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Original article

Improvement in renal function after switching from entecavir to tenofovir alafenamide in chronic hepatitis B patients with low estimated glomerular filtration rates

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ABSTRACT

Introduction and Objectives: Tenofovir alafenamide (TAF) and entecavir (ETV) are both considered renal-friendly nucleoside/nucleotide analogs (NAs). However, the difference between ETV and TAF in terms of renal function remains unclear. This study aims to compare the renal safety profiles of two antiviral medications directly and evaluate the impact of switching from ETV to TAF treatment on renal function in chronic hepatitis B (CHB) patients with low estimated glomerular filtration rates (eGFR).

Patients and Methods: A total of 179 CHB patients who received TAF (n = 84) or ETV (n = 95) between 2019 and 2023 were included in the study. Changes in eGFR levels between two treatment groups from baseline to 72 weeks were compared to measure the influence of these NAs on renal function.

Results: At baseline, 84 patients were included in each treatment group after a 1:1 propensity score matching process. At week 48, a notable different changes in eGFR were observed between the two groups. Gender, baseline eGFR, and medication (TAF/ETV) were significantly correlated with eGFR abnormalities. Furthermore, eGFR abnormalities at week 48 led to the transition of 6 patients in the ETV group to TAF. eGFR significantly increased (83.60 ± 5.45 vs. 93.39 ± 9.88 mL/min/1.73 m^2; p = 0.031) and serum creatinine significantly decreased (81.47 ± 11.36 vs. 74.9 ± 10.67 μmol/L; p = 0.046) from week 48 to 60. At week 48, the incidence of low-level viremia (LLV) was 19.0 % in the ETV group and 16.7 % in the TAF group, respectively ($p > 0.05$). Pairwise comparisons revealed no significant difference in the percentage of LLV between the ETV continued group and the TAF continued group at week 48, 60, and 72. Additionally, there was also no significant difference in the proportion of LLV between the ETV + TAF combination group and the TAF + ETV combination group at week 48, 60, and 72.

Conclusions: There was a substantial difference in eGFR between ETV and TAF treatments at week 48. Gender, baseline eGFR, and medication (TAF/ETV) were all remarkably positive indicators of eGFR abnormalities. In patients receiving ETV, an early switch to TAF may result in the reversal of early-stage renal damage.

1. Introduction

Hepatitis B virus (HBV) infection affected approximately 296 million people worldwide in 2019, leading to 820,000 fatalities, making it a serious public health concern [1]. Chronic hepatitis B (CHB) is closely associated with cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [2,3]. Nucleoside/nucleotide analogs (NAs) have been demonstrated to efficiently inhibit HBV replication, lessen fibrosis, and reduce mortality rates [1,4]. However, due to the presence of the viral nuclear reservoir, which contains transcriptionally active covalently closed circular DNA (cccDNA), NAs cannot eradicate HBV

Abbreviations: ALT, Alanine transaminase; AST, Aspartate transaminase; BMI, Body mass index; BUN, Blood urea nitrogen; CHB, Chronic hepatitis B; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration creatinine; cccDNA, Covalently closed circular DNA; eGFR, Estimated glomerular filtration rates; ETV, Entecavir; HBV, Hepatitis B virus; HBsAg, Hepatitis B surface antigen; HCC, Hepatocellular carcinoma; LLV, Low-level viremia; LSM, Liver stiffness measurement; NAs, Nucleoside/nucleotide analogs; PEG-IFN, Platelets; PLT, Serum creatinine; PS, Propensity score; TAF, Tenofovir alafenamide; TDF, Tenofovir disoproxil fumarate; TG, Triglycerides

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[3,5,6], hence for the majority of patients need long-term NA treatment.

According to current international guidelines, the first-line nucleotide analog medications for CHB include entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) [7–10]. Due to the long-term use of NAs, safety concerns have become increasingly important. The close association between TDF and proximal renal tubular dysfunction has been well-documented [11]. ETV or TAF, which have a lower risk of nephrotoxicity compared to TDF, are usually recommended for patients with high renal risk [7,9,12]. There is extensive literature on the renal safety profiles of both TAF and ETV [7,13]. According to a comparative study, TAF poses a lower risk of renal function deterioration than ETV [14]. However, there is still limited information on the long-term effects and the impact of switching from ETV to TAF due to impaired renal function.

Therefore, this study aims to investigate the effects on renal function of long-term ETV or TAF administration in CHB patients, as well as the impact on renal function after switch from ETV to TAF.

2. Patients and methods

2.1. Study design

This is a single-center, retrospective study. The study included 557 CHB patients aged 18 and above who received either ETV or TAF treatment, which was conducted at the First Affiliated Hospital of Nanchang University between September 2019 and November 2023. Patients were followed for a minimum of 48 weeks to assess their clinical outcomes.

The process of switching antiviral regimens was detailed: after completing renal function and HBV-DNA tests at week 48, some patients switched their antiviral regimen under the guidance of their doctor, while other continued with their original antiviral therapy due to expenses and other factors. We analyzed changes in renal function and HBV-DNA 24 weeks after either switching to TAF or maintaining the original regimen (ETV or TAF).

