

# COMPARATIVE EFFECTIVENESS OF ENTECAVIR VERSUS TENOFOVIR FOR PREVENTING HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS B: A COMPREHENSIVE SYSTEMATIC REVIEW

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## ABSTRACT

**Background:** Chronic hepatitis B (CHB), a hepatotropic infection affecting over 250 million people worldwide is associated with a long-term risk of hepatocellular carcinoma (HCC), the most common primary cancer of the liver. HCC incidence is increasing; it is the fifth most common cause of cancer worldwide, and the third leading cause of cancer-related death.

**The aim:** The aim of this study to show about comparative effectiveness of entecavir versus tenofovir for preventing hepatocellular carcinoma in patients with chronic hepatitis B.

**Methods:** By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Google Scholar were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

**Result:** In the PubMed database, the results of our search get 20 articles, whereas the results of our search on SagePub get 47 articles, on Google Scholar 8810 articles. Records remove before screening are 6028, so we get 2849 articles for screening. After we screened based on record exclude, we compiled a total of 12 papers. We included five research that met the criteria.

**Conclusion:** Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have remained the first-line antiviral agents in several international guidelines. These two antiviral agents have shown similar short to intermediate-term efficacy, including virologic, biochemical, serologic, and histologic responses. However, huge controversies regarding the antiviral efficacy of ETV and TDF in preventing the development of hepatocellular carcinoma (HCC).

**Keyword:** Entecavir, tenofovir, hepatocellular carcinoma (HCC), chronic hepatitis B.

## INTRODUCTION

Chronic hepatitis B virus infection affects more than 250 million people around the world, causing nearly 1 million deaths per year. Chronic hepatitis B (CHB) is the leading cause of hepatocellular carcinoma (HCC) worldwide, which can occur even in the absence of cirrhosis in a subset of patients. HCC is the third-most common cause of cancer-related death in the world. Improved understanding of Hepatitis B (HBV)-related HCC may help reduce the burden of morbidity and mortality due to HCC.<sup>1</sup>

Over the past two decades, researchers have identified several modifiable and non-modifiable risk factors for HBV-related HCC including Hepatitis B e-antigen (HBeAg) status, cirrhosis, and serum HBV DNA levels. This recognition has led to achieving a virologic response with undetectable HBV DNA as one of the key treatment endpoints in patients with chronic HBV infection. The currently approved oral treatment regimens for chronic HBV infection are the nucleos(t)ide analogues lamivudine, adefovir, entecavir, tenofovir disoproxil or alafenamide, and telbivudine. These antiviral agents achieve biochemical and virologic response with varying efficacy.<sup>1</sup>

Chronic hepatitis B virus (CHBV) affects more than 250 million individuals worldwide and is the dominant risk factor for hepatocellular carcinoma (HCC). Nucleos(t)ide analogues reduce the risk of HCC in patients with CHBV by inhibiting viral replication and preventing fibrosis. Tenofovir and entecavir are highly potent nucleos(t)ide analogues with high genetic barriers to resistance and are both recommended by major society guidelines as first-line agents for the treatment of patients with CHB at higher risk for disease progression. However, the comparative effectiveness of tenofovir and entecavir in preventing HCC remains a matter of controversy and debate.<sup>2,3</sup>

Among the available NAs, entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are equally recommended as first-line treatments for CHB by practice guidelines because of their similarly high antiviral efficacy and low rate of resistance. These 2 treatments have been reported to have comparable efficacy on intermediate clinical end points, such as the rates of HBV DNA suppression, hepatitis B e Ag seroconversion, and the normalization of alanine aminotransferase levels. However, there has been no randomized clinical trial (RCT) comparing the efficacy on long-term clinical outcomes such as HCC between ETV and TDF.<sup>4,5</sup>

Nucleos(t)ide analogs (NAs) with a high barrier to HBV resistance, entecavir (ETV) or tenofovir disoproxil fumarate (TDF), are currently recommended as the first-line treatments for adults with immune-active CH. Long-term antiviral treatments are associated with a significantly lower HCC incidence in CHB patients by reducing HBV DNA concentrations. However, HCC may still develop after antiviral treatment. Recent studies have suggested that there may be differences in the effects of ETV and TDF on the occurrence of HCC among CHB patients. However, it is still controversial whether antiviral strategies affect HCC development in CHB patients.<sup>6</sup>

## METHODS

### Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

### Criteria for Eligibility

For the purpose of this literature review, we compare and contrast comparative effectiveness of entecavir versus tenofovir for preventing hepatocellular carcinoma in patients with chronic hepatitis B. It is possible to accomplish this by researching or investigating comparative effectiveness of entecavir versus tenofovir for preventing hepatocellular carcinoma in patients with chronic hepatitis B. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about comparative effectiveness of entecavir versus tenofovir for preventing hepatocellular carcinoma in patients with chronic hepatitis B. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

