Comparing the efficacy and safety of tenofovir and adefovir or combined drug treatment for the treatment of chronic hepatitis B infection: a systematic review and meta-analysis

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Background: Chronic hepatitis B (CHB) affects a vast population globally. A variety of drugs are available for the treatment of CHB, including tenofovir (TDF) and adefovir (ADV). However, the efficacy of monotherapy drug treatment is inconclusive, the safety and efficacy of TDF remain unclear, more data are needed to be included and combined drug treatment is considered to exhibit higher efficacy. To explore this issue, we performed a current literature review and meta-analysis to compare the efficacy and safety of ADV *vs.* TDF, TDF *vs.* ADV + lamivudine (LAM); TDF *vs.* ADV + entecavir (ETV).

Methods: We systematically searched China National Knowledge Infrastructure, the Cochrane Library, Embase, PubMed, Chinese VIP, and Wanfang Data, for relevant clinical trials since July 2015, all included studies were based on PICOS principles and evaluated independently by the reviewers in accordance with the Cochrane Handbook (Rob2.0). A meta-analysis was performed by using Review Manager 5.4.

Results: We included a total of 32 studies, including 31 randomized controlled trials and one retrospective study involving 2,473 patients. The results revealed a low risk of bias in included studies, that the virologic response of TDF was superior to ADV ($P<0.05$). And TDF was also superior to ADV in Serum creatinine levels, Immunologic function, and safety profile. However, when ADV was combined with other medications, it was superior to TDF in alanine aminotransferase (ALT) level and Tbil level and adverse reactions, but on other indicators, TDF was superior to drug combination therapy.

Conclusions: Results showed that TDF was superior to ADV in the parameters of ALT, hepatitis B virus (HBV)-DNA reduction, HBeAg-negative conversion rate, safety, and total bilirubin levels in patients with CHB. However, when ADV was combined with LAM or ETV, they often showed the same therapeutic effect as TDF in parameters such as ALT level and Tbil level and combined therapy can effectively reduce the occurrence of adverse reactions. In this study, because the sample source countries were limited, a greater number of global studies are needed in the future to verify the current findings.

Keywords: Adefovir (ADV); tenofovir (TDF); drug combination; chronic hepatitis B (CHB); meta-analysis

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Introduction

Hepatitis B virus (HBV) infection (defined as hepatitis B surface antigen-positive) affects 240 million people worldwide and causes 686,000 deaths annually (1). Moreover, nearly 93 million HBV patients live in China (2). Long-term HBV infection is associated with a risk of cirrhosis and hepatocellular carcinoma (HCC) (3). After several years of infection, approximately 15–40% of chronically infected patients develop serious sequelae (4): 24% of patients with HBV may progress to liver cirrhosis, 2–5% may experience decompensated liver cirrhosis due to HBV infection each year, and of these, 15–20% are likely to decompensate within five years (5). Furthermore, HCC is a significant cause of mortality. Therefore, it is essential to suppress the replication of HBV-DNA to treat chronic HBV infection, prevent liver disease, cirrhosis, HCC, and other HBV-causing diseases, and finally eradicate HBV (6).

HBV is a partially circular double-stranded DNA virus with a limited host range and high species specificity (7). Owing to its biostructure, it can integrate into the host genome as covalently closed circular DNA (cccDNA), making it challenging to eliminate (8). Indeed, cccDNA is the template for all HBV mRNAs, liver are sufficient to (re) initiate HBV infection with only a few copies of cccDNA (9). to reduce the risk of progression to cirrhosis and liver-related complications become great vital (10). Thus, two currently available therapeutic options have been proposed: nucleos(t)ide analogs (NAs) and pegylated interferon (PEG-IFN). NAs specifically target HBV reverse transcriptase, thereby inhibiting progeny virus formation. PEG-IFN can inhibit viral transcription independently of immune cells and play an immunomodulator role mainly through cell-mediated immune stimulation. However, it appears to have higher costs and limited therapeutic efficacy and is not widely adopted, making NUCs (nucleotide analogs) the preferred choice (11). The most commonly used NUCs include tenofovir (TDF) disoproxil fumarate, entecavir (ETV), and telbivudine. It is often unclear which is the optimal drug treatment for the disease. In most cases, doctors make subjective judgments based on the patient's condition and drug resistance status. TDF is recommended as first-line drug therapy in the guidelines for chronic hepatitis B (CHB) treatment domestically and overseas (12,13). According to Marcellin *et al.*, after 48 weeks of TDF treatment, 76% of hepatitis e antigen (HBeAg)-positive CHB patients achieved HBV-DNA levels <400 copies/mL, a 21% HBeAg serological conversion rate, and a 68% serum alanine aminotransferase (ALT) normalization rate (the final serum ALT level of all patients with CHB is within the range of 0–40 U/L after treatment). In HBeAg-negative CHB patients, 93% achieved HBV-DNA levels <400 copies/mL ratio and the ALT normalization rate was 76% (14).

In recent years, the success of direct-acting antivirals (DAAs) for hepatitis C treatment has rejuvenated the search for a cure for CHB. Low genetic barrier DAAs include lamivudine (LAM), telbivudine, and adefovir dipivoxil (ADV) (15). ADV is a pentacyclic purine nucleotide analog that inhibits HBV replication (16). But with the advent of new drugs, the use of ADV has gradually decreased. Recent studies reveal that the curative effect of TDF was superior to ADV in patients with CHB, but there is a lack of evidence-based medical evidence. This study aimed to aggregate existing findings about the efficacy of TDF versus ADV. Before undertaking this study, we only found one existing networked meta-analysis. However, its years of reference were relatively long, and its scope was somewhat limited. On the one hand, ADV is used more commonly as a control group in current studies on the efficacy of TDF, Besides, whether there's any difference regarding the safety between TDF and ADV is not well concluded. And on the other hand, drug resistance has become a concern with the frequent use of new drugs. Unfortunately, long-term use of ADV monotherapy for LAM-R will probably cause a high resistance to ADV (17) and ETV monorescue therapy can also cause about 50% of these patients developing ETV-resistance (ETV-R) after 5 years of treatment (18). A combination of ADV with LAM or ADV with ETV therapy has become a choice for the treatment of LAM resistance and which can also reduce the development of ADV resistance. However, these therapies, on the one hand, have limited effectiveness in patients with LAM-R, on the other hand, most of patients have poor virological responses, these may contribute to multidrug resistant HBV variants and the progression of liver disease (19). As rescue therapies TDF, shows a better potent activity against HBV and a high level of genetic barrier (20), Good virological results were demonstrated. Several recent studies have shown that TDF monotherapy is highly effective in patients with LAM-R and NA-naive patients, and the presence of resistant mutations to LAM did not alter the response rate (21,22). Until now which one is the best to treat CHB in different treatments remains unclear. Besides, ADV is currently a viable alternative TDF for CHB infection when TDF disoproxil fumarate cannot be used because

of a relative or absolute contraindication, Therefore, The efficacy of ADV combined with other drugs versus TDF should also be considered. So we decided to study the efficacyof TDF versus ADV when combined with other drugs as an alternative therapy. Regardless, the efficacy of this therapeutic method compared to TDF is inconclusive and needs further determination.

Therefore, the study aims to evaluate the efficacy and safety between TDF and ADV in the treatment of CHB through Meta-analysis, and efficacy and safety of ADV combined with other drugs are also taken into consideration. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3747/rc).

Methods

Inclusion and exclusion criteria

Eligible studies were included based on PICOS (population, intervention/exposure, control, outcomes, and study design) principles with the following criteria: (I) randomized controlled trials and prospective comparative cohort study or retrospective study that reported CHB as time-to-event data; (II) studies with subjects over 18 years old; (III) studies with subjects who received TDF (300 mg per day orally) or ADV (10 mg per day orally) monotherapy or combined with other drugs intervention therapies included: TDF, ADV, ETV plus ADV, or LAM plus ADV therapy. based on previous reports (23,24).

Studies were excluded if they contained: (I) patients co-infected with other hepatitis viruses (A, C, D, or E), Epstein-Barr virus, cytomegalovirus, or human immunodeficiency virus (HIV); (II) patients infected with other concomitant liver diseases; (III) patients with past or present HCCs or liver transplantation; (IV) pregnant or breastfeeding patients; (V) small sample sizes (to avoid unreliable estimates caused by a few events within a small cohort); (VI) the absence of necessary intervention or information concerning the subjects.

