reported the baseline of two groups in detail<sup>[13-15,17,19,20,22-24]</sup>, the other 4 presented no significant differences in gender, age and duration of treatment between the two groups<sup>[12,16,18,21]</sup>. Three described the methods of randomization in detail<sup>[13,14,24]</sup>,

nine reported randomization, but did not describe the method of randomization in detail<sup>[12,15,17-23]</sup>, one reported allocation concealment<sup>[24]</sup> and two presented blinding method<sup>[22,24]</sup>. None of the trials referred to incomplete outcome data addressed, free of selective reporting, and free of other bias. Various risks of bias in the 13 trials. In addition, none of the trials reported mortality, life quality and liver cancer incidence are shown in Figure 1.

### HBV DNA undetectability

All the trials reported the rate of HBV DNA undetectability.  $\chi^2$  and  $I^2$  analyses showed no heterogeneity ( $\chi^2 = 35.37$ ,  $P = 0.74$ ,  $I^2 = 0\%$ ); therefore, we used the fixed-effect method to analyze the data. The results showed that in various treatment durations of 4 wk, 8 wk, 12 wk, 24 wk, 36 wk, 48 wk, 52 wk, 60 wk and 72 wk, there were no statistical differences in the rate of HBV DNA undetectability between the two groups (RR 1.04, 95% CI 0.72, 1.49,  $P = 0.85$ ; RR 0.98, 95% CI 0.74, 1.28,  $P = 0.86$ ; RR 1.01, 95% CI 0.89, 1.15,  $P = 0.83$ ; RR 1.06, 95% CI 0.99, 1.14,  $P = 0.12$ ; RR 1.03, 95% CI 0.86, 1.37,  $P = 1.24$ ; RR 1.02, 95% CI 0.95, 1.09,  $P = 0.63$ ; RR 0.95, 95% CI 0.86, 1.05,  $P = 0.29$ ; RR 1.02, 95% CI 0.83, 1.24,  $P = 0.88$ ; and RR 0.95, 95% CI 0.80, 1.12,  $P = 0.54$ ) (Figure 2A).

### ALT normalization

Eleven trials reported the rate of ALT normalization<sup>[12,13,15-20,22-24]</sup>.  $\chi^2$  and  $I^2$  analysis showed no heterogeneity ( $\chi^2 = 32.22$ ,  $P = 0.51$ ,  $I^2 = 0\%$ ). At various treatment durations of 4 wk, 8 wk, 12 wk, 24 wk, 36 wk, 48 wk, 52 wk, 60 wk and 72 wk, there were no statistical differences in the rate of ALT normalization between the two groups (RR 1.08, 95% CI 0.81, 1.43,  $P = 0.59$ ; RR 1.05, 95% CI 0.77, 1.43,  $P = 0.77$ ;

Table 1 Characteristics of included trials

Trials	Sample size (n)		Mean age (yr)		Regimen (mg/d)		Duration (wk)	Observation time (wk)	Outcome parameters	HBV DNA undetectability (copy/mL)
	LDT	ETV	LDT	ETV	LDT	ETV				
Zhao <i>et al</i> <sup>[12]</sup>	36	36	34.30		600	0.5	48	24, 48	ABDE	-
Zhu <i>et al</i> <sup>[13]</sup>	30	30	28.00 ± 9.10	31.80 ± 7.10	600	0.5	24	12, 24	ABCDE	1000
Zhou <i>et al</i> <sup>[14]</sup>	52	63	46.30 ± 9.00		600	0.5	48	12, 24, 36, 48	ACD	-
Xu <i>et al</i> <sup>[15]</sup>	30	30	32.70 ± 10.60	33.60 ± 8.80	600	0.5	24	12, 24, 48	ABCDEF	1000
Ye <i>et al</i> <sup>[16]</sup>	46	46	32.20		600	0.5	48	12, 24, 48	ABCDE	100
Zhang <i>et al</i> <sup>[17]</sup>	75	65	31.93 ± 7.96		600	0.5	72	8, 12, 24, 52, 72	ABDEF	500
Liu <sup>[18]</sup>	20	20	33.50		600	0.5	48	4, 12, 24, 48	ABCDEF	1000
Zhao <i>et al</i> <sup>[19]</sup>	42	39	33.56 ± 10.25		600	0.5	60	8, 12, 24, 48, 60	ABD	1000
Shi <i>et al</i> <sup>[20]</sup>	40	40	30.50 ± 7.11	31.50 ± 7.95	600	0.5	24	12, 24	ABCD	500
Yu <i>et al</i> <sup>[21]</sup>	92	85			600	0.5	48	4, 8, 12, 24, 48	ACD	500
Huang <i>et al</i> <sup>[22]</sup>	90	90	28.80 ± 9.80		600	0.5	52	52	ABCDE	500
Ding <i>et al</i> <sup>[23]</sup>	30	30	37.20 ± 7.96	36.10 ± 7.12	600	0.5	48	4, 8, 12, 24, 36, 48	ABCDEF	1000
Zheng <i>et al</i> <sup>[24]</sup>	65	66	31.60 ± 8.70	33.50 ± 9.10	600	0.5	24	12, 24	AFCDF	500

A: Hepatitis B virus DNA undetectability; B: Alanine aminotransferase normalization; C: Hepatitis B e antigen loss; D: Hepatitis B e antigen seroconversion; E: Drug-resistance; F: Increased creatine kinase. LDT: Telbivudine; ETV: Entecavir; HBV: Hepatitis B virus.

RR 1.05, 95% CI 0.94, 1.16,  $P = 0.40$ ; RR 1.00, 95% CI 0.93, 1.08,  $P = 0.91$ ; RR 0.95, 95% CI 0.67, 1.34,  $P = 0.78$ ; RR 1.01, 95% CI 0.92, 1.11,  $P = 1.08$ ; RR 0.94, 95% CI 0.86, 1.02,  $P = 0.14$ ; RR 0.96, 95% CI 0.77, 1.19,  $P = 0.69$ ; and RR 0.98, 95% CI 0.84, 1.13,  $P = 0.76$ ) (Figure 2B).

