Systematic Review and Meta-Analysis

Medicine®

OPEN

# Entecavir-based combination therapies for chronic hepatitis B

## A meta-analysis

Aoran Luo, PhD, Xiaoyan Jiang, MM, Hong Ren, MD, PhD*

**Abstract**

**Background:** Currently, there is no consensus on the efficacy and safety of the entecavir (ETV) monotherapy versus the ETV-based combination therapy for chronic hepatitis B.

**Methods:** A comprehensive literature search was performed on the comparison of ETV-based combination therapy and monotherapy for chronical hepatitis B (CHB) patients in the PubMed, Embase, Web of Science, the Cochrane Libraries, and the Chinese BioMedical Literature Database. Both dichotomous and continuous variables were extracted, and pooled outcomes were expressed as odds ratio (OR) or mean difference (MD).

**Results:** We included randomized clinical trials (RCTs) and cohorts involving Group A: nucleos(t)ide-naive patients (four RCTs, n = 719 patients), Group B: nucleos(t)ide-resistant patients (four cohorts, n = 196 patients), and Group C: entecavir-treated patients with undetectable hepatitis B virus DNA (two RCTs and two cohorts, n = 297). Group A. ETV monotherapy was better for rates of undetectable HBV DNA, while the rates of the HBV DNA levels at the end of treatment, HBeAg Loss, ALT normalization were similar between the two groups [MD, −0.85 (95% CI, −0.173–0.03); OR, 0.92 (95% CI, 0.24–3.56); OR, 1.31 (95% CI, 0.17–9.82)]; Group B. ETV monotherapy was better for rates of undetectable HBV DNA, while the rates of the HBV DNA levels at the end of treatment, HBeAg Loss, ALT normalization were similar; Group C. The ETV-based combination therapy was better for the rate of HBV DNA relapse.

**Conclusion:** Based on the current data, ETV-based combination therapy seemed to be no better than ETV monotherapy. Further studies are needed to verify this conclusion.

**Abbreviations:** ADV = adefovir, CHB = chronic hepatitis B, CI = confidence interval, ETV = entecavir, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IFN = interferon, LAM = lamivudine, LdT = telbivudine, MD = mean difference, NOS = Newcastle–Ottawa scale, OR= odds ratio, RCT = randomized controlled trial, TDF = tenofovir.

**Keywords:** chronic hepatitis B, combination therapy, entecavir, monotherapy

### 1. Introduction

Chronic hepatitis B virus (HBV) infection remains a serious global health problem. Currently, approximately two billion people have been infected with HBV, and approximately 3.6% of the world's population are suffering from chronic hepatitis B (CHB) worldwide.[1] Like patients with hepatitis C will develop into end-stage liver disease,[2–4] 15% to 40% of patients with CHB are expected to develop cirrhosis, liver failure, and/or hepatocellular carcinoma (HCC).[5] Chronic hepatitis B cannot be completely cured because the covalently closed circular DNA persists in the nuclei of infected hepatocytes. Therefore, the main purpose of antiviral therapy is sustained viral suppression.[6]

Currently, the available antiviral drugs for HBV include immunomodulatory drugs (interferon-alpha and pegylated interferon-alpha) and HBV polymerase inhibitors (nucleoside analogs: lamivudine [LAM], telbivudine [LdT], and entecavir [ETV] and nucleotide analogs: adefovir [ADV] and tenofovir [TDF]).[7] Entecavir is a new cyclopentyl guanosine NUC which is efficiently phosphorylated to the active triphosphate form by host cellular kinases. It hinders HBV replication by inhibiting all three steps of the HBV reverse transcriptase: base priming, reverse transcription of the negative-strand DNA from the pregenomic messenger RNA, and DNA-dependent plus-strand DNA synthesis.[8] Entecavir treatment is more favorable compared to other NUCs other than tenofovir, because it has a higher genetic barrier to resistance with more than three sites are required for drug resistance to develop, and a safer profile. In addition, the efficacy of entecavir is not worse than tenofovir. Therefore, ETV is now recommended as a first choice for CHB patients by most international guidelines.[9,10]

Despite these advantages, ETV monotherapy is not sufficient for some special patients. For example, ETV combination treatment is more potent than ETV monotherapy for patients with lamivudine/adefovir resistance. Because of a further decrease in HBV DNA following the addition of another

Editor: Sherief Abd-Elsalam.

Supplemental Digital Content is available for this article.

The authors have no conflicts of interest to disclose.

Key Laboratory of Molecular Biology for Infectious Diseases (Ministry of Education), Institute for Viral Hepatitis, Department of Infectious Diseases, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, PR China.

* Correspondence: Hong Ren, Key Laboratory of Molecular Biology for Infectious Diseases (Ministry of Education), Institute for Viral Hepatitis, Department of Infectious Diseases, The Second Affiliated Hospital, Chongqing Medical University, 1 Yixueyuan Road, Chongqing 400010, PR China (e-mail: renhong0531@vip.sina.com).



Medicine (2018) 97:51(e13596)

Received: 26 July 2018 / Accepted: 16 November 2018

http://dx.doi.org/10.1097/MD.0000000000013596

NA.[11] So, it remains controversial whether ETV-based combination therapy induces better outcomes than ETV monotherapy in CHB patients. At present, the meta-analysis on ETV mainly focused on ETV monotherapy versus other nucleos(t)ide analogs monotherapy;[12] ETV monotherapy versus ETV and interferon combination therapy;[13] other nucleos(t)ide analogs monotherapy versus other nucleos(t)ide analogs and ETV combination therapy;[14] ETV monotherapy versus other nucleos(t)ide analogs combination therapy, for example, lamivudine and adefovir combination therapy.[15] However, no relevant meta-analyses have directly compared ETV monotherapy and ETV-based combination therapy. Thence, our meta-analysis aimed to compare the relative efficacy of the two treatment strategies in CHB patients.