2.2. Patients

The inclusion criteria were as follows: (1) age over 18 years; (2) diagnosed with CHB [7]; (3) have been on ETV or TAF monotherapy for more than 48 weeks at the time of presentation (September 2019 to November 2023).

The exclusion criteria were as follows: (1) combined with other liver diseases, such as alcoholic liver disease, autoimmune liver disease, and drug-induced liver injury; (2) coinfected with hepatitis C virus and/or HIV; (3) chronic kidney disease or kidney transplantation; (4) concomitant with diabetes or hypertension; (5) prior use of antiviral drugs; (6) patients with missing data; (7) less than 48 weeks of follow-up.

2.3. Outcome assessment and measurement

Diagnosed CHB patients attended outpatient clinic sessions every 3-6 months. During these visits, detailed information on laboratory parameters, such as HBV DNA, viral markers, and blood chemistry tests, were collected. Abdominal imaging, such as ultrasonography, was also performed.

Creatinine and estimated glomerular function rate (eGFR) were used to measure renal impairment. The Chronic Kidney Disease Epidemiology Collaboration creatinine (CKD-EPI) equation was used to compute eGFR [15]. Serum HBV DNA was quantitatively measured using the Cobas TaqMan assay, which has a detection limit of 20 IU/ml. ALT normalization is defined as ALT < 40 U/L regardless of gender, in accordance with the APASL guidelines [12].

eGFR < 90 ml/min/1.73 m^2 is considered indicative of renal abnormalities [16]. According to a recent study [14], there was a statistically significant difference in eGFR between ETV and TAF treatment at week 48. Additionally, prolonged ETV treatment resulted in further deterioration of renal function. Consequently, when patients experienced renal abnormalities at week 48, we switched treatment regimen from ETV to TAF. Serum HBV DNA ranging from 20 to 2000 IU/mL are referred to as low-level viremia (LLV). Rescue therapy must be considered for patients with LLV at week 48 [17]. Some patients continued their antiviral medication due to expense and other concerns, while others switched from ETV to ETV and TAF combination, and from TAF to TAF and ETV combination.

2.4. Statistical analysis

The propensity score (PS) was employed to adjust for baseline differences. The covariates included in the PS model were baseline age, gender, HBV DNA, hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) positivity, total bilirubin, albumin, alanine transaminase (ALT), alanine transaminase (AST), and eGFR.

Statistical analyses were conducted using SPSS 26.0. The plots were created using GraphPad Prism 8.0. Continuous variables were presented as mean (± standard deviation) or median (interquartile range), while categorical variables were presented as frequencies and percentages. The student *t*-test and rank sum test were used for the comparison of continuous variables, while the chi-squared test was applied for categorical variables. All statistical tests were two-tailed, with a significance level set at $p < 0.05$.

2.5. Ethical statement

The study was carried out under the ethical guidelines outlined in the Declaration of Helsinki and received approval from the institutional review board at The First Affiliated Hospital of Nanchang University (approval No:(2023)CDYFYYLK(01-006)). The Ethics Committee of The First Affiliated Hospital of Nanchang University waived the requirement for informed consent due to the retrospective nature of the study.

3. Results

3.1. Baseline characteristics

A total of 179 CHB patients who received ETV (n = 95) or TAF (n = 84) monotherapy were enrolled in this study between September 2019 and November 2023. A total of 378 patients were excluded for the following reasons: 17 patients had a history of renal disease or kidney transplantation, 9 had diabetes or hypertension, 164 were monitored for less than 1 year, 21 had alcoholic liver disease, 101 had previously received other NAs or pegylated interferon (PEG-IFN) therapy, 14 were co-infected with other hepatitis viruses, and 52 had incomplete data (Fig. 1).

The baseline characteristics of the study subjects are presented in Table 1. Before matching, the median age, mean body mass index (BMI), and median liver stiffness measurement (LSM) were comparable between the ETV and TAF groups (all $p > 0.05$). Furthermore, the proportions of male patients (58.9 % vs. 57.1 %), HBeAg positive (46.3 % vs. 50.0 %), and those with compensated cirrhosis (11.6 % vs. 14.3 %) did not exhibit statistically significant differences between the ETV and TAF groups (all $p > 0.05$).

Moreover, the median HBsAg level in the ETV group was significantly lower than that in the TAF group ($p = 0.039$). No significant differences were observed in the other laboratory variables, including HBV DNA, total bilirubin, serum albumin, ALT, AST, triglycerides (TG), serum creatinine, baseline eGFR, blood urea nitrogen (BUN), and platelets (PLT) (all $p > 0.05$).

