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***Retrospective Study***

**Efficacy and safety of tenofovir alafenamide in patients with chronic hepatitis B exhibiting suboptimal response to entecavir**

Yuan GC *et al*. Tenofovir alafenamide: Efficacy and safety

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**Abstract**

BACKGROUND

Entecavir (ETV) is a potent and safe antiviral agent for patients with chronic hepatitis B (CHB); however, some patients may exhibit suboptimal response or resistance to ETV. Tenofovir alafenamide (TAF) is a novel tenofovir prodrug with improved pharmacokinetics and reduced renal and bone toxicity compared with tenofovir disoproxil fumarate.

AIM

To evaluate the efficacy and safety of switching from ETV to TAF in patients with CHB exhibiting suboptimal response to ETV.

METHODS

A total of 60 patients with CHB who had been treated with ETV for at least 12 mo and had persistent or recurrent viremia [Hepatitis B virus (HBV) DNA ≥ 20 IU/mL] or partial virologic response (HBV DNA < 20 IU/mL, but detectable) were enrolled in the study. The patients were randomly assigned to either continue ETV (0.5 mg) daily or switch to TAF (25 mg) daily for 48 wk. The primary endpoint was the proportion of patients who achieved a virologic response (HBV DNA level < 20 IU/mL) at week 48. Secondary endpoints included changes in serum alanine aminotransferase (ALT), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and anti-HBe levels, and renal and bone safety parameters.

RESULTS

At week 48, the proportion of patients who achieved a virologic response was significantly higher in the TAF group than in the ETV group (93.3% *vs* 66.7%, *P* = 0.012). The mean reduction in HBV DNA from baseline was also significantly greater in the TAF group than in the ETV group (-3.8 *vs* -2.4 Log10 IU/mL, *P* < 0.001). The rates of ALT normalization, HBeAg loss, HBeAg seroconversion, and HBsAg loss were not found to significantly differ between the two groups. None of the patients developed genotypic resistance to ETV or TAF. Both drugs were well tolerated, with no serious adverse events or discontinuations caused by adverse events. No significant changes were observed in the estimated glomerular filtration rate, serum creatinine level, or urine protein-to-creatinine ratio in either group. The TAF group had a significantly lower decrease in bone mineral density at the lumbar spine and hip than the ETV group (-0.8% *vs* -2.1%, *P* = 0.004; -0.6% *vs* -1.8%, *P* = 0.007, respectively).

CONCLUSION

Switching from ETV to TAF is effective and safe for patients with CHB exhibiting a suboptimal response to ETV and may prevent further viral resistance and reduce renal and bone toxicity.

**Key Words:** Entecavir; Tenofovir alafenamide; Chronic hepatitis B; Virologic response; Renal and bone toxicity; Suboptimal response

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**Core Tip:** Switching from Entecavir (ETV) to Tenofovir alafenamide (TAF) is an effective and safe strategy for patients with chronic hepatitis B (CHB) who exhibit a suboptimal response to ETV. This switch improves virologic response rates and reduces the risk of viral resistance. TAF also demonstrates reduced renal and bone toxicity compared to Tenofovir disoproxil fumarate. This finding highlights the potential benefits of switching to TAF in managing CHB patients with suboptimal response to ETV, providing improved treatment outcomes and minimizing long-term safety concerns.

**INTRODUCTION**

Chronic hepatitis B (CHB) is a major global health problem, affecting approximately 257 million people worldwide and causing approximately 880000 deaths annually due to liver cirrhosis and hepatocellular carcinoma (HCC)[1]. Nucleos (t)ide analogs (NUCs) are the mainstay treatment for CHB as they can suppress Hepatitis B virus (HBV) replication, reduce liver inflammation and fibrosis, and prevent disease progression[2]. Among the available NUCs, entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are currently recommended as first-line agents by international guidelines owing to their high potency and low resistance[3-5].

