



# Tenofovir Disoproxil Fumarate and Entecavir in Patients with Chronic Hepatitis B: Efficacy and Safety Comparison

Kronik Hepatit B Hastalarında Tenofovir Disoproksil Fumarat ve Entecavir: Etkinlik ve Güvenlik Karşılaştırması

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## ABSTRACT

**Objectives:** Two potent nucleoside analogues frequently used to treat chronic hepatitis B (CHB) are entecavir (ETV) and tenofovir disoproxil fumarate (TDF). The purpose of this study was to examine the virological and biochemical therapeutic responses to TDF and ETV in CHB patients and to assess their effects on renal function.

**Materials and Methods:** This was a single-center retrospective study. The study comprised patients diagnosed with CHB who had been treated with TDF or ETV for at least a year.

**Results:** A total of treatment-naïve 269 patients were analyzed, of whom 29% were hepatitis B e antigen positive. Among the patients, 26% (n=70/269) received ETV, whereas 74% (n=199/269) received TDF treatment. Patients receiving TDF were younger than those treated with ETV. The TDF group had significantly higher baseline hepatitis B virus DNA levels (log<sub>10</sub> IU/mL) than the ETV group. Complete virological response was achieved in 232 (86.2%) of patients. Antiviral efficacy was comparable between treatments; however, a greater decline in estimated glomerular filtration rate was observed among patients receiving TDF.

**Conclusion:** This study showed that TDF and ETV had comparable antiviral effectiveness. These findings provide updated real-world evidence supporting individualized selection of first-line antiviral therapy based on patients' renal profiles.

**Keywords:** Chronic hepatitis B, nucleos(t)ide analogues, entecavir, tenofovir disoproxil fumarate, virological response

## ÖZ

**Amaç:** Kronik hepatit B (KHB) tedavisinde sıklıkla kullanılan iki güçlü nükleozit analogu entecavir (ETV) ve tenofovir disoproksil fumarattır (TDF). Bu çalışmanın amacı, KHB hastalarında TDF ve ETV'ye karşı virolojik ve biyokimyasal tedavi yanıtlarını incelemek ve böbrek fonksiyonları üzerindeki etkilerini değerlendirmektir.

**Gereç ve Yöntemler:** Bu çalışma tek merkezli, retrospektif bir araştırma olarak tasarlanmıştır. Çalışmaya, en az bir yıl süreyle TDF veya ETV tedavisi alan KHB tanılı hastalar dahil edilmiştir.

**Bulgular:** Toplamda tedavi görmemiş 269 hasta analiz edildi; bunların %29'u hepatit B e antijeni pozitifiti. Hastaların %26'sı (n=70/269) ETV alırken, %74'ü (n=199/269) TDF tedavisi aldı. TDF alan hastalar, ETV ile tedavi edilenlerden daha gençti. TDF grubunun, ETV grubuna göre anlamlı derecede daha yüksek başlangıç hepatit B virüsü DNA seviyelerine (log<sub>10</sub> IU/mL) sahip olduğu görüldü. Hastaların 232'sinde (%86,2) tam virolojik yanıt elde edildi. Antiviral etkinlik her iki tedavi grubu arasında benzer bulunmakla birlikte, tahmini glomerüler filtrasyon hızındaki düşüş TDF kullanan hastalarda daha belirgin olarak saptandı.

**Sonuç:** Bu çalışmanın sonuçları, TDF ve ETV'nin antiviral etkinliklerinin benzer olduğunu göstermektedir. Bulgularımız, ilk basamak antiviral tedavinin hastaların renal profilleri dikkate alınarak bireyselleştirilmesi gerektiğini destekleyen güncel gerçek yaşam verileri sunmaktadır.

**Anahtar Kelimeler:** Kronik hepatit B, nükleoz(t)id analogları, entecavir, tenofovir disoproksil fumarat, virolojik yanıt

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## Introduction

Chronic hepatitis B (CHB) continues to represent a major global health burden, affecting 254 million individuals worldwide, with 1.2 million new cases reported each year (1). In about 5% of adults and more than 90% of newborns infected with hepatitis B virus (HBV), the infection results in chronicity (2,3). Patients with CHB remain at lifelong risk for complications such as cirrhosis and hepatocellular carcinoma (HCC) (4).