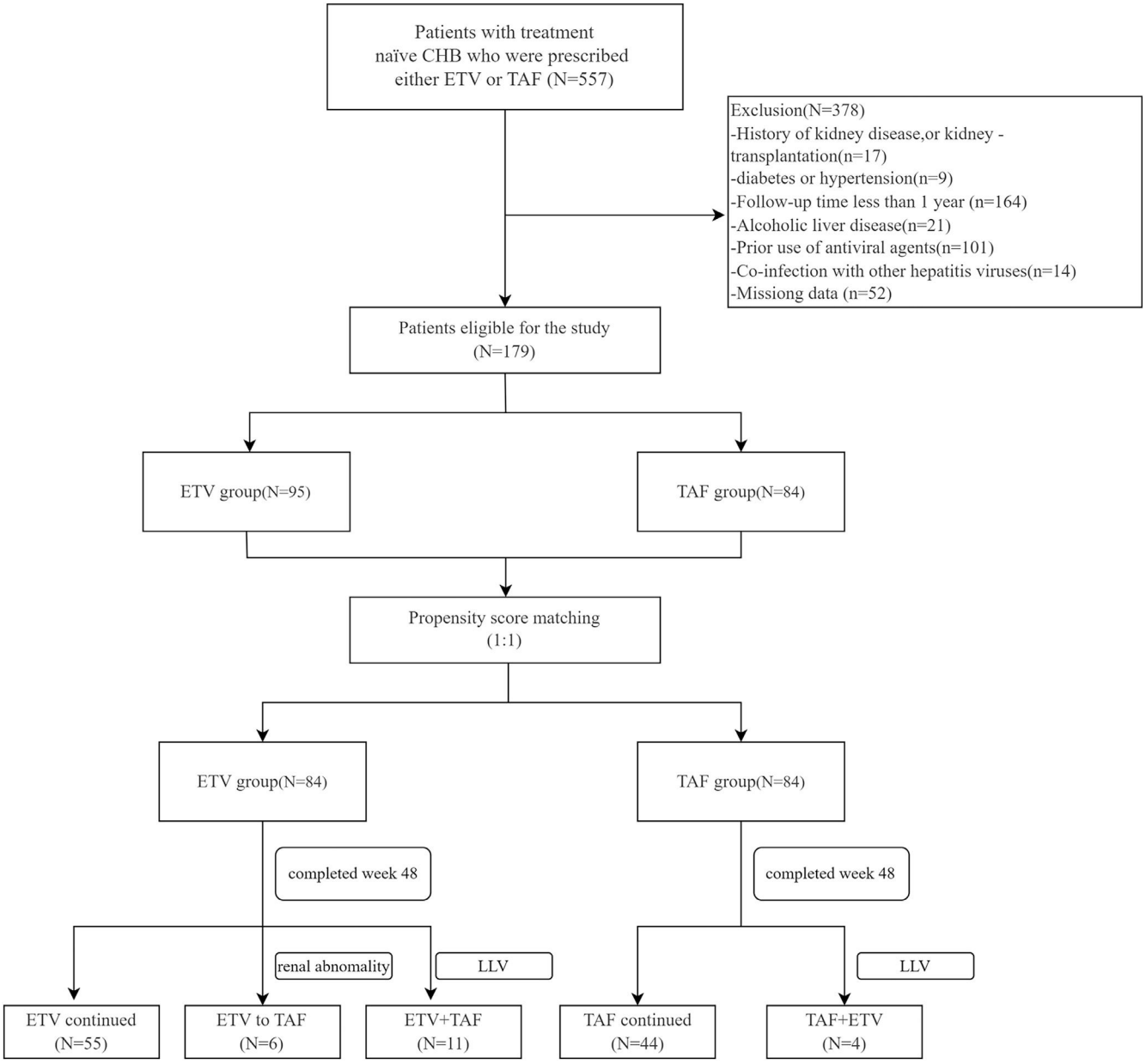

Fig. 1. Flow diagram of the study. CHB, chronic hepatitis B; ETV, entecavir; TAF, tenofovir alafenamide; LLV, low-level viremia; ETV continued group, ETV maintained therapy; ETV to TAF group, switching from ETV to TAF at week 48; ETV + TAF group, ETV combined with TAF at week 48; TAF continued group, TAF maintained therapy; TAF + ETV group, TAF combined with ETV at week 48. Patients in the TAF group with renal function abnormalities continue to use TAF at week 48.

A 1:1 matching method based on propensity scores was employed to pair a group of 84 patients receiving ETV treatment with 84 patients receiving TAF treatment, as detailed in Table 1. After propensity score matching (PSM), the baseline characteristics of the two groups were well-balanced across all variables included in the propensity score model (all $p > 0.05$).

3.2. Clinical outcomes of patients at week 48

The clinical outcomes at week 48 for the ETV and TAF groups are shown in Table 2. The median eGFR level was significantly lower in the ETV group compared to the TAF group (110.0 ml/min/1.73 m^2 vs. 115.9 ml/min/1.73 m^2, $p = 0.015$). No significant differences were observed between the two groups in the other laboratory variables, including HBV DNA, total bilirubin, serum albumin, ALT, AST, TG, BUN, serum creatinine, PLT, and LSM (all $p > 0.05$).