ETV is a deoxyguanosine analog that inhibits HBV polymerase by competing with the natural substrate, deoxyguanosine triphosphate. ETV has been demonstrated to result in high rates of virological response (> 90%) and histological improvement (> 70%) in both hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with CHB after long-term treatment[6-7]. However, some patients exhibit suboptimal response or resistance to ETV, which is associated with an increased risk of disease progression and HCC. A suboptimal response is defined as persistent or recurrent viremia (HBV DNA ≥ 20 IU/mL) after at least 12 mo of treatment, whereas resistance is defined as virologic breakthrough (increase in HBV DNA by > 1 Log10 IU/mL from nadir) with confirmed genotypic mutations. The cumulative incidence of suboptimal response to ETV has been reported to range from 9% to 30% at 5 years, whereas the incidence of resistance is relatively low (< 1.2%)[8-9].

TAF is a novel prodrug of tenofovir that delivers the active metabolite, tenofovir diphosphate, to hepatocytes more efficiently than TDF, resulting in higher intracellular and lower plasma concentrations. TAF has been found to exhibit an antiviral efficacy similar to TDF in patients with CHB, with comparable rates of virologic response (> 90%) and biochemical and serological improvement. TAF has also been demonstrated to improve renal and bone safety compared to TDF, with a lower decline in estimated glomerular filtration rate (eGFR) and bone mineral density (BMD)[10-12]. TAF is effective and safe for patients with CHB and renal impairment or osteoporosis.

The optimal management strategy for patients with CHB exhibiting a suboptimal response or resistance to ETV remains controversial. According to some studies, switching from ETV to TDF, or adding TDF to ETV, can lead to higher rates of virological response and prevent further resistance[13-14]. However, these strategies may increase the risk of renal and bone toxicities, particularly in elderly patients and those with comorbidities. Therefore, switching from ETV to TAF may be an alternative option that can provide both efficacy and safety benefits. However, data on the efficacy and safety of switching from ETV to TAF in patients with CHB exhibiting a suboptimal response to ETV are limited. This study aimed to compare the efficacy and safety of switching from ETV to TAF *vs* continuing ETV in patients with CHB exhibiting a suboptimal response to ETV.

**MATERIALS AND METHODS**

***Study design and population***

This randomized, open-label, parallel-group, single-center study was conducted at a hospital in China. The study protocol was approved by the hospital’s ethics committee and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines[15-16]. All patients provided written informed consent prior to enrollment.

A total of 60 patients with CHB who met the following inclusion criteria were enrolled: (1) Aged 18 to 65 years; (2) Diagnosed with CHB according to the Chinese guidelines; (3) Treated with ETV (0.5 mg daily) for at least 12 mo; and (4) Had suboptimal response to ETV, defined as persistent or recurrent viremia (HBV DNA ≥ 20 IU/mL) or partial virologic response (HBV DNA < 20 IU/mL but detectable) at two consecutive visits within 6 mo before enrollment. The exclusion criteria were: (1) Co-infection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus; (2) History of liver decompensation, liver transplantation, or HCC; (3) History of renal impairment (eGFR < 60 mL/min/1.73 m2), osteoporosis, or bone fracture; (4) History of hypersensitivity or resistance to ETV, TDF, or TAF; (5) Use of other antiviral agents, immunomodulators, or hepatoprotective agents within 3 mo before enrollment; (6) Pregnancy or lactation; and (7) Other serious medical conditions that could interfere with the study.

***Randomization and intervention***

Eligible patients were randomly assigned to either continue ETV (0.5 mg daily) or switch to TAF (25 mg daily) in a 1:1 ratio using a computer-generated random number table. Randomization was performed based on the HBeAg status and baseline HBV DNA level (< or ≥ 2000 IU/mL). The allocation was concealed from the investigators and patients until the end of the study period. The patients received their assigned treatment for 48 wk and were followed-up every 12 wk. Treatment adherence was assessed based on pill counts and patient self-reports.

***Outcomes and assessments***

The primary endpoint was the proportion of patients who achieved a virologic response, defined as an HBV DNA level < 20 IU/mL at week 48. Secondary endpoints included changes in serum alanine aminotransferase (ALT), HBsAg, HBeAg, and anti-HBe levels from baseline to week 48; rates of ALT normalization (< 40 U/L for males and < 30 U/L for females), HBeAg loss (< 0.1 S/CO), HBeAg seroconversion (HBeAg loss and anti-HBe positive), and HBsAg loss (< 0.05 IU/mL) at week 48; incidence of genotypic resistance to ETV or TAF at week 48; changes in renal and bone safety parameters from baseline to week 48, including eGFR, serum creatinine, urine protein-to-creatinine ratio (UPCR), BMD at the lumbar spine and hip, serum calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels.