Literature search and Search strategy

A comprehensive search of relevant peer-reviewed articles and dissertations published from 2015 to 2022 was conducted. We searched Mesh terms “chronic hepatitis B”, “tenofovir disoproxil fumarate” “adefovir” and “drug combination” and free words of the above terms using the critical search terms like “hepatitis B virus,” in the Embase, PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chinese VIP databases published from 2015 to 2022 , without language restrictions. Any discrepancies were resolved by consensus and discussion with the third and senior investigators.

Data extraction

In the first search, all studies were included in EndNote X9. The titles and abstracts were then reviewed and identified. Two authors independently extracted the data, which consisted of the data source, male-female ratio, methods, sample size, interventions, and experimental duration. If there was a discrepancy in the data extracted from one of the articles, it was resolved by negotiation between the two authors.

Patient reported outcomes definition

In this study, the treatment results were divided according to the intervention time included in the article, and the same outcome was divided among different subgroups. Treatment outcomes included the first 24 and 48 weeks. This is because, after 48 weeks, the design of many studies and the disease status of the patients have changed. In this study, all outcomes included the following: ALT recovery rate (biochemistry response), defined as the number of patients with serum ALT levels <40 IU/mL; virological response, defined as the number of patients with <400 copies/mL of serum HBV-DNA; the HBV-DNA negative rate (where the standard value of HBV-DNA is less than 10^3 copies/mL: if the value exceeds the average value, it is considered positive. Whether the HBV-DNA turns negative or not is judged according to whether the test result changes from positive to negative after the treatment and the magnitude of HBV-DNA reduction); HBeAg-negative rate (the average value of HBeAg is 0–1 S/CO: if the value exceeds the normal range, it is considered as positive; otherwise it is negative); the level of total bilirubin, serum creatinine, and prothrombin activity, the ratio of CD4+/CD8+, and the adverse reaction rate.

Quality assessment

All included studies were assessed using the Cochrane Collaboration’s risk-of-bias tool (25). According to the Cochrane Handbook, we carefully determined that each study had a low, high, or unclear risk of bias. In some

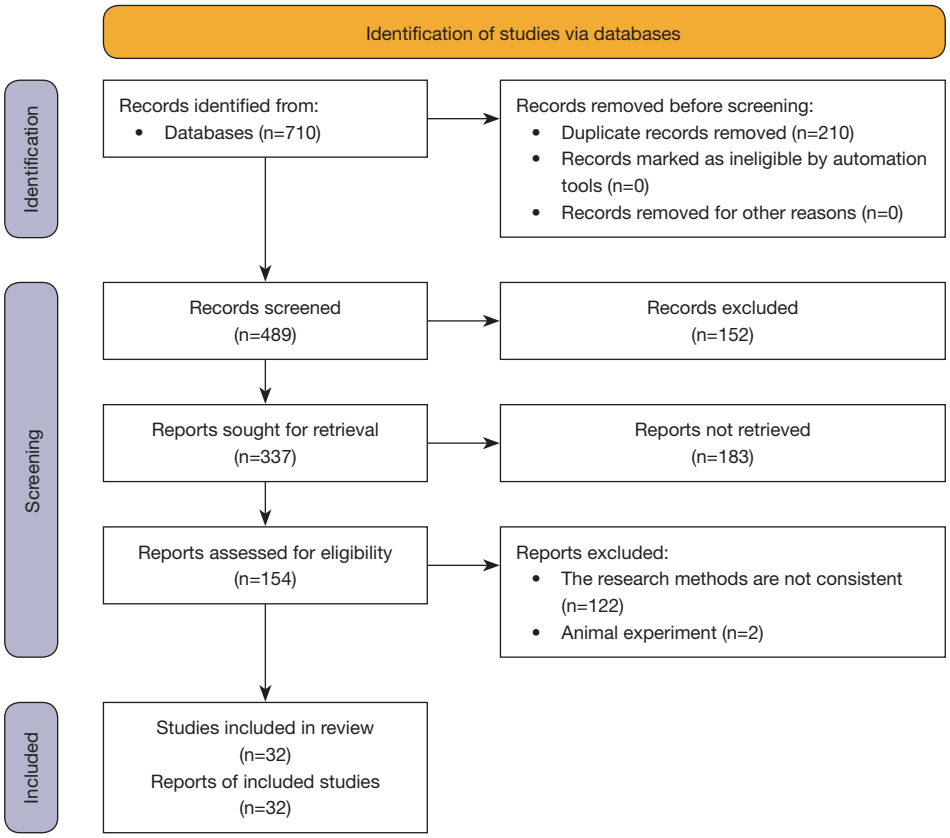

Figure 1 Flow diagram of the literature search strategy used in this study.

studies, the risk of bias was unclear because of the lack of sufficient information or uncertainty about potential bias. A single point showed each study with a regression line running through the forest plot. On the Y-axis, it was expressed as the log-transformed effect size divided by SE (z score), and on the X-axis, as the reciprocal of SE. STATA version 16.0 (Stata Corp, College Station, Texas, USA) and Review Manager version 5.4 (RevMan, The Cochrane Collaboration, Oxford, UK) were used to process the data.

Statistical analysis

A fixed effects model was applied when the data was homogenous and heterogeneous. The heterogeneity of the included studies was analyzed using the Cochrane Q test and the I^2 statistic, where $P<0.1$ or $I^2>50\%$ represented significant heterogeneity. For dichotomized outcomes, we calculated risk ratios (RRs) and 95% confidence intervals (95% CI) using a binomial distribution. Publication bias was assessed using funnel plots and the Begg statistical test. Finally, the results of the subgroup comparisons were represented using P values (subgroup difference test). To explore heterogeneity, we conducted a subgroup analysis for studies with different therapeutic regimens; we performed stratified analysis for the following groups: ADV *vs.* TDF, TDF *vs.* ADV + LAM; TDF + ETV *vs.* ADV + ETV. If there are a sufficient number of studies for each outcome (>20), and the heterogeneity was low. We than used Egger regression asymmetry test and constructed funnel plot to explore the effect of publication bias (26).

Results

Search results and study characteristics

According to the retrieval strategy (see *Figure 1*), 710 articles were retrieved, including 311 from CNKI, 199 from Wanfang, 66 from VIP, 13 from PubMed, 57 from Embase, and 64 from Cochrane. A total of 210 duplicated articles were excluded. Initial screening was conducted according to the article titles. In total, 138 review articles or

meta-analysis essays and 14 conference papers and animal experiments were excluded. The remainder were evaluated based on the abstract or full text. Among them, 183 were excluded because they were non-clinical trials or the study subjects had other disease co-infections. The remainder were considered carefully according to the inclusion and exclusion criteria. After screening, 122 were excluded because there was no correlation between the outcomes and the research purpose. Finally, 32 were included, one of which was retrospective study. The studies included in the meta-analysis are summarized in *Table 1*.

All 32 trials had clearly stated inclusion and exclusion criteria (see *Table 1*), and all these trials had comparable baseline demographics in the treated groups, including age, sex, etc. A total of 2,473 patients were enrolled, with 1,701 males and 772 females, and the ratio of males to females was approximately 2:1. A total of 1,249 patients were treated with TDF, and the remaining 1,224 patients received ADV. The average age of the patients was approximately 45 years, and the intermediate course of the disease spanned seven years. Out of the 32 studies, eight studies used combined treatment with ETV, and nine studies used combined treatment with LAM.

Study quality

We evaluate the quality of non-randomized and randomized controlled studies included in the meta-analysis. The risk of bias of all included studies were shown in *Figures 2,3*. We carefully determined each study's low, high, or unclear risk of bias, according to the Cochrane Handbook. In some studies, the risk of bias was unclear because of the lack of sufficient information or uncertainty about potential bias. A single point showed each study with a regression line running through the forest plot. On the Y-axis, it is expressed as the log-transformed effect size divided by SE (z score), and on the X-axis, as the reciprocal of SE.

Serological examination results of HBeAg-negative rates

After TDF versus ADV monotherapy, 7 trials reported the number of HBeAg-negative patients. A total of 670 patients were included. According to the P and I^2 analyses, no heterogeneity was observed in monotherapy (P=0.95, I^2=0.0%). Therefore, a fixed-effects model was used to analyze the data. The incidence of HBeAg-negative status was statistically significant in monotherapy (RR =1.89, 95% CI: 1.48–2.42) (see *Figure 4*).