## 2. Materials and methods

### 2.1. Ethics statement

As all the data were from previously published studies, no ethical approval or patient consent was required.

### 2.2. Search strategy

Relevant studies regarding the comparison of ETV-based combination therapy and ETV monotherapy for CHB patients were identified by searching the PubMed, Embase, Web of Science, the Cochrane Libraries, and the Chinese BioMedical Literature Database using the following strategy: (((((Lamivudine) OR Tenofovir) OR Adefovir) OR Telbivudine) AND Entecavir) AND (HBV OR hepatitis B). The search was restricted to "human." The reference lists of all the retrieved documents were manually searched for potentially relevant reports missed by the intelligent retrieval systems mentioned above. The search was carried out in May 2018, and the entire selection process was implemented independently by two investigators (ARL and XYJ). Inconsistent search results were resolved with the assistance of an arbiter (HR) where necessary.

### 2.3. Selection criteria

Inclusion criteria for the meta-analysis were as followed: Study design: randomized controlled trials (RCTs), retrospective, and prospective cohort study designs (each group sample size >10); Subjects: patients with CHB (defined as a positive serum HBsAg test for at least 6 months); Treatment strategy: including a ETV plus other nucleoside analogs combination therapy group and a ETV monotherapy group as a control group. Outcome: including virological responses such as rates of undetectable HBV DNA, levels of HBV DNA at the end of treatment; Serological responses such as the rates of HBeAg loss, HBeAg seroconversion and HBsAg seroconversion. Biochemical response such as rates of ALT and AST normalization; levels of ALT AST and TBil at the end of treatment. The exclusion criteria were as follows: duplicated data; coinfection with other viruses such as hepatitis A, C, D, or E viruses or human immunodeficiency virus; autoimmune hepatitis, alcoholic liver disease, primary biliary cirrhosis, Wilson's disease, hepatocellular carcinoma, etc.; any report has no available outcome measures.

### 2.4. Outcome measures

The virological responses, serological responses, and biochemical responses were used as primary efficacy measures. Virological responses included virological suppression defined as achievement of undetectable HBV DNA levels to below the detection level. In addition, HBV DNA levels were comparable between the two groups at baseline, so HBV DNA levels at the end of treatment was also used. "Biochemical response" included ALT and AST normalization, defined as the proportion of subjects with normal ALT and AST levels after treatment, where patients had had abnormal ALT and AST levels at baseline. Moreover, ALT, AST and TBil levels after treatment were also applied as efficacy measures. "Serological response" included rates of HBeAg loss, HBeAg seroconversion, and HBsAg loss. The incidence of adverse events during treatment was used as a safety measure.

### 2.5. Study quality assessment

The quality of included RCTs was evaluated using the revised Jadad quality scale, which graded the quality of a study by examining randomization, blinding, allocation concealment, and drop-out. The quality of included cohort studies was assessed using the Newcastle–Ottawa scale (NOS) based on several standards including selection of cohorts, comparability of cohorts, and assessment of the outcomes.

### 2.6. Data extraction

Two reviewers (ARL and XYJ) independently used inclusion criteria, selected the studies, and extracted data and outcomes. The following data were extracted from each study: study characteristics (author, year of publication, geographic locale, study design, regimen, duration of follow-up, and sample size); patient demographics (age, sex) and baseline characteristics (HBeAg-positive percentage, alanine aminotransferase levels, and serum HBV DNA levels); and the study outcomes (virological responses, serological responses, and biochemical responses) after treatment. Any disagreement between the reviewers was resolved by the third party (HR).

### 2.7. Statistical analysis

All the statistical analyses were performed with Review Manager Software 5.3 (Cochrane Collaboration, Oxford, UK) and Stata (version 12.0). Both the dichotomous and continuous variables were extracted. For the dichotomous outcomes, the results were presented as the odds ratio (OR) with a 95% confidence interval (95% CI), while the continuous results were presented as a mean difference (MD) with a 95% confidence interval (95% CI). The statistical heterogeneity was evaluated by using chi-square and *I*-square ($I^2$) tests. Since the $\chi^2$ test lacks power when the number of studies is low, we considered heterogeneity was significant when both the $\chi^2$ value was within the 10% level of significance ($P < .10$) and the $I^2$ value exceeded 50%. If the $I^2$ value exceeded 50%, then the random effect model was used on combined results. Otherwise, the fixed effect model was used. If no heterogeneity was identified among the studies, the two models would generate identical results. However, when heterogeneity is found, the 95%CI of the summary estimate calculated by the random-effects model will be wider than that calculated using the fixed-effects model. A sensitivity analysis was then performed through the sequential omission of individual studies to investigate the effect of each study on the heterogeneity. The possible publication bias was assessed by Funnel plot and Egger's tests.[16] All the *P* values were two-sided. Apart from Cochran's *Q*-test, the significance level was 0.05.

## 3. Results

### 3.1. Search results and study characteristics

The search strategy resulted in the identification of 1916 records in total. Around 243 duplicates were excluded. 1649 records were excluded after scanning titles and abstracts. As a result, 24 full-text articles were subjected to detailed evaluation, of which, two have no relevant outcomes; four have no ETV monotherapy groups; in one study, patients were coinfected with viruses; patients were with liver cancer and cirrhosis in other five studies. Finally, six randomized-controlled trials and six cohorts were chosen for inclusion in the meta-analysis, which comprised a total of 1212 patients. Figure 1 shows the study selection process. The basic characteristics of the 12 studies and the included patients are listed in Table 1. Six of these studies were from China,[17–22] five studies were from South Korea.[23–27] The remaining one study was performed in multi-centers in Western countries.[28] The included studies were published between 2011 and 2018. The sample size for each study ranged from 30 to 200. The mean age ranged from 35 to 53 years old. The duration of follow-up ranged from 12 to 96 weeks. The percentage of males ranged from 55% to 85%.