The key objective of treatment is to achieve a functional cure, which is defined as the complete elimination of hepatitis B surface antigen, with or without seroconversion, as current antiviral drugs cannot completely eliminate HBV due to the persistence of covalently closed circular DNA in hepatocytes (5,6). Additional treatment goals, as outlined in international guidelines, include long-term virological suppression, normalization of serum aminotransferase levels, and achievement of serological endpoints (7,8).

Effective suppression of serum HBV-DNA has been as been related to a reduced risk of HCC and progressive liver disease (9,10). Nevertheless, a functional cure may still be achieved during long-term therapy. This usually follows a period of treatment during which HBV-DNA and hepatitis B e antigen (HBeAg) remain continuously undetectable (11,12). The purpose of this study was to assess and compare the therapeutic efficacy of tenofovir disoproxil fumarate (TDF) and entecavir (ETV) in patients with CHB, with a focus on suppression of HBV-DNA levels and normalization of alanine aminotransferase (ALT). Additionally, the impact of both drugs on renal function was examined by assessing changes in estimated glomerular filtration rate (eGFR). The study investigated evolving patterns in the choice of oral antiviral drugs for the management of CHB.

## Materials and Methods

Between January 2015 and January 2022, a retrospective study was performed at a 507-bed tertiary hospital in İstanbul, Türkiye. Patients' demographic characteristics, biochemical and hematological laboratory parameters, and radiological imaging findings were obtained from the hospital's institutional clinical database. Treatment-naïve patients with CHB who were started on TDF (300 mg once daily) or ETV (0.5 mg once daily) as initial treatment were included in the study. Patients who had co-infections with hepatitis C, hepatitis D, and human immunodeficiency viruses were excluded. Additional exclusion criteria included the presence of chronic liver diseases other than CHB and prior or ongoing immunosuppressive therapy during the study period. Real-time polymerase chain reaction assays were used to quantify serum HBV-DNA levels. The Artus HBV QS-RGQ Kit (Qiagen GmbH, Germany; lower limit of detection: 10.2 IU/mL) and COBAS AmpliPrep/COBAS TaqMan HBV assay version 2.0 (Roche Molecular Diagnostics, Pleasanton, CA, USA; lower limit of detection: 20 IU/mL) were used to measure viral load. The nucleic acid extraction and amplification procedures followed the manufacturer's standard protocols.

A complete virological response (CVR) was defined as undetectable serum HBV-DNA levels after 12 months of therapy. A partial virological response was defined as a decrease in HBV-DNA levels of more than  $1 \log_{10}$  IU/mL. Classification of HBeAg-negative and HBeAg-positive CHB was defined according to the 2025 European Association for the Study of the Liver guidelines, and HBV-DNA values  $>5 \log_{10}$  IU/mL were considered as high viral load (13).

The Ishak-modified histological activity index was used to assess necroinflammatory and fibrotic activity in liver biopsy specimens (14). The biochemical response was determined by ALT normalization. Biochemical and virological responses were evaluated and compared between treatment groups at weeks 24 and 48. Achievement of a complete virological and biochemical response at one year was defined as the primary endpoint, while secondary endpoints included partial virological response and changes in renal function.

## Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Chicago, IL, USA). Continuous variables were expressed as mean  $\pm$  standard deviation or median (interquartile range), as appropriate, while categorical variables were presented as frequencies and percentages. Data distribution was assessed using the Kolmogorov-Smirnov test. Group comparisons were conducted using the Student's t-test or Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. A two-sided p-value  $<0.05$  was considered statistically significant.

## Ethics Statement

The study received ethical approval from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2023-02-19, date: 23.01.2023).

## Results

The study comprised 269 patients, 60.2% of whom were male, with a mean age of  $44.1 \pm 13.4$  years. HBeAg positivity was present in 29% of patients; 74% were treated with TDF and 26% with ETV. The median ALT level was 44 IU/L, whereas the median serum HBV-DNA level was  $6.16 \log_{10}$  IU/mL. Patients treated with TDF were younger than those receiving ETV ( $41.9 \pm 12.9$  vs.  $50.4 \pm 12.8$  years;  $p=0.001$ ). Table 1 summarizes the demographic, biochemical, viral, and histopathological features of the patients.