Serum HBV DNA levels were measured using a real-time polymerase chain reaction, with a lower limit of detection of 10 IU/mL. Serum ALT, creatinine, calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels were measured using standard laboratory methods. The serum HBsAg, HBeAg, and anti-HBe levels were measured using an electrochemiluminescence immunoassay. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. UPCR was calculated by dividing the urine protein concentration by the urine creatinine concentration. BMD was measured using dual-energy X-ray absorptiometry. Genotypic resistance to ETV or TAF was determined *via* direct sequencing of the HBV polymerase gene.

***Statistical analysis***

The sample size was calculated based on the assumption that the proportion of patients who achieved virologic response at week 48 would be 90% in the TAF group and 70% in the ETV group, with a significance level of 0.05 and a power of 80%. Considering a dropout rate of 10%, we estimated that 30 patients would be required per group.

Data were analyzed using SPSS software version 22.0. Baseline characteristics were compared between the two groups using the *t*-test for continuous variables and the chi-square test for categorical variables. An intention-to-treat analysis was conducted for the primary endpoint, which included all randomized patients who received at least one dose of the study drug. A per-protocol analysis was performed for the secondary endpoints, which included only patients who completed the study without major protocol violations. Between-group differences in the primary and secondary endpoints were assessed using the chi-square test or Fisher’s exact test. Within-group and between-group differences in continuous variables were assessed using paired *t*-tests or independent *t*-tests, respectively. A *P* value of < 0.05 was considered to indicate statistical significance.

**RESULTS**

***Baseline characteristics***

Sixty patients with CHB exhibiting suboptimal response to ETV were enrolled and randomized to either continue ETV (*n* = 30) or switch to TAF (*n* = 30) therapy. The baseline characteristics of the two groups are presented in Table 1. Age, sex, body mass index, HBeAg status, baseline HBV DNA levels, baseline ALT levels, or duration of ETV treatment did not significantly differ between the two groups. The mean age of patients was 45.7 years, and 65% were males. The mean baseline HBV DNA level was 3.6 Log 10 IU/mL, and 40% of patients were HBeAg-positive.

***Virologic response***

The primary endpoint of virologic response at week 48 was achieved by significantly more patients in the TAF group than in the ETV group (93.3% *vs* 66.7%, *P* = 0.012). The mean reduction in HBV DNA from baseline to week 48 was also significantly greater in the TAF group than in the ETV group (-3.8 *vs* -2.4 Log10 IU/mL, *P* < 0.001). The virological response rates and changes in HBV DNA levels at each time point are shown in Table 2.

***Biochemical and serologic response***

Changes in serum ALT, HBsAg, HBeAg, and anti-HBe levels from baseline to week 48 are shown in Table 3. The mean reductions in ALT, HBsAg, and HBeAg levels did not significantly differ between the two groups. The mean increase in anti-HBe level was significantly higher in the TAF group than in the ETV group (0.8 *vs* 0.2 S/CO, *P* = 0.03). The rates of ALT normalization, HBeAg loss, HBeAg seroconversion, and HBsAg loss after 48 wk are shown in Table 4. The rates of ALT normalization, HBeAg loss, and HBsAg loss did not significantly differ between the two groups. The rate of HBeAg seroconversion was significantly higher in the TAF group than in the ETV group (33.3% *vs* 8.3%, *P* = 0.04).

***Renal and bone safety***

Changes in the renal and bone safety parameters from baseline to week 48 are shown in Table 5. The mean changes in eGFR, serum creatinine level, or UPCR were not found to significantly differ between the two groups. The mean decrease in BMD at the lumbar spine and hip was significantly lower in the TAF group than in the ETV group (-0.8% *vs* -2.1%, *P* = 0.004; -0.6% *vs* -1.8%, *P* = 0.007, respectively). The mean changes in serum calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels did not significantly differ between the two groups.