### 3.2. Virological responses

The seven included studies, which involved 700 patients, reported the undetectable rates of HBV DNA.[17,19,20,23–25,28] Because the heterogeneity was not significant among these studies (group A: $P=.16$, $I^2=45\%$; group B: $P=.23$, $I^2=30\%$; overall: $P=.24$, $I^2=24\%$), the fixed-effect method was applied to calculate the overall effects. For both group A and group B, the rate of undetectable HBV DNA was higher in the ETV monotherapy group than in the combination therapy group (OR = 1.92, 95% CI: 1.20–3.05, $P=.006$; OR = 1.76, 95% CI: 0.97–3.97, $P=.06$; Fig. 2). When ORs of two groups were pooled, it showed that the rate of undetectable HBV DNA was also higher in the ETV monotherapy group than in the combination therapy group (OR = 1.86, 95% CI: 1.29–2.68, $P=.0009$; Fig. 2). In addition, the sensitivity analysis was performed through the sequential omission of every studies, it turned out that the significance of the ORs was not influenced excessively. Based on a symmetrical funnel plot (Figure S1, http://links.lww.com/MD/C693) and Egger's tests ($P=.49$), no evidence of publication bias was found (Table 2).

Four studies including 338 patients reported the serum HBV DNA levels at the end of the therapy.[18,19,24,25] Because the HBV DNA levels are comparable in these studies at the baseline, the difference in therapeutic effects can be illustrated by comparing the HBV DNA level of the treatment endpoint. Because the heterogeneity was significant among these studies ($P<.00001$, $I^2=89\%$), the random-effect method was applied to calculate the overall effects. For both group A and group B, the meta-analysis showed that the HBV DNA levels at the end of treatment were similar between the two groups (group A: MD = −0.85, 95% CI: −0.173–0.03, $P=.06$; group B: MD = −0.98, 95% CI: −2.37–0.42, $P=.17$; Figure S2, http://links.lww.com/MD/C693). But when results of the two groups were pooled, HBV DNA levels at

