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META-ANALYSIS

Comparison of the Effects of Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF) on Liver Function in Patients with Hepatitis B: A Meta-analysis

Longda Chen, MM; Qingqing Jiang, MM; Xun Xu, MD

ABSTRACT

Objective • This is a meta-analysis comparing the efficacy of Tenofovir disoproxil fumarate (TDF) and Tenofovir alafenamide (TAF) in the treatment of chronic hepatitis B (CHB) so as to provide a reference for clinical medication.
Methods • Relevant literature about TDF and TAF in the treatment of CHB was searched in the literature databases, and two researchers two researchers conducted independent cross-screening conducted independent cross-screening according to the inclusion and exclusion criteria. The authors, publication time, research subjects. The literature quality was evaluated by, and outcome measures of the selected literature were extracted. The literature quality was evaluated using the Jadad scale and Cochrane risk-of-bias tool. Meta-analysis was conducted using the RevMan 5.3 software.
Results • After screening, 5 references were included, with a total of 5324 subjects. Patients who were treated with TDF and TAF were included in the TDF group and TAF group, respectively. The meta-analysis showed no significant difference in viral suppression between groups after 12 months of treatment ($P > .05$). Still, the alanine transaminase (ALT) normalization rate was higher, and the incidence of adverse reactions was lower in TAF group versus TDF group at 12 months after treatment ($P < .05$).
Conclusions • Both TAF and TDF are effective in the treatment of CHB, but the former is preferred due to its higher safety profile. (*Altern Ther Health Med.* 2025;31(1):124-127).

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INTRODUCTION

Chronic hepatitis B (CHB), a viral hepatitis caused by the hepatitis B virus (HBV), is highly endemic, with approximately 257 million CHB-infected cases worldwide, according to the World Health Organization (WHO), of which approximately 887,000 die each year from HBV.[1,2] Although HBV vaccination can effectively prevent infection, the efficacy of the vaccine can decrease over time, with statistics showing that HBV vaccines are currently effective for 10 to 15 years.[3] Most CHB patients are infected with HBV precisely because the vaccine is not supplemented in time after failure.[4] According to a survey conducted by the Chinese Center for Disease Control and Prevention in 2014, the number of HBV surface antigen-positive people in all age groups decreased significantly compared with 10 years ago, which proves that people pay insufficient attention to CHB in modern society.[5] At present, the clinical treatment of CHB is mainly divided into two categories: interferon and nucleoside (acid).[6] Tenofovir disoproxil fumarate (TDF) is currently the most widely used drug, which inhibits HBV replication mainly by hydrolysis into tenofovir (TFV) after entering the human body, with its effect repeatedly demonstrated.[7,8] However, in patients on long-term use of TDF, there are high bone-related adverse reactions and potential nephrotoxicity.[9] Tenofovir alafenamide (TAF), as a new nucleoside (acid) drug, has higher clinical safety than interferon drugs,[10] but its inhibitory effect on HBV needs further evidence.

Currently, there is still a lack of unified reference for the selection of therapeutic drugs for CHB in clinical practice, and there has been a dispute between TDF and TAF. To provide more accurate medication guidance for future clinical use, this study conducts a meta-analysis of the effect of TDF and TAF in the treatment of CHB to confirm the best treatment choice for CHB.

MATERIALS AND METHODS

Inclusion criteria

(1) Randomized controlled trial (RCT) or cohort study of TDF and TAF in the treatment of CHB; (2) The subjects

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were diagnosed with CHB and met the relevant diagnostic criteria; (3) The treatment plan was carried out in strict accordance with the drug instructions; (4) The subjects' heart and kidney functions were normal; (5) The follow-up time was ≥12 months.

Exclusion criteria

(1) Subjects receiving solid organ or bone marrow transplantation; (2) Subjects were co-infected with hepatitis C virus, hepatitis D virus, or HIV; (3) Literature with incomplete data; (4) Literature with selective reporting potential; (5) Literature with authors who could not be contacted for complete data.