The number of HBeAg-negative patients was reported in two studies when treatment was combined with LAM. After a fixed-effects model, no heterogeneity was observed (P=0.50, I^2=0.0%). The incidence of HBeAg-negative was similar to monotherapy (RR =1.63, 95% CI: 0.99–2.68) (see *Figure 5*). The results suggest that TDF was superior in both monotherapy and combination therapy. Egger's test also showed no publication bias amongst the subgroups.

Virologic response

The study included 519 patients. The trials evaluating ADV or TDF were divided into two parts: TDF *vs.* ADV (see *Figure 6*); TDF *vs.* ADV+LAM (see *Figure 7*) as an alternative option.

In the treatment of ADV *vs.* TDF with CHB patients, a total of 368 patients were included. The number of patients treated with ADV or TDF was 184 in each group. Of the 184 patients in the TDF group, 174 (95%) had HBV-DNA levels <400 copies /mL, compared with only 131 out of 184 patients (71%) in the ADV group. The results also indicated a significant between-group difference (RR: 1.33, 95% CI: 1.20–1.46, I^2=0%). Egger's test revealed the no existence of publication bias (P=0.02).

When compared to treatment with ADV + LAM, 54 out of 72 patients (75%) in the TDF group had a virologic response compared with 27 out of 79 patients (34%) in the ADV + LAM group. No publication bias was found using Egger's test (P=0.063). The results also showed a significant difference (RR =2.28, 95% CI: 1.63–3.18, I^2=0%), which suggests that TDF can effectively change the virologic response of patients, which is consistent with the results of previous clinical trials. The results indicated that differences in ADV+LAM and ADV monotherapy may have been due to the limited sample size and the different experimental design used in Tian Qinglian's study.

There was no heterogeneity in the two groups. Four studies showed similar results, indicating that TDF was superior to ADV, while ADV combined with other therapies showed no improvement compared with TDF, which suggests that combined drug treatment did not significantly improve the virologic response in CHB.

HBV-DNA levels

The HBV-DNA level is used to evaluate the infection status and recovery of CHB. As a continuous variable corresponding to the virological response data, the HBV-

Table 1 Summary of the 32 clinical trials included in the analysis

Author	Year	Disease	Method	Intervention		Course of treatment	Sample size (male/female)		Age (y)	
							TDF group	ADV group	TDF group	ADV group
Hou JL *et al.* (14)	2015	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	48 w	257 (214/43)	252 (210/42)	Mean (SD): 36.1 (20.0)	Mean (SD): 36.4 (20.0)
Chang B *et al.* (27)	2018	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	24 w	24 (14/10)	24 (12/12)	Mean (SD): 49.55 (13.32)	Mean (SD): 50.27 (14.64)
Zhang J *et al.* (28)	2016	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	24 w	32 (17/15)	32 (16/16)	Mean (SD): 56.85 (3.25)	Mean (SD): 56.72 (3.31)
Yan YR *et al.* (29)	2017	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Tenofovir	Lamivudine + adefovir	48 w	29 (19/10)	32 (16/16)	Mean (SD): 40.71 (9.71)	Mean (SD): 42.35 (9.36)
Sarkar Jayeeta *et al.* (30)	2018	Chronic hepatitis B	Randomized controlled trial	Lamivudine + tenofovir	Lamivudine + adefovir	120 w	39 (29/10)	39 (32/7)	35 [23–62]	35 [21–55]
Yang DH *et al.* (31)	2015	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Tenofovir	Lamivudine + adefovir	48 w	28 (26/2)	31 (28/3)	Mean (SD): 35.81 (9.85)	Mean (SD): 32.06 (8.36)
Lee HW *et al.* (35)	2016	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	48 w	16 (6/10)	16 (10/6)	Mean (SD): 51 (5.8)	Mean (SD): 53.5 (8.0)
Lai MC *et al.* (36)	2019	Chronic hepatitis B	Randomized controlled trial	Entecavir + tenofovir	Adefovir	96 w	48(36/12)	52 (41/11)	Mean (SD): 33.81 (9.01)	Mean (SD): 33.87 (7.9)
Rodríguez Manuel *et al.* (40)	2017	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Lamivudine + adefovir	48 w	22 (17/5)	24 (22/2)	Mean (SD): 53.14 (11.95)	Mean (SD): 56.35 (11.86)
Annikki de Niet *et al.* (43)	2017	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	72 w	45 (21/24)	46 (28/18)	Mean (SD): 43 (12.00)	Mean (SD): 44 (12.00)
Bai YR *et al.* (44)	2019	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir + entecavir	12 w	16 (10/6)	16 (9/7)	Mean (SD): 45.36 (3.22)	Mean (SD): 45.28 (3.19)
Chen XR *et al.* (45)	2019	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	24 w	36(21/15)	36(19/17)	Mean (SD): 55.3 (3.6)	Mean (SD): 55(3.4)
De Francesco *et al.* (46)	2015	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Lamivudine + tenofovir	Lamivudine + adefovir	24 w	16 (8/8)	19 (10/9)	/	/
Dong B *et al.* (47)	2020	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	24 w	30 (17/13)	30 (16/14)	Mean (SD): 52.53 (14.47)	Mean (SD): 52.19 (14.51)
Yuan G *et al.* (48)	2017	Multiple drug-resistant chronic hepatitis B	Retrospective study	Tenofovir	Adefovir + entecavir	48 w	21 (18/3)	19 (16/3)	Mean (SD): 51 (11)	Mean (SD): 51 (12)
Lee HJ *et al.* (49)	2018	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Tenofovir	Lamivudine + adefovir	96 w	111 (71/40)	58 (38/20)	Mean (SD): 53.35 (9.91)	Mean (SD): 49.47 (10.87)
Park JG *et al.* (50)	2015	Chronic hepatitis B	Randomized controlled trial	Entecavir + tenofovir	Lamivudine + adefovir	48 w	33 (24/9)	30 (26/4)	Mean (SD): 49 (10.0)	Mean (SD): 49 (10.0)

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Disease	Method	Intervention		Course of treatment	Sample size (male/female)		Age (y)	
							TDF group	ADV group	TDF group	ADV group
Li ZB *et al.* (51)	2017	Chronic hepatitis B	Randomized control trial	Entecavir + tenofovir	Lamivudine + adefovir	48 w	50 (34/16)	50 (38/12)	Mean (SD): 41.5 (12.4)	Mean (SD): 43.6 (11.5)
Liu HQ *et al.* (52)	2017	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir + entecavir	48 w	28 (20/8)	45 (36/9)	Mean (SD): 37.6 (7.15)	Mean (SD): 35 (7.44)
Lu T *et al.* (53)	2016	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Lamivudine + adefovir	48 w	31(30/1)	30(29/1）	Mean (SD): 50.97 (8.83)	Mean (SD): 49.24 (7.82)
Luo HY *et al.* (54)	2019	HBeAg positive chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	48 w	52	52	/	/
Lee SH *et al.* (55)	2018	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir + entecavir	48 w	30 (21/9)	30 (21/9)	33–69	24–66
Su L *et al.* (56)	2019	HBeAg positive chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	24 w	78 (39/39)	78 (40/38)	Mean (SD): 43.56 (1.35)	Mean (SD): 43.43 (1.38)
Tian QL *et al.* (57)	2018	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir + entecavir/ lamivudine	48 w	27 (25/2)	31 (27/4)	Mean (SD): 49.27 (7.64)	Mean (SD): 50.91 (8.52)
Xu JM *et al.* (58)	2016	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Entecavir + tenofovir	Adefovir + entecavir	48 w	52 (36/16)	51 (35/16)	Mean (SD): 63.88 (24.14)	Mean (SD): 62.21 (22.77)
Yang GX *et al.* (59)	2020	HBeAg positive chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	48 w	36 (19/17)	36 (20/16)	Mean (SD): 46.32 (2.56)	Mean (SD): 46.37 (2.5)
Yu YJ *et al.* (60)	2017	chronic hepatitis B	Randomized control trial	Tenofovir	Adefovir	48 w	30 (18/12)	30 (21/9)	Mean (SD): 41.02 (7.63)	Mean (SD): 40.57 (7.48)
Yuan Y *et al.* (61)	2019	chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir + entecavir	48 w	40 (17/23)	40 (19/21)	Mean (SD): 58.16 (0.66)	Mean (SD): 58.09 (0.57)
Zang W *et al.* (62)	2018	chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	48 w	36 (19/17)	36 (20/16)	/	/
Zhang N *et al.* (63)	2021	HBeAg positive chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	48 w	40 (27/13)	40 (24/16)	Mean (SD): 48.48 (1.46)	Mean (SD): 47.64 (1.73)
Zhang W *et al.* (64)	2018	Chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir + entecavir	48 w	40 (24/16)	40 (22/18)	Mean (SD): 45.5 (5.3)	Mean (SD): 45.2 (5.2)
Zhao N *et al.* (65)	2020	Multiple drug-resistant chronic hepatitis B	Randomized controlled trial	Tenofovir	Adefovir	24 w	50 (26/24)	50 (28/22)	Mean (SD): 48.23 (3.84)	Mean (SD): 49.05 (3.68)