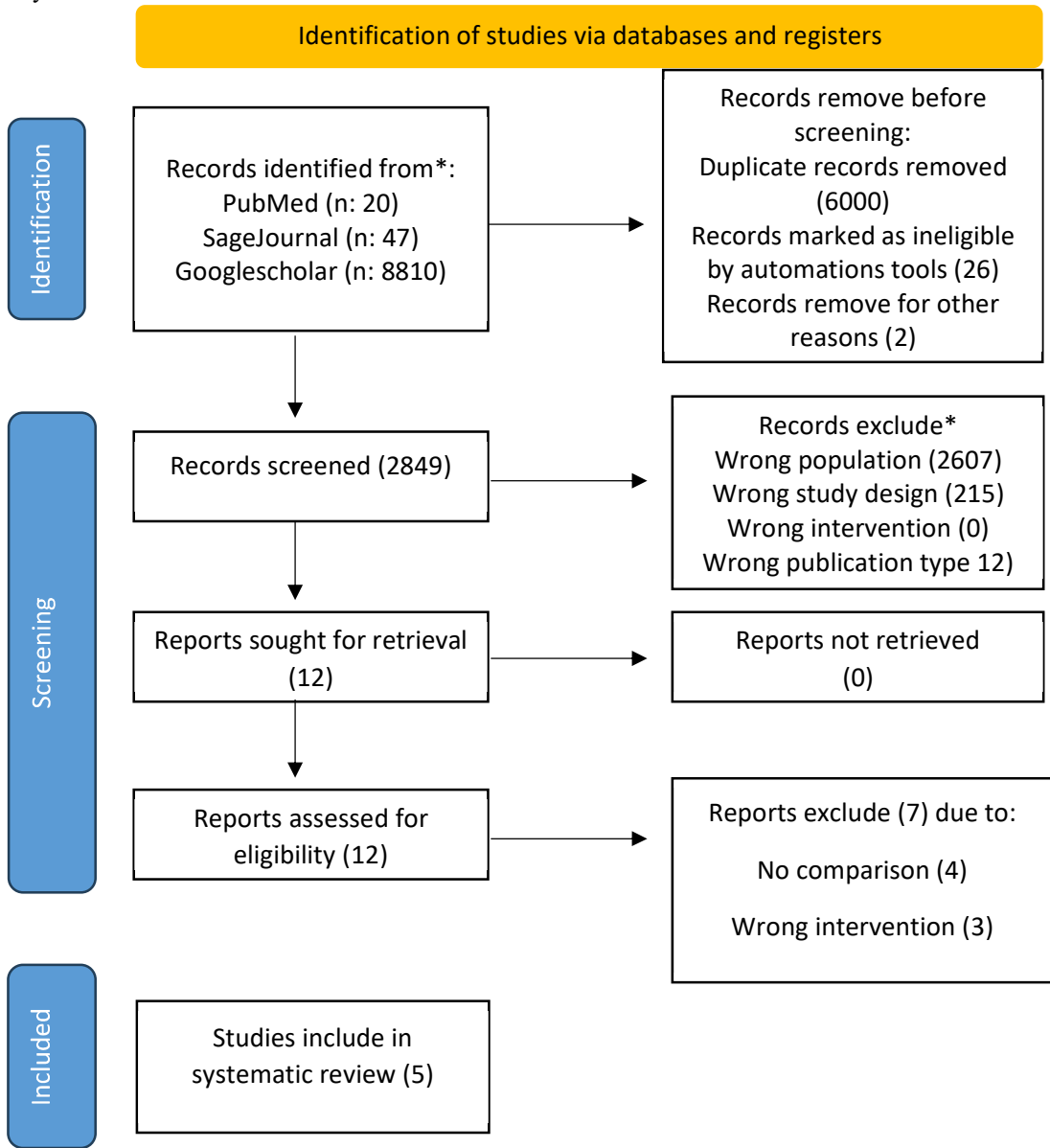
### Search Strategy

We used " comparative effectiveness of entecavir versus tenofovir for preventing hepatocellular carcinoma in patients with chronic hepatitis B." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *("Hepatitis B"[MeSH Subheading] OR "Chronic hepatitis B"[All Fields] OR "Hepatocellular carcinoma" [All Fields]) AND ("Risk of hepatocellular carcinoma"[All*

Fields] OR " treatment of hepatitis B"[All Fields]) AND ("Entecavir"[All Fields]) OR ("Tenofovir" [All Fields])) used in searching the literature.

**Data retrieval**

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.