### HBeAg loss

Ten trials reported the rate of HBeAg loss<sup>[13-16,18,20-24]</sup>.  $\chi^2$  and  $I^2$  analyses found no heterogeneity ( $\chi^2 = 38.84$ ,  $P = 0.04$ ,  $I^2 = 36\%$ ). At 4 wk and 8 wk of the treatment, no statistical differences in the rate of HBeAg loss were observed between the two groups (RR 2.89, 95% CI 0.31, 27.23,  $P = 0.35$ ; and RR 1.50, 95% CI 0.50, 4.46,  $P = 0.47$ ). At 12 wk, 24 wk, 48 wk and 52 wk, the rate of HBeAg loss was higher in the LDT group than in the ETV group, and the difference between two groups was statistically significant (RR 2.28, 95% CI 1.16, 7.03,  $P = 0.02$ ; RR 1.45, 95% CI 1.16, 1.82,  $P = 0.001$ ; RR 1.45, 95% CI 1.11, 1.89,  $P = 0.006$ ; RR 1.86, 95% CI 1.04, 3.32,  $P = 0.04$ ) (Figure 2C).

### HBeAg seroconversion

All the trials reported the rate of HBeAg seroconversion.  $\chi^2$  and  $I^2$  analyses showed no heterogeneity ( $\chi^2 = 22.15$ ,  $P = 0.85$ ,  $I^2 = 0\%$ ). At 4 wk, 8 wk, 60 wk and 72 wk of the treatment, the rate of HBeAg seroconversion in the two groups was similar, and no statistical significances were observed (RR 2.34, 95% CI 0.55, 9.92,  $P = 0.25$ ; RR 1.55, 95% CI 0.77, 3.12,  $P = 0.22$ ; RR 1.56, 95% CI 0.91, 2.67,  $P = 0.1$ ). However, at 12 wk, 24 wk, 48 wk and 52 wk, the rate of HBeAg loss was higher in the LDT group than in the ETV group, with statistically significant difference between two groups (RR 2.1, 95% CI 1.36, 3.24,  $P = 0.0008$ ; RR 1.71, 95% CI 1.29, 2.28,  $P = 0.0002$ ; RR 1.86, 95% CI 1.36, 2.54,  $P < 0.0001$ ; RR 1.87, 95% CI 1.21, 2.90,  $P = 0.005$ ) (Figure 2D).

### Drug-resistance

Six trials reported drug-resistance<sup>[12,13,16,17,22,23]</sup>.  $\chi^2$  and  $I^2$  analyses showed no heterogeneity ( $\chi^2 = 0.63$ ,  $P = 0.96$ ,

$I^2 = 0\%$ ). The rate of drug-resistance was higher in the LDT group than in the ETV group, and the difference between two groups was statistically significant (RR = 3.76, 95% CI 1.28, 11.01,  $P = 0.02$ ) (Figure 2E).

### Adverse reactions

Ten trials reported on the adverse reactions<sup>[12-18,20,23,24]</sup>. No severe adverse reactions were observed in both groups. Common adverse reactions in the two groups included influenza-like symptoms such as fever, headache, fatigue, muscular stiffness, gastrointestinal upset such as nausea and diarrhea, alopecia and rash. Five of the trials reported the rate of increased creatine kinase (CK)<sup>[15,17,18,23,24]</sup>.  $\chi^2$  and  $I^2$  analyses showed no heterogeneity ( $\chi^2 = 1.06$ ,  $P = 0.94$ ,  $I^2 = 0\%$ ). The rate of increased CK was higher in the LDT group than in the ETV group, the difference being statistically significant (RR 5.58, 95% CI 2.22, 13.98,  $P = 0.0002$ ). But the increased CK recovered without any intervention, and did not influence the anti-HBV treatment (Figure 2F).

### Statistical analysis

Meta-analysis was performed based on the rate of HBeAg seroconversion, using the fixed-effect model, and the minimum sample size trials were excluded<sup>[18]</sup>. Odds ratio (OR) of all sensitivity analyses was higher than 1 and statistically significant ( $P < 0.05$ ) (Table 2).