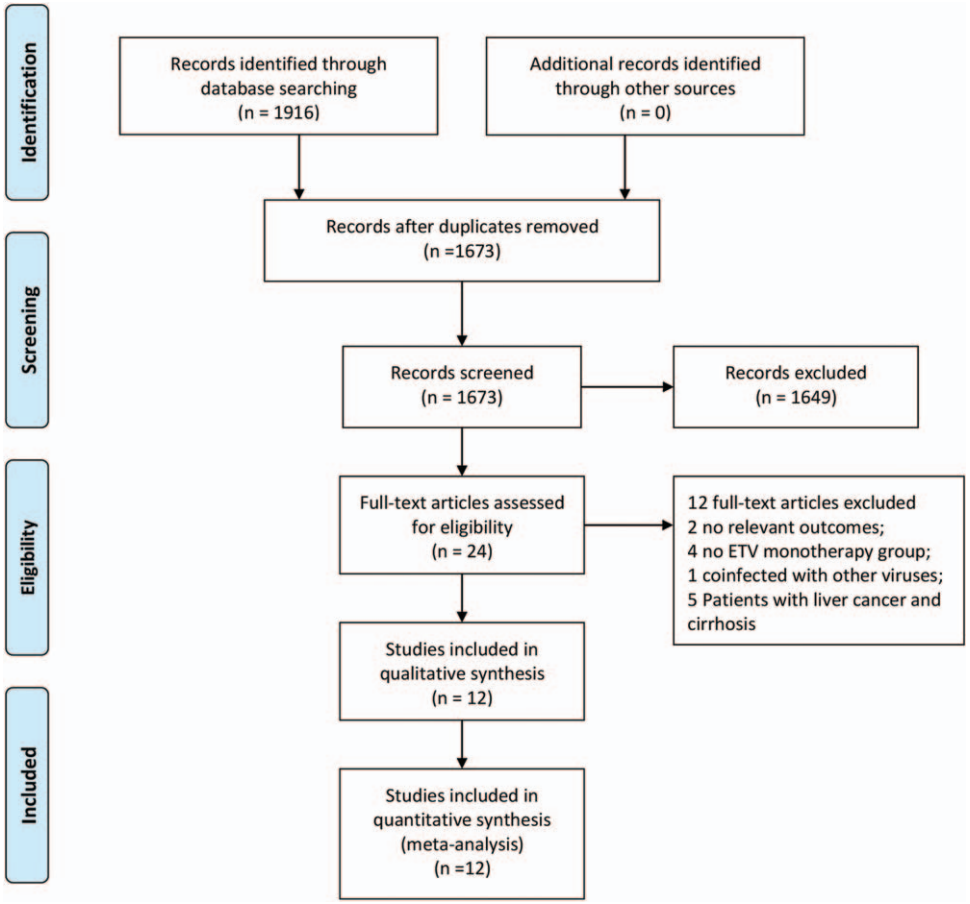


**Figure 1.** Study selection process.

**Table 1**

**Characteristics of the trials included in this meta-analysis.**

| Author | Year | Geographic locale | Patient grouping | Study design | Regimen | Sample size | Duration, weeks |
|---|---|---|---|---|---|---|---|
| An | 2017 | South Korea | Group C | Cohort | ETV, ETV+LdT | 97 | 36 |
| Chen | 2018 | China, Jiangxi province | Group A | RCT | ETV, ETV+ADV | 60 | 96 |
| Fung | 2011 | China, Hong Kong, | Group C | RCT | ETV, ETV+LAM | 50 | 96 |
| Kang | 2014 | South Korea | Group B | Cohort | ETV, ETV+ADV | 28 | 32 |
| Kim | 2017 | South Korea | Group C | RCT | ETV, ETV+LdT | 60 | 96 |
| Liu | 2016 | China, Hunan province | Group B | Cohort | ETV, ETV+ADV | 108 | 48 |
| Lok | 2012 | Multicenters in Western countries | Group A | RCT | ETV, ETV+TDF | 379 | 96 |
| Oh | 2016 | South Korea | Group B | Cohort | ETV, ETV+ADV | 30 | 48 |
| Park | 2013 | South Korea | Group B | Cohort | ETV, ETV+ADV | 30 | 23 |
| Yeh | 2016 | China, Taiwan | Group C | Cohort | ETV, ETV+LAM | 90 | 48 |
| Zhang | 2014 | China, Hubei province | Group A | RCT | ETV, ETV+ADV | 80 | 96 |
| Zhang | 2017 | China, Jiangsu province | Group A | RCT | ETV, ETV+ADV | 200 | 12 |

ADV = adefovir, ETV = entecavir, LAM = lamivudine, RCT = randomized controlled trial.

the end of treatment were lower in the combination group than the ETV monotherapy group (MD = −0.89, 95% CI: −1.61–−0.16, $P = .02$; Figure S2, http://links.lww.com/MD/C693).

The four included studies, which involved 297 patients, reported the rates of HBV DNA relapse.[21,22,26,27] Because the heterogeneity was not significant among these studies (group C: $P = .98$, $I^2 = 0\%$), the fixed-effect method was applied to calculate the overall effects. The rate of HBV DNA relapse was higher in the combination therapy group than in ETV monotherapy group (OR = 19.57, 95% CI: 4.60–83.37, $P < .0001$; Figure S3, http://links.lww.com/MD/C693).

### 3.3. Serological responses

The four included studies involving 397 patients reported the rates of HBeAg loss.[19,24,25,28] Because the heterogeneity was significant among these studies (group A: $P = .57$, $I^2 = 0\%$; group B: $P = .01$, $I^2 = 85\%$; overall: $P = .07$, $I^2 = 57\%$), the random-effect method was applied to calculate the overall effects. For group A, group B and overall effect, the rate of HBeAg Loss was all similar between the ETV monotherapy group and the combination therapy group (OR = 0.92, 95% CI: 0.24–3.56, $P = .91$; OR = 0.89, 95% CI: 0.57–1.41, $P = .63$; OR = 0.90, 95% CI: 0.58–1.38, $P = .62$; Fig. 3).

The three included studies involving 374 patients reported the rates of HBeAg seroconversion.[19,25,28] The heterogeneity was significant among these studies ($P = .004$, $I^2 = 82\%$). Therefore, the random-effect method was applied to calculate the overall effects. The rate of HBeAg seroconversion was similar between the two groups (OR = 1.59, 95% CI: 0.40–6.43, $P = .5$; Figure S4, http://links.lww.com/MD/C693).

The two included studies involving 487 patients reported the rates of HBsAg Loss.[20,28] As there was not significant heterogeneity among these studies ($P = .23$, $I^2 = 30\%$), the fixed-