Document retrieval

The literature related to TDF and TAF in the treatment of CHB was searched in Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Web of science (http://webofscience.com) and other literature databases. The time frame is set from 1 January 2010 to 1 June 2023, and the language was limited to English. The search keywords included Tenofovir disoproxil Fumarate, Tenofovir alafenamide, hepatitis B, hepatitis B virus, etc. Taking Pubmed as an example, the retrieval formula is as follows: Search((tenofovir disoproxil fumarate[Title/Abstract]) AND tenofovir alafenamide[Title/Abstract]) AND CHB[Title/Abstract]). Two researchers conducted independent screening according to the inclusion and exclusion criteria, after which discussion and checking were performed; a third researcher judged documents with inconsistent screening results.

Quality evaluation

The modified Jadad Scale[11] was used for quality evaluation, and high literature quality was indicated by a score ≥4. Bias was assessed using the Cochrane risk-of-bias tool. Two researchers independently completed the evaluation and the results were cross-checked.

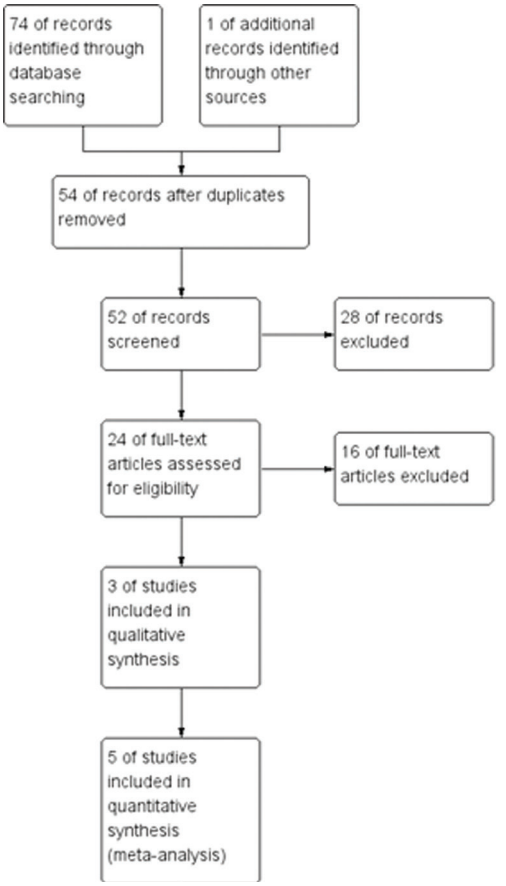
Data extraction

The authors, published years, number of subjects, basic information of subjects (age, sex, etc.), and outcome measures [e.g., viral suppression (number of people who tested negative for hepatitis B antigen after treatment), normalization rate of alanine transaminase (ALT) (number of people whose ALT returned to normal values (5-40 U/L for men and 5-35 U/L for women) after treatment), and incidence of adverse reactions during treatment) were extracted.

Statistical analyses

Risk ratio (RR) and 95% confidence interval (CI) were calculated for statistical analyses. Heterogeneity was tested, with $P \geq .1$ and $I^2 < 50\%$ indicating the absence of heterogeneity among studies, in which case a fixed-effects model (FEM) would be used for analysis; conversely, the source of heterogeneity needs to be analyzed in depth if $P < .1$ or $I^2 > 50\%$. A random-effects model (REM) can be used for analysis if heterogeneous effects are eliminated. RevMan 5.3 software was used for data merging and plotting during statistical analysis.

Figure 1. The search process of the literature.



RESULTS

Literature screening results

After searching, a total of 75 relevant papers were found in various literature databases. After removing duplicate publications, 54 were manually screened. Five articles that met the inclusion and exclusion criteria were finally confirmed (12-16), of which 1 was RCTs (Figure 1).

Quality evaluation and basic data of literature

All the included studies had a modified Jadad score of ≥4 and were of high quality. Cochrane risk-of-bias assessment results, shown in Figure 2, suggested low risk of publication of the literature, indicating high reference value. There were 5324 subjects in total in the 5 articles, including 4351 patients treated with TDF (TDF group) and 973 patients treated with TAF (TAF group) (Table 1).

