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Evaluation of the Efficacy of Tenofovir Alafenamide in Patients with Low-Level Viremia Under Chronic Hepatitis B Treatment

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Abstract

In a multicenter, retrospective study of 62 patients, we aimed to investigate whether switching from entecavir (ETV) or tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) is a superior treatment strategy for patients with chronic hepatitis B (CHB) experiencing low-level viremia (LLV). The study found that TAF significantly improved virological and biochemical outcomes. At 48 weeks, the sustained virological response was 77.8% for those who switched from ETV and 81.8% for those who switched from TDF, with HBV DNA negativity reaching 81% by month 12. Significant normalization of liver enzymes, albumin, and platelets was also observed. While switching from TDF was associated with a significant increase in triglycerides and HDL and a decrease in eGFR, no such changes were noted in the ETV group. This evidence suggests that TAF provides better virological control, promotes the regression of liver fibrosis, and may reduce the risk of hepatocellular carcinoma (HCC), making it a more advantageous option than continuing prior monotherapy.

Keywords: low level viremi; hepatitis b; tenofovir; tenofovir alafenamide; taf; entecavir; efficiency; hepatocellular carcinoma

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1. Introduction

Hepatitis B virus (HBV) is a hepatotropic DNA virus that primarily infects hepatocytes and causes liver disease [1]. Although the widespread introduction of neonatal vaccination worldwide has significantly reduced the incidence of HBV infection, 257 million people worldwide are living with chronic HBV infection, and approximately 25% of these patients die from liver cancer or complications of liver failure [2]. Chronic hepatitis B (CHB) remains the leading cause of liver-related morbidity and mortality worldwide. Understanding the natural history of HBV has led to significant advances in the development of antiviral therapies and the management of patients with CHB. Effective antiviral treatment of patients with CHB using potent nucleoside/nucleotide analogue (NNA) drugs with high genetic barriers, such as entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), has been shown to regress liver fibrosis, prevent liver-related complications and improve patient survival [3–5]. However, even with potent drugs, the risk of hepatic complications, particularly the development of hepatocellular carcinoma (HCC), has not been completely eliminated in patients with CHB [6]. Low-level viremia (LLV) may be a possible cause of HCC in NNA-treated patients [7,8]. LLV is not mentioned in most guidelines, with the exception of the American Association for the Study of Liver Diseases (AASLD) guideline (2018). In this guideline, LLV is defined as detectable HBV DNA < 2000 IU/mL (detection limit 10 IU/mL) after 48 weeks of antiviral treatment [9]. If a patient develops LLV, it has not yet been determined whether they should continue their original treatment or switch to other therapies. Guidelines recommend that patients with partial virological response to non-first-line agents should be switched to the most effective antiviral agent without cross-resistance [9–12]. In patients with LLV, the AASLD recommends that patients treated with ETV or TDF monotherapy continue with monotherapy, but the quality and certainty of the evidence are low [9]. The European Association for the Study of the Liver (EASL) does not recommend changing the initial treatment strategy in patients with low HBV DNA levels (HBV DNA < 69 IU/mL) and/or decreasing HBV DNA concentrations on potent NNA monotherapy; if HBV DNA has plateaued (69 < DNA < 2000 IU/mL), the possibility of switching to another drug or the combination of ETV+TDF/TAF should be considered [11]. Recent studies have shown that switching from ETV to TAF helps to achieve undetectable HBV DNA in patients with LLV at some point after switching [13–15]. However, it is still unclear whether switching from ETV to TAF can achieve and maintain a complete virological response (CVR) during treatment with TAF in patients with LLV or occasionally detectable HBV DNA. In this study, we first aimed to investigate whether switching from ETV and TDF to TAF is effective in achieving CVR in patients with LLV. Most CHB patients treated with NNA are well controlled, but long-term nucleotide analogue therapy carries a high risk of nephrotoxicity and bone toxicity. TAF has high plasma stability, which allows efficient delivery of the active metabolite to hepatocytes at a dose of 25 mg with low circulating tenafovir levels and reduces the risk of renal and bone damage with long-term use [16,17]. However, studies have shown that TAF is worse than TDF in terms of fasting lipid changes, and the exact mechanism of these changes has not been determined [1]. Our second aim was to evaluate the virological/biochemical effects and renal safety when patients were switched from ETV or TDF to TAF.