The TDF group had higher initial HBV-DNA levels than the ETV group ( $6.43$  vs.  $5.78 \log_{10}$  IU/mL;  $p=0.016$ ). A CVR was observed in 86.2% of patients and was comparable between the TDF and ETV groups ( $p=0.339$ ). There was no significant difference between treatment groups ( $p=0.905$ ), and most patients (68.5%) who achieved CVR had high baseline HBV-DNA levels. At 12 months, the median HBV-DNA level in patients without CVR was 1,490 IU/mL (minimum:

**Table 1.** Demographic characteristics, biochemical and virological responses of patients with chronic hepatitis B

	Total	ETV	TDF	p
Number of patients (%)	269 (100)	70 (26)	199 (74)	
Age (mean ± SD)	44.1±13.4	50.4±12.8	41.9±12.9	0.001
Gender, n (%)				
Male	162 (60.2)	38 (54.3)	124 (62.3)	0.238
Female	107 (39.8)	32 (45.7)	75 (37.7)	
HBeAg-positive (%)	78 (29)	19 (27.9)	59 (30.3)	0.719
Anti HBe-positive (%)	186 (69.1)	49 (72.1)	137 (70.3)	0.779
ALT (IU/L) (median)	44	42	44	0.960
AST (IU/L) (median)	34	39	34	0.385
Creatinin (mg/dL) (median)	0.7	0.7	0.7	0.310
AFP (IU/mL) (median)	3.1	3.1	3.1	0.761
Albumin (g/dL) (median)	43	42	44	0.076
PLT (103/μL) (median)	218	226	215	0.692
HAI (median)	6	6	6	0.575
Fibrosis (median)	2	2	2	0.233
HBV-DNA PCR (log <sub>10</sub> IU/mL) (median)	6.16	5.78	6.43	0.016
HBV-DNA PCR-negative at 24 weeks (%)	168 (71.8)	47 (77)	121 (69.9)	0.289
CVR (%)	232 (86.2)	58 (82.9)	174 (87.4)	0.339
ALT normalization at 48 weeks (%)	88 (86.3)	20 (83.3)	68 (87.2)	0.632

ETV: Entecavir, TDF: Tenofovir disoproxil fumarate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alfa feto protein, PLT: Platelet count, HAI: Histology activity index, CVR: Complete virological response, HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen, Anti HBe: Antibodies against hepatitis B e antigen, SD: Standard deviation, PCR: Polymerase chain reaction

51, maximum: 10348) for patients without a CVR. Initially, 43.9% of patients had elevated ALT levels. ALT normalization occurred in 21.2% of these patients at month 6 and increased to 74.6% by the end of the first year (p=0.632). However, when comparing the groups with respect to ALT normalization, no statistically significant differences were observed at either the six-month [p=0.394, odds ratio (OR): 0.65, 95% confidence interval (CI): 0.24-1.73] or the one-year (p=0.735, OR: 1.36, 95% CI: 0.38-4.80) follow-ups.

Clinical and virological characteristics were compared between patients achieving partial and CVRs. Patients older than 40 years and those with elevated baseline HBV-DNA levels showed higher CVR rates; however, these differences were not statistically significant (p=0.16 and p=0.14).

Histological activity index scores (p=0.98) and fibrosis stages (p=0.34) were similar between patients with partial and CVRs (Table 2).

At 12 months, renal function data were available for 242 patients (180 in the TDF group and 62 in the ETV group). The mean eGFR in the TDF group decreased considerably from 115.2±14.9 mL/min/1.73 m<sup>2</sup> at baseline to 109.1±8.7 mL/min/1.73 m<sup>2</sup> after one year (p<0.001) (Figure 1a). Patients receiving ETV did not have a significant change in renal function, with mean eGFR values of 107.0±16.1 mL/min/1.73 m<sup>2</sup> at treatment initiation and 109.8±9.3 mL/min/1.73 m<sup>2</sup> at one-year follow-up (p=0.586). (Figure 1b). Changes in eGFR differed significantly between the treatment groups (p<0.001) (Figure 1c).

## Discussion

Due to their potent antiviral activity and high genetic barriers to resistance, ETV and TDF are frequently used as first-line treatments (15,16). Although both agents are well established, treatment selection should balance antiviral efficacy with long-term safety considerations. In the current study, we evaluated the efficacy and clinical outcomes of TDF or ETV in treatment-naive patients, offering valuable insights that could shape treatment decisions and improve patient care.