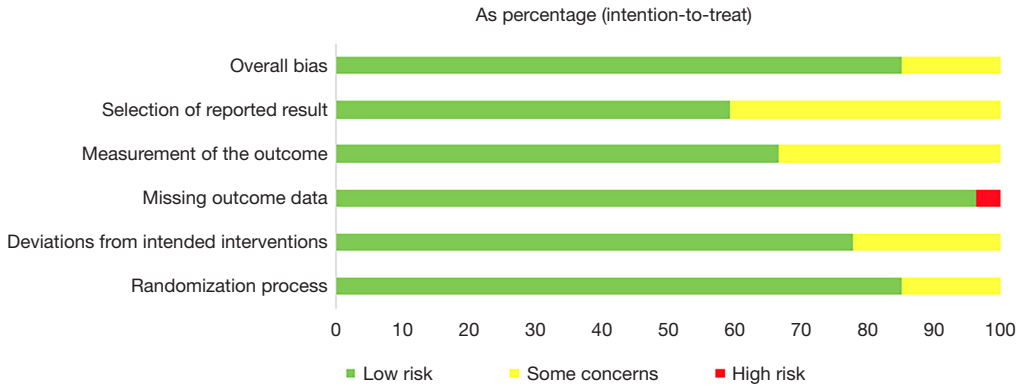

Figure 2 Risk of bias graph.

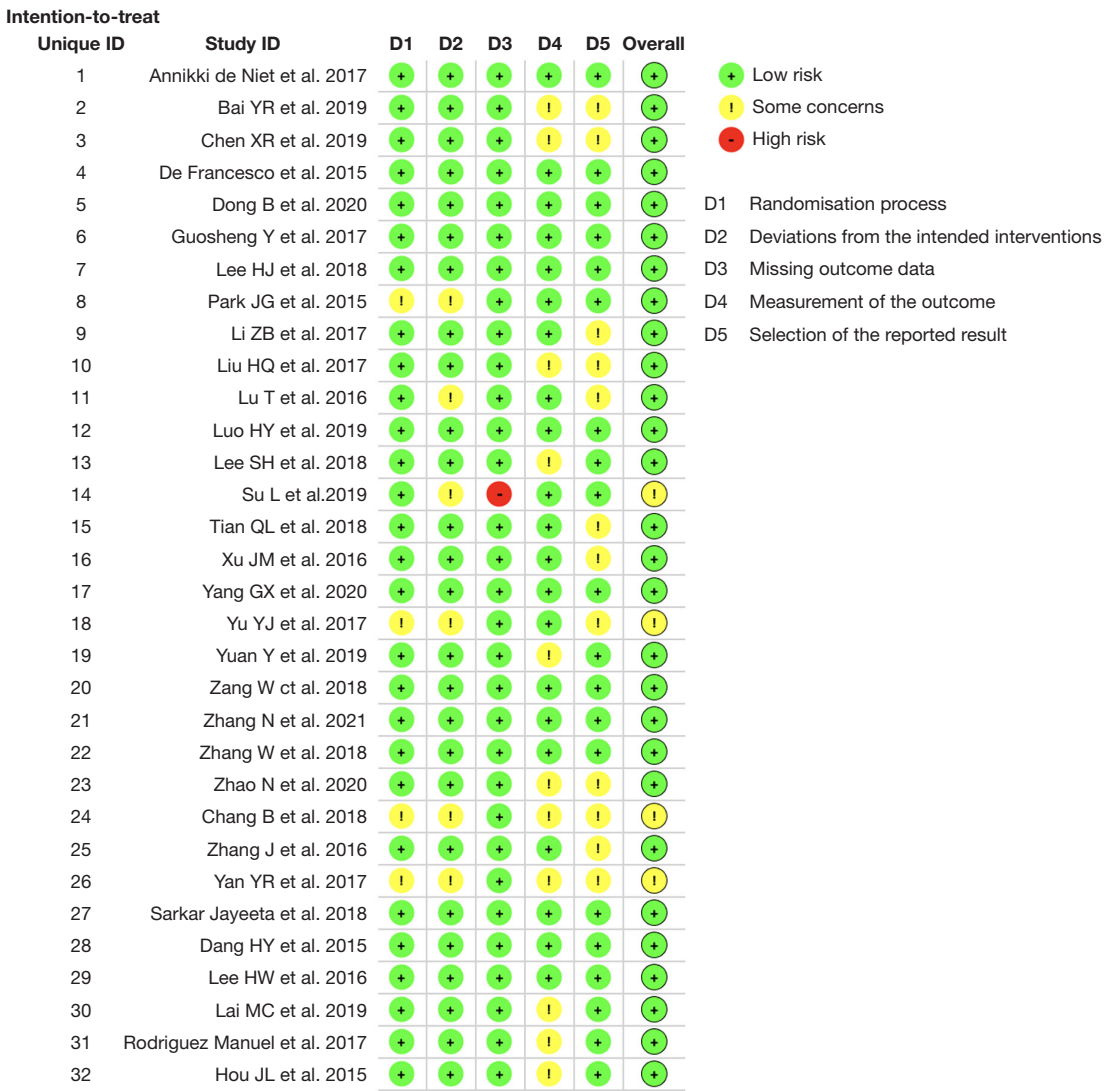

Figure 3 Assessment of risk of bias.

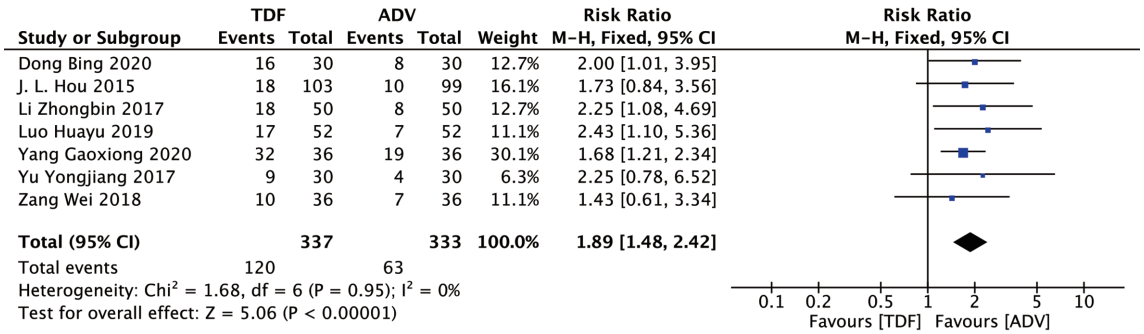

Figure 4 Forest plots showing the HBeAg-negative rates after treatment with tenofovir or adefovir using a fixed-effects meta-analysis of the efficacy of both drugs. HBeAg, hepatitis e antigen; TDF, tenofovir; ADV, adefovir.