2. Materials and Methods

Between 1 January 2018 and 1 January 2024, the files of patients aged ≥18 years who presented to the Infectious Diseases and Clinical Microbiology outpatient clinic in the participating centers between 1 January 2018 and 1 January 2024 and who received ETV or TDF treatment for CHB infection for at least 48 weeks and developed LLV (HBV DNA >20 IU/mL monitored at every 12-week interval under treatment) during follow-up, were retrospectively reviewed. Records of patients whose treatment was switched to TAF due to LLV and who were followed up for at least 48 weeks were analyzed. Patients with a history of interferon treatment, coinfection with hepatitis C virus or human immunodeficiency virus, autoimmune liver disease, other liver diseases including drug-

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induced liver injury, decompensated cirrhosis (complicated by ascites, variceal bleeding, or encephalopathy), any cancer, poor medication compliance, and pregnant or breastfeeding women were excluded.

Physical examination and blood tests (virological and biochemical parameters) were evaluated at baseline, 12, 24 and 48 weeks. Serum HBV DNA levels were measured using the COBAS TaqMan HBV Test (Roche, USA), with a lower limit of detection of 20 IU/mL. HBV serological markers were measured by chemiluminescent immunoassay (Abbott, Germany). Estimated glomerular filtration rate (eGFR) was determined by the Cockcroft-Gault method. aspartate aminotransferase platelet ratio index (APRI) scores were calculated for all patients using the formula APRI = ([AST/ULN]/PLT) × 100.

The primary efficacy endpoint was complete virological response, defined as a serum HBV DNA level <20 IU/mL at week 48. Secondary efficacy endpoints were the degree of reduction in serum HBV DNA levels in patients with detectable HBV DNA, alanine aminotransferase (ALT), normalisation, HBeAg seroconversion and changes in liver fibrosis as measured by APRI.

Patient data collected in the study were analysed using IBM Statistical Package for the Social Sciences (SPSS) for Macos 30.0 (IBM Corp., Armonk, NY). Descriptive values included frequencies and percentages for categorical data and medians, 25% and 75% quartiles for continuous data. Chi-square or Fisher's exact test was used to compare categorical variables. Friedman's two-way analysis of variance with ranks was used to assess differences between dependent measures. For pairwise comparisons between dependent measures, multiple testing was evaluated with Bonferroni correction. Results were considered statistically significant if the p-value was less than 0.05.

3. Results

In our study, 62 patients who fulfilled the inclusion and exclusion criteria were evaluated. Of these patients, 67.7% (n = 42) were male. The age of the patients ranged from 26 to 77 years, with a median age of 43 years. Before TAF treatment, 29% (n = 18) of the patients were taking ETV and 71% (n = 44) were taking TDF. Treatment duration ranged from 12 to 162 months, with a median of 44 months (Table 1).

Table 1. Distribution of patient demographics and clinical findings.

Variables	n (%) or Median (IQR)
Age (years)	43 (36-54)
Gender	
Female	20 (32,3)
Male	42 (67,7)
Pre-TAF treatment	
ETV	18 (29)
TDF	44 (71)
Duration of treatment before TAF (months)	44 (30-80)

Abbreviations: ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

The results of the data from the patients who were followed up for low viremia before and after TAF treatment at three, six and twelve months are shown in Table 2. After TAF treatment, HBV DNA negativity was 67.3% (n = 37), 67.9% (n = 38) and 81% (n = 50) at 3, 6 and 12 months, respectively. There was no difference in HBeAg seroconversion at any time point after treatment switch. ALT, aspartate aminotransferase (AST), albumin and platelet levels were significantly normalised with TAF treatment. Although alpha-fetoprotein (AFP) and APRI, which give an indication of liver damage, normalised with treatment change, the results were not statistically significant. High density lipoprotein (HDL) cholesterol was significantly improved, while no difference was observed in low density lipoprotein (LDL) cholesterol. Triglyceride levels increased significantly from the first few

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months after switching to TAF. The eGFR values, which we used to monitor changes in patients' kidney function, decreased significantly during follow-up (Table 2).

Table 2. Distribution of patients' laboratory values before and after treatment.