In treatment-naive patients with CHB, TDF and ETV have shown similar and high rates of CVR (17,18,19). CVR rates at week 48 were reported to be 92.5% in the TDF group and 83.3% in the ETV group in a large cohort study by Riveiro-Barciela et al. (20) involving 611 treatment-naive patients. Park et al. (21) found CVR rates of 81% in patients receiving TDF and 72% in those receiving ETV, whereas Batirel et al. (22) reported lower rates of 74.7% and 58.4%, respectively. Variations among studies may result from differences in HBV-DNA level thresholds, treatment adherence, or patient characteristics.

Ha et al. (23) reported that patients treated with TDF were younger than those treated with ETV, while Alkan et al. (24) found no significant age difference. The younger age of patients receiving TDF may reflect a clinical preference to avoid potential renal and bone toxicity in older individuals. Despite higher baseline HBV-DNA levels in the TDF group, pretreatment viral load did not

**Table 2.** Evaluation of the parameters affecting CVR

	PVR	CVR	p
Number of patients, n (%)	37 (13.8)	232 (86.2)	
Gender, n (%)			
Male	19 (51.4)	143 (61.6)	0.23
Female	18 (48.6)	89 (38.4)	
Age (mean ± SD)	46.35±13.87	43.81±13.33	0.28
Age ≥40 years, n (%)	26 (70.3)	135 (58.2)	0.16
HBV-DNA>100000 IU/mL, n (%)	21 (56.8)	160 (69)	0.14
Higher baseline ALT level, n (%)	13 (44.8)	105 (54.1)	0.35
HAI, n (%)			0.98
<6	11 (31.4)	65 (29.8)	
6-8	18 (51.4)	115 (52.8)	
≥9	6 (17.1)	38 (17.4)	
Fibrosis, n (%)			0.34
0-2	31 (86.1)	173 (79.7)	
3-4	3 (8.3)	37 (17.1)	
≥5	2 (5.6)	7 (3.2)	
ALT, median (IQR)	39 (22.5-74)	44 (26.75-90)	0.43
HAI, median (IQR)	6 (5-7)	6 (5-7)	0.71
Fibrosis, median (IQR)	2 (2-2)	2 (2-2)	0.15
PLT, median (IQR)	225.5 (176.5-283.75)	216.5 (182-248)	0.32

IQR: Interquartile range, ALT: Alanine aminotransferase, HAI: Histology activity index, SD: Standard deviation, CVR: Complete virological response, PVR: Partial virological response, PLT: Platelet count, HBV: Hepatitis B virus

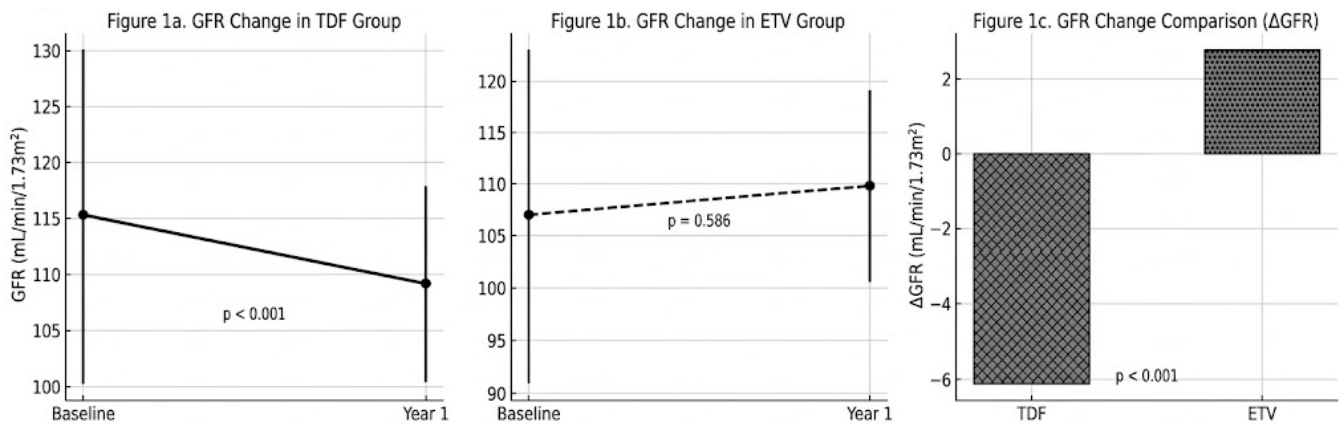


Figure 1a. Change in estimated glomerular filtration rate (GFR) between baseline and 1st year in TDF group.  
Figure 1b. Change in estimated GFR between baseline and 1st year in ETV group.  
Figure 1c. Comparison of ΔGFR (1st year - baseline) between TDF and ETV groups. Error bars represent mean ± SD.