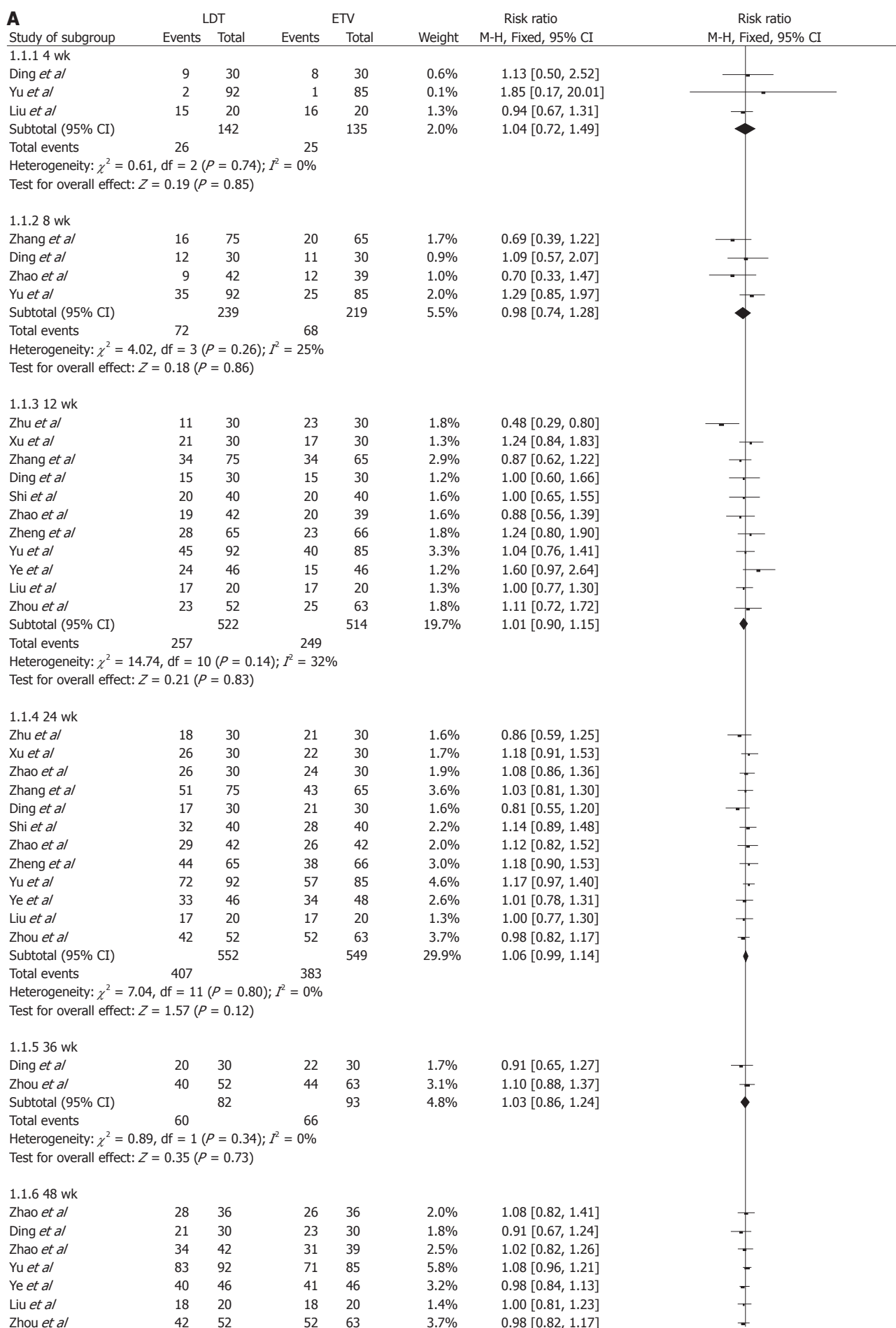
### Funnel plots

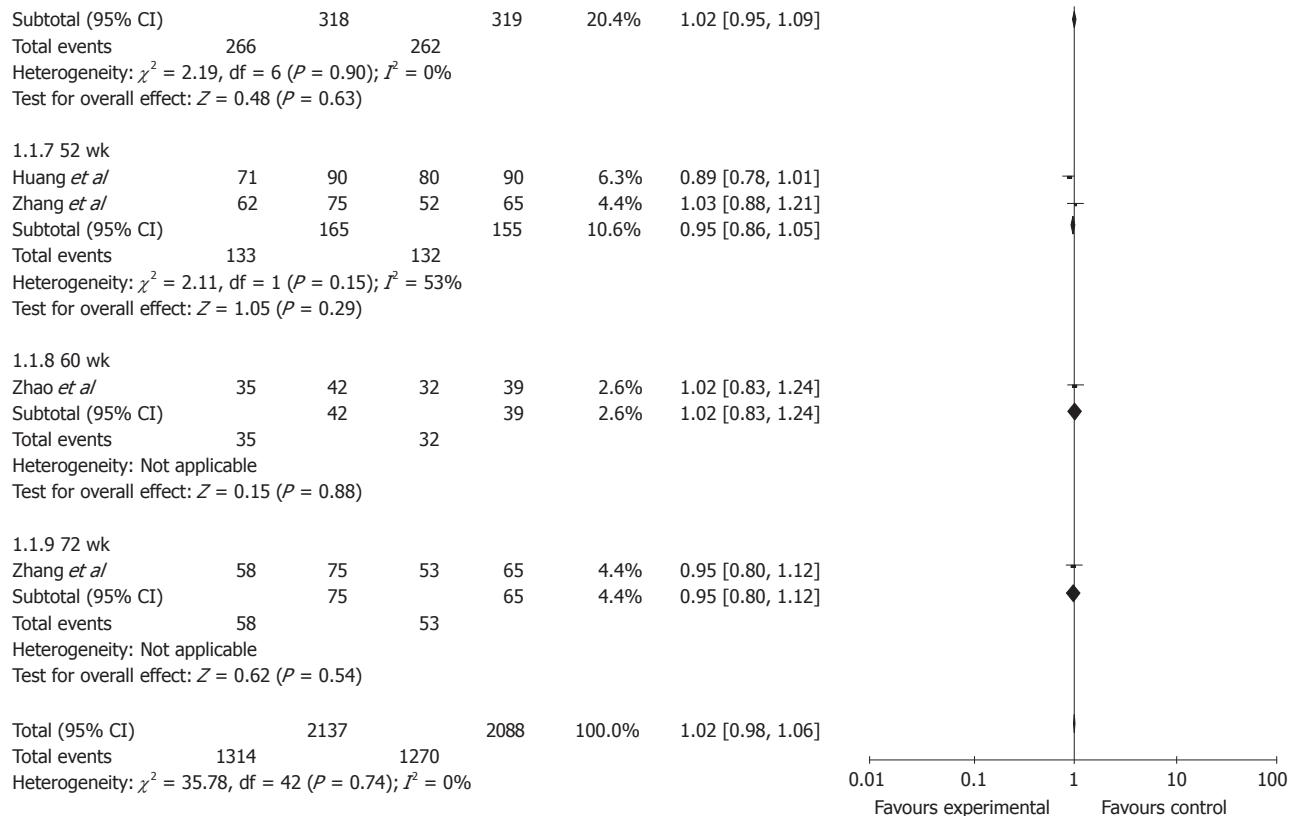
Funnel plots were performed based on the rate of HBV DNA undetectability. The results showed that funnel plots were symmetric and suggested that there was no publication bias (Figure 3).

## DISCUSSION

The RCTs comparing LDT with ETV for patients with HBeAg-positive chronic hepatitis B were included, and meta-analyses on virology, serology, biochemical respons-







Study of subgroup	LDT		ETV		Weight	Risk ratio	Risk ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.2.1 4 wk							
Ding <i>et al</i>	8	30	7	30	0.7%	1.14 [0.47, 2.75]	
Liu <i>et al</i>	19	20	18	20	1.8%	1.06 [0.88, 1.26]	
Subtotal (95% CI)		50		50	2.5%	1.08 [0.81, 1.43]	
Total events	27		25				
Heterogeneity: $\chi^2 = 0.08$ , df = 1 ( $P = 0.78$ ); $I^2 = 0\%$							
Test for overall effect: $Z = 0.53$ ( $P = 0.59$ )							
1.2.2 8 wk							
Zhang <i>et al</i>	27	75	23	65	2.4%	1.02 [0.65, 1.59]	
Ding <i>et al</i>	13	30	12	30	1.2%	1.08 [0.59, 1.97]	
Zhao <i>et al</i>	15	42	13	39	1.3%	1.07 [0.59, 1.95]	
Subtotal (95% CI)		147		134	4.9%	1.05 [0.77, 1.43]	
Total events	55		48				
Heterogeneity: $\chi^2 = 0.03$ , df = 2 ( $P = 0.98$ ); $I^2 = 0\%$							
Test for overall effect: $Z = 0.30$ ( $P = 0.77$ )							
1.2.3 12 wk							
Zhu <i>et al</i>	16	30	22	30	2.0%	0.73 [0.49, 1.08]	
Xu <i>et al</i>	15	30	18	30	1.8%	0.83 [0.53, 1.32]	
Zhang <i>et al</i>	56	75	43	65	4.5%	1.13 [0.91, 1.40]	
Ding <i>et al</i>	15	30	16	30	1.6%	0.94 [0.57, 1.53]	
Shi <i>et al</i>	21	40	24	40	2.4%	0.88 [0.59, 1.29]	
Zhao <i>et al</i>	30	42	27	39	2.7%	1.03 [0.78, 1.37]	
Zheng <i>et al</i>	56	65	38	65	3.7%	1.47 [1.17, 1.85]	
Ye <i>et al</i>	23	46	25	46	2.5%	0.92 [0.62, 1.36]	
Liu <i>et al</i>	19	20	18	20	1.8%	1.06 [0.88, 1.26]	
Subtotal (95% CI)		378		365	23.0%	1.05 [0.94, 1.16]	
Total events	251		231				
Heterogeneity: $\chi^2 = 14.80$ , df = 8 ( $P = 0.06$ ); $I^2 = 46\%$							
Test for overall effect: $Z = 0.84$ ( $P = 0.40$ )							
1.2.4 24 wk							
Zhu <i>et al</i>	22	30	27	30	2.6%	0.81 [0.64, 1.04]	
Xu <i>et al</i>	23	30	27	30	2.6%	0.85 [0.68, 1.07]	
Zhao <i>et al</i>	28	36	26	36	2.5%	1.08 [0.82, 1.41]	
Zhang <i>et al</i>	57	75	44	65	4.6%	1.12 [0.91, 1.39]	
Ding <i>et al</i>	16	30	18	30	1.8%	0.89 [0.57, 1.39]	