Variables	Pre-TAF [1] (n=62)	TAF 3rd month[2] (n=55)	TAF 6th month[3] (n=56)	TAF 12th month[4] (n=62)	p-value	Post-HOC
	n (%) or Median (IQR)	n (%) or Median (IQR)	n (%) or Median (IQR)	n (%) or Median (IQR)		
HBV-DNA (log10)	2,46 (1,48-2,83)	1,83 (1,3-3,02)	1,46 (1,14-1,81)	1,6 (1,12-2,22)	0,143	
HBV-DNA (+)	62 (100)	18 (32,7)	18 (32,1)	12 (19,4)	<0,001	
HBeAg (+)	12 (19,4)	11 (20)	11 (19,6)	13 (21)	0,996	
Anti-HBe (HBeAb) (+)	50 (80,6)	44 (80)	45 (80,4)	49 (79)	0,996	
AST (U/L)	29 (21-41)	26 (21-30)	27,5 (21,5-33)	27,5 (21-33)	0,046	1-2;1-4
ALT (U/L)	34 (20-45)	26 (20-33)	28 (18-41,5)	28 (18-36)	0,002	1-2;1-3; 1-4
Albümin (g/L)	4 (3,8-4,5)	4 (3,6-4,6)	4,1 (3,6-4,4)	4,3 (3,7-4,6)	0,004	1-4;2-4; 3-4
Total Bilirubin (mg/dL)	0,7 (0,5-0,9)	0,7 (0,5-1)	0,8 (0,5-0,9)	0,8 (0,5-1)	0,598	
AFP (µg/L)	2,8 (1,8-3,2)	2,5 (2-3,7)	2,6 (1,8-3,9)	2,5 (2-3,7)	0,477	
HDL (mg/dL)	43 (40-46)	44 (41-47)	44 (41-51)	46 (41-52)	0,032	1-4;2-4
LDL (mg/dL)	114 (99-126)	109 (96-125)	111 (93,5-130)	102 (88-125)	0,233	
Total Kolesterol (mg/dL)	207 (199-209)	205 (188-217)	201 (183-215)	203 (196-211)	0,475	
Trigliserit (mg/dL)	189 (166-208)	199 (163-211)	200 (168-217)	201 (174-222)	<0,001	1-2;1-3; 1-4;2-4
Trombosit (x10³)	237,5 (210-302)	241 (194-282)	244,5 (192,5-290,5)	252,5 (195-302)	0,040	1-2;2-4
eGFR (mL/dk/1.73m2)	94 (88-104)	93 (88-101)	90 (85,5-99)	90 (87-97)	0,016	1-3;1-4
Fosfor (mg/dL)	3 (2,9-3,3)	3 (2,8-3,5)	3 (2,9-3,5)	3 (2,8-3,4)	0,724	
APRI	0,4 (0,2-0,8)	0,3 (0,2-0,9)	0,4 (0,2-0,9)	0,3 (0,2-0,9)	0,921	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; APRI, aspartate aminotransferase platelet ratio index; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HBeAb, Hepatitis B virus e antibody; HBeAg, Hepatitis B virus e antigen; HBV-DNA, Hepatitis B virus deoxyribonucleic acid; HDL, High density lipoprotein; LDL, Low density lipoprotein; TAF, Tenofovir alafenamide.

When the data of the patients who switched from ETV and TDF to TAF were analysed individually in Tables 3 and 4, HBV DNA negativity was significant in 77.8% and 81.8% of the LLV patients in the ETV and TDF groups, respectively, at the end of the twelfth month. ALT normalisation was significantly observed after switching from both drugs to TAF. Although no significant differences were observed in comparisons analysing changes in drug levels, a significant increase in triglycerides and HDL was observed in the TDF group with the switch to TAF, while no change was observed in the ETV group. While eGFR decreased significantly in the TDF group with the switch to TAF, no change was observed in the ETV group.

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Table 3. Distribution of laboratory measurements in patients treated with ETV before and after treatment.