3.3. Renal abnormality-related factors at week 48

Logistic regression analysis was conducted to identify factors associated with renal abnormalities at week 48. The independent variables included age, gender, and baseline eGFR. Among these, Gender, baseline eGFR, and the treatment regimens were identified as independent predictors of renal abnormalities at week 48 (Table 3).

3.4. Renal function changes after switching from ETV to TAF

Renal function changes over the 72-weeks follow-up period were illustrated in Fig. 2. At week 48, 6 patients switched from ETV to TAF due to GFR below 90 mL/min/1.73 m^2, and the eGFR levels of these patients switched from ETV to TAF were all ranged between 60 and 89 mL/min/1.73 m^2. From baseline to week 48, serum creatinine level was significantly increased (70.33 ± 9.84 vs.

Table 1
Baseline characteristics of the study population before and after propensity score matching.

Variables	Before matching (n = 179)			After matching (n = 168)		
	ETV (n = 95)	TAF (n = 84)	*P*	ETV (n = 84)	TAF (n = 84)	*P*
Age, years	35 (30,45)	34 (30,42)	0.610	35 (30,45)	34 (30,42)	0.626
Male,%	56 (58.9)	48 (57.1)	0.807	50 (59.0)	48 (57.1)	0.754
Body mass index, kg/m^2	22.9 (20.5,24.5)	22.2 (20.2,25.0)	0.999	22.9 (20.6,24.5)	22.2 (20.2,25.0)	0.842
DNA, log10 IU/mL	5.19 (3.59,7.43)	4.80 (3.31,7.65)	0.594	5.27 (3.60,7.50)	4.80 (3.31,7.65)	0.725
HBsAg, log10 IU/mL	3.30 (2.56,3.82)	3.50 (3.01,4.14)	0.039	3.32 (2.83,3.84)	3.50 (3.01,4.14)	0.103
HBeAg, positive%	44 (46.3)	42 (50.0)	0.622	40 (47.6)	42 (50.0)	0.758
Total bilirubin, μmol/L	17.80 (12.47,31.85)	15.15 (11.30,25.10)	0.141	17.4 (12.5,29.9)	15.1 (11.3,25.1)	0.250
Serum albumin, g/dL	44.9 (40.6,47.4)	44.0 (40.9,47.0)	0.293	44.9 (40.6,47.7)	44.0 (40.9,47.0)	0.244
ALT, U/L	51.4 (27.8,111.3)	46.2 (23.8,103.0)	0.586	50.0 (27.8,95.8)	46.2 (23.8,103.0)	0.730
AST, U/L	35.5 (27.0,76.4)	32.8 (22.0,78.2)	0.301	35.2 (27.1,72.6)	32.8 (22.0,78.2)	0.370
TG, mmol/L	1.24 (0.82,1.80)	1.18 (0.87,1.75)	0.931	1.19 (0.82,1.77)	1.18 (0.87,1.75)	0.704
BUN, mmol/L	4.14 ± 0.98	4.10 ± 1.24	0.805	4.14 ± 0.98	4.10 ± 1.24	0.825
Serum creatinine, μmol/L	65.94 ± 12.47	66.18 ± 15.36	0.911	66.05 ± 12.67	66.18 ± 15.36	0.951
eGFR, mL/min/1.73 m^2	115.5 (106.0,122.6)	116.0 (106.3,123.6)	0.945	115.5 (104.9,123.1)	115.7 (106.2,123.0)	0.919
PLT, 10^9/L	191 ± 59	201 ± 56	0.251	189 ± 59	201 ± 56	0.198
LSM, kPa	6.9 (5.9,10.4)	6.2 (5.5,9.8)	0.199	7.0 (6.1,10.5)	6.2 (5.5,9.8)	0.450
Liver cirrhosis,%	11 (11.6)	12 (14.3)	0.589	9 (10.7)	12 (14.3)	0.484

Table 2
Clinical outcomes after 48 weeks of treatment.

Variables	Total (n = 168)	ETV (n = 84)	TAF (n = 84)	Z/χ^2/t	*P*
DNA,log10 IU/mL	1.30 (1.30,1.75)	1.30 (1.30,1.90)	1.30 (1.30,1.68)	−0.778	0.436
HBsAg, log10 IU/mL	3.23 (2.76,3.60)	3.23 (2.83,3.52)	3.25 (2.71,3.67)	0.070	0.944
HBeAg, positive%	73 (52.6)	41 (53.9)	39 (51.3)	0.106	0.745
Total bilirubin, μmol/L	14.7 (11.0,19.0)	14.9 (10.8,19.0)	14.5 (11.0,19.1)	−0.086	0.932
Serum albumin, g/dL	45.6 (43.7,47.1)	45.9 (44.1,47.6)	45.3 (43.0,47.0)	−1.350	0.177
ALT, U/L	23.1 (17.1,33.2)	22.8 (16.9,31.5)	23.8 (18.0,34.7)	0.722	0.470
AST, U/L	24.0 (19.3,29.9)	25.0 (19.7,31.2)	23.6 (19.0,28.9)	−1.015	0.310
TG, mmol/L	1.23 (1.00,1.67)	1.20 (0.99,1.51)	1.36 (1.02,1.88)	1.886	0.059
BUN, mmol/L	4.38 (3.76,4.97)	4.41 (3.86,4.94)	4.35 (3.73,5.11)	−0.151	0.880
Serum creatinine, μmol/L	68.69 ± 13.46	70.72 ± 13.45	66.67 ± 13.24	1.970	0.051
eGFR, mL/min/1.73 m^2	113.2 (102.1,120.0)	111.0 (98.9,118.2)	115.9 (107.1,121.5)	2.430	0.015
PLT, 10^9/L	198 ± 56	193 ± 58	203 ± 54	−1.180	0.240
LSM, kPa	6.5 (5.4,8.1)	6.6 (5.2,8.2)	6.4 (5.5,8.0)	0.008	0.994
Liver cirrhosis,%	24 (14.3)	12 (14.3)	12 (14.3)	0.001	1.000