Su QM *et al.* Telbivudine and entecavir for CHB treatment

Shi <i>et al</i>	31	40	30	40	2.9%	1.03 [0.81, 1.32]
Zhao <i>et al</i>	32	42	29	39	2.9%	1.02 [0.80, 1.32]
Zheng <i>et al</i>	51	65	49	66	4.8%	1.06 [0.87, 1.28]
Ye <i>et al</i>	39	46	40	46	3.9%	0.97 [0.83, 1.15]
Liu <i>et al</i>	18	20	17	20	1.7%	1.06 [0.84, 1.34]
Subtotal (95% CI)		414		402	30.5%	1.00 [0.93, 1.08]

Total events 317 307

Heterogeneity:  $\chi^2 = 7.01$ ,  $df = 9$  ( $P = 0.64$ );  $I^2 = 0\%$

Test for overall effect:  $Z = 0.11$  ( $P = 0.91$ )

1.2.5 36 wk

Ding <i>et al</i>	20	30	21	30	2.1%	0.95 [0.67, 1.34]
Subtotal (95% CI)		30		30	2.1%	0.95 [0.67, 1.34]

Total events 20 21

Heterogeneity: Not applicable

Test for overall effect:  $Z = 0.28$  ( $P = 0.78$ )

1.2.6 48 wk

Zhao <i>et al</i>	30	36	28	36	2.7%	1.07 [0.85, 1.35]
Ding <i>et al</i>	23	30	24	30	2.4%	0.96 [0.73, 1.25]
Zhao <i>et al</i>	33	42	31	39	3.2%	0.99 [0.79, 1.24]
Ye <i>et al</i>	43	46	42	46	4.1%	1.02 [0.91, 1.15]
Liu <i>et al</i>	18	20	18	20	1.8%	1.00 [0.81, 1.23]
Subtotal (95% CI)		174		171	14.1%	1.01 [0.92, 1.11]

Total events 147 143

Heterogeneity:  $\chi^2 = 0.50$ ,  $df = 4$  ( $P = 0.97$ );  $I^2 = 0\%$

Test for overall effect:  $Z = 0.24$  ( $P = 0.81$ )

1.2.7 52 wk

Huang <i>et al</i>	75	90	86	90	8.4%	0.87 [0.79, 0.97]
Zhang <i>et al</i>	62	75	52	65	5.5%	1.03 [0.88, 1.21]
Subtotal (95% CI)		165		155	13.9%	0.94 [0.86, 1.02]

Total events 137 138

Heterogeneity:  $\chi^2 = 3.29$ ,  $df = 1$  ( $P = 0.07$ );  $I^2 = 70\%$

Test for overall effect:  $Z = 1.46$  ( $P = 0.14$ )

1.2.8 60 wk

Zhao <i>et al</i>	33	42	32	39	3.3%	0.96 [0.77, 1.19]
Subtotal (95% CI)		42		39	3.3%	0.96 [0.77, 1.19]

Total events 33 32

Heterogeneity: Not applicable

Test for overall effect:  $Z = 0.39$  ( $P = 0.69$ )

1.2.9 72 wk

Zhang <i>et al</i>	62	75	55	65	5.8%	0.98 [0.84, 1.13]
Subtotal (95% CI)		75		65	5.8%	0.98 [0.84, 1.13]

Total events 62 55

Heterogeneity: Not applicable

Test for overall effect:  $Z = 0.31$  ( $P = 0.76$ )

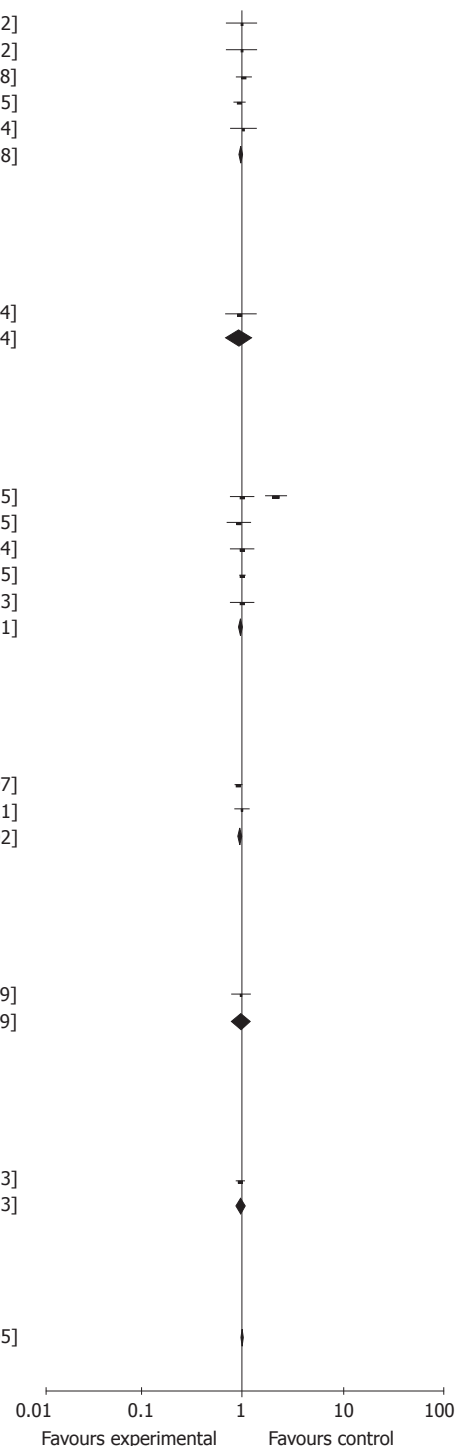
Total (95% CI)		1475		1411	100.0%	1.01 [0.96, 1.05]
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Total events 1049 1000

Heterogeneity:  $\chi^2 = 32.22$ ,  $df = 33$  ( $P = 0.51$ );  $I^2 = 0\%$

Test for overall effect:  $Z = 0.23$  ( $P = 0.82$ )

Test for subgroup differences: Not applicable.