Variables	Pre-TAF [1] (n=18)	TAF 3rd month[2] (n=17)	TAF 6th month[3] (n=15)	TAF 12th month[4] (n=18)	p-value	Post-HOC
	n (%) or Median (IQR)	n (%) or Median (IQR)	n (%) or Median (IQR)	n (%) or Median (IQR)		
HBV-DNA (log10)	1,9 (1,8-2)	1,9 (1,8-2)	1,3 (1,2-1,9)	1,9 (1,5-2,8)	0,122	
HBV-DNA (+)	18 (100)	5 (29,4)	7 (46,7)	4 (22,2)	<0,001	
HBeAg (+)	6 (33,3)	5 (29,4)	5 (33,3)	6 (33,3)	0,993	
Anti-HBe (HBeAb) (+)	12 (66,7)	12 (70,6)	10 (66,7)	12 (66,7)	0,993	
AST (U/L)	24 (22-41)	23 (19-30)	27 (19-36)	27 (19-28)	0,028	1-4; 3-4
ALT (U/L)	29,5 (19-56)	25 (23-31)	26 (17-45)	26 (14-45)	0,026	1-2; 1-3; 1-4
Albümin (g/L)	4,5 (3,9-5,1)	4,3 (4,1-4,9)	4,4 (4,2-4,6)	4,5 (4,3-5,1)	0,155	
Total Bilirubin (mg/dL)	0,6 (0,5-0,6)	0,6 (0,5-0,7)	0,6 (0,5-0,8)	0,7 (0,5-0,9)	0,119	
AFP (µg/L)	2 (1,5-2,8)	1,8 (1,7-2,8)	1,8 (1,7-2,6)	2,1 (1,7-3)	0,735	
HDL (mg/dL)	41 (39-45)	42 (40-45)	44 (39-51)	42,5 (41-46)	0,419	
LDL (mg/dL)	109,5 (90-126)	113 (89-120)	111 (90-125)	110 (88-126)	0,191	
Total Kolesterol (mg/dL)	208,5 (201-219)	211 (180-233)	211 (165-233)	209 (201-233)	0,920	
Trigliserit (mg/dL)	183 (152,9-211)	180 (163-201)	176 (92-206)	194,5 (172-211)	0,095	
Trombosit (x10³)	253,5 (210-302)	250 (205-308)	262 (222-301)	268 (227-310)	0,241	
eGFR (mL/dk/1.73m2)	88 (84-104)	92 (88-102)	90 (75-109)	89,5 (74-97)	0,688	
Fosfor (mg/dL)	3 (2,9-3,9)	3,1 (3-4)	3,2 (3-3,9)	3 (2,7-3,7)	0,197	
APRI	0,2 (0,2-0,4)	0,2 (0,2-0,3)	0,2 (0,2-0,4)	0,2 (0,2-0,2)	0,377	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; APRI, aspartate aminotransferase platelet ratio index; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ETV, entecavir; HBeAb, Hepatitis B virus e antibody; HBeAg, Hepatitis B virus e antigen; HBV-DNA, Hepatitis B virus deoxyribonucleic acid; HDL, High density lipoprotein; LDL, Low density lipoprotein; TAF, Tenofovir alafenamide.

Table 4. Distribution of laboratory values in TDF-treated patients before and after treatment.

Variables	Pre-TAF [1] (n=44)	TAF 3rd month[2] (n=38)	TAF 6th month[3] (n=41)	TAF 12th month[4] (n=44)	p-value	Post-HOC
	n (%) or Median (IQR)	n (%) or Median (IQR)	n (%) or Median (IQR)	n (%) or Median (IQR)		
HBV-DNA (log10)	1,8 (1,2-3)	1,8 (1,2-3)	1,5 (0,8-1,8)	1,5 (1,1-2)	0,469	
HBV-DNA (+)	44 (100)	13 (34,2)	11 (26,8)	8 (18,2)	<0,001	
HBeAg (+)	6 (13,6)	6 (15,8)	6 (14,6)	7 (15,9)	0,990	
Anti-HBe (HBeAb) (+)	38 (86,4)	32 (84,2)	35 (85,4)	37 (84,1)	0,990	

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AST (U/L)	30 (21-42,5)	26 (22-32)	28 (22-33)	29,5 (21-33,5)	0,224	
ALT (U/L)	34 (21-40)	29 (20-37)	28 (20-40)	27 (18-35,5)	0,046	1-2; 1-3; 1-4
Albümin (g/L)	3,9 (3,7-4,3)	3,7 (3,5-4,3)	4 (3,6-4,4)	4 (3,6-4,6)	0,030	2-4
Total Bilirubin (mg/dL)	0,8 (0,6-1)	0,8 (0,6-1)	0,8 (0,6-1)	0,8 (0,5-1)	0,608	
AFP (µg/L)	2,8 (2-3,3)	2,9 (2,2-3,9)	2,8 (2-4)	2,7 (2,1-3,8)	0,675	
HDL (mg/dL)	42,5 (41-46)	44 (42-48)	44 (42-51)	46 (42-53,5)	0,034	1-2; 1-3; 1-4
LDL (mg/dL)	115 (101-126)	108 (99-125)	108 (98-132)	102 (88-125)	0,275	
Total Kolesterol (mg/dL)	204,5 (195-209)	201 (188-211)	200 (188-211)	200 (192,5-208,5)	0,458	
Trigliserit (mg/dL)	196 (170,5-208)	201 (176-212)	202 (186-241)	202,5 (177,5-231,5)	<0,001	1-2; 1-3; 1-4; 2-4
Trombosit (x10³)	230 (209,5-304,5)	237 (193-277)	241 (187-288)	243 (183-301)	0,098	
eGFR (mL/dk/1.73m2)	96 (90-103,5)	93,5 (89-99)	90 (87-98)	90 (88,5-97)	0,006	1-3; 1-4
Fosfor (mg/dL)	3 (2,9-3,3)	3 (2,8-3,2)	3 (2,9-3,3)	3 (2,9-3,4)	0,648	
APRI	0,6 (0,2-0,9)	0,8 (0,3-0,9)	0,7 (0,3-0,9)	0,7 (0,2-1)	0,895	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; APRI, aspartate aminotransferase platelet ratio index; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HBeAb, Hepatitis B virus e antibody; HBeAg, Hepatitis B virus e antigen; HBV-DNA, Hepatitis B virus deoxyribonucleic acid; HDL, High density lipoprotein; LDL, Low density lipoprotein; TAF, Tenofovir alafenamide. TDF, tenofovir disoproxil fumarate.