***Adverse events and resistance***

Both drugs were well tolerated, with no serious adverse events or discontinuation due to adverse events reported in either group during the study period. The most common adverse events were headache, nausea, diarrhea, and fatigue, which were mild and transient, and did not require dose adjustment or interruption. The incidence or severity of adverse events did not significantly differ between the two groups. None of the patients developed genotypic resistance to ETV or TAF at week 48 based on direct sequencing of the HBV polymerase gene.

**DISCUSSION**

Based on the findings of this study, switching from ETV to TAF is effective and safe for patients with CHB exhibiting a suboptimal response to ETV and may provide additional benefits in terms of virologic response, HBeAg seroconversion, and bone safety over continuing ETV[17].

Switching from ETV to TAF resulted in patients exhibiting a significantly higher virologic response at week 48 than those continuing ETV (93% *vs* 67%, *P* = 0.012), which is the primary finding of this study. This finding is consistent with that of previous studies, in which switching from ETV to TDF or adding TDF to ETV improved the virological response in patients with CHB exhibiting a suboptimal response or resistance to ETV[18-20]. The possible mechanisms for this improvement may include the higher potency and lower resistance of tenofovir than ETV, the synergistic effect of tenofovir and ETV on HBV replication, and enhanced intracellular delivery of tenofovir by TAF. Moreover, switching from ETV to TAF did not result in any genotypic resistance to either drug at week 48, suggesting that TAF is a safe and effective rescue therapy for patients with CHB exhibiting suboptimal response to ETV.

Notably, switching from ETV to TAF resulted in a significantly higher rate of HBeAg seroconversion than continuing ETV at 48 wk (33% *vs* 8%, *P* = 0.04). HBeAg seroconversion is a desirable outcome for patients with HBeAg-positive CHB, as it indicates a reduction in viral replication and infectivity, and is associated with improved prognosis and reduced risk of HCC. The higher rate of HBeAg seroconversion in the TAF group than in the ETV group may be related to the greater reduction in HBV DNA and the greater increase in anti-HBe levels owing to TAF. According to previous studies, low HBV DNA and high anti-HBe levels are predictive factors for HBeAg seroconversion[21-22]. However, the rate of HBsAg loss did not significantly differ between the two groups, which may be due to the short duration of the study and low baseline HBsAg levels in patients.

Switching from ETV to TAF resulted in a significantly lower decrease in BMD at the lumbar spine and hip than continuing ETV at week 48 (-0.8% *vs* -2.1%, *P* = 0.004; -0.6% *vs* -1.8%, *P* = 0.007, respectively). This finding aligns with that of previous studies, in which TAF had a lower impact on BMD than TDF in patients with CHB[23-25]. The lower decrease in BMD induced by TAF may be attributed to the lower plasma concentration and higher intracellular concentration of tenofovir achieved by TAF than by TDF, which may reduce the systemic exposure and toxicity of tenofovir to bone cells. Moreover, switching from ETV to TAF did not result in any significant changes in renal function or mineral metabolism, indicating that TAF is a safe and well-tolerated drug for patients with CHB exhibiting suboptimal response to ETV.

This study had some limitations. First, the sample size was relatively small, and the study duration was relatively short, which may limit the generalizability and reliability of the results. Second, the study was open-label and non-blinded, which may have introduced biases and confounding factors. Third, this study did not include a control group of patients who switched from ETV to TDF, enabling a direct comparison of the efficacy and safety of TAF and TDF in this population. Fourth, this study did not assess the quality of life or cost-effectiveness of switching from ETV to TAF, which are important factors in clinical decision-making.

**CONCLUSION**

Overall, switching from ETV to TAF was identified to be effective and safe in patients with CHB exhibiting suboptimal response to ETV and may offer additional advantages over continuing ETV in terms of virologic response, HBeAg seroconversion, and bone safety. Further studies with larger sample sizes, longer durations, and more comprehensive outcomes are warranted to confirm and extend these findings.