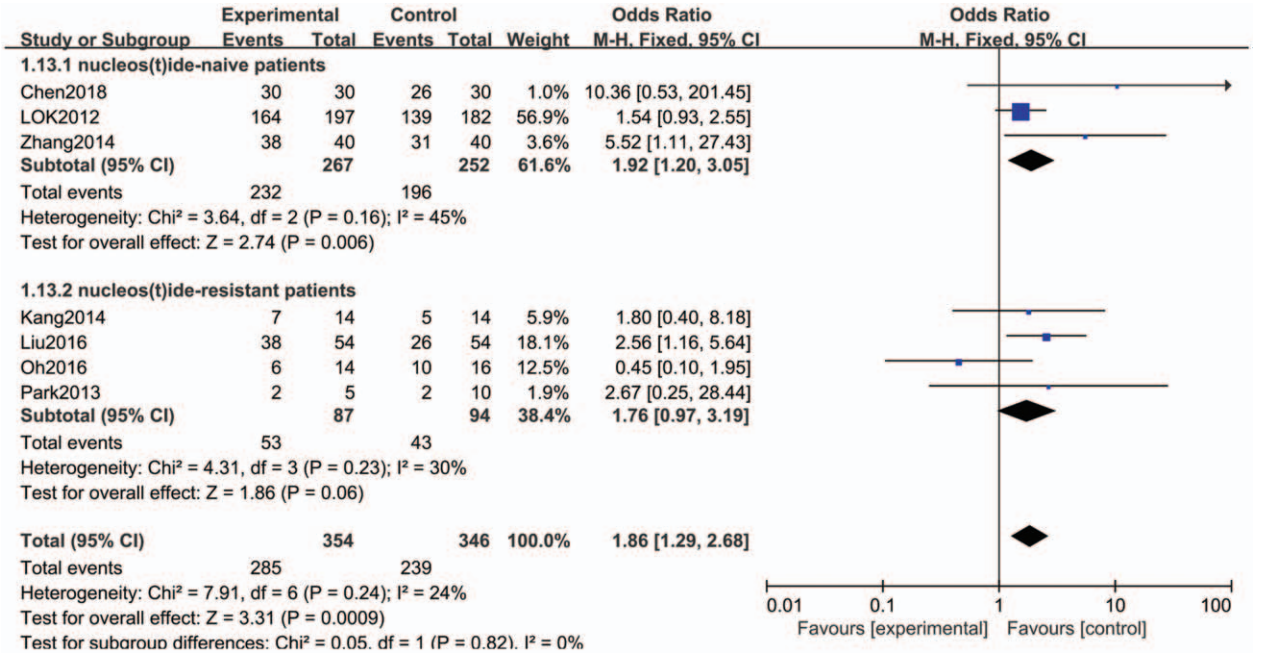


**Figure 2.** Effect of ETV-based combination therapy vs ETV monotherapy on HBV suppression in nucleos(t)ide-naive patients and nucleos(t)ide-resistant patients. ETV = entecavir, HBV = hepatitis B virus.

**Table 2**

**Characteristics of the patients included in this meta-analysis.**

| Author | Year | Age | Sex (male%) | HBV DNA (log10) | HBeAg(+), % | ALT, U/L |
|---|---|---|---|---|---|---|
| An | 2017 | 47 | 69.1 | <60 IU | 75.3 | 20 |
| Chen | 2018 | 51 | 63.3 | NR | 0 | 116.9 |
| Fung | 2011 | 50 | 72 | <61 IU | 18 | 24.5 |
| Kang | 2014 | 44 | 85.7 | 5.64 | 71.4 | 147.8 |
| Kim | 2017 | 53 | 66.7 | <20 IU | 18.3 | 24.5 |
| Liu | 2016 | 45 | 54.6 | NR | NR | 818.1 |
| Lok | 2012 | 39 | 69.1 | 7.5 | 69.7 | 143.1 |
| Oh | 2016 | 43 | 73.3 | 4.47 | 96.7 | 279 |
| Park | 2013 | 45 | 89.2 | 5.84 | 82.1 | 92.5 |
| Yeh | 2016 | 48 | 72.2 | 5.95 | 24.4 | 23.5 |
| Zhang | 2014 | 35 | 82.5 | 8.05 | 100 | 181.4 |
| Zhang | 2017 | 46 | 70 | 6.65 | 0 | 116.4 |

HBV DNA, HBeAg, and ALT were all expressed as mean.
ALT = alanine transaminase, HBV = hepatitis B virus, NR = not report.

effect method was applied to combine the overall effects. The rate of HBsAg Loss was higher in the ETV monotherapy group than in the combination therapy group (OR = 2.25, 95% CI: 1.05–4.81, $P = .04$; Figure S5, http://links.lww.com/MD/C693).

### 3.4. Biochemical responses

The five included studies involving 599 patients reported the rates of ALT normalization.[19,20,24,25,28] The between-study heterogeneity was significant when the five studies were pooled into a meta-analysis ($P = .003$, $I^2 = 78\%$); thus, the random-effects model was used to pool the results. For group A, group B and overall effect, The results suggested that the rate of ALT normalization was all similar between the two groups (group A: OR = 1.31, 95% CI: 0.17–9.82, $P = .79$; group B: OR = 1.41, 95% CI: 0.48–4.13, $P = .53$; overall: OR = 1.32, 95% CI: 0.40–4.33, $P = .65$; Fig. 4).

The three included studies involving 368 patients reported the levels of ALT at the end of treatment.[17,18,20] Because the ALT levels are comparable in these studies at the baseline, the difference in therapeutic effects can be illustrated by comparing the ALT level of the treatment endpoint. The between-study heterogeneity was significant when the three studies were pooled into a meta-analysis ($P < .00001$, $I^2 = 99\%$); thus, the random-effects model was used to pool the results. The results suggested that the level of ALT at the end of treatment was similar between the two groups (OR = 8.11, 95% CI: −28.56–12.35, $P = .44$; Figure S6, http://links.lww.com/MD/C693).

The two included studies involving 260 patients reported the levels of AST at the end of treatment.[17,18] Because the AST levels are comparable in these studies at the baseline, the difference in therapeutic effects can be illustrated by comparing the AST level of the treatment endpoint. The between-study heterogeneity was not significant when the two studies were pooled into a meta-analysis ($P = 1$, $I^2 = 0\%$); thus, the fixed-effects model was used to pool the results. The results suggested that the level of AST at the end of treatment was higher in the ETV monotherapy group than combination group