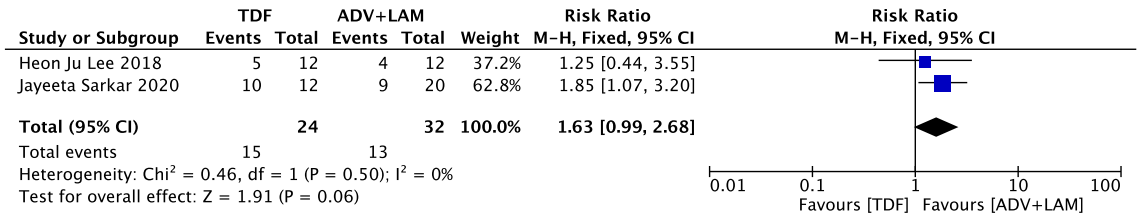

Figure 5 Forest plots showing the HBeAg-negative rates after treatment with tenofovir or adefovir plus lamivudine using a fixed-effects meta-analysis of the efficacy of both drugs. HBeAg, hepatitis e antigen; TDF, tenofovir; ADV, adefovir.

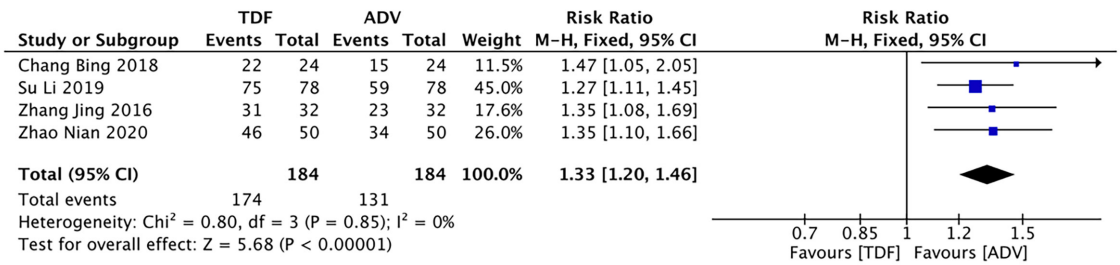

Figure 6 Forest plots showing the virologic response after treatment with tenofovir TDF or adefovir ADV. Using a fixed-effects model, the efficacy of both drugs is indicated in the plots. TDF, tenofovir; ADV, adefovir.

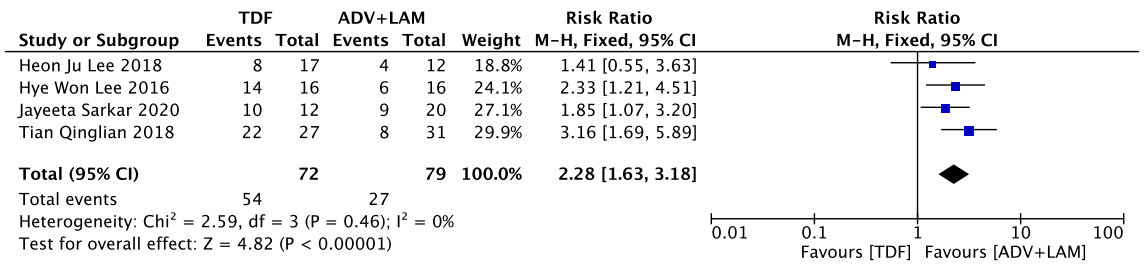

Figure 7 Forest plots showing the virologic response after treatment with tenofovir TDF or adefovir ADV plus LAM. Using a fixed-effects model, the efficacy of both drugs is indicated in the plots. TDF, tenofovir; ADV, adefovir; LAM, lamivudine.

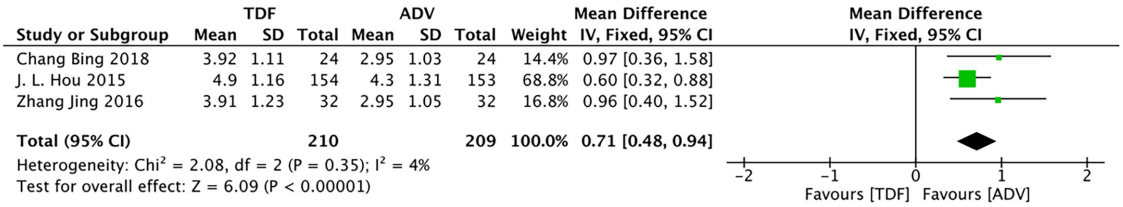

Figure 8 Forest plots show the levels of HBV-DNA after treatment with TDF or ADV; the plots show a fixed-effects meta-analysis of the efficacy of both drugs. HBV, hepatitis B virus; TDF, tenofovir; ADV, adefovir.

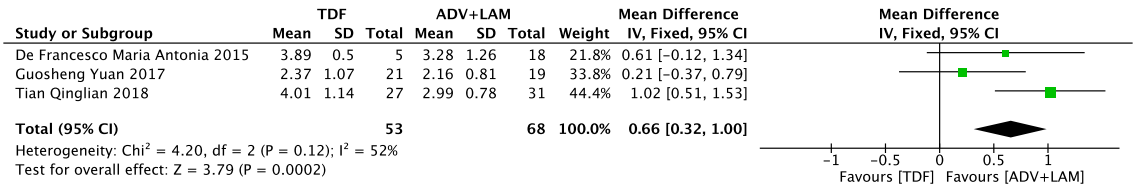

Figure 9 Forest plots show the levels of HBV-DNA after treatment with TDF or ADV plus LAM; the plots show a fixed-effects meta-analysis of the efficacy of both drugs. HBV, hepatitis B virus; TDF, tenofovir; ADV, adefovir; LAM, lamivudine.

DNA level also reflects changes in the amount of virus in patients with hepatitis B. The HBV-DNA level study included six studies involving 540 patients.

In this study, we analyze the efficacy of TDF versus ADV monotherapy (see *Figure 8*), and TDF versus ADV plus LAM as an alternative therapy (see *Figure 9*).

Depending on the treatment, patients were divided into TDF versus ADV monotherapy, or ADV were combined with other drugs as interventions versus TDF. In the comparison of TDF versus ADV monotherapy, The results show no heterogeneity between the two methods (I^2=4%, P=0.35), and the decrease in HBV-DNA was statistically significant in the monotherapy group (MD =0.71, 95% CI: 0.48–0.94). Egger's test revealed the existence of publication bias (P=0.001).

The decrease of HBV-DNA in the combined treatment group was statistically significant (MD =0.66, 95% CI: 0.32–1.00). Both results could be matched with the virologic response results and suggested that TDF can effectively change the content of the virus *in vivo*.

Liver function tests

ALT is an important serum liver marker exhibiting prognostic value with regard to CHB outcomes. We summarized the results from 572 patients with CHB and detected biochemical reactions at 24 and 48 weeks (see *Figure 10*). TDF showed a significant difference from ADV in the ALT recovery rate of CHB patients (RR: 1.33, 95% CI: 1.22–1.45, I^2=0%), indicating that TDF can efficiently reduce the level of ALT and significantly improve liver function. Seven studies compared the rate at which ALT levels returned to normal after 48 weeks, which was similar to that after 24 weeks. TDF demonstrated a significant difference in CHB treatment compared with the control group.

A significant difference was shown in two alternative option studies of CHB patients that included TDF *vs.* LAM+ADV (see *Figure 11*) (RR: 1.42, 95% CI: 1.13–1.78, I^2=0%) and TDF *vs.* ETV+ADV (see *Figure 12*) (RR: 0.94, 95% CI: 0.75–1.18, I^2=0%), which indicated that the curative effect of the ALT recovery rate using ETV + ADV was superior to TDF when treating CHB patients and ADV+LAM can slightly change the recovery rate of ALT.

Corresponding to the results of the biochemical response rates, we also analyze the studies on the change of ALT content in patients consisting of 2 studies using TDF *vs.* ETV+ADV (see *Figure 13*). The results also showed significant differences, which indicated that ETV + ADV was superior to TDF when treating CHB patients as an alternative option.