C

Study of subgroup	LDT		ETV		Weight	Risk ratio M-H, Random, 95% CI	Risk ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
1.3.1 4 wk							
Ding <i>et al</i>	1	30	0	30	0.5%	3.00 [0.13, 70.83]	
Yu <i>et al</i>	1	92	0	85	0.5%	2.77 [0.11, 67.19]	
Liu <i>et al</i>	0	20	0	20		Not estimable	
Subtotal (95% CI)		142		135	0.9%	2.89 [0.31, 27.23]	
Total events	2		0				
Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 0.00$ , $df = 1$ ( $P = 0.97$ ); $I^2 = 0\%$							
Test for overall effect: $Z = 0.93$ ( $P = 0.35$ )							
1.3.2 8 wk							
Ding <i>et al</i>	2	30	1	30	0.8%	2.00 [0.19, 20.90]	
Yu <i>et al</i>	6	92	4	85	2.6%	1.39 [0.40, 4.74]	
Subtotal (95% CI)		122		115	3.4%	1.50 [0.50, 4.46]	
Total events	8		5				

Heterogeneity:  $\text{Tau}^2 = 0.00$ ;  $\chi^2 = 0.07$ ,  $\text{df} = 1$  ( $P = 0.79$ );  $I^2 = 0\%$   
 Test for overall effect:  $Z = 0.73$  ( $P = 0.47$ )

## 1.3.3 12 wk

Zhu <i>et al</i>	6	30	14	30	4.7%	0.43 [0.19, 0.96]
Xu <i>et al</i>	11	30	5	30	4.0%	2.20 [0.87, 5.57]
Ding <i>et al</i>	5	30	3	30	2.2%	1.67 [0.44, 6.36]
Shi <i>et al</i>	12	40	2	40	2.0%	6.00 [1.43, 25.11]
Zheng <i>et al</i>	13	65	2	66	2.0%	6.60 [1.55, 28.10]
Yu <i>et al</i>	27	97	4	85	3.5%	5.91 [2.16, 16.22]
Ye <i>et al</i>	3	46	0	46	0.5%	7.00 [0.37, 131.81]
Liu <i>et al</i>	3	20	0	20	0.5%	7.00 [0.38, 127.32]
Subtotal (95% CI)		358		347	19.5%	2.86 [1.16, 7.03]
Total events	80		30			

Heterogeneity:  $\text{Tau}^2 = 1.10$ ;  $\chi^2 = 25.62$ ,  $\text{df} = 7$  ( $P = 0.0006$ );  $I^2 = 73\%$   
 Test for overall effect:  $Z = 2.29$  ( $P = 0.02$ )

## 1.3.4 24 wk

Zhu <i>et al</i>	8	30	10	30	5.0%	0.80 [0.37, 1.74]
Xu <i>et al</i>	14	30	6	30	4.7%	2.33 [1.04, 5.25]
Ding <i>et al</i>	7	30	5	30	3.4%	1.40 [0.50, 3.92]
Shi <i>et al</i>	18	40	13	40	7.2%	1.38 [0.79, 2.43]
Zheng <i>et al</i>	24	65	19	66	8.0%	1.28 [0.78, 2.10]
Yu <i>et al</i>	44	92	27	85	9.7%	1.51 [1.03, 2.20]
Ye <i>et al</i>	10	46	3	46	2.6%	3.33 [0.98, 11.33]
Liu <i>et al</i>	4	20	2	20	1.7%	2.00 [0.41, 9.71]
Subtotal (95% CI)		353		347	42.3%	1.45 [1.16, 1.82]
Total events	129		85			

Heterogeneity:  $\text{Tau}^2 = 0.00$ ;  $\chi^2 = 5.83$ ,  $\text{df} = 7$  ( $P = 0.56$ );  $I^2 = 0\%$   
 Test for overall effect:  $Z = 3.22$  ( $P = 0.001$ )

## 1.3.6 48 wk

Ding <i>et al</i>	10	30	6	30	4.3%	1.67 [0.69, 4.00]
Yu <i>et al</i>	47	92	35	85	10.5%	1.24 [0.90, 1.71]
Ye <i>et al</i>	20	46	10	46	6.3%	2.00 [1.05, 3.79]
Liu <i>et al</i>	8	20	2	20	2.0%	4.00 [0.97, 16.55]
Zhou <i>et al</i>	8	52	7	63	3.8%	1.38 [0.54, 3.56]
Subtotal (95% CI)		240		244	27.0%	1.45 [1.11, 1.89]
Total events	93		60			

Heterogeneity:  $\text{Tau}^2 = 0.00$ ;  $\chi^2 = 4.06$ ,  $\text{df} = 4$  ( $P = 0.40$ );  $I^2 = 2\%$   
 Test for overall effect:  $Z = 2.75$  ( $P = 0.006$ )

## 1.3.7 52 wk

Huang <i>et al</i>	26	90	14	90	7.0%	1.86 [1.04, 3.32]
Subtotal (95% CI)		90		90	7.0%	1.86 [1.04, 3.32]
Total events	26		14			

