Comparison of the side effects of antivirals in chronic hepatitis B patients: a single-center experience

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Abstract

Background and study aim: **Entecavir (ETV), Tenofovir Disoproxil Fumarate (TDF), and Tenofovir Alafenamide (TAF) have been approved for treating Chronic Hepatitis B (CHB) and recommended due to their high safety profile and high resistance barriers. This study aimed to evaluate the kidney functions, bone, and metabolic parameters in CHB patients receiving ETV, TDF, and TAF treatment.**

Patients and methods: **In this retrospective cohort study, a total of 469 CHB patients who were treated with TDF (n = 256), ETV (n = 184), or TAF (n = 129) for at least six months between March 2012 and March 2022, were enrolled.**

Results: **No significant difference was observed between three groups regarding ALT normalization, HBV DNA suppression, and HBs Ag seroconversion (p = 0.15, p = 0.26, p = 0.72). After the treatment, there was a significant decrease in GFR values in the TDF, ETV, and TAF groups (p<0.01, p = 0.01, p = 0.01, respectively). No significant improvement was observed in the GFR values after TAF treatment in 77 patients who had switched from TDF to TAF (p = 0.51). Moreover, no significant decrease in bone mineral densities was observed in the TDF, ETV, and TAF groups (p = 0.24, p = 0.41, p = 0.95, respectively). There was no significant difference between the three groups in metabolic parameters (serum glucose, lipid profile, calcium and phosphorus levels, etc.) when the data were adjusted for underlying comorbidities.**

Conclusions: **ETV, TDF, and TAF are comparably safe and effective antiviral agents against CHB.** (Acta gastroenterol. belg., **2022,** 85, **587-592**).

Keywords: Entecavir, Tenofovir Disoproxil Fumarate, Tenofovir Alafenamide, Chronic Hepatitis B.

Introduction

Chronic Hepatitis B (CHB) infection is a serious public health concern causing liver cirrhosis and hepatocellular cancer (HCC) (1). According to the World Health Organization, 296 million individuals suffered from Chronic Hepatitis B infection in 2019, with 1.5 million new cases yearly (2). Therefore, the primary goal of chronic infection treatment is to limit viral replication and successfully prevent liver damage, cirrhosis, liver failure, and HCC (3). Effective antiviral treatment for sustained HBV DNA suppression has been an important research subject for years (4). Three different nucleos(t)ide (NA) analogs, Tenofovir Disoproxil Fumarate (TDF), Entecavir (ETV), and Tenofovir Alafenamide (TAF), have been approved for the treatment of Chronic Hepatitis B. Current international guidelines have recommended these antivirals because of their high safety profile and high resistance barriers (3,4). Moreover, during long-term treatment with nucleos(t)ide analogs, these agents depict an excellent suppressing effect on HBV replication, healing histology, and decreasing HCC incidence (5).

These agents are generally safe and well-tolerated, but long-term treatment has raised concerns about adverse outcomes. The guidelines have recommended periodic monitoring of renal safety using serum creatinine, serum phosphorus, urine protein, and urine glucose in TDF patients due to Tenofovir (TFV) accumulation in the proximal renal tubules (3,4). TAF is a bioavailable prodrug with a TFV concentration 90% lower than TDF and a resistance barrier as high as TDF, with excellent efficacy. It was also associated with enhanced renal function, phosphorus blood levels, and bone metabolism (4,6,7). However, there are some concerns involving previous HIV patient experiences that the TAF-related lipid profile could worsen (8,9). Mild improvements in kidney or bone parameters with TAF in CHB patients could counterbalance side effects such as dyslipidemia, elevated fasting glucose, and clinical obesity (10,11). On the other hand, TDF has a lipid-lowering impact compared to other NAs (12,13). Entecavir maintains its reliability on renal and bone parameters and is prescribed in naive patients without any previous experience with Lamivudine. However, there is limited data on metabolic side effects (14,15).

Only a few studies have compared the side effects of these three drugs in the literature (16,17). Therefore, the present study retrospectively compared the kidney functions, bone, and metabolic parameters in our center of CHB patients treated with TDF, ETV, and TAF.