Serum creatinine levels

After 48 weeks of treatment, a total of five trials with 291 participants reported changes in serum creatinine levels (see *Figure 14*). Using a fixed-effects model, the results

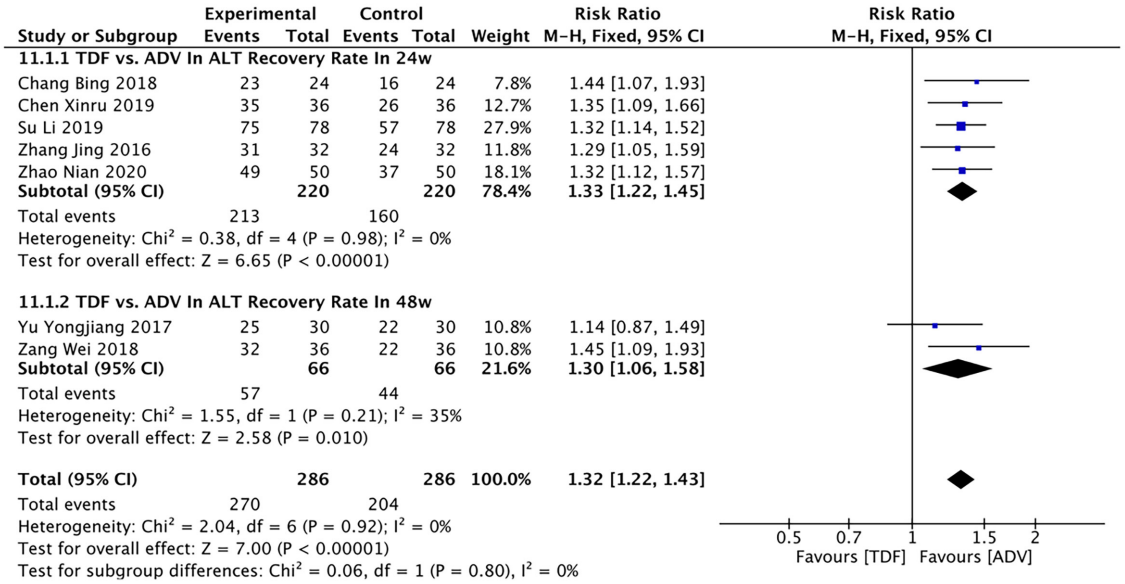

Figure 10 The ALT recovery rate was analyzed using forest plots at 24 and 48 weeks after therapy commencement using a fixed-effects meta-analysis of TDF and ADV antiviral therapy in chronic HBV. Squares represent the risk estimate of the individual study; diamonds represent the summary risk estimate; horizontal lines indicate 95% CI. An overall tendency toward the right side of the reference line (RR =1) suggested that TDF was superior to ADV. ALT, alanine aminotransferase; TDF, tenofovir; ADV, adefovir; HBV, hepatitis B virus; RR, risk ratio.

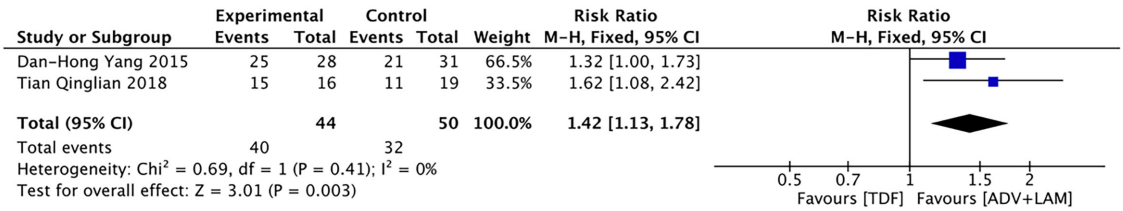

Figure 11 The ALT recovery rate was analyzed using forest plots at 24 weeks after therapy commencement using a fixed-effects meta-analysis of TDF and ADV+LAM antiviral therapy in chronic HBV. ALT, alanine aminotransferase; TDF, tenofovir; ADV, adefovir; HBV, hepatitis B virus; LAM, lamivudine.

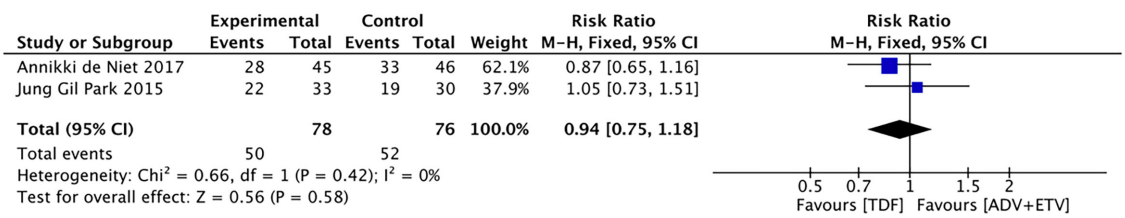

Figure 12 Forest plots show the ALT recovery rate after treatment with TDF or ADV plus ETV; the plots show a fixed-effects meta-analysis of the efficacy of both drugs. ALT, alanine aminotransferase; TDF, tenofovir; ADV, adefovir; ETV, entecavir.

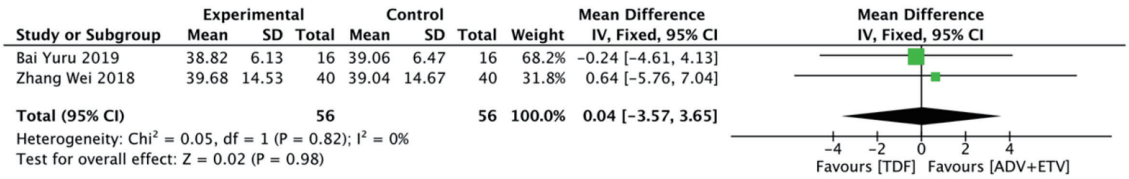

Figure 13 Forest plots show ALT levels after 48 weeks of treatment. ALT, alanine aminotransferase; TDF, tenofovir; ADV, adefovir; ETV, entecavir.

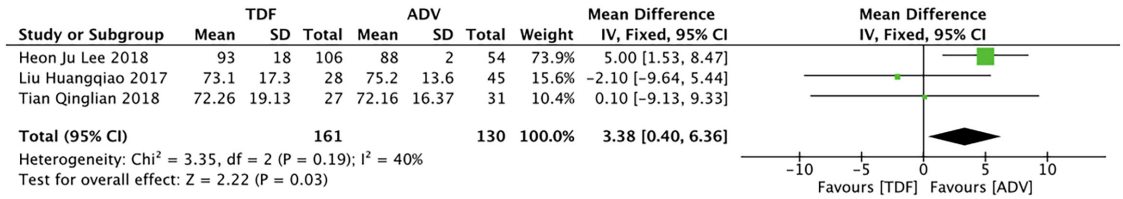

Figure 14 Forest plot of serum creatinine levels during treatment with ADV or TDF. ADV, adefovir; TDF, tenofovir.

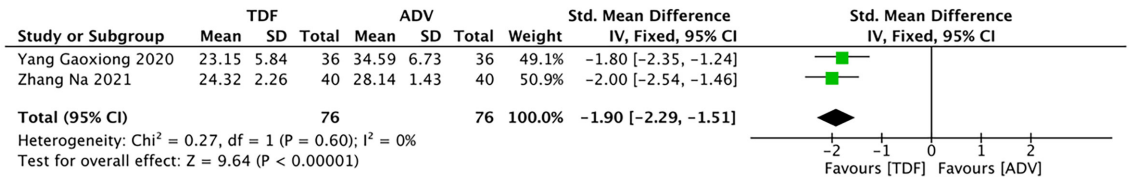

Figure 15 Forest plot of Tbil levels at 48 weeks after treatment with TDF or ADV. The plots show a fixed-effects meta-analysis of the efficacy of ADV and TDF antiviral therapy in chronic hepatitis B. Tbil, total bilirubin; TDF, tenofovir; ADV, adefovir.

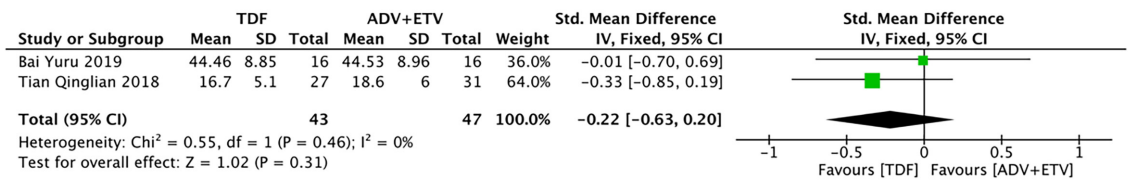

Figure 16 Forest plot of Tbil levels at 48 weeks after treatment with TDF or ADV plus ETV. The plots show a fixed-effects meta-analysis of the efficacy of ADV plus ETV and TDF antiviral therapy in chronic hepatitis B. Tbil, total bilirubin; TDF, tenofovir; ADV, adefovir; ETV, entecavir.

indicated that TDF showed a significant improvement over ADV (MD =3.38, 95% CI: 0.40–6.36, P=0.19), indicating that TDF had a better effect in changing CHB patients' serum creatinine levels compared with ADV.