4. Discussion

Low-level viremia may be a possible cause of HCC in patients receiving NNA treatment [7,8]. Therefore, management of LLV and ensuring CVR with treatment is important to reduce the risk of HCC. When LLV develops in a patient, it is not clear whether monotherapy should be continued or other drugs should be switched. Guidelines recommend that patients with partial virological responses using non-first-line drugs should switch to the most effective antiviral agent without cross-resistance [9,11,12]. We analysed the efficacy and safety of TAF monotherapy as an alternative treatment in patients who developed LLV under ETV, TDF and combination therapies. In the literature, He et al. In a group of 351 patients with LLV, after 48 weeks of treatment, CVR was 75.3% in the TAF (n=183) group compared to 11.4% in the ETV group ($P < 0.001$)[19]. Zhong et al. In a study including 211 patients with LLV, CVR was 62% in the TAF group and 9% in the ETV group, which was significantly higher in the TAF group [13]. Ogawa et al. studied 313 consecutive CHB patients treated with a combination of ETV or NNA for more than two years and then switched to TAF monotherapy and achieved a CVR of 73.9% in the ETV group and 77.8% in the NNA combination group [14]. The fact that we achieved a CVR of 81% (n=50) in our 62 patients who were followed for a median of 44 months despite receiving ETV and TDF treatment, 48 weeks after switching to TAF, is consistent with the literature. Achievement of CVR is important for long-term clinical benefit and was therefore the primary endpoint of our study.

In terms of drug-related factors, TAF has less potential for side effects due to its high potency, liver-targeting properties and high plasma stability, providing the theoretical basis for the better response in the TAF group [13]. In LLV, Zhong et al. showed an ALT normalisation of 47% vs 10% in the TAF group compared to ETV at 24 weeks and the difference was significant in favour of the TAF group [13]. He et al. again compared patients receiving TAF and ETV in patients with low viremia and found that ALT normalisation was significantly higher in the TAF arm [19]. In our study, ALT normalisation after switching to TAF treatment in patients receiving long-term ETV or TDF but progressing to LLV was found to be significant, in agreement with the literature. ALT normalisation

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was significantly observed in patients who switched from both TDF and ETV to TAF. This difference is probably due to the superior viral suppression observed in the TAF group.

Achieving a sustained viral response is the most important and first step in improving long-term clinical benefit. Our study has provided clinical evidence that may attract further attention and encourage long-term studies. Considering the difference in viral suppression with TAF after ETV and TDF, a higher rate of ALT normalisation should be expected in patients receiving TAF. Long-term follow-up is needed to confirm whether faster ALT normalisation, reflecting faster resolution of necroinflammation, translates into faster regression of liver fibrosis. In addition, the lower HBeAg seroconversion rates in naive patients treated with TDF or ETV compared to previous studies [17,18] may be due in part to lower HBV DNA and ALT levels as patients received ETV or TDF for longer periods, or to the shorter duration of treatment in this study.

Both APRI and Fibrosis-4 index (FIB-4) are also recommended by the WHO guidelines for clinical assessment of fibrosis [20]. Therefore, we used APRI to assess liver fibrosis because it is convenient, non-invasive and quantitative. Our results showed that after 48 weeks of treatment, the changes after TAF treatment in patients with LLV were not significantly different. In this study, all enrolled patients received ETV or TDF treatment for a median of 44 months, which resulted in a significant reduction in liver fibrosis in most patients. It is therefore difficult to achieve a significant reduction after 48 weeks of follow-up; however, after remission of the liver inflammation, liver fibrosis should theoretically improve after prolonged observation.