Methods

Patients: CHB patients treated with TDF, ETV, and TAF at the Zonguldak Bulent Ecevit University Hospital gastroenterology outpatient department between March 2012 and March 2022 were recruited retrospectively. Data were collected from the electronic database of the hospital. The study included CHB patients over 18 years

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Table 1. — **Baseline demographic characteristics of the TDF, ETV, and TAF treatment groups**

		TDF (n=256)	ETV (n=84)	TAF (n=129)	p-value
Age, years median (IQR)		52 (42-62)	55 (44-63)	59 (48-65)	**<0.001**
Gender	Males, n (%)	133 (%52)	57 (%67.9)	79 (%61.2)	**0.02**
	Females, n (%)	123 (%48)	27 (%32.1)	50 (%38.8)	
Waist Circumference, cm median (IQR)		95 (85-103.5)	96.5 (89-103)	95 (85-105)	0.22
BMI, kg/m2 median (IQR)		27.7 (25.39-30.8)	27.76 (26.1-31.4)	27.2 (25-31.2)	0.44
Follow-Up time, months mean±SD		71.8±36.1	84.6±47	30.6±11.2	**<0.001**
Comorbidities	DM, n (%)	35 (%13.7)	13 (%15.5)	36 (%27.9)	**0.02**
	Cirrhosis, n (%)	39 (%15.2)	16 (%19)	30 (%23.3)	0.15
	CKD, n (%)	13 (%5.1)	6 (%7.1)	24 (%18.6)	**<0.001**
Immunosuppressive therapy, n (%)		37 (%14.6)	12 (%14.3)	22 (%17.1)	0.78

Values are expressed as numbers (%), medians (interquartile ranges), or means (±standard deviations). ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease, BMI: Body Mass Index, SD: Standard Deviation, IQR: interquartile range. $p < 0.05$ is considered statistically significant

who were treated with TDF, ETV, or TAF for at least six months. Pregnant women and patients co-infected with Hepatitis C or HIV, decompensated liver cirrhosis, organ transplantation history, hepatocellular cancer, alcoholic liver disease, and autoimmune liver disease were excluded from the present study. Age, gender, body mass index, waist circumference, latest bone mineral density, serum calcium, phosphorus, 25-OH-Vit D levels, fasting blood glucose, fasting insulin, HbA1C, renal function tests, liver function tests, urine proteinuria, duration of the current antiviral treatment, history of immunosuppressants, and antiviral switch were recorded. A quantitative polymerase chain reaction assay determined the HBV DNA, and the viral suppression was defined as an HBV DNA level below 300 copy/mL. The ALT normalization (40 IU/mL) and HBsAg seroconversion (HBsAg loss and the appearance of HBs antibody) rates were also recorded. The Homeostatic Model Assessment Insulin Resistance (HOMA-IR) scores ≥ 2.5 were set as insulin resistant. GFR was calculated with diet modification in the renal disease (MDRD) formula. The L1-L4 total score or hip density, whichever was the lowest, was recorded in the bone mineral density assessments.

Statistics: Statistical Package for Social Sciences (SPSS) version 22 was used for statistical analysis. Numbers (%), medians (interquartile ranges), and means (standard deviations) were used to represent the data. The $\chi 2$ test was used to examine the categorical variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the data were normally distributed. Parametric tests (Student's t-test) were used to analyze normally distributed data, while non-normally distributed data were analyzed using the non-parametric test (Kruskal-Wallis test). Wilcoxon Signed Ranks Test was employed for repeated measurements. Statistical significance was defined as a p-value of less than 0.05.

Ethics: An approval from the Non-Interventional Clinical Research Ethics Committee of the Zonguldak Bulent Ecevit University Faculty of Medicine was obtained for the study (Protocol No: 2022/04, Approval date: 23/02/2022). The study protocol conforms with the ethical guidelines of the 1964 Declaration of Helsinki.

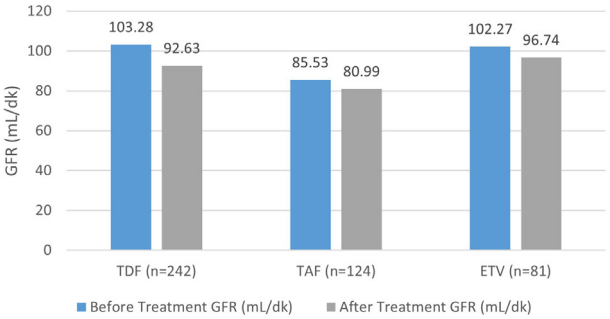

Figure 1. — GFR alterations with TDF, ETV, and TAF treatment. ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; GFR: Glomerular Filtration Rate.