Total bilirubin levels

Four randomized controlled studies reported changes in patients' total bilirubin levels, depending on their treatment regimen. We divided the studies into two groups: those who received TDF *vs.* ADV (see *Figure 15*) and those who received TDF *vs.* ADV combined with ETV (see *Figure 16*). A standardized mean difference (SMD) was used to compare the total bilirubin levels in ADV *vs.* TDF and TDF *vs.* the drug combination group in patients receiving antiretroviral therapy for the first time. The results show slight differences

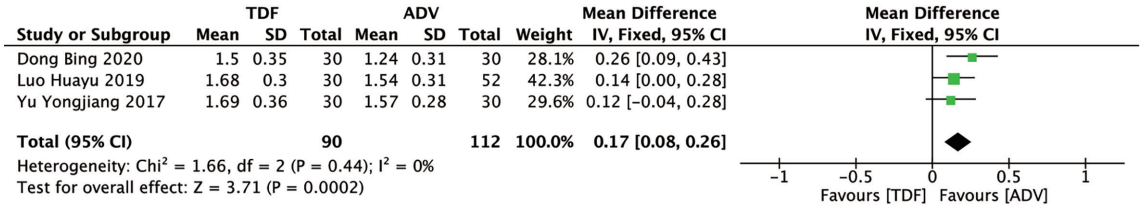

Figure 17 Forest plot of CD4+/CD8+ during treatment with ADV or TDF. ADV, adefovir; TDF, tenofovir.

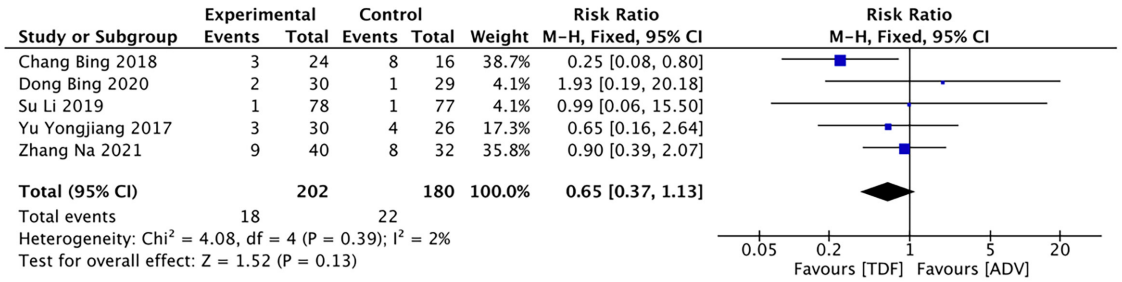

Figure 18 Forest plot of adverse reactions during treatment with ADV or TDF. Subgroups are shown based on the duration and method of treatment. TDF, tenofovir; ADV, adefovir.

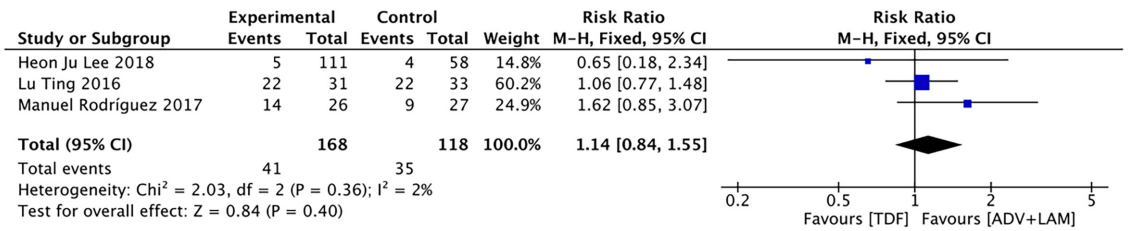

Figure 19 Forest plot of adverse reactions during treatment with ADV or TDF plus LAM. TDF, tenofovir; ADV, adefovir; LAM, lamivudine.

between two groups, suggesting TDF exhibited a more significant improvement in total bilirubin levels (SMD =−1.90, 95% CI: −2.29 to −1.51) and an alternative option like ADV combined with ETV shows a similar efficacy of TDF (SMD =0.22, 95% CI: −0.63 to 0.20).

Immunologic function

A total of three articles reported changes in CD4+/CD8+ levels, and the fixed-effects model showed significant differences (MD =0.17, 95% CI: 0.08–0.26) (see *Figure 17*), which indicated that TDF effectively improved immune function.

Safety profile

Adverse reactions included, muscle pain, allergic reactions, headache, vomiting elevated serum creatinine kinase, nausea and acute kidney failure.

The occurrence of adverse reactions in CHB patients treated with TDF versus ADV was reported in five studies. There were 40 adverse events, of which TDF accounted for 45%, and ADV accounted for 55%. The study showed no heterogeneity (I^2=2%, P=0.39), and the result suggested that TDF can reduce adverse events compared with ADV (RR =0.65, 95% CI: 0.37–1.13) (see *Figure 18*).

As alternative options for TDF, we respectively study different treatments: ADV + LAM (see *Figure 19*), ADV

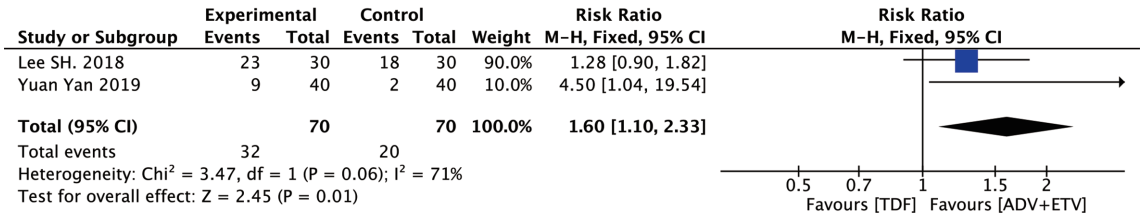

Figure 20 Forest plot of adverse reactions during treatment with ADV or TDF plus ETV. TDF, tenofovir; ADV, adefovir; ETV, entecavir.

+ ETV (see *Figure 20*). In the study of ADV+ LAM, in three trials involving 286 patients that compared TDF with combined treatment, 41 (24%) patients treated with TDF and 35 (30%) treated with ADV + LAM experienced adverse side effects. Adverse reactions were reported in two studies that combined ADV with ETV; however, the subgroup study showed no heterogeneity (I^2=2%, P=0.36). When analyzed with a fixed-effects model. In combination therapy, however, AVD combined with other NAs partially reduced the incidence of adverse reactions; ADV + LAM (RR =1.14, 95% CI: 0.84–1.55) and ADV + ETV (RR =1.60, 95% CI: 1.10–2.33). This result suggested that combined drug treatment can effectively reduce the occurrence of adverse reactions. Regardless, the long-term safety of both TFD and ADV should be monitored during extended treatment.

Discussion

The rationale for drug use in HBV and the curative effect of NAs versus DAAs present challenges for clinicians and patients in daily practice. To address these questions, we performed an extensive literature search, selecting studies that included comparison groups and data on clinical outcomes. Subsequently, we rated the quality of the evidence. We found sufficient comparative evidence to answer the questions posed.

To prevent complications such as HCC and cirrhosis in patients with CHB, it is necessary to administer NUC treatment. According to current guidelines, ADV and TDF are widely used for first-line antiretroviral therapy in China (7). Concurrently, a growing number of treatment studies are considering the efficacy and safety of combined treatment for hepatitis B. We performed a systematic meta-analysis using data published over a recent 5-year period to compare the effectiveness of ADV and TDF in patients with chronic HBV. In previous literature reviews, a systematic comparison of the efficacy of the two drugs has rarely been reported. The safety of both drugs was evaluated in a network meta-analysis conducted by Shen and colleagues (25). Their study reported that TDF was more effective and safer than ADV. However, because of the limited amount of data, the study only reported the incidence of adverse reactions for the two drugs. There was no discussion of other indicators, suggesting possible deviation and omission. Additionally, only 11 of the 38 studies included in their study reported on ADV and TDF, and six were prospective cohort studies instead of RCTs (26). To carefully and comprehensively evaluate the efficacy and safety of TDF and ADV in treating CHB, we used 32 articles from different countries with a total of 7,447 participants. A systematic meta-analysis was conducted, and 12 indicators were extracted for analysis. In an analysis of the outcomes of both drugs, our study showed that TDF was superior to ADV in more aspects and an alternative option for TDF like ADV + LAM, ADV + ETV had a better effect in HBV-DNA level and adverse reactions.