TDF is actively secreted by the kidneys via organic anion transporters (OAT1 and OAT3) and causes high tenofovir exposure in the proximal renal tubules [21,22]. In contrast, TAF is not a substrate of renal OATs and does not exhibit OAT-dependent cytotoxicity [22]. Although there are publications showing rapid recovery of lost renal function with increased eGFR after switching from TDF to TAF [23,24], Hishijima et al. found that long-term TDF use and subsequent discontinuation, especially when used for more than two years, significantly increased the likelihood of causing renal tubular damage compared to those who never used TDF. They showed that cumulative TDF exposure, independent of TDF use, was strongly and robustly associated with renal damage [25]. In two studies showing the change in eGFR over time after switching from TDF to TAF, a significant decrease in eGFR was observed in the group of patients with eGFR≥90 at 144 weeks and 18 months respectively, whereas increases in eGFR were observed in the lower eGFR groups after switching from TDF to TAF [26,27]. In our study, the duration of treatment before TAF in the TDF group was 44 months, and the decline in eGFR continued during follow-up in our patient population, which consisted of patients with high cumulative TDF exposure and eGFR≥90. This situation supports the literature with the deterioration of renal function in the group of patients who continued TAF after TDF in two aspects. Tsai et al. showed that eGFR remained stable in the ETV group during the first three years and improved significantly in years four and five [28]. Our study was consistent with the literature in that there was no change in eGFR in those who switched from ETV to TAF.

In terms of lipid safety, as previously described, TDF treatment is known to have a 'lipid-lowering effect'. According to clinical trials, in patients who switched from TDF to TAF, a greater increase in triglycerides, LDL and HDL cholesterol was seen in TDF-treated patients compared to those who continued TDF treatment due to high plasma tenofovir levels; this was associated with lipid reduction in patients receiving TDF [29,30]. Over forty-eight weeks, no significant increases in HDL, LDL and triglycerides were observed in the group switched from ETV to TAF in terms of lipid profiles. No significant changes were observed in the ETV to TAF group compared to baseline. In the group switched from TDF to TAF, HDL and triglycerides increased significantly compared to baseline, while no significant change was observed in LDL. While no change in lipid levels was observed in the group switched from ETV to TAF and the increase in lipid tests in the group switched from TDF to TAF supported the lipid-lowering effect of TDF, TAF showed a "normal blood lipid level" effect compared to TDF. This has shown that the clinical significance of the lipid effect of TAF is unclear, and that a definitive mechanism for these changes has not been identified. The effects of antiviral drugs on the metabolism of patients should not be underestimated. Monitoring of blood

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lipid parameters is recommended for follow-up of TAF treatment. Future studies should focus on the actual cardiovascular risk and not only on changes in lipid parameters. Considering that most CHB patients require lifelong treatment and the prevalence of comorbidities increases with age, changes in both renal function and lipid parameters need to be seriously monitored and managed.

One of the shortcomings of our study is the small number of patients, especially in the ETV group, although it was a multicentre study. In our study, in which we investigated the efficacy and effect of TAF in patients with LLV after treatment change, there was no information on whether the reason for the decision to change TAF treatment in patients was due to physician preference, drug ineffectiveness, drug side effects, or secondary causes that developed in patients. Although we used non-invasive methods to assess liver fibrosis, these methods provide indirect measurements and cannot provide the definitive histological evidence that liver biopsy would provide. The 48-week observation period may not be long enough to assess difficult clinical endpoints such as cirrhosis progression and HCC incidence. Uchida et al. have shown that HBV genotype (B vs. C) is an important factor influencing treatment efficacy [31]. Although genotypic analysis may provide more accurate guidance for salvage therapies in LLV patients, our other shortcoming was the lack of HBV genotype information. Therefore, future studies with larger sample sizes and improved genotyping techniques are crucial to better understand the role of HBV genotype in LLV treatment outcomes. Another missing point is the lack of data on weight gain in patients switched to TAF. The increase in body mass index (BMI) after switching to TAF is associated with a decrease in eGFR, but we could not analyse the effect of BMI on the decrease in eGFR in patients switching to TAF after TDF because we did not have data on this.