Results

A total of 469 patients with 256 using TDF for at least six months, 84 using ETV, and 129 using TAF were included in the present study. The male gender comprised 57.4% (269) of the patients. The mean age of the patients was 53.36 (±12.91) years, and the mean treatment duration was 62.79 (±39.46) months. 15.2% (71) of the patients received concomitant immunosuppressive treatment, and the treatment rates were similar among the groups ($p = 0.78$). Compensated cirrhosis was observed in 18.1% (85) of the patients, and cirrhosis rates were similar among the groups ($p = 0.15$). The rate of the patients with chronic kidney disease (CKD) (18.6%) ($p<0.001$) and diabetes mellitus (DM) (27.9%) ($p = 0.02$) was significantly higher in the TAF group (Table 1).

In the TDF group, the mean duration of treatment was 71.8 (±36.1) months. HBV DNA levels remained detectable during the total treatment period in 17 (6.6%) of the patients using TDF, and HBs Ag seroconversion occurred in 8 (3.7%). There was a significant decrease in the post-treatment transaminase levels compared to the

Table 2. — **Comparison of liver enzymes alterations with TDF, ETV, and TAF**

	TDF			ETV			TAF		
	Pre-Treatment	**Post-Treatment**	**p-value**	**Pre-Treatment**	**Post-Treatment**	**p-value**	**Pre-Treatment**	**Post-Treatment**	**p-value**
AST	68.8±146.3	23±9.5	**<0,001**	96.8±217.6	19.8±5.7	**<0,001**	26.1±15	21.7±12.5	**<0,001**
ALT	92.5±199.4	23±17.3	**<0,001**	118.9±299.1	18.2±9.4	**<0,001**	28.5±31	20.4±15	**<0,001**
GGT	41±71.8	25.6±33.3	**<0,001**	60.9±59.2	26.4±19.4	**<0,001**	24.1±20.6	23.2±19.7	0.49
ALP	90.2±39.8	89.1±32.6	0.12	101.3±51.6	83.1±24.3	**<0,001**	86.3±35.3	85.8±34.3	0.65

Values are expressed as means (±standard deviations). ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase. Normal reference ranges are as follows; ALT: 0-41 U/L, AST: : 0-41 U/L, ALP: 25–100 U/L, GGT: 0–45 U/L. $p < 0.05$ is considered statistically significant.

Table 3. — **A comparison of the GFR in ETV, TDF, and TAF groups according to comorbidities**

	ETV			TDF			TAF		
	GFR, Pre-Treatment	GFR, Post-Treatment	**p-Value**	GFR, Pre-Treatment	GFR, Post-Treatment	**p-Value**	GFR, Pre-Treatment	GFR, Post-Treatment	**p-Value**
CKD (+)	57.4 (37.5-69.8)	60.52 (54.4-77.69)	0.35	66.7 (61.8-77.2)	56.7 (47.4-59.7)	**0.001**	45.6 (37.9-62.75)	41.7 (34-54.8)	0.079
CKD (-)	106.45 (85.1-119)	97.8 (82.4-114.9)	**0.01**	103.4 (91.4-115.9)	92.7 (82-109.9)	**<0.001**	89.7 (76.2-109.6)	81.75 (72.5-105.9)	**0.002**
DM (+)	69.3 (65.4-110.6)	75.6 (60.54-103.4)	0.86	93.7 (79.4-110.6)	83.05 (70.1-107.3)	**<0.001**	80.9 (62.6-105.7)	80.46 (54.8-98.3)	0.242
DM (-)	106.6 (89.8-119.1)	97.8 (84.77-113.65)	**0.01**	100.9 (89.3-116.2)	92.55 (80.55-109.7)	**<0.001**	86.4 (66.78-107.8)	80.2 (68.2-103.4)	**0.001**

Values are expressed as medians (interquartile ranges). DM: diabetes mellitus; CKD: chronic kidney disease; ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; GFR: Glomerular filtration rate. Normal reference range for GFR: 90-120 ml/min. $p < 0.05$ is considered statistically significant

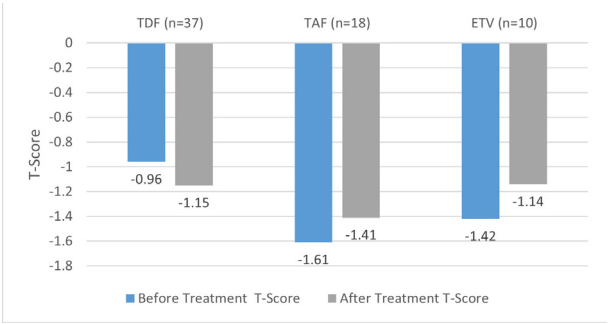

Figure 2. — Bone mineral density alterations with TDF, ETV, and TAF treatment. ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide.