**Figure 1. Article search flowchart**

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised

in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

**RESULT**

From the PubMed database, the results of our search get 20 articles, whereas the results of our search on SagePub get 47 articles, on Google Scholar 8810 articles. Records remove before screening are 6028, so we get 2849 articles for screening. After we screened based on record exclude, we compiled a total of 12 papers. We included five research that met the criteria.

Huang, Yh et al (2023)<sup>7</sup> showed TDF/TAF treatment was associated with a significantly lower risk of cirrhosis-related complications, and mortality, in patients with HBV-related cirrhosis compared with ETV treatment. However, no statistically significant difference in death and liver transplantation was seen in treatment-experienced patients. Further studies are necessary to ensure the replicability of our findings.

Choi, HK & Seo, GH (2021)<sup>8</sup> showed ETV treatment was inferior to TDF treatment for the prevention of HCC. We suggest that the index date and follow-up period may be residual confounding factors when comparing ETV and TDF. Therefore, to compare the effect of ETV and TDF treatment on HCC incidence, the index date and follow-up period should be controlled. Additional studies with in-depth analyses of clinical, socioeconomic, and lifestyle data are needed to further confirm our results.

**Table 1. The literature include in this study**

Author	Origin	Method	Sample Size	Result
Huang, YH et al., 2023 <sup>3</sup>	Taiwan	A retrospective study	7316	A total of 7,316 propensity score-matched treatment-naïve patients and 3,524 propensity score-matched treatment-experienced patients were included. Within treatment-naïve patients, those receiving tenofovir showed significantly lower hazards of developing the composite outcome (HR, 0.79; $p < 0.0001$ ), hepatocellular carcinoma (HR, 0.86; $p = 0.027$ ), mortality (HR, 0.75; $p < 0.0001$ ), and liver transplantation (HR, 0.70; $p = 0.0189$ ) than those receiving entecavir. As for treatment-experienced patients, tenofovir was associated with a significantly lower risk of the composite outcome (HR, 0.82; $p = 0.0033$ ) and hepatocellular carcinoma (HR, 0.60; $p < 0.0001$ ), but it did not show a significantly different risk of all-cause mortality (HR, 0.93; $p = 0.3374$ ) or liver transplantation (HR, 1.17; $p = 0.5112$ ) compared to entecavir.
Choi, HK & Seo, GH., 2021 <sup>8</sup>	Korea	A retrospective cohort study	76285	The matched participants (18,491 in the ETV and 36,982 in the TDF groups) were a part of the study for, on average, 41.2 months. The incidence of HCC did not differ significantly between the ETV (1.46 per 100 patient-years) and the TDF (1.36 per 100 patient-years) treatments (hazard ratio, 0.93; 95%

				confidence interval, 0.86–1.01; $P = 0.081$ ). By contrast, HCC incidence was significantly higher in the ETV group than tenofovir group of cohort 2.
<b>Su, F et al., 2019<sup>9</sup></b>	USA	A retrospective cohort study	3287	We identified 2193 ETV-treated and 1094 TDF-treated patients who were followed for a mean of 5.4 years. We found no difference in the risk of HCC in ETV-treated versus TDF-treated patients (adjusted HR (aHR) 1.00, 95% CI 0.76 to 1.32). Results were similar in propensity score adjusted and competing risks analysis, and in multiple sensitivity analyses. We also found no difference in the risk of death or liver transplantation (aHR 1.16, 95% CI 0.98 to 1.39).
<b>Choi, J et al., 2019<sup>10</sup></b>	Republic of Korea	A nationwide historical population cohort study	24156	Among the population cohort of 24 156, the mean (SD) age was 48.9 (9.8) years, and 15 120 patients (62.6%) were male. Among the hospital cohort of 2701, the mean (SD) age was 48.8 (10.5) years and 1657 patients (61.3%) were male. In the population cohort, the annual incidence rate of HCC was significantly lower in the tenofovir group (0.64 per 100 person-years [PY]) than in the entecavir group (1.06 per 100 PY). By multivariable-adjusted analysis, tenofovir therapy was associated with a significantly lower risk of HCC (hazard ratio [HR], 0.61; 95% CI, 0.54-0.70) and all-cause mortality or transplant (HR, 0.77; 95% CI, 0.65-0.92) compared with entecavir. The tenofovir group also showed a significantly lower risk of HCC in the 10 923-pair propensity score-matched population cohort (HR, 0.62; 95% CI, 0.54-0.70) and 869-pair propensity score-matched hospital cohort (HR, 0.68; 95% CI, 0.46-0.99) compared with the entecavir group.
<b>Yip, TCF et al., 2020<sup>11</sup></b>	China	A retrospective study	29350	We analyzed data from 29,350 patients (mean age, 52.9±13.2 years; 18,685 male (63.7%); 1309 were first treated with TDF (4.5%) and 28,041 were first treated with entecavir (95.5%). TDF-treated patients were younger (mean age, 43.2 years vs 53.4 years) and a