Meta-analysis of therapeutic effects

A comparison of the viral suppression rate at 12 months showed no heterogeneity among the literature (I^2=0%), and the meta-analysis revealed no significant difference in viral suppression between TDF and TAF groups (P = .55,

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Table 1. Basic information of the literature

Author & Year	TAF group	TDF group	Jadad score	Outcome measures
Agarwal K 2018[12]	60	60	5	(1)(2)(3)
Jeong S 2022[13]	46	154	4	(1)(2)(3)
Lee HW 2021[14]	285	1832	5	(1)(2)(3)
Li J 2021[15]	80	60	6	(1)(3)
Lin J 2022[16]	502	2245	5	(1)(2)(3)

Note: (1) viral suppression, (2) normalization rate of ALT, (3) incidence of adverse reactions during treatment.

Figure 2. Cochrane offset risk assessment results.

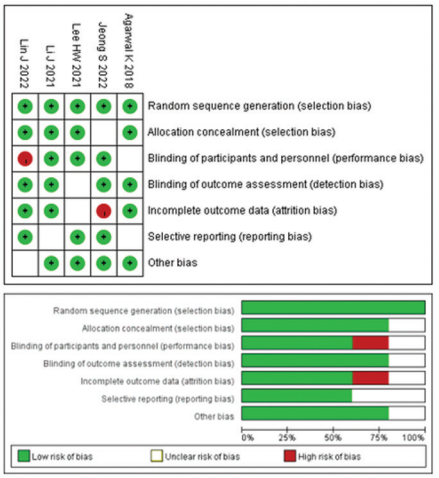


Figure 3. Meta-analysis of therapeutic effects. The differences between the TAF and TDF groups were not statistically significant.

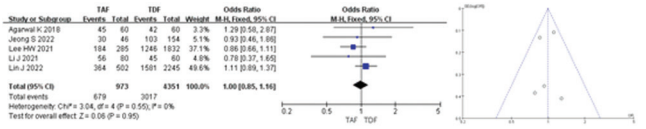


Figure 4. Meta-analysis of ALT normalization rate. The ALT normalization rate was higher in the TAF group than in the TDF group.

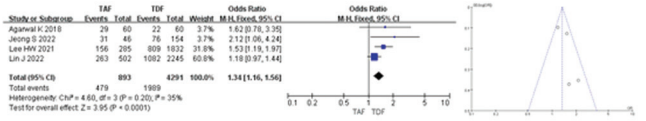
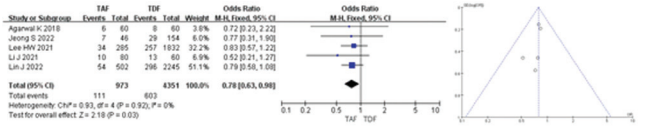


Figure 5. Meta-analysis of treatment safety. The incidence of adverse reactions was lower in the TAF group than in the TDF group.



95%CI=0.85-1.16), indicating similar therapeutic effects of TDF and TAF on CHB with no significant difference. Furthermore, the funnel plot of treatment effects was basically symmetrical, confirming low publication bias (Figure 3).

Meta-analysis of ALT normalization rate

There were four articles reporting the normalization rate of ALT after 12 months of treatment, and no heterogeneity was identified among them (I^2=35%). Meta-analysis shows that the ALT normalization rate was higher in the TAF group than in the TDF group after 12 months of treatment (P < .001, 95%CI=1.16-1.56), with an ALT normalization rate increased by about 1.34% in the TAF group after 12 months of treatment. The funnel plot of this outcome measure was also symmetrical, with no publication bias (Figure 4).

Meta-analysis of treatment safety

The incidence of adverse reactions during treatment was compared, and no heterogeneity was found in the literature (I^2 =0%). According to FEM analysis, the TAF group had a lower incidence of adverse reactions than the TDF group (P = .03, 95%CI=0.63-0.98), indicating higher treatment safety of TAF. After drawing the funnel plot, it can be seen that the graph was also basically symmetrical (Figure 5).