pre-treatment levels among patients who received TDF treatment for at least six months ($p<0.001$). A significant decrease was observed in GGT values compared to the pre-treatment period ($p<0.001$). However, no significant alterations were detected in the ALP values ($p = 0.12$) (Table 2). The mean GFR of the patients was 92.63 mL/min (±21.83). A statistically significant difference was identified when the mean GFR of the 242 patients before TDF treatment was compared with GFR for at least six months after treatment ($p<0.001$) (Figure 1). A statistically significant decrease was observed after TDF treatment, regardless of underlying CKD or DM, as shown in Table 3. The 135 patients receiving TDF for at least six months had a current bone mineral density mean T score of -1.15 (±1.16). Moreover, after at least six months of antiviral therapy, the mean serum phosphorus level of 244 patients was 3.4 mg/dL (±0.6). In addition, the mean total cholesterol level of 236 patients was 166 mg/dL (±36.97). Additionally, the mean HOMA-IR level of 207 patients was 4.08 (±4.89). Finally, the mean 25-OH-D Vit level of 224 patients was 16.9 mg/dL (±9.7). When comparing the bone mineral density of the patients who underwent at least six months of TAF treatment, whose pre- and post-treatment results were available, no statistically significant difference was found ($p = 0.24$) (Figure 2).

The mean treatment duration was 84.6 (±47) months in the ETV group. HBV DNA levels were detectable in 3 (3.6%) of the patients who utilized ETV during the total treatment period, and HBs Ag seroconversion occurred in 3 (4.2%). A significant decrease was observed in the post-treatment transaminase levels compared to the pre-treatment values among patients receiving ETV treatment for at least six months ($p<0.001$). A significant reduction was detected in the GGT and ALP values after treatment ($p<0.001$) (Table 2). The mean GFR of the patients was 96.74 mL/min (±23.48). A statistically significant difference was identified when the mean GFR of 81 patients before ETV treatment was compared with the GFR for patients receiving at least six months of treatment ($p = 0.01$) (Figure 1). However, when we

Table 4. — **After at least six months of antiviral therapy, a comparison of the latest laboratory parameters in TDF, ETV, and TAF groups**

	TDF	ETV	TAF	p-value	Adjusted p-value
Fasting Glucose, mg/dl	100 (92-111)	100 (92-113)	105 (96-132)	**0.003**	0.149
HbA1C	5.60 (5.3-6.1)	5.7 (5.4-6)	5.75 (5.4-6.5)	0.177	0.769
HOMA-IR,	2.7 (1.93-4.14)	2.89(2.09-5.44)	4.23 (2.25-6.98)	**0.001**	0.265
GFR, ml/dak	95.6 (82-109)	95 (79-109.2)	83.5 (64.5-98)	**<0.001**	**0.012**
ALT, U/L	19 (14-26.5)	16 (13-22)	17 (13-23)	**0.017**	**0.039**
Triglyceride, mg/dl	106 (77-151)	108 (82-180)	110 (77-143)	0.599	0.708
Total Cholesterol, mg/dl	163 (141-191)	169 (150-190)	177 (157-202)	**0.016**	0.539
LDL, mg/dl	95 (77-118)	96 (83-115)	103 (82-121)	0.229	0.198
HDL, mg/dl	44 (37-52)	46.5 (38-53)	46 (40-57)	0.059	0.795
Calcium, mg/dl	9.6 (9.3-9.8)	9,5 (9.3-9.8)	9.5 (9.2-9.8)	0.501	0.093
Phosphorus, mg/dl	3.4 (3.05-3.8)	3.2 (2.9-3.7)	3.1 (2.7-3.6)	**<0.001**	**0.505**
25-OH D_3, ng/mL	14.8 (10.6-20.8)	15.35 (10.65-21.6)	17.8 (12.3-24.2)	**0.017**	**0.487**
Proteinuria, n (%)	28 (%11.3)	8 (%9.6)	50 (%39.7)	**<0.001**	