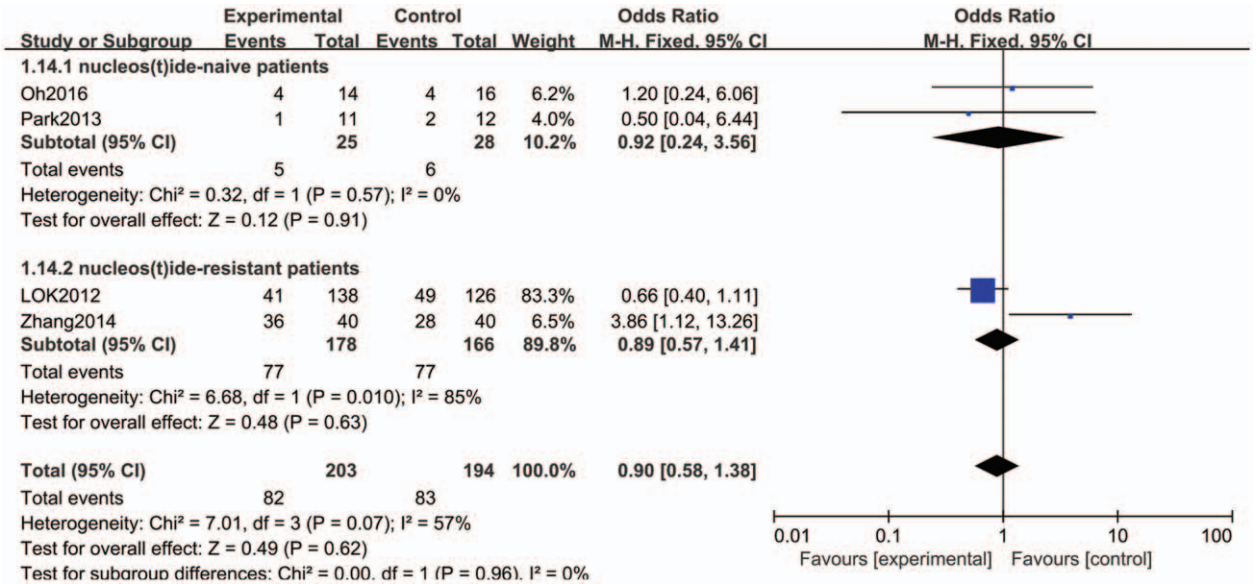


**Figure 3.** Effect of ETV-based combination therapy vs ETV monotherapy on HBeAg loss in nucleos(t)ide-naive patients and nucleos(t)ide-resistant patients. ETV = entecavir.

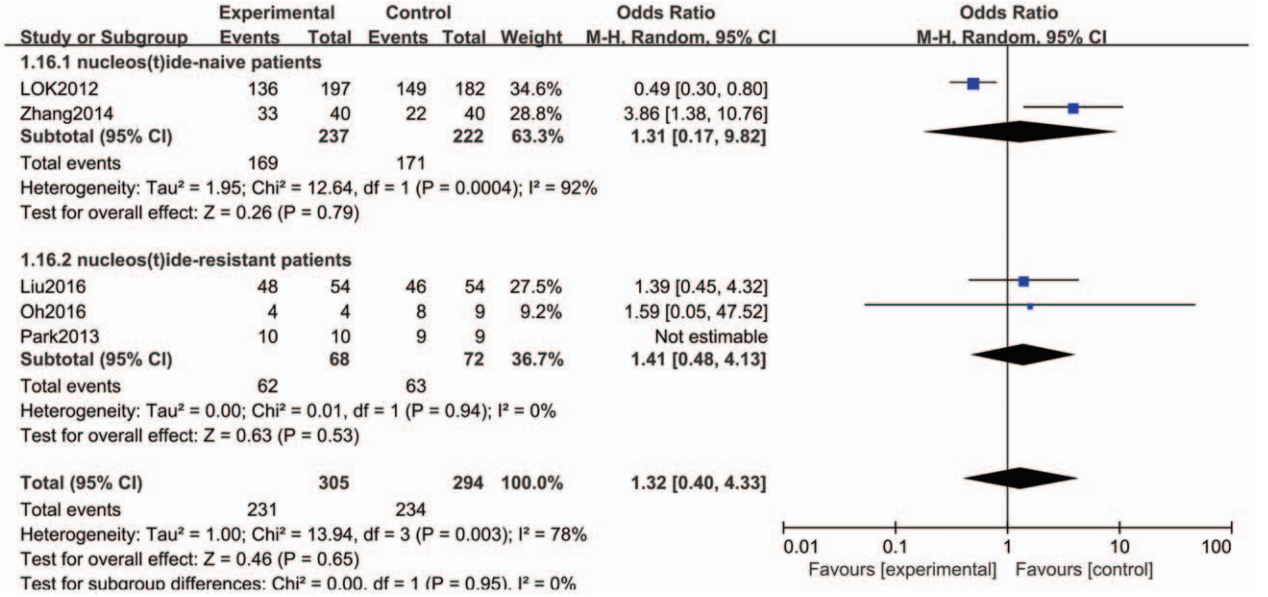


**Figure 4.** Effect of ETV-based combination therapy vs ETV monotherapy on ALT normalization in nucleos(t)ide-naive patients and nucleos(t)ide-resistant patients. ETV = entecavir.

(MD = −41.40, 95% CI: −49.44 – −33.36, $P = .44$; Figure S7, http://links.lww.com/MD/C693).

The three included studies involving 368 patients reported the levels of TBil at the end of treatment.[17,18,20] Because the TBil levels are comparable in these studies at the baseline, the difference in therapeutic effects can be illustrated by comparing the TBil level of the treatment endpoint. The between-study heterogeneity was significant when the studies were pooled into a meta-analysis (group A: $P = 1$, $I^2 = 0\%$; overall: $P < .00001$, $I^2 = 89\%$); thus, the random-effects model was used to pool the results. The results suggested that the level of TBil at the end of treatment was higher in the ETV monotherapy group than the combination group (MD = −47.32, 95% CI: −68.09– −26.54, $P < .00001$; Figure S8, http://links.lww.com/MD/C693).

### 3.5. Safety

The four studies included here reported some of the adverse events that occurred over the course of treatment, including dizziness, nausea, myelosuppression, constipation, elevated blood lipids and etc.[17–19,28] The between-study heterogeneity was not significant when the four studies were pooled into the meta-analysis ($P = .28$, $I^2 = 21\%$); thus, the fixed-effects model was used to pool the results. The meta-analysis showed that the incidence of adverse events was similar between the two groups (OR = 0.72, 95% CI: 0.53–1.07, $P = .12$; Fig. 5).