Serum ALT levels can reflect the Immune system function to viral infection in liver cells. Thus, normalization of ALT usually indicates that ongoing liver damage has stopped and viral infection has reduced. In this study, TDF significantly improved ALT normalization rates and ALT levels compared to ADV at 24 and 48 weeks of treatment (P=0.80, RR =1.32, 95% CI: 1.22–1.43). These findings are consistent with several other studies. Chang *et al.* showed that treatment with TDF improved serum biochemical and virological responses in patients with CHB compared to ADV (27). Zhang *et al.* showed that TDF was highly valued in treating patients with chronic multidrug-resistant hepatitis B (28). As an alternative option for TDF, TDF showed similar efficacy to ADV + ETV (P=0.58, RR =0.94, 95% CI: 0.75–1.18). Yan *et al.* also reported no significant difference in the effectiveness of TDF versus ADV + ETV in combination therapy (29). The results showed that both drug regimens could significantly improve the liver function of patients, which suggested that ADV + ETV can deal with situations when TDF disoproxil fumarate cannot be used

because of a relative or absolute contraindication. Finally, in the study of TDF versus ADV + LAM, a study by Sarkar *et al.* have shown that ADV combined with LAM is an effective alternative to TDF + LAM in the long-term treatment of patients with HIV/HBV co-infections (30). However, in a meta-analysis of the treatment of CHB patients, the effect of TDF was significantly better than LAM + ADV (P=0.003, RR =1.42, 95% CI: 1.13–1.78). Dang *et al.* also concluded that TDF monotherapy is superior to continuous dosing with LAM; plus, ADV is inadequate for CHB (31). So we can draw a conclusion that TDF is superior to LAM + ADV. TDF is a kind of nucleoside reverse transcriptase inhibitor that can specifically bind the transcriptase of HBV to reduce the number of viruses that proliferate. The exact molecular mechanism of ADV in clearing HBV is unknown, but ADV is one of several DAA agents that can change the structure of the HBV protein to eliminate HBV. In this case, TDF may have a better curative effect compared with ADV.

Also, in this study, we found that the overall efficacy of TDF was superior to ADV in reducing serum HBV-DNA levels and virologic responses at 48 weeks (P<0.001, RR =0.71, 95% CI: 0.48–0.94). Additionally, As an alternative option for TDF, different treatments revealed that TDF is more effective than ADV combined with other drugs in CHB patients (P=0.0002, RR =0.66, 95% CI: 0.31–1.00). Another study by He *et al.* found that, at 24 weeks, patients treated with LAM+ADV had higher serum HBV-DNA negative rates and HBeAg conversion rates than patients treated with LAM or ADV monotherapy (32). However, in this meta-analysis, ETV and LAM showed no significant difference when combined with ADV. The reason for the difference may be related to the trial design and baseline of the patients; concomitantly, more studies are needed to verify these results. Our findings are consistent with several other studies. The meta-analysis of Ke *et al.* concluded that among the five approved nucleoside (t) mimics for chronic HBV, TDF was most likely undetectable for HBV-DNA in HBeAg-positive patients at 12 months of treatment (33). Finally, Lin *et al.* reported that total virus suppression was significantly higher in patients treated with TDF for 12 months than those treated with ETV, LAM, or ADV (34). In addition, Lee *et al.* reported that switching from ADV to TDF may provide better virological outcomes in patients who exhibit a poor response to ADV + NA therapy for NA-resistant CHB (35). Another study given by Lai *et al.* reported that both ETV + ADV combination therapy and TDF monotherapy provided effective treatments in chronic ADV-resistant hepatitis B (36).

Our significant serological results showed that TDF performed better in causing HBeAg-negative changes than ADV (P<0.0001, RR =1.84, 95% CI: 1.42–2.39). As an alternative option for TDF, the three analyses results were the same, indicating that TDF is more likely to cause HBeAg-negative changes than ADV combined with other drugs (P=0.06, RR =1.63, 95% CI: 0.99–2.68). Similar to the virological response, this study found that the efficacy of ADV combined with LAM (P<0.0001, RR =2.28, 95% CI: 1.63–3.18) was slightly better than TDF (P<0.0001, RR =1.33, 95% CI: 1.20–1.46). In a recently published meta-analysis by Liu *et al.*, the combination of LAM and ADV significantly increased HBeAg serum conversion 96 weeks after treatment compared to ETV (37).

There were few statistically significant differences in adverse events for ADV or TDF in the included studies. We found no previous studies have compared TDF and ADV from a safety perspective. The major adverse events previously reported in association with ADV given by Matthews *et al.* were reversible nephrotoxicity and antiviral resistance with warnings of high doses of nephrotoxicity (38). There have also been reports by Sun *et al.* of severe hypophosphatemia associated with ADV treatment (39). TDF is like ADV in structure, and there was no statistical difference in adverse reactions to TDF compared to ADV in Rodríguez *et al.* study (40). A total of 10 studies were included in this study. Reports of adverse reactions mainly focused on nausea, dizziness, vomiting, liver discomfort, renal function changes, etc. Among all studies included in this analysis, we observed no significant differences in the incidence of adverse events in patients treated with TDF compared to ADV, which indicates that TDF may showed fewer adverse events during treatment. But when ADV was combined with LAM to treat patients with hepatitis, there was no significant difference in the incidence of adverse reactions between the two groups (P=0.4, RR =1.14, 95% CI: 0.84–1.55), suggesting that LAM may change the incidence of adverse reactions in ADV monotherapy. When ADV was combined with ETV to treat patients with hepatitis, a significant difference was found (P=0.01, RR =1.60, 95% CI: 1.10–2.33), suggesting that ETV may change the incidence of adverse reactions in ADV monotherapy.

Furthermore, other analyses showed that TDF was superior to ADV in total bilirubin levels (P<0.0001, RR =0.19, 95% CI: 2.29–1.51) and CD4+/CD8+ levels (P=0.0002, RR =0.17, 95% CI: 0.08–0.26) in patients with hepatitis B. CD4+ T cells complete HBV clearance by inducing cytotoxic CD8+ T cells, B cells and natural

killer T cells, which are also involved in the pathogenesis of inflammatory progression by producing a series of proinflammatory and profibrotic cytokines (41,42). The mechanism by which T cells regulate CHB is still being investigated. However, the equilibrium of CD4+ T cells contributes to the disease cure. Our study suggests that TDF can better maintain the level of CD4+ T cells to slow down the progression of the disease compared with ADV. Regardless, there was no significant difference in serum creatinine levels between the two drugs. The molecular mechanism remains unclear.

A meta-analysis is intended to provide a comprehensive evaluation and quantitative analysis of the results of multiple studies by reviewing the published literature. However, owing to the limited quantity and quality of reference studies, the meta-analysis of this study has some limitations. First, because of the differences in research methods between countries, the studies on hepatitis B in China are more likely to be randomized controlled trials rather than RCTs. Ideally, more RCTs are needed in the future to better compare TDF and ADV. Second, limited by the included literature, most of the samples were from China, which may have led to a significant difference in the outcome indicators and conclusions in different studies. As a result, the heterogeneity of the studies and the differences in subgroups were prominent in the subsequent analyses. Finally, the quality of the studies included in this study was limited, and the data need to be supplemented with more high-quality clinical reports in the future.

In conclusion, the results of this meta-analysis showed that TDF was superior to ADV in the parameters of ALT, HBV-DNA reduction, HBeAg-negative conversion rate, safety, and total bilirubin levels in patients with CHB. However, when ADV was combined with other drugs as an alternative option for TDF, such as LAM, they often showed the same therapeutic effect as TDF in some of these parameters such as ALT level and Tbil level when ADV was combined with ETV and ADV combined with other drugs can effectively reduce the occurrence of adverse reactions. But in other outcomes, TDF was more efficient to the drug combination options. Although hepatitis B infection is a global problem, China is particularly affected. Our analysis provides new insights into the treatment of chronic HBV infection in China.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3747/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3747/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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