Heterogeneity: Not applicable

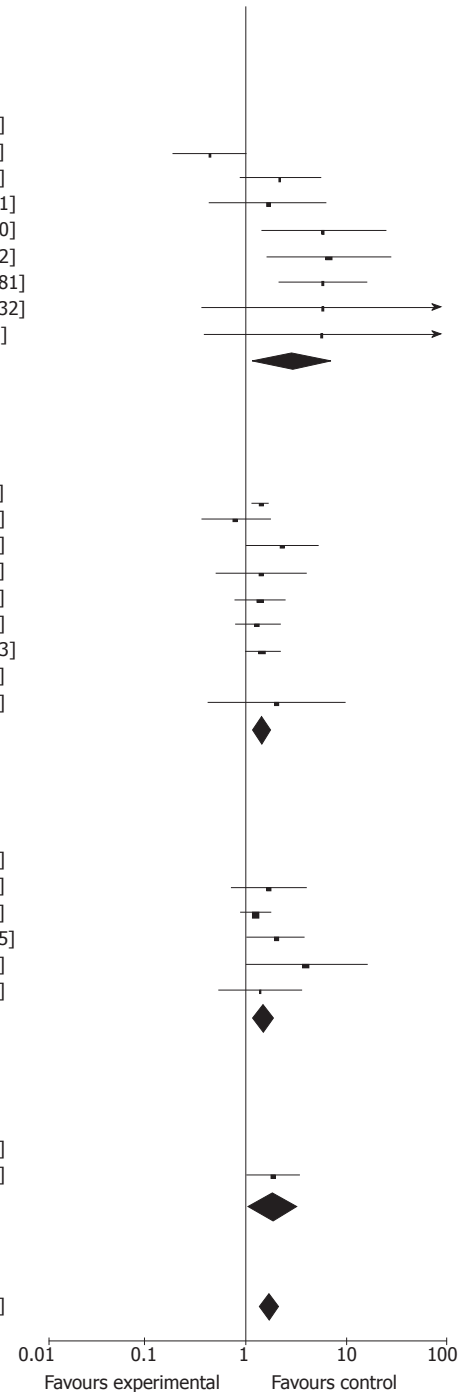
Test for overall effect:  $Z = 2.09$  ( $P = 0.04$ )

Total (95% CI)		1305		1278	100.0%	1.68 [1.35, 2.09]
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Total events 338 194

Heterogeneity:  $\text{Tau}^2 = 0.09$ ;  $\chi^2 = 38.84$ ,  $\text{df} = 25$  ( $P = 0.04$ );  $I^2 = 36\%$

Test for overall effect:  $Z = 4.66$  ( $P < 0.00001$ )



## D

Study of subgroup	LDT		ETV		Weight	Risk ratio M-H, Fixed, 95% CI	Risk ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
1.4.1 4 wk							
Yu <i>et al</i>	0	92	0	85		Not estimable	
Liu <i>et al</i>	0	20	0	20		Not estimable	
Subtotal (95% CI)		112		105		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.4.2 8 wk							
Zhang <i>et al</i>	3	75	1	65	0.6%	2.60 [0.28, 24.39]	
Zhao <i>et al</i>	2	42	1	39	0.5%	1.86 [0.18, 19.68]	
Yu <i>et al</i>	1	92	0	85	0.3%	2.77 [0.11, 67.19]	
Subtotal (95% CI)		209		189	1.4%	2.34 [0.55, 9.92]	
Total events	6		2				
Heterogeneity: $\chi^2 = 0.06$ , $\text{df} = 2$ ( $P = 0.97$ ); $I^2 = 0\%$							
Test for overall effect: $Z = 1.16$ ( $P = 0.25$ )							



## 1.4.3 12 wk

Zhu <i>et al</i>	4	30	11	30	5.8%	0.36 [0.13, 1.01]
Xu <i>et al</i>	8	30	2	30	1.1%	4.00 [0.92, 17.30]
Zhang <i>et al</i>	6	75	3	65	1.7%	1.73 [0.45, 6.66]
Shi <i>et al</i>	8	40	2	40	1.1%	4.00 [0.90, 17.68]
Zhao <i>et al</i>	3	42	2	39	1.1%	1.39 [0.25, 7.90]
Zheng <i>et al</i>	9	65	2	66	1.0%	4.57 [1.03, 20.34]
Yu <i>et al</i>	21	92	5	85	2.7%	3.88 [1.53, 9.83]
Ye <i>et al</i>	0	46	0	46		Not estimable
Liu <i>et al</i>	0	20	0	20		Not estimable
Subtotal (95% CI)		440		421	14.5%	2.10 [1.36, 3.24]
Total events	59		27			

Heterogeneity:  $\chi^2 = 15.69$ ,  $df = 6$  ( $P = 0.02$ );  $I^2 = 62\%$ Test for overall effect:  $Z = 3.36$  ( $P = 0.0008$ )

## 1.4.4 24 wk

Zhu <i>et al</i>	8	30	6	30	3.2%	1.33 [0.53, 3.38]
Xu <i>et al</i>	12	30	6	30	3.2%	2.00 [0.86, 4.63]
Zhao <i>et al</i>	7	36	6	36	3.2%	1.17 [0.43, 3.13]
Zhang <i>et al</i>	12	75	6	65	3.4%	1.73 [0.69, 4.36]
Shi <i>et al</i>	11	40	7	40	3.7%	1.57 [0.68, 3.64]
Zhao <i>et al</i>	6	42	4	39	2.2%	1.39 [0.42, 4.57]
Zheng <i>et al</i>	16	65	9	66	4.7%	1.81 [0.86, 3.79]
Yu <i>et al</i>	26	92	14	85	7.7%	1.72 [0.96, 3.06]
Ye <i>et al</i>	7	46	2	46	1.1%	3.50 [0.77, 15.96]
Liu <i>et al</i>	2	20	0	20	0.3%	5.00 [0.26, 98.00]
Subtotal (95% CI)		476		457	32.6%	1.71 [1.29, 2.28]
Total events	107		60			

Heterogeneity:  $\chi^2 = 2.52$ ,  $df = 9$  ( $P = 0.98$ );  $I^2 = 0\%$ Test for overall effect:  $Z = 3.71$  ( $P = 0.0002$ )

## 1.4.5 48 wk

Zhao <i>et al</i>	10	36	7	36	3.7%	1.43 [0.61, 3.34]
Ding <i>et al</i>	8	30	5	30	2.6%	1.60 [0.59, 4.33]
Zhao <i>et al</i>	15	42	9	39	4.9%	1.55 [0.77, 3.12]
Yu <i>et al</i>	37	92	18	85	9.9%	1.90 [1.18, 3.07]
Ye <i>et al</i>	12	46	4	46	2.1%	3.00 [1.04, 8.62]
Liu <i>et al</i>	4	20	0	20	0.3%	9.00 [0.52, 156.91]
Zhou <i>et al</i>	3	52	3	63	1.4%	1.21 [0.26, 5.75]
Subtotal (95% CI)		318		319	25.0%	1.86 [1.36, 2.54]
Total events	89		46			

Heterogeneity:  $\chi^2 = 2.97$ ,  $df = 6$  ( $P = 0.81$ );  $I^2 = 0\%$ Test for overall effect:  $Z = 3.89$  ( $P < 0.0001$ )

## 1.4.6 52 wk

Huang <i>et al</i>	25	90	13	90	6.9%	1.92 [1.05, 3.52]
Zhang <i>et al</i>	23	75	11	65	6.2%	1.81 [0.96, 3.43]
Subtotal (95% CI)		165		155	13.1%	1.87 [1.21, 2.90]
Total events	48		24			