## 4. Discussion

ETV monotherapy is now recommended as a first-line therapy for CHB patients by most international guidelines. But for nucleos(t)ide-resistant patients or entecavir-treated patients with undetectable hepatitis B virus DNA to maintain treatment effect, it is uncertain that ETV-based combination therapy or ETV monotherapy will be a better choice. Therefore, we performed this present meta-analysis including studies that involved the comparison between ETV-based combination therapy and monotherapy, to investigate the controversy.

The current meta-analysis reached the following results: For both group A and group B, ETV monotherapy was more effective in improving the rate of undetectable HBV DNA than ETV-based combination therapy. The result was consistent when we pooled the rates of the two groups. For group C, ETV monotherapy was also more effective in maintain treatment effect than combination group. However, for group A, group B or overall effect, HBV DNA levels at the end of treatment were all similar between the

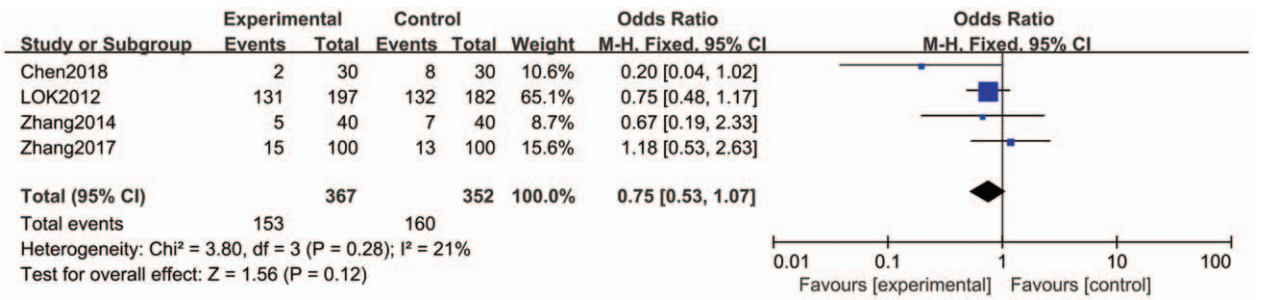


**Figure 5.** Effect of ETV-based combination therapy vs ETV monotherapy on the incidence of adverse events. ETV = entecavir.

two groups. Compared with other outcomes, there may be too few studies reporting HBV DNA levels at the end of treatment to achieve significant difference. Both of the rates of HBeAg loss and HBeAg seroconversion were similar between the two groups, while the monotherapy group was more effective in improving the rates of HBsAg loss than the combination therapy group. ETV-based combination therapy was more effective in reducing levels of AST and TBil than monotherapy group. But both ALT levels at the end of treatment and the rates of ALT normalization were similar between the two groups. Within a certain treatment period, the incidence of adverse events was similar between the two groups.

In the treatment of nucleoside analogs, we should not only use the imaging, biochemical indicators and other means to monitor the patients' treatment response,[29–32] but also pay attention to side effects caused by treatment. Despite that the incidences of adverse events were comparable between the ETV-based combination therapy group and the ETV monotherapy group, the potential for an increased risk of toxicity must always be noted especially when instituting ETV-based combination therapy. It was reported that the most common adverse events in phase III clinical trials were headache, fatigue, dizziness, and nausea.[33,34] Our present study reported some of the adverse events that occurred over the course of treatment, including dizziness, nausea, myelosuppression, constipation, elevated blood lipids, etc. As the ETV-901 rollover study including 1051 patients reported an overall discontinuation rate in our meta-analysis as AEs was extremely low (<1%).[35] In the present study, a cost-effectiveness analysis was not done because costs of medications were not included.

Several limitations to our meta-analysis should be considered. First, most studies came from Asia, and only one report came from Western countries. Although the sample size of this study from Western countries is the largest, it is not enough to balance the bias brought about by too little research; Second, six randomized controlled trials and six cohorts were included, so not all the studies included in this meta-analysis were randomized controlled trials; Third, as the revised Jadad quality scale showed, the randomized controlled trials included here was not of high quality; Fourth, detailed information of individual patients was insufficient to access the treatment effects in the different subgroups.

In conclusion, based on the available data, our results show that in terms of most outcomes (virological responses, serological responses, ALT normalization, ALT levels at the end of treatment, safety), ETV monotherapy is superior to or similar to ETV-based combination therapy. However, significant observations were found primarily for Asians but not for other populations, so large and elaborately designed studies from other areas are needed to confirm to these conclusions.

## Author contributions

**Methodology:** Hong Ren.
**Supervision:** Hong Ren.
**Validation:** Xiaoyan Jiang, Hong Ren.
**Writing – original draft:** Aoran Luo.
**Writing – review & editing:** Aoran Luo.