Values are expressed as medians (interquartile ranges). ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide. HbA1C: glycosylated hemoglobin; HOMA-IR: the homeostatic model assessment insulin resistance; GFR: Glomerular filtration rate; ALT: alanine aminotransferase; LDL: Low-density lipoprotein; HDL: high-density lipoprotein; 25-OH D_3: 25-hydroxyvitamin D_3; $p < 0.05$ is considered statistically significant. Normal reference ranges are as follows; Fasting blood glucose: 70-110 mg/dl; HbA1C: 4-5.9%; HOMA-IR <2.5 mg/dl; GFR: 90-120 ml/min; ALT: 0-41 U/L; Triglyceride: 0-150 mg/dl; Total cholesterol: 0-200 mg/dl; LDL: 0-200 mg/dl; HDL: 40-100 mg/dl; Calcium: 8.6-10.5 mg/dl; Phosphorus: 2.5-4.5 mg/dl; 25-OH-D3: 20-100 ng/mL; Proteinuria: 0-150 mg/24 hours.

separated patients according to underlying DM and CKD, we observed a significant change in GFR values in the group of patients without underlying DM and CKD, as shown in Table 3. The mean current bone mineral density T score of 41 patients who received ETV for at least six months was -1.14 (±1.12). Moreover, after at least six months of antiviral therapy, the mean serum phosphorus level in 82 patients was 3.3 mg/dL (±0.59), the mean total cholesterol level in 79 patients was 174 mg/dL (±40.15), the mean HOMA-IR level in 68 patients was 4.12 (±4.03). The mean 25-OH-D Vit level among 68 patients was 16.58 mg/dL (±7.71). When comparing the bone mineral density of the patients who underwent at least six months of ETV treatment, whose pre- and post-treatment results were available, no statistically significant difference was found (p = 0.41) (Figure 2).

Among the 129 patients in the TAF group, 25 were naive and did not receive antiviral treatment before, 77 were switched from TDF to TAF, 23 were switched from ETV to TAF, and three were switched from Lamivudine to TAF. One patient was switched from Telbivudin to TAF. The mean treatment duration was 30.6 (±11.2) months. HBV DNA levels remained detectable during the total treatment duration in 4 (3.1%) of the patients using TAF, and HBs Ag seroconversion was found in 6 (5.6%). A significant decrease was detected in post-treatment transaminase levels when compared to the pre-treatment levels among patients receiving TAF treatment for at least six months (treatment-experienced and naive patients) (p<0.001). No significant changes were observed in the GGT (p = 0.49) and ALP values when compared with the pre-treatment period (p = 0.65) (Table 2). The mean GFR among the patients was 80.99 mL/min (±30.04). Statistically significant decreases were detected when the mean GFR of 124 patients before the TAF treatment was compared with the GFR after treatment for at least six months (p = 0.01) (Figure 1). However, when we separated patients according to underlying DM and CKD, we observed a significant change in GFR values in the group of patients without underlying DM and CKD, as shown in Table 3. There was no significant change in GFR values of 77 patients who switched from TDF to TAF (p = 0.51). The mean latest available bone mineral density T score of the 40 patients receiving TAF for at least six months was -1.42 (±1.41). In addition, after at least six months of antiviral therapy, the mean serum phosphorus level of 129 patients was 3.18 mg/dL (±0.86), the mean total cholesterol level among 121 patients was 177 mg/dL (±40.69) mean HOMA-IR level among 102 patients was 5.9 (±5.87). The mean 25-OH-D Vit level among 114 patients was 19.59 mg/dL (±10.35). Furthermore, when comparing the bone mineral density of the patients who underwent at least six months of TAF treatment, whose pre- and post-treatment results were available, no statistically significant difference was found (p = 0.95) (Figure 2).

When the three groups were compared, after at least six months antiviral therapy, the latest serum fasting glucose (p = 0.003), fasting insulin (p = 0.005), HOMA-IR (p = 0.01), serum urea (p<0.001), creatinine (p<0.001), GFR (p<0.001), ALT (p = 0.017), total cholesterol (p = 0.016), serum phosphorus (p<0.001), presence of proteinuria (p<0.001), and 25-OH-D Vit (p = 0.017) levels of the patients were significantly different. However, when the data were adjusted according to the underlying DM and CKD, it was observed that the significant difference in

these metabolic parameters between the three groups disappeared (Table 4).

No significant differences were observed between the three groups regarding ALT normalization, HBV DNA suppression, and HBs Ag seroconversion ($p = 0.15$, $p = 0.26$, $p = 0.72$).

Discussion

The present study presented retrospective 10-year comparative data of patients receiving TDF, ETV, and TAF treatments for at least six months for CHB. Most patients received TDF, possibly due to lower cost and higher resistance barrier efficacy. TAF has been used in our country for the last three years, and the majority of TAF patients were those who switched from TDF to TAF. All three groups revealed similar efficacy in ALT normalization, HBV DNA suppression, and HBs Ag seroconversion. Therefore, the current findings differed from the recently published meta-analysis (18). Consistent with our results, no significant difference was observed in the efficacy of these three antivirals in Jeong et al.'s retrospective cohorts (17).