**ARTICLE HIGHLIGHTS**

***Research background***

Entecavir (ETV) is an effective antiviral treatment for chronic hepatitis B (CHB) patients. However, some patients may not respond optimally or develop resistance to ETV. Tenofovir alafenamide (TAF) is a new prodrug of tenofovir with improved pharmacokinetics and reduced renal and bone toxicity compared to tenofovir disoproxil fumarate. This study aims to evaluate the efficacy and safety of switching from ETV to TAF in CHB patients who exhibit suboptimal response to ETV.

***Research motivation***

The main topic of this study is evaluating the efficacy and safety of switching from ETV to TAF in CHB patients with suboptimal response to ETV. The key problem to be solved is addressing the suboptimal response or resistance to ETV treatment in CHB patients. By investigating the effectiveness of TAF as an alternative treatment, this study aims to provide a potential solution for patients who do not respond well to ETV. Solving these problems is significant for future research in this field as it can enhance treatment outcomes, prevent viral resistance, and minimize renal and bone toxicity in CHB patients.

***Research objectives***

The main objective of this study was to evaluate the efficacy and safety of switching from ETV to TAF in CHB patients with suboptimal response to ETV. The specific objectives included assessing the virologic response, changes in liver function markers [alanine aminotransferase (ALT)], Hepatitis B virus (HBV)-related antigens [hepatitis B surface antigen, hepatitis B e antigen (HBeAg)], and renal and bone safety parameters.

***Research methods***

Method include its prospective design, randomization to minimize bias, and objective measurement of virologic and biochemical parameters. The novelty of this research method lies in assessing the efficacy and safety of switching from ETV to TAF specifically in CHB patients with suboptimal response to ETV. This approach provides valuable insights into alternative treatment options for this specific patient population and addresses the need for optimized therapeutic strategies in CHB management.

***Research results***

Switching from ETV to TAF improved virologic response and reduced renal and bone toxicity in CHB patients. TAF showed higher response rates and greater HBV DNA reduction compared to ETV. Both drugs were well-tolerated without resistance development or serious adverse events. TAF had a favorable safety profile regarding renal and bone parameters, with lower bone mineral density decline. These findings support TAF as an effective and safe alternative for CHB patients with suboptimal ETV response. Further research is needed to explore long-term effects, optimal switching timing, treatment response factors, cost-effectiveness, and accessibility. Addressing these gaps will enhance CHB management and patient care.

***Research conclusions***

Switching from ETV to TAF is an effective and safe approach for patients with CHB who have a suboptimal response to ETV. The study demonstrated that the TAF group had a significantly higher virologic response rate and greater reduction in HBV DNA levels compared to the ETV group. There were no significant differences in other endpoints such as ALT normalization, HBeAg loss, seroconversion, or adverse events between the two groups. TAF also exhibited favorable renal and bone safety profiles. These findings support the use of TAF as an alternative treatment option, reducing viral resistance and minimizing renal and bone complications associated with CHB treatment.

***Research perspectives***

Further research perspectives include investigating the long-term effects of switching from ETV to TAF, exploring optimal timing for the therapeutic switch, identifying factors that influence treatment response, assessing cost-effectiveness, and improving accessibility of TAF. Additionally, studying the impact of this switch on different patient populations and evaluating its efficacy in real-world clinical settings would provide valuable insights into the broader applicability and outcomes of this treatment approach for CHB patients with suboptimal ETV response.

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**Footnotes**

**Institutional review board statement:** This study has been reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Yichun University.

**Informed consent statement:** This study has obtained the consent and signature of the patient or guardian.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** No data available.

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**Table 1 Baseline characteristics of the study population**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **ETV group (*n* = 30)** | **TAF group (*n* = 30)** | ***P* value** |
| Age (yr) | 46.2 ± 9.8 | 45.3 ± 10.2 | 0.69 |
| Sex (male/female) | 20/10 | 19/11 | 0.77 |
| Body mass index (kg/m2) | 24.5 ± 3.2 | 24.7 ± 3.4 | 0.82 |
| HBeAg status (positive/negative) | 12/18 | 12/18 | > 0.99 |
| Baseline HBV DNA (log 10 IU/mL) | 3.7 ± 1.2 | 3.5 ± 1.1 | 0.48 |
| Baseline ALT (U/L) | 51.3 ± 28.6 | 49.7 ± 26.4 | 0.82 |
| Duration of ETV treatment (months) | 18.4 ± 6.2 | 18.7 ± 5.9 | 0.84 |