## References

[1] Vaage J, Agarwal S. Stimulation or inhibition of immune resistance against metastatic or local growth of a C3H mammary carcinoma. Cancer Res 1976;36:1831–6.
[2] Besheer T, Arafa M, Elmaksoud MA, et al. Diagnosis of cirrhosis in patients with chronic hepatitis C genotype 4: role of ABCB11 genotype polymorphism and plasma bile acid levels. Turk J Gastroenterol 2018; 29:299.
[3] Besheer T, Elbendary M, Elalfy H, et al. Prediction of fibrosis progression rate in patients with chronic hepatitis c genotype 4: role of cirrhosis risk score and host factors. J Interferon Cytokine Res 2017;37:3.
[4] Besheer T, Razek AA, El BM, et al. Does steatosis affect the performance of diffusion-weighted MRI values for fibrosis evaluation in patients with chronic hepatitis C genotype 4? Turk J Gastroenterol 2017;28:4.
[5] Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med 2004;350:1118–29.
[6] European Association for the Study of the LiverEASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol 2012;57:167–85.
[7] Lok ASF, Mcmahon BJ. Chronic hepatitis B: update 2009. Hepatology 2010;50:661–2.
[8] Lee HW, Park JY, Sang HA. An evaluation of entecavir for the treatment of chronic hepatitis B infection in adults. Expert Rev Gastroenterol Hepatol 2015;10:2.
[9] Liaw YF, Leung N, Kao JH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Chin J Gastroenterol Hepatol 2012;2:263.
[10] Yang L, Lun-Gen LU. Introduction: EASL Clinical Practice Guidelines: Management of Chronic Hepatitis B Virus Infection (2012). 1999; Springer,
[11] Osborn M. Safety and efficacy of entecavir for the treatment of chronic hepatitis B. Infect Drug Resist 2011;4:55–64.
[12] Yu S, Luo H, Pan M, et al. Comparison of entecavir and lamivudine in preventing HBV reactivation in lymphoma patients undergoing chemotherapy: a meta-analysis. Int J Clin Pharm 2016;38:1035–43.
[13] Xie QL, Zhu Y, Wu LH, et al. The efficacy and safety of entecavir and interferon combination therapy for chronic hepatitis B virus infection: a meta-analysis. PLoS One 2015;10:e132219.
[14] Chen J, Zhao SS, Liu XX, et al. Comparison of the efficacy of tenofovir versus tenofovir plus entecavir in the treatment of chronic hepatitis B in patients with poor efficacy of entecavir: a systematic review and meta-analysis. Clin Ther 2017;39:1870–80.
[15] Huang ZB, Zhao SS, Huang Y, et al. Comparison of the efficacy of Lamivudine plus adefovir versus entecavir in the treatment of Lamivudine-resistant chronic hepatitis B: a systematic review and meta-analysis. Clin Ther 2013;35:1997–2006.
[16] Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[17] Chen Li. Clinical analysis of entecavir and adefovir dipivoxil in the treatment of patients with HBeAg-negative chronic hepatitis B. Contempor Med 2018;24:22–4. [in Chinese].
[18] Zhang X, Zhang H, Pan T, et al. Efficacy of entecavir combined with adefoxil dipivoxil in treatment of HBeAg negative patients with chronic hepatitis B. Jiangsu Med 2017;43:414–7. [in Chinese].
[19] Zhang W, Yu J, Zhu G, et al. Clinical efficacy of entecavir combined with adefovir in chronic hepatitis B patients with high viral load. Clin Hepatobiliary 2014;30:1169–72. [in Chinese].
[20] Liu S. Efficacy evaluation of entecavir combined with adefovir dipivoxil in patients with chronic lamivudine resistant chronic hepatitis B. Commun Med J 2016;14:73–5. [in Chinese].
[21] Fung J, Lai CL, Yuen J, et al. Randomized trial of lamivudine versus entecavir in entecavir-treated patients with undetectable hepatitis B virus DNA: outcome at 2 Years. Hepatology 2011;53:1148–53.
[22] Yeh ML, Huang CI, Hsieh MY, et al. Lamivudine switch therapy in chronic hepatitis B patients achieving undetectable hepatitis B virus DNA after 3 years of entecavir therapy: a prospective, open-label, multicenter study. Kaohsiung J Med Sci 2016;32:559–66.
[23] Kang SH, Yim HJ, Kim HR, et al. Comparison of lamivudine plus adefovir therapy versus entecavir with or without adefovir therapy for adefovir-resistant chronic hepatitis B. J Clin Gastroenterol 2014;48:889–95.
[24] Park MS, Kim BK, Kim KS, et al. Antiviral efficacies of currently available rescue therapies for multidrug-resistant chronic hepatitis B. Clin Mol Hepatol 2013;19:29–35.
[25] Oh MJ, Lee HJ. Antiviral efficacy of entecavir versus entecavir plus adefovir for hepatitis B virus rtA181V/T mutants alone. Saudi J Gastroenterol 2016;22:37–42.
[26] An J, Lim YS, Kim GA, et al. Telbivudine versus entecavir in patients with undetectable hepatitis B virus DNA: a randomized trial. BMC Gastroenterol 2017;17:15.
[27] Kim DH, Choi JW, Seo JH, et al. Entecavir to telbivudine switch therapy in entecavir-treated patients with undetectable hepatitis B viral DNA. Yonsei Med J 2017;58:552–6.

[28] Lok AS, Trinh H, Carosi G, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naive patients with chronic hepatitis B. Gastroenterology 2012;143:619–28.
[29] Razek AA, Massoud SM, Azziz MR, et al. Prediction of esophageal varices in cirrhotic patients with apparent diffusion coefficient of the spleen. Abdom Imaging 2015;40:1465–9.
[30] Razek A, Khashaba M, Abdalla A, et al. Apparent diffusion coefficient value of hepatic fibrosis and inflammation in children with chronic hepatitis. Radiol Med 2014;119:903–9.
[31] Razek AA, Abdalla A, Omran E, et al. Diagnosis and quantification of hepatic fibrosis in children with diffusion weighted MR imaging. Eur J Radiol 2011;78:129–34.
[32] Razek A, Abdalla A, Barakat T, et al. Assessment of the liver and spleen in children with Gaucher disease type I with diffusion-weighted MR imaging. Blood Cells Mol Dis 2018;68:139–42.
[33] Chang TT, Gish RG, De MR, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. Digest World Core Med J 2006;354:1001–10.
[34] Fattovich G. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. Digest World Core Med J 2006;354: 1011–20.
[35] Manns MP, Akarca US, Chang TT, et al. Long-term safety and tolerability of entecavir in patients with chronic hepatitis B in the rollover study ETV-901. Expert Opin Drug Safety 2012;11:361–8.