DISCUSSION

The change in people's living habits and the lack of medical and health knowledge in modern society have driven the increasing risk of HBV infection[17] Although HBV vaccination is mandatory for newborns in China, vaccination in adulthood is not explicitly prescribed, which also leads to HBV infection occurring in the gap between the disappearance of vaccine efficacy and the second injection.[18] Despite the fact that both TAF and TDH are highly effective in the treatment of CHB, there is still a lot of controversy over the preferred protocol for CHB. Therefore, this meta-analysis can provide reliable insights for future clinical treatment of CHB patients.

In this analysis, we finally included 5 articles[12-16] through screening, which is a small number that may cause the risk of accidental analysis results. However, in the literature quality evaluation, all the literature included was confirmed to be of high quality with a low risk of bias, indicating the high reference value of the analysis results. First, the meta-analysis results of the therapeutic effects showed no significant difference in viral suppression between TAF and TDH, which indicates that both drugs have excellent therapeutic effects on CHB. Many previous studies have also demonstrated the effects of TAF and TDH,[19,20] supporting the accuracy of the results of the above analysis. However, it is well known that the treatment cycle of TAF and TDH is generally long, with the best effect only being obtained after 2 years of treatment.[21,22] Given the difference in the follow-up time among the studies, we uniformly observed the effect of patients after one year's treatment to ensure the credibility of the analysis results. Second, in the comparison of ALT normalization rate and treatment safety, we can see that the TAF group had a higher ALT normalization rate and a lower incidence of adverse reactions after 12 months of treatment, which suggests that TAF treatment is more conducive to the recovery of patients' liver function while being safer. However, although there was no heterogeneity in the analysis of treatment safety in the current study, we still suspect the possibility of bias in the

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results of this analysis. This is because the counting of adverse reactions is very subjective, which may result in the final count of the types of adverse reactions being different in some different literature. For example, headache was considered an adverse effect in the study of Agarwal K et al,[12] while headache was not included as an adverse effect in the study of Lee HW et al.[14] As a result, this may lead to biased results in the analysis.

As prodrugs of TFV, TAF, and TDF are highly effective anti-HBV therapeutics.[23] Compared to TDF, which is rapidly absorbed and released in the intestine, TAF is better targeted to hepatocytes and hydrolyzed to TFV.[24] Meanwhile, TFV in cells is phosphorylated to form TFV diphosphate, which has good pharmacological activity.[25] HBV reverse transcriptase integrates TFV diphosphate into viral DNA, causing DNA breakage in the HBV virus.[26] Through the long-term use of drugs, the virus replication can be continuously inhibited, and the prognosis of CHB patients can be clinically improved. But it is worth noting that at present, a number of trials and literature have reported that TAF has more obvious advantages in the protection of bones and kidneys.[27] Replacing TDF with TAF may be a better treatment option if we consider better kidney and bone safety.

The controversy of TAF in lipid metabolism and cardiovascular risk also warrants continuous attention.[28,29] However, as none of the literature included in this meta-analysis involved a comparison of these measures, we have not analyzed them for the time being. In addition, this study also has the following limitations: the existing TAF studies are mainly carried out in Europe and the United States, and the patients included are predominantly Caucasian with few Asians/Chinese. Considering the differences in drug metabolic background and living habits among different races, the conclusions obtained in this study need to be validated by more clinical randomized controlled trials conducted in the Chinese population. In addition, the criteria for achieving efficacy endpoints are not completely consistent across studies, which may also affect the reliability of the analysis results. It is hoped that more researchers can carry out clinical studies of TAF and TDF in the treatment of CHB in the future so as to provide more reference opinions for subsequent meta-analyses and clinical medication.

CONCLUSION

Through meta-analysis, TAF and TDF are confirmed to have ideal effects in the treatment of CHB. Still, the former is more conducive to the recovery of patients' liver function and has a higher safety profile. In the future, TAF is recommended to be the first choice in the treatment of CHB patients, thus providing more reliable protection for the treatment effect and safety of patients. However, because the analysis of adverse reactions is highly subjective and not standardized, this may bias the results of the analysis of treatment safety. At the same time, future studies should increase the number of included studies in order to analyze our views more rigorously.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Xun Xu designed the study. Longda Chen wrote and revised the manuscript. Qingqing Jiang collected and analyzed data. Longda Chen and Qingqing Jiang made equal contributions in this work. All authors read and approved the final submitted manuscript.

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Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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