Heterogeneity:  $\chi^2 = 0.02$ ,  $df = 1$  ( $P = 0.89$ );  $I^2 = 0\%$ Test for overall effect:  $Z = 2.80$  ( $P = 0.005$ )

## 1.4.7 60 wk

Zhao <i>et al</i>	15	42	9	39	4.9%	1.55 [0.77, 3.12]
Subtotal (95% CI)		42		39	4.9%	1.55 [0.77, 3.12]
Total events	15		9			

Heterogeneity: Not applicable

Test for overall effect:  $Z = 1.22$  ( $P = 0.22$ )

## 1.4.8 72 wk

Zhang <i>et al</i>	27	75	15	65	8.5%	1.56 [0.91, 2.67]
Subtotal (95% CI)		75		65	8.5%	1.56 [0.91, 2.67]
Total events	27		15			

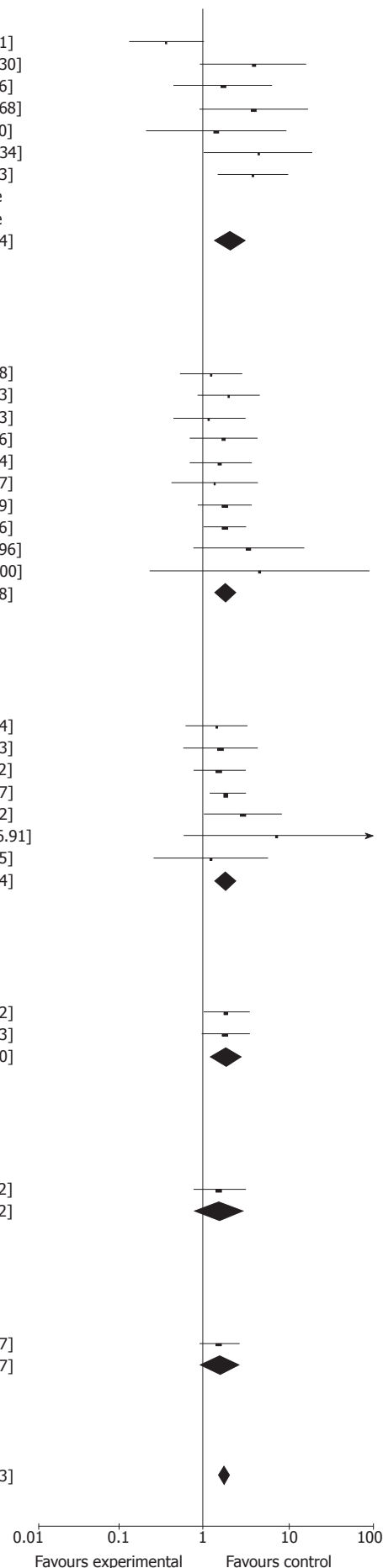
Heterogeneity: Not applicable

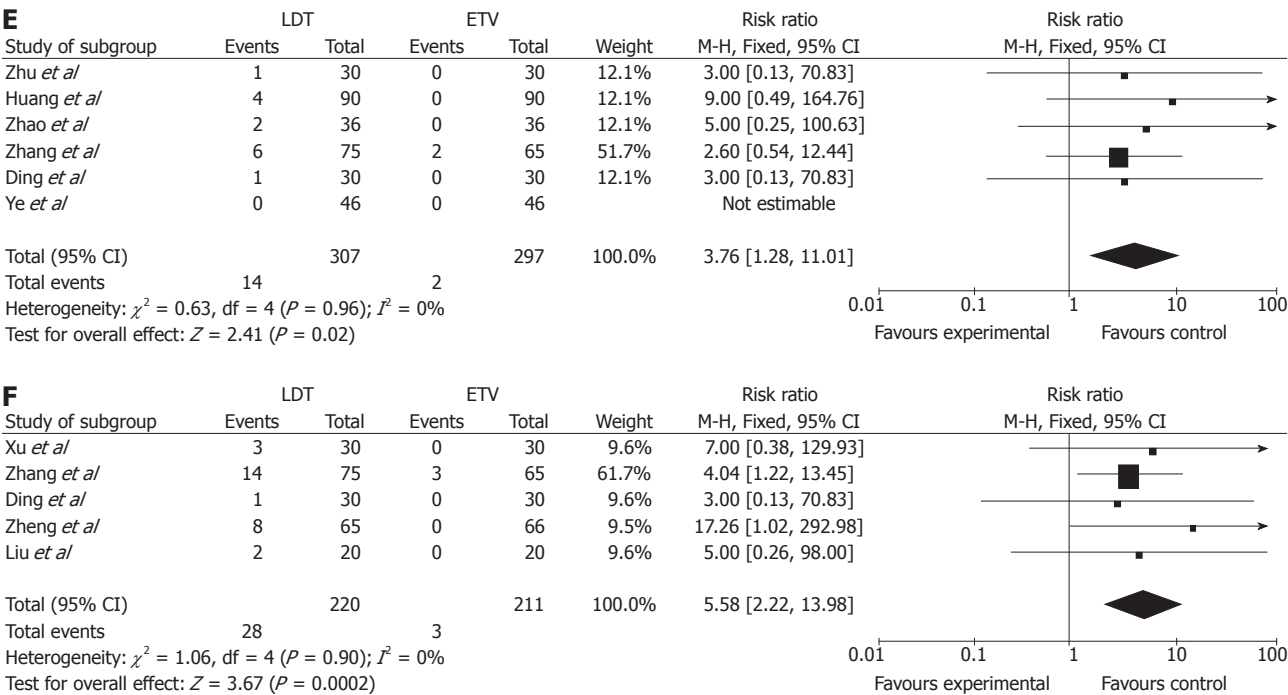
Test for overall effect:  $Z = 1.62$  ( $P = 0.10$ )

Total (95% CI)		1837		1750	100.0%	1.81 [1.55, 2.13]
Total events	351		183			

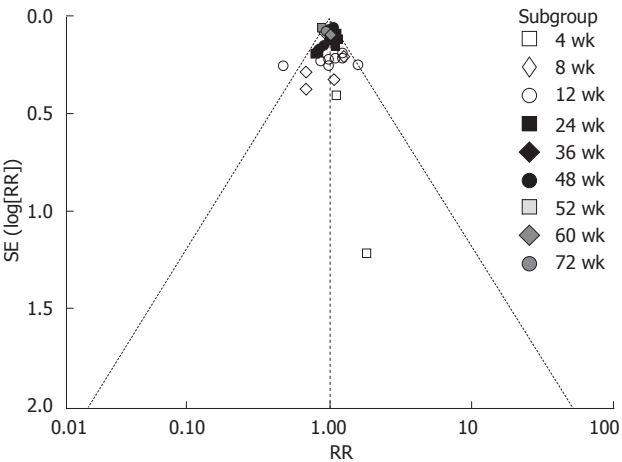
Heterogeneity:  $\chi^2 = 22.15$ ,  $df = 30$  ( $P = 0.85$ );  $I^2 = 0\%$ Test for overall effect:  $Z = 7.29$  ( $P < 0.00001$ )

Test for subgroup differences: Not applicable.