81.47 ± 11.36 μmol/L; p = 0.028), while eGFR was significantly decreased (96.99 ± 6.53 vs. 83.60 ± 5.45 mL/min/1.73 m^2; p = 0.028). Following the switch from ETV to TAF at week 48, serum creatinine level was decreased (81.47 ± 11.36 vs. 74.9 ± 10.67 μmol/L; p = 0.046), and eGFR was significantly improved (83.60 ± 5.45 vs. 93.39 ± 9.88 mL/min/1.73 m^2; p = 0.031) between week 48 to 60. However, no statistically significant changes in serum creatinine level or eGFR were observed between week 60 to 72 (all $p > 0.05$) (Fig. 2a; 2c). No statistically significant differences in renal function were observed between the ETV-continued and TAF-continued group during follow-up period.

Notably, after switching from ETV to TAF, serum creatinine levels decreased, and the difference in creatinine levels (Δcreatinine) was more pronounced compared to during ETV treatment (p = 0.0313, Wilcoxon signed rank test; Fig. 2b), and eGFR levels increased, the difference in eGFR levels (ΔeGFR) was more pronounced compared to during ETV treatment (p = 0.0313, Wilcoxon signed rank test; Fig. 2d).

Table 3
Risk factor analysis for renal abnormality* at week 48.

	Univariable analysis		Multivariable analysis	
	Odds ratio (95 %CI)	*P*	Odds ratio (95 %CI)	*P*
Age (years)	1.058 (1.011∼1.107)	0.015	0.977 (0.911∼1.047)	0.506
Male sex	0.233 (0.071∼0.762)	0.016	0.091 (0.016∼0.511)	0.006
Baseline eGFR	0.885 (0.830∼0.945)	<0.001	0.867 (0.795∼0.945)	0.001
Drug (TAF/ETV)	0.256 (0.070∼0.942)	0.040	0.206 (0.043∼0.981)	0.047

* Renal abnormality, eGFR<90 mL/min/1.73 m^2

3.5. Dynamic changes of HBV DNA levels under NA combination treatment

At week 0, 48, 60, and 72, the median HBV-DNA ($\log_{10}$ IU/ml) in the ETV + TAF combination group was 8.08 (IQR 7.68-8.23), 2.44 (IQR 2.22-2.88), 2.14 (IQR 1.84-2.21), 1.30 (IQR 1.30-1.30), respectively. In the TAF + ETV combination group, the median HBV-DNA levels ($\log_{10}$ IU/ml) were 7.72 (IQR 7.43-8.23), 2.38 (IQR 2.12-2.45), 2.12 (IQR 1.46-3.00), and 1.43 (IQR 1.30-2.23) at the same time points. For the ETV-continued group, the median HBV-DNA levels ($\log_{10}$ IU/ml) at week 0, 48, 60, and 72 were 4.55 (IQR 3.28-6.36), 1.30 (IQR 1.30-1.30), 1.30 (IQR 1.30-1.30), and 1.30 (IQR 1.30-1.30). Similarly, in the TAF-continued group, the median HBV-DNA ($\log_{10}$ IU/ml) at the same intervals was 4.54 (IQR 3.20-7.43), 1.30 (IQR 1.30-1.30), 1.30 (IQR 1.30-1.30), and 1.30 (IQR 1.30-1.30), respectively (Fig. 3a).