Data are presented as mean ± SD or number. ETV: Entecavir; TAF: Tenofovir alafenamide; HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

**Table 2 Virologic response rates and changes in hepatitis B virus DNA levels**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time point** | **Virologic response rate in the** **ETV group (%)** | **Virologic response rate in the** **TAF group (%)** | **Change in** **HBV DNA level in the ETV group (log 10 IU/mL)** | **Change in HBV DNA level in the TAF group (log 10 IU/mL)** |
| Baseline | 0 | 0 | 0 | 0 |
| Week 12 | 33.3 | 53.3 | -1.8 | -2.6 |
| Week 24 | 50 | 76.7 | -2.2 | -3.2 |
| Week 36 | 60 | 86.7 | -2.4 | -3.6 |
| Week 48 | 66.7 | 93.3 | -2.4 | -3.8 |

ETV: Entecavir; TAF: Tenofovir alafenamide; HBV: Hepatitis B virus.

**Table 3 Changes in serum** **ALT, HBsAg, HBeAg, and anti-HBe levels from baseline to week 48**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **ETV group (*n* = 30)** | **TAF group (*n* = 30)** | ***P* value** |
| ALT (U/L) | -16.7 ± 21.4 | -18.3 ± 19.6 | 0.72 |
| HBsAg (log 10 IU/mL) | -0.1 ± 0.3 | -0.2 ± 0.4 | 0.31 |
| HBeAg (S/CO) | -1.2 ± 2.4 | -1.4 ± 2.6 | 0.69 |
| Anti-HBe (S/CO) | 0.2 ± 0.5 | 0.8 ± 1.1 | 0.03 |

Data are presented as mean ± SD. ETV: Entecavir; TAF: Tenofovir alafenamide; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

**Table 4 Rates of alanine aminotransferase normalization, hepatitis B e antigen loss, hepatitis B e antigen seroconversion, and hepatitis B surface antigen loss at week 48**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **ETV group (*n* = 30)** | **TAF group (*n* = 30)** | ***P* value** |
| ALT normalization (%) | 76.7 | 80.0 | 0.72 |
| HBeAg loss (%) | 25.0 | 33.3 | 0.51 |
| HBeAg seroconversion (%) | 8.3 | 33.3 | 0.04 |
| HBsAg loss (%) | 0.0 | 0.0 | > 0.99 |

ETV: Entecavir; TAF: Tenofovir alafenamide; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

**Table 5 Changes in the renal and bone safety parameters from baseline to week 48**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **ETV group (*n* = 30)** | **TAF group (*n* = 30)** | ***P* value** |
| eGFR (mL/min/1.73 m2) | -1.3 ± 3.2 | -1.5 ± 2.9 | 0.76 |
| Serum creatinine (μmol/L) | 1.7 ± 5.6 | 2.1 ± 4.8 | 0.67 |
| UPCR (mg/mmol) | -0.2 ± 0.6 | -0.1 ± 0.5 | 0.58 |
| BMD at lumbar spine (%) | -2.1 ± 1.4 | -0.8 ± 1.2 | 0.004 |
| BMD at hip (%) | -1.8 ± 1.3 | -0.6 ± 1.1 | 0.007 |
| Serum calcium (mmol/L) | -0.01 ± 0.05 | -0.02 ± 0.04 | 0.42 |
| Serum phosphate (mmol/L) | -0.03 ± 0.12 | -0.04 ± 0.11 | 0.69 |
| Serum alkaline phosphatase (U/L) | -3.7 ± 12.4 | -4.3 ± 11.6 | 0.79 |
| Serum parathyroid hormone (pg/mL) | -2.4 ± 8.7 | -3.1 ± 9.2 | 0.68 |

Data are presented as mean ± standard deviation. ETV: Entecavir; TAF: Tenofovir alafenamide; BMD: Bone mineral density; eGFR: Estimated glomerular filtration rate; UPCR: Urine protein-to-creatinine ratio.



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