**Figure 1.** a. Changes in estimated glomerular filtration rate (GFR) between baseline and the first year in the TDF group. b. Changes in estimated GFR between baseline and the first year in the ETV group. c. Comparison of GFR change (ΔGFR) between the TDF and ETV groups

TDF: Tenofovir disoproxil fumarate, ETV: Entecavir

independently affect virological response, indicating that ETV and TDF are comparably effective across different viral load levels. In accordance with our findings, Yang et al. (25) reported higher baseline HBV-DNA levels in patients treated with TDF than in those receiving ETV, while similar trends were observed by Li et al. (26). These data highlight differences in baseline viral load distribution

between treatment groups and underscore the clinical importance of HBV-DNA monitoring in therapeutic decision-making.

Biochemical response, as reflected by normalization of serum ALT levels, is among the earliest treatment outcomes observed in clinical practice. ALT levels are often used as an indirect marker of hepatic activity, and their normalization after antiviral therapy

suggests improvement in liver inflammation. Ha et al. (23) evaluated 557 treatment-naive patients and reported ALT normalization rates of 80.1% and 85.6% with TDF and ETV, respectively, at week 48. According to Güzelbulut et al. (18), there was not a significant difference in ALT normalization rates between TDF and ETV (79.2% vs. 85%). ALT normalization rates were similar between TDF and ETV in our study (87.2% vs. 83.3%,  $p=0.632$ ), consistent with previous studies (17,27,28).

TDF treatment was associated with higher serum creatinine levels and a more marked decline in eGFR at one year compared with ETV. Long-term exposure to TDF is associated with a higher decline in renal function than ETV in patients with CHB, according to prior studies by Jung et al. (29) and Lee et al. (30). Therefore, for patients with baseline renal impairment or those at risk for nephrotoxicity, ETV should be considered a safer therapeutic option. Overall, these results support current evidence and emphasize that careful, sustained monitoring of renal function is essential when TDF is used for long-term antiviral therapy.

### Study Limitations

Our study had some limitations. Initially, it was designed as a retrospective study, was carried out at a single-center, and included patients followed in an infectious diseases outpatient clinic. Second, the follow-up period was limited to 48 months, which prevented the assessment of long-term outcomes such as liver decompensation, HCC, or overall survival. Moreover, the lack of detailed data regarding concomitant medications with potential renal effects may have influenced renal outcome assessments. Therefore, studies with longer follow-up and larger patient populations are required. This study is strengthened by its large sample size and the high proportion of patients who underwent liver biopsy.

### Conclusion

The research presented here reveals our preference for ETV and TDF as well as a comprehensive review of their therapeutic efficacy, highlighting the advantages of each in therapy. High and comparable rates of virological and biochemical responses were observed with TDF and ETV. However, TDF was associated with a significantly greater decline in eGFR compared with ETV, indicating a greater adverse effect on renal function. These findings are consistent with previous studies but provide updated evidence from a contemporary real-world cohort, reflecting current treatment practices. By simultaneously evaluating antiviral efficacy and renal safety, this study contributes to a more balanced understanding of the risk–benefit profile. ETV may be preferred in patients with pre-existing renal impairment, while TDF remains an effective option for patients with preserved renal function requiring potent viral suppression. This study, therefore, contributes timely clinical data to the ongoing discussion on optimizing the management of CHB in the era of lifelong antiviral therapy.

### Ethics

**Ethics Committee Approval:** The study received ethical approval from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2023-02-19, date: 23.01.2023).

**Informed Consent:** Retrospective study.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: D.B., A.İ.S., F.B.E., E.C.Ü., Concept: D.B., Y.E.Ö., S.Ş., Z.Ç., H.K.K., K.K.Y., Design: D.B., Y.E.Ö., Z.Y., Data Collection or Processing: D.B., E.S.D., A.S.D., Analysis or Interpretation: D.B., Y.E.Ö., Z.Y., S.Ş., Z.Ç., H.K.K., K.K.Y., Literature Search: D.B., Writing: D.B.

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