The percentage of patients with low-level viremia (LLV) throughout the study was presented in Fig. 3b. At week 48, the incidence of LLV was 19.0 % in the ETV groups and 16.7 % in the TAF group ($p > 0.05$). Among the groups, LLV is sustained by 5 out of 67 patients (7.5 %) in the ETV-continued group, 9 out of 79 patients (11.4 %) in

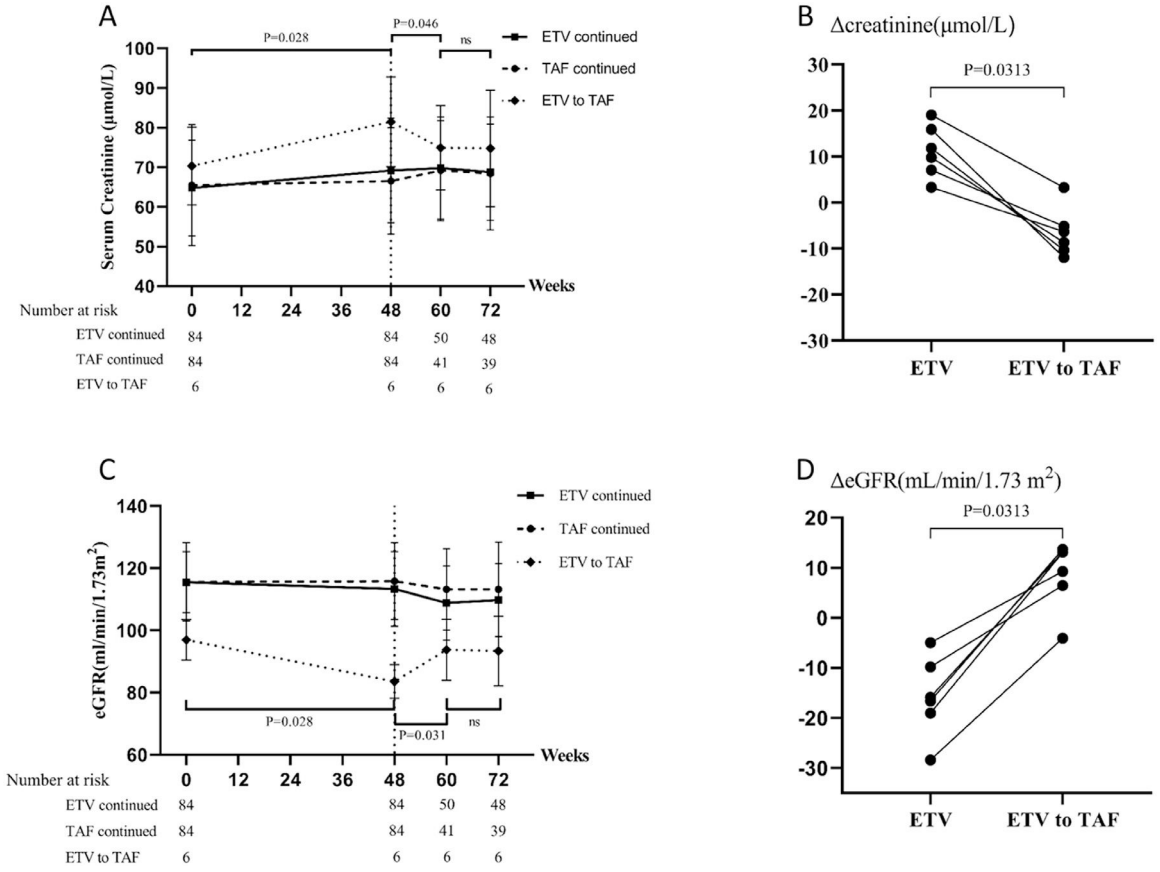

Fig. 2. Renal function in patients who switched from entecavir (ETV) to tenofovir alafenamide fumarate (TAF) from baseline to 72 weeks. (A) serum creatinine levels and (C) Estimated glomerular filtration rate (eGFR) at baseline, 48, 60, and 72 weeks by ETV or TAF therapy. The points and error bars represent the median values and quartiles (Q1 and Q3). (B) Changes in serum creatinine level and (D) changes in eGFR during the 48-week ETV treatment period and the 12-week TAF treatment period in patients who switched from ETV to TAF. The comparisons of changes in serum creatinine levels and eGFR were compared within the same patients. ns, no significance.

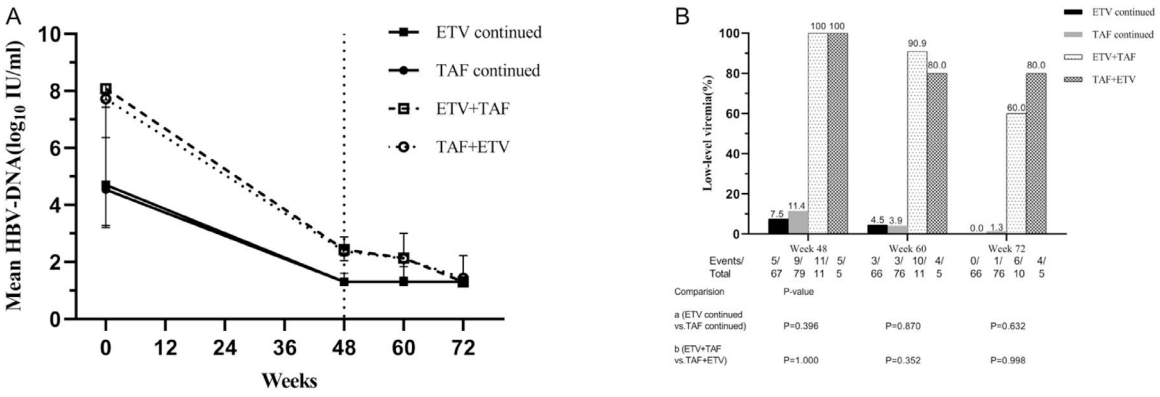

Fig. 3. The change in HBV-DNA and the rate of low-level viremia throughout the study. (A) the change of HBV-DNA level after combination therapy. (B) the rate of low-level viremia after combination therapy. The number of patients with the event/total patients is shown below the bar chart. "a" ETV continued versus TAF continued; "b" ETV + TAF versus TAF + ETV. LLV, low-level viremia.