5. Conclusions

Switching to TAF is a superior option for patients who develop low levels of viremia on ETV and TDF monotherapy. This is because TAF promotes regression of liver fibrosis, reduces the risk of HCC, provides better virological and biochemical responses, and has a similar safety profile to ETV and TDF. For these reasons, switching to TAF treatment is more advantageous than continuing ETV or TDF treatment. Large prospective studies evaluating histological changes, renal and bone safety and the incidence of HCC are needed to clarify the clinical benefits of switching to TAF therapy.

Author Contributions: This project involved a collaborative effort across multiple teams, with AT and FY leading the initial stages of Conceptualization, Methodology, Original Draft Preparation, and Visualization. The Software aspect was a joint effort between AT, FY, and MYD, while AT and MYD were solely responsible for Data Curation and Validation. The most extensive tasks—Formal Analysis, Investigation, and management of Resources—were carried out by a large team including AT, FY, TÖK, OK, MKÇ, SAl, TDÇ, FA, SAk, EG, ŞÖB, MÇe, and MÇa. For the Writing – Review & Editing phase, AT, FY, OK, SAl, and TDÇ collaborated. Finally, FY, OK, MKÇ, and SAk provided Supervision, and AT single-handedly managed Project Administration and Funding Acquisition.

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Institutional Review Board Statement: This study was approved by the Ethics Committee of Antalya Training and Research Hospital (Ethics committee decision no: 3/30, date: 21/03/2024) and followed the principles of the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The Excel and SPSS datasets, as well as the SPSS data outputs related to this study, are kept by the corresponding author.

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Abbreviations

The following abbreviations are used in this manuscript:

HBV	**Hepatitis B virus**
CHB	**Chronic hepatitis B**
NNA	**Nucleoside/nucleotide analogue**
ETV	**Entecavir**
TDF	**Tenofovir disoproxil fumarate**
TAF	**Tenofovir alafenamide**
HCC	**Hepatocellular carcinoma**
LLV	**Low-level viremia**
AASLD	**American Association for the Study of Liver Diseases**
EASL	**European Association for the Study of the Liver**
CVR	**Complete virological response**
eGFR	**Estimated glomerular filtration rate**
APRI	**Aspartate aminotransferase platelet ratio index**
ALT	**Alanine aminotransferase**
SPSS	**Statistical Package for the Social Sciences**
AST	**Aspartate aminotransferase**
AFP	**Alpha-fetoprotein**
HDL	**High density lipoprotein**
LDL	**Low density lipoprotein**
HBeAb	**Hepatitis B virus e antibody**
HBeAg	**Hepatitis B virus e antigen**
HBV DNA	**Hepatitis B virus deoxyribonucleic acid**
FIB-4	**Fibrosis-4 index**
OAT1	**Organic anion transporters 1**
OAT4	**Organic anion transporters 4**
BMI	**Body mass index**

References

1. Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. *Lancet*. 2018;392(10161):2313-2324.
2. Hutin Y, Nasrullah M, Easterbrook, P.; et al. Access to treatment for hepatitis B virus infection worldwide, 2016. *Am J Transplant*. 2018;18(10):2595-2598.
3. Wang X, Liu X, Dang Z; et al. Nucleos (t) ide analogues for reducing hepatocellular carcinoma in chronic hepatitis B patients: A systematic review and meta-analysis. *Gut Liver*. 2019;14(2):232.
4. Grossi G, Viganò M, Loglio A, Lampertico P. Hepatitis B virus long-term impact of antiviral therapy nucleot (s) ide analogues (NUC s). *Liver Int*. 2017;37:45-51.
5. Coffin CS, Rezaeeaval M., Pang JX; et al. The incidence of hepatocellular carcinoma is reduced in patients with chronic hepatitis B on long-term nucleos (t) ide analogue therapy. *Aliment Pharmacol Ther*. 2014;40(11-12):1262-1269.
6. Hosaka T, Suzuki F, Kobayashi M.; et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*. 2013;58(1):98-107.
7. Kim JH, Sinn DH, Kang W.; et al. Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment. *Hepatology*. 2017;66(2):335-343.
8. Sinn DH, Lee J., Goo J.; et al. Hepatocellular carcinoma risk in chronic hepatitis B virus–infected compensated cirrhosis patients with low viral load. *Hepatology*. 2015;62(3):694-701.
9. Terrault NA, Lok ASF, McMahon BJ; et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560-1599.