**Figure 2** Meta-analysis of the two groups. A: Hepatitis B virus DNA undetectability; B: Alanine aminotransferase normalization; C: Hepatitis B e antigen (HBeAg) loss; D: HBeAg seroconversion; E: Drug-resistance; F: Increased creatine kinase (CK). ETV: Entecavir; LDT: Telbivudine.



**Figure 3** Funnel plots of the two groups in hepatitis B virus DNA undetectability. RR: Relative risk;

es, drug-resistance and adverse reactions were performed to examine the association between pre-specified characteristics (treatment duration) and the therapeutic effect of the two drugs.

HBV DNA level is a primary prognostic marker for the treatment of patients with CHB<sup>[25,26]</sup>. The early and sustained suppression of HBV DNA replication is associated with improved long-term rates of virological, serological and biochemical responses. Rapidly and effectively suppressing HBV DNA replication can decrease the incidence of liver cirrhosis (LC), HCC and drug-resistance<sup>[27,28]</sup>. The results of the meta-analysis showed that in various treatment durations (4 wk, 8 wk, 12 wk, 24 wk, 36 wk, 48 wk, 52 wk, 60 wk and 72 wk), there were no statistical differences in the rate of HBV DNA undetect-

Table 2 Sensitivity analysis		
Index	Total HBeAg loss	
	OR (95% CI)	P value
Excluding the minimum sample size trials <sup>[18]</sup>	1.64 (1.31, 2.05)	< 0.00 010
Using random-effect model	1.68 (1.35, 2.09)	< 0.00 001
Using fixed-effect model	1.69 (1.46, 1.97)	< 0.00 001

OR: Odds ratio; HBeAg: Hepatitis B e antigen.

ability between the two groups. This suggested that both LDT and ETV have rapid and effective anti-viral activity and the result is similar with a large sample size study<sup>[29]</sup>. In addition, there was also no significant difference in the rate of ALT normalization between the two drugs.

HBeAg is a protein expressed by *pre-C* gene. HBeAg loss occurs with the rise of immunomodulatory effect which can suppress HBV DNA replication. HBeAg seroconversion has been established as a key marker of treatment response and is associated with improved clinical outcomes. It is one of the significant withdrawal standards for HBeAg-positive patients and suggests that patients can obtain sustained immune response<sup>[30]</sup>. The results of the meta-analysis showed that at 4 wk and 8 wk of the treatment, the rates of HBeAg loss and HBeAg seroconversion were similar, with no statistical difference between the two groups, while at 12 wk, 24 wk, 48 wk and 52 wk, the rate was higher in the LDT group than in the ETV group, the difference being statistically significant. At 60 wk and 72 wk, there was no significant difference in the rate of HBeAg seroconversion between the two groups. These results suggested that the rates of HBeAg loss and HBeAg seroconversion in the short-term and medium-

term treatment were higher in the LDT group than in the ETV group. So LDT can be used as a primary drug for HBeAg-positive patients. However, its long-term efficacy needs to be further explored.

The higher rate of HBeAg seroconversion during LDT treatment might be associated with the potential immunomodulatory effect of LDT. CHB is a viral as well as an immunological disease. Specific immune function is impaired in the patients with CHB. Many studies suggested that LDT promoted T-helper 1 cytokine and CD4+/CD8+ cell production, but only downregulated programmed death ligand 1, regulatory T cell and T-helper 2 cytokine production<sup>[31-33]</sup>. These immunomodulatory effects increase the rate of HBeAg seroconversion.

ETV has a high genetic barrier to resistance<sup>[34-36]</sup>. The meta-analysis (Figure 2E) showed that the rate of drug-resistance was higher in the LDT group (4.69%) than in the ETV group (0.75%), the difference being statistically significant between the two groups. ETV has a lower drug-resistance than LDT and it is preferred for long-term anti-HBV activity.

The meta-analysis (Figure 2F) showed no severe adverse reactions in the two groups. Although the rate of increased CK in the LDT group was higher than in the ETV group, CK can recover without any intervention, and does not influence the anti-HBV treatment. These results suggest that both LDT and ETV are safe and well tolerated.

## COMMENTS

### Background

Chronic hepatitis B (CHB) infection is a major health problem affecting over 350 million people worldwide. CHB can lead to a number of life-threatening conditions such as liver failure, liver cirrhosis and hepatocellular carcinoma. Recent studies have shown that telbivudine (LDT) and entecavir (ETV) are the strongest nucleoside analogues in the treatment of CHB. But there are few systematic reviews about the comparison of LDT and ETV.

### Research frontiers

LDT is an orally bioavailable L-nucleoside. It can rapidly and effectively suppress HBV DNA replication, but it has a higher drug-resistance. ETV is a new generation nucleoside analogues. It has the advantage of a higher rate of HBV DNA suppression, low drug-resistance and high safety, especially in lamivudine-resistant CHB patients. But the rate of hepatitis B e antigen (HBeAg) loss and HBeAg seroconversion was very low, which is difficult to meet the withdrawal standards.

### Innovations and breakthroughs

There are few systematic reviews about the efficacy of LDT and ETV in the CHB treatment. The authors conducted a meta-analysis of the included randomized controlled trials using the Cochrane methodology and explored the efficacy of LDT and ETV for clinical treatment of HBeAg-positive chronic hepatitis B.

### Applications

The results of this meta-analysis suggest that LDT and ETV have similar virological and biomedical response, and both are safe and well tolerated. However, LDT has better serological response and higher rate of drug-resistance.

### Peer review

This study reviewed 13 trials comparing the effects of telbivudine and entecavir for patients with chronic HBeAg-positive chronic hepatitis B infection. Based on their analyses, the authors conclude that LDT and ETV exert an effective antiviral effect on HBV. Regarding the undetectability and ALT normalization, there was no big difference between the two drugs. The analysis was carefully performed, and the results were clearly presented and summarized, which provided valuable advice for clinical treatment of CHB.

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