the TAF-continued group, 11 in the ETV + TAF combination group, and 5 in the TAF + ETV combination group. Pairwise comparisons showed that there was no significant difference in the percentage of LLV between the ETV-continued group and the TAF-continued group: 7.5 % vs. 11.4 % at week 48 (p = 0.396), 4.5 % vs. 3.9 % at week 60 (p = 0.870), and 0.0 % vs. 1.3 % at week 72 (p = 0.632). Similarly, there was no significant difference in the percentage of LLV between the ETV + TAF combination group and the TAF + ETV combination group: 90.9 % vs. 80.0 % at week 60 (p = 0.352), and 60.0 % vs. 80.0 % at week 72 (p = 0.998) (Fig. 3b). Notably, 28 out of the 29 LLV patients were HBeAg positive.

3.6. Longitudinal changes in ALT level and ALT normalization

At baseline and 48 weeks of TAF treatment, the median ALT levels were 50.0 U/L and 22.8 U/L; for ETV treatment, the median ALT levels at baseline and 48 weeks were 46.2 U/L and 23.8 U/L, respectively (Tables 1 and 2). There was no significant difference between the ETV and TAF group at either baseline or 48 weeks (p = 0.730; p = 0.470) (Table S1). Notably, the median ALT in the TAF group was statistically lower at 48 weeks compared to baseline (22.8 U/L vs. 50.0 U/L; $p < 0.001$). Similarly, the ALT level in the ETV group showed a comparable reduction (23.8 U/L vs. 46.2 U/L; $p < 0.001$) (Table S1).

Regarding ALT normalization at different time points, no significant differences were observed between the TAF group and ETV groups at baseline (44.0 % vs. 41.7 %; $p > 0.05$) or at 48 weeks (83.3 % vs. 83.3 %; $p > 0.05$) (Figure S1). However, after 48 weeks of TAF or ETV treatment, the ALT normalization rate increased compared to baseline (for the TAF group, from 44.0 % to 83.3 %; for the ETV group, from 41.7 % to 83.3 %; all $p < 0.001$) (Figure S1).

Additionally, when patients were switched from ETV to TAF at 48 weeks due to eGFR abnormalities, the median ALT level at 48, 60, and 72 weeks of TAF treatment were 19.5 U/L, 14.4 U/L, 15.8 U/L, respectively. There was no significantly difference in the median ALT level at 48 weeks compared to those at 60 weeks (19.5 U/L vs. 14.4 U/L; $p = 0.14$) or at 72 weeks (19.5 U/L vs. 15.8 U/L; $p = 0.24$) (Table S2).

4. Discussion

The recommended course of treatment for chronic hepatitis B is long-term usage of strong nucleotide analogs such as ETV, TDF, or TAF [7,12,13]. The effect of these medications on kidney function must also be taken into consideration, as this has been recognized as a clinical problem [18]. In high-risk patients, the guidelines advise using less nephrotoxic drugs, including ETV or TAF, rather than TDF [7,19]. Due to possible differences in renal effects brought on by different drug metabolic pathways [20], the renal safety of ETV and TAF is a clinical concern.

In this study, we assessed the renal outcomes of CHB patients receiving 48 weeks of ETV or TAF treatment. During the 48 weeks following ETV or TAF treatment, serum creatinine levels increased and eGFR decreased. At week 48, there was a statistically significant difference in eGFR between the TAF and ETV groups, but no such difference was found in serum creatinine level. This result aligned with a previous retrospective analysis conducted by Jung et al. [14], which included 1988 individuals with CHB who had not received prior treatment. Patients with diabetes mellitus and hypertension-conditions associated with renal function deterioration-were excluded from our study. Interestingly, our findings differed from earlier study, which showed that TAF and ETV treatment had comparable effects on renal function [21,22]. These discrepancies may stem from different definitions of renal abnormalities or differences in the baseline stages of chronic kidney. Thus, eGFR is more sensitive than serum creatinine as an indicator of renal function. Based on these findings, patients undergoing ETV treatment should have regular closer monitoring of eGFR, compared to those receiving TAF treatment.