				<p>lower proportion had cirrhosis (38 patients [2.9%] vs 3822 patients treated with entecavir [13.6%]). At a median follow-up time of 3.6 years after treatment began (inter-quartile range, 1.7–5.0 years), 8 TDF-treated patients (0.6%) and 1386 entecavir-treated patients (4.9%) developed HCC. Patients’ clinical characteristics were comparable after propensity score weighting. TDF treatment was associated with a lower risk of HCC than entecavir treatment after propensity score weighting (weighted subdistribution hazard ratio, 0.36, 95% CI, 0.16–0.80; P=.013) and 1:5 matching (weighted subdistribution hazard ratio, 0.39, 95% CI, 0.18–0.84; P=.016).</p>
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Su, F et al (2019)<sup>9</sup> showed in a large cohort of patients with CHB in the USA, there was no difference in the risk of HCC in patients treated with ETV versus TDF. Given the conflicting results of our study and several recent observational studies, there may be sufficient clinical equipoise to justify prospective, randomised trials to definitively determine whether first-line antiviral agents differ meaningfully with respect to their effectiveness in preventing HCC and other long-term CHB-related complications. However, such a trial may be practically difficult as it would require many years of follow-up and large sample sizes to achieve adequate statistical power. In the absence of randomised studies, observational studies must be relied on to inform practice decisions. Our results support current guideline recommendations that consider both ETV and TDF as first-line agents for treatment of CHB.

Choi, J et al (2019)<sup>10</sup> showed tenofovir treatment may be associated with a significantly lower risk of HCC in patients with CHB compared with entecavir treatment. Given the poor prognosis of HCC, our findings might have considerable clinical implications for preventing the occurrence of HCC in patients with CHB. Further studies are needed to ensure the replicability of our findings.

Yip, TCF et al (2020)<sup>11</sup> showed Tenofovir disoproxil fumarate treatment is associated with a lower risk of hepatocellular carcinoma than entecavir treatment in a territory-wide cohort of Chinese patients with chronic hepatitis B.

**DISCUSSION**

Chronic hepatitis B (CHB) is known to be the most common chronic viral infection, affecting approximately 350 million people worldwide. Since the persistent replication with necroinflammation by the hepatitis B virus (HBV) significantly raises the risk of developing compensated cirrhosis and hepatocellular carcinoma (HCC), antiviral therapy to suppress HBV replication, which can prevent the progression of liver disease by stabilizing necroinflammation and inducing fibrosis regression, has been the mainstay in the management of patients with CHB. Several recent studies have proven that oral antiviral agents, particularly entecavir (ETV), reduce the risk of long-term complications such as liver cirrhosis and HCC, ultimately improving survival compared to controls.<sup>12</sup>

For example, for patients receiving initial treatment, some studies found TDF to be significantly better than entecavir at preventing HCC, but other studies involving first- or second-line treatment found them to be similarly effective for this outcome. Even meta-analyses have come to divergent conclusions: several indicated the superiority of TDF for preventing HCC, while another reported similar efficacy for the two drugs. These considerations highlight the need for a large, rigorously designed trial to compare the two monotherapies with long follow-up.<sup>13,14</sup>

Similarly, the literature is unclear about how well either monotherapy prevents viral reactivation or recurrence of HCC after patients with HBV-associated HCC have undergone curative hepatectomy. The drugs are often given prophylactically to such patients after hepatic resection in order to inhibit viral replication and thereby reduce risk of HCC recurrence. Indeed, we and others have shown that preoperative levels of HBV DNA or surface antigen HBsAg are associated with risk of HCC recurrence, and that entecavir monotherapy can reduce this risk.<sup>13</sup>

Although both entecavir and tenofovir disoproxil fumarate reduce hepatocellular carcinoma risk, the comparative effectiveness of these two drugs remains unclear. Between 2019 and 2020, several metaanalyses synthesised the evidence, but findings comparing the two drugs are still conflicting. The pooled results reported to date were often drawn from studies with heterogeneous populations, making results difficult to interpret. In addition, previous meta-analyses have included only a few comparative studies, pooled unadjusted data with adjusted data, did not exclude articles with overlapping populations, analysed hepatocellular carcinoma data as a dichotomous outcome as opposed to time-to-event data, and lacked detailed subgroup analysis, all of which have restricted the study conclusions.<sup>15</sup>

## CONCLUSION

Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have remained the first-line antiviral agents in several international guidelines. These two antiviral agents have shown similar short to intermediateterm efficacy, including virologic, biochemical, serologic, and histologic responses. However, huge controversies regarding the antiviral efficacy of ETV and TDF in preventing the development of hepatocellular carcinoma (HCC).

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