The current guidelines recommend switching to ETV or TAF in patients with worsening renal and bone parameters under TDF (3,4). It was observed that this preference was utilized for TAF in our center. However, no significant changes were identified in the mean GFR value in our patients switching from TDF to TAF. These results are consistent with the retrospective findings of Su et al. (19) and contradict the studies of Farag et al. and Kaneko et al. (20,21). However, the patient profile in the TAF group was older and had more DM and CKD in this study. A significant decrease was detected in mean GFR values after at least six months of treatment in all three antiviral arms in the present study. However, when we divided the patients into subgroups according to underlying DM and CKD, we observed a significant decrease in GFR values in the ETV and TAF groups in the patient group without DM and CKD. We did not observe a substantial reduction after ETV and TAF treatment in patients with baseline DM and CKD. Moreover, those with DM and CKD constituted a small group of patients. In the retrospective cohorts of Jeong et al., no significant changes were observed in the GFR values in all three antiviral groups with a 48-week follow-up (17). Moreover, in the study of Trinh et al., during the follow-up period, TDF did not deteriorate kidney function more than ETV in individuals with no substantial renal impairment (22). The patients' physiological losses in the GFR over the years should be considered based on the long-term follow-up.

Although the tendency to decrease in bone density in TDF patients under treatment and the tendency to increase in TAF and ETV patients was observed, no significant changes were detected in bone mineral density measurements under antiviral therapy in the present study cohort in all three groups. The guidelines recommend switching to ETV or TAF in at-risk patients due to the risk of bone mineral loss in TDF. There are better results reported in T scores in TAF patients than in TDF, as well as retrospective studies in which no significant changes were noted in bone mineral density measurements of TDF and ETV patients in 4-5 years of follow-up (23). The ALP levels of the patients did not increase significantly in all three groups. However, studies reported that serum ALP, representing increased osteoblast activation after bone resorption, was elevated in patients using TDF (24,25). The baseline calcium, phosphorus, and 25-OH-Vit D levels in patients should also be evaluated for a more accurate evaluation. However, the unavailability of these values was a limitation of the present study. In addition, when the latest available values were compared, after at least six months of therapy, although we could not reach statistical significance when the underlying comorbidities were taken into account, the phosphorus level was lower in the TAF group than in the other groups, which could be related to TAF switching, particularly in the hypophosphatemic patient group. Calcium levels were found to be similar among the three groups. The low 25-OH-Vit D levels observed in all three groups may be related to the fact that our center, where this study was conducted, is located in the Black Sea Region with less sun exposure.

Finally, it was identified that the metabolic parameters of the patients associated with lipid and glucose were the worst in the TAF group. Although the baseline values of these parameters were not available, an important limitation of the present study, the total cholesterol level of these parameters was the lowest in the TDF group, under treatment for at least six months. Although not statistically significant, it was observed that the highest LDL and triglyceride levels were in the TAF group. These results are in line with the cohort of Jeong et al. (17). The lipid-lowering mechanism of TDF is unknown (12). Higher insulin resistance and fasting serum glucose in the TAF group may be associated with a higher preference for TAF therapy in diabetic patients. However, when the data were adjusted according to the underlying DM and CKD, the significant difference in these metabolic parameters between the three groups disappeared. Buti et al. and Chan et al. determined that the hyperglycemia and glycosuria rates were higher in the TAF than in the TDF group (10,11).

Other study limitations were the lack of similar follow-up times between all three groups due to the retrospective design; the most extended duration of treatment was 85 months in the ETV group and 30 months in the TAF group. Moreover, there was significant heterogeneity in favor of TDF regarding the number of patients between the groups. The single-center experience reflects the geographical conditions of our center and prevents the results from being generalizable. Related concomitant drugs (diabetes mellitus medications, proton pump inhibitor therapy, vitamin D, calcium supplements, etc.) that could affect different parameters measured in the

treatment groups were not evaluated. Finally, it was challenging to interpret these results after the intervention because some baseline data could not be accessed before treatment started (e.g., glucose and lipid parameters).

In conclusion, based on data analysis over at least a 24-week follow-up period, ETV, TDF, and TAF are comparably safe and effective antiviral agents against CHB.

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