Renal function at week 48 was found to be independently influenced by gender, baseline eGFR, and treatment regimen (ETV/TAF). When Lim et al. [23] assessed risk factors for eGFR declines greater than 20 %, the findings indicated that female was a significant risk factor for renal insufficiency. Similarly, Ogawa et al. [24] demonstrated that patients with CKD had a significantly higher risk of eGFR decline than patients without CKD, and the differences in the slope coefficient of eGFR between the two groups were significant. Furthermore, Gish et al. [25] found that eGFR decrease was associated with pre-existing renal inadequacy during ETV treatment, suggesting that low baseline eGFR is a significant predictor of eGFR decline. Using both univariate and multivariate analysis, we assessed renal function at week 48 between eGFR $\geq$ 90 mL/min/1.73 m^2 and eGFR < 90 mL/min/1.73 m^2. Our study verified that at week 48, baseline eGFR, treatment regimen (TAF/ETV), and female were significant risk factors for eGFR abnormalities. Early detection and intervention are crucial to mitigate or delay adverse outcomes caused by renal impairment. Thus, patients who are female, receiving ETV treatment, or have lower baseline eGFR levels should all be closely monitored for the potential of eGFR impact.

There are different opinions about the safety of switching from ETV to TAF in terms of renal function [24,26,27]. According to AASLD guidelines and the European Association for the Study of the Liver (EASL), patients with eGFR is less than 60 mL/min/1.73 m^2 should switch to TAF or ETV [7,19]. However, patients with CKD stage 2 (range of 60–89 mL/min/1.73 m^2) receiving ETV treatment have not been given enough attention. According to Jung et al. [14], there is a statistically significant difference in eGFR between ETV and TAF treatment at week 48, with ETV treatment further worsening renal function. Consequently, patients in our study were switched from ETV to TAF when renal abnormality (eGFR < 90 mL/min/1.73 m^2) were observed at week 48. Although the eGFR level at week 60 remained below the baseline eGFR, it was shown that patients with CKD stage 2 who switched from the ETV to TAF regimen showed a significantly improvements in eGFR during the 48–60 week. However, the changes in eGFR were minimal during the 60–72 week period. These findings suggest that, an early switch to TAF may benefit stage 2 CKD patients receiving ETV by preventing further renal deterioration. In addition, Hur et al [28] developed and validated a Machine Learning Model that can provide tailored treatment options for each patient with chronic hepatitis B, indicating a highly crucial role for machine learning models in individualized medication selection. We will expand the dataset of cases, then develop and validate machine learning models to facilitate the precise selection of optimal antiviral drugs for CHB patients with different levels of renal function, further validating our findings.

Another issue for patients on long-term NA treatment is LLV. Currently, 10–30 % of CHB patients who had received NAs treatment fail to achieve viral response within 48 weeks [29,30]. In our study, the effectiveness of ETV and TAF for CHB patients over 48 weeks was retrospectively evaluated (19.0 % vs. 16.7 %; $p > 0.05$). We found that the incidence of low-level viremia was comparable between the two groups. After treatment modification, no significant difference was observed in LLV rates between the ETV continued group and the TAF continued group at 72 weeks (0 % vs. 1.3 %; $p = 0.632$). Similarly, there was no significant difference in the percentage of LLV between the ETV + TAF combination group and the TAF + ETV combination group (60 % vs. 80 %; $p = 0.998$). It is noteworthy that monotherapy (the ETV or TAF continued groups) seems to produce a more favorable viral response than combination groups (the ETV + TAF or TAF + ETV combination groups), as lower HBV-DNA level were observed in the monotherapy group at week 48 (Fig. 3a), which was found to be slightly higher than 20 IU/ml. Furthermore, among the 29 LLV patients, 28 are HBeAg positive. This highlights the risk of LLV in CHB patients with high viral loads and HBeAg positivity, emphasizing the need for prolonged treatment to achieve complete virological response.

Our study has several limitations. First of all, the analysis might have been impacted by possible biases and confounders because it was a retrospective single-center study that relied on observational data. Secondly, only serum creatinine and eGFR were assessed as markers of renal function, given the study's retrospective design. Incorporating additional indicators on kidney tubular damage, such as NAG, α1-MG, and β2-MG, would have improved the robustness of the results, given the nephrotoxic consequences of long-term NAs therapy in CHB patients, which largely manifest as kidney tubular toxicity. Thirdly, further research is necessary given the very limited number of patients who transition from ETV to TAF in our study.

5. Conclusions

In summary, there was a significant difference in eGFR between ETV and TAF treatments at week 48, and gender, baseline eGFR, and treatment regimen (TAF/ETV) were identified as risk factors for eGFR abnormalities. Patients with CKD stage 2 undergoing ETV treatment experienced significant improvements in renal function after switching to TAF.

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Declaration of interests

None.

CRediT authorship contribution statement

Liang Wang: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Shipeng Ma:** Data curation, Writing – original draft. **Lajpat Rai Malhi:** Writing – review & editing. **Xiaoping Wu:** Resources, Writing – review & editing. **Liping Liu:** Data curation. **Xin Wan:** Data curation. **Yuliang Zhang:** Data curation. **Xiaopeng Li:** Resources. **Shanfei Ge:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2025.101925.

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