 doi:10.20944/preprints202509.2075.v1

10. Jia JD, Hou JL, Wei L., Zhuang H. Highlights of the guidelines of prevention and treatment for chronic hepatitis B (2019 version). *Zhonghua gan zang bing za zhi= Zhonghua ganzangbing zazhi= Chinese J Hepatol*. 2020;28(1):21-23.
11. Lampertico P, Agarwal K, Berg T; et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67(2):370-398.
12. Sarin SK, Kumar M., Lau GK; et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: A 2015 update. *Hepatol Int*. 2016;10(1):1-98.
13. Li Z., Li L., Niu X.; et al. Switching from entecavir to tenofovir alafenamide for chronic hepatitis B patients with low-level viraemia. *Liver Int*. 2021;41(6):1254-1264.
14. Ogawa E, Nomura H, Nakamuta M.; et al. Tenofovir alafenamide after switching from entecavir or nucleos (t) ide combination therapy for patients with chronic hepatitis B. *Liver Int*. 2020;40(7):1578-1589.
15. Ogawa E, Nakamuta M, Koyanagi T.; et al. Switching to tenofovir alafenamide for nucleos (t) ide analogue-experienced patients with chronic hepatitis B: Week 144 results from a real-world, multi-centre cohort study. *Aliment Pharmacol Ther*. 2022;56(4):713-722.
16. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. *Mol Pharm*. 2013;10(2):459-466.
17. Murakami E, Wang T, Park Y; et al. Implications of efficient hepatic delivery by tenofovir alafenamide (GS-7340) for hepatitis B virus therapy. *Antimicrob Agents Chemother*. 2015;59(6):3563-3569.
18. Chan HLY, Fung S., Seto WK; et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: A randomised, double-blind, phase 3, non-inferiority trial. *lancet Gastroenterol Hepatol*. 2016;1(3):185-195.
19. He MW, Cui L., Chen DD; et al. Efficacy and safety of switching from entecavir to tenofovir alafenamide in chronic hepatitis B patients with low-level viremia: A real-world 48-week extension study. *Antimicrob Agents Chemother*. Published online 2025:e01827-24.
20. Organization WH. Guidelines for the Prevention Care and Treatment of Persons with Chronic Hepatitis B Infection: Mar-15. World Health Organization; 2015.
21. Ray AS, Cihlar T., Robinson KL; et al. Mechanism of active renal tubular efflux of tenofovir. *Antimicrob Agents Chemother*. 2006;50(10):3297-3304.
22. Bam RA, Yant SR, Cihlar T. Tenofovir alafenamide is not a substrate for renal organic anion transporters (OATs) and does not exhibit OAT-dependent cytotoxicity. Published online 2014.
23. Kalkan I, Karasahin O, Sarigul F.; et al. Comparison of tenofovir alafenamide and entecavir therapy in patients with chronic hepatitis B initially treated with tenofovir disoproxil: A retrospective observational survey. *Hepat Mon*. 2021;21(10).
24. Kaneko S, Kurosaki M, Tamaki N.; et al. Tenofovir alafenamide for hepatitis B virus infection including switching therapy from tenofovir disoproxil fumarate. *J Gastroenterol Hepatol*. 2019;34(11):2004-2010.
25. Nishijima T, Mutoh Y, Kawasaki Y; et al. Cumulative exposure of TDF is associated with kidney tubulopathy whether it is currently used or discontinued. *Aids*. 2018;32(2):179-188.
26. Abe K, Obara T, Kamio S; et al. Renal function in Japanese HIV-1-positive patients who switch to tenofovir alafenamide fumarate after long-term tenofovir disoproxil fumarate: A single-center observational study. *AIDS Res Ther*. 2021;18:1-12.
27. Surial B, Ledergerber B, Calmy A.; et al. Changes in renal function after switching from TDF to TAF in HIV-infected individuals: A prospective cohort study. *J Infect Dis*. 2020;222(4):637-645.
28. Tsai MC, Chen CH, Tseng PL; et al. Comparison of renal safety and efficacy of telbivudine, entecavir and tenofovir treatment in chronic hepatitis B patients: Real world experience. *Clin Microbiol Infect*. 2016;22(1):95-e1.
29. Tungsiripat M, Kitch D, Glesby MJ; et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. *Aids*. 2010;24(11):1781-1784.

 doi:10.20944/preprints202509.2075.v1

30. Santos JR, Saumoy M., Curran A.; et al. The lipid-lowering effect of tenofovir/emtricitabine: A randomized, crossover, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2015;61(3):403-408.
31. Uchida Y, Nakao M, Tsuji S; et al. Significance of switching of the nucleos (t) ide analog used to treat Japanese patients with chronic hepatitis B virus infection from entecavir to tenofovir alafenamide fumarate. *J Med Virol*. 2020;92(3):329-338.