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ORIGINAL RESEARCH

# Effect of Entecavir, Tenofovir Disoproxil Fumarate, and Tenofovir Alafenamideantiviral Therapy on Renal Function in Chronic Hepatitis B Patients: A Real-World Retrospective Study

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**Background:** Entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide(TAF) are first-line nucleos(t)ide analogs (NUCs) with chronic hepatitis B (CHB). This study aimed to assess the renal safety profile in NUC-experienced CHB patients who received ETV, TDF or TAF therapy.

**Methods:** This retrospective observational cohort study investigated factors related to renal function in 154 patients with NUC-experienced CHB who received ETV, TDF, and TAF therapy for 48 weeks. Changes in UREA, uric acid (UA), creatinine (Cr), and estimated glomerular filtration rate (eGFR) were analyzed using a one-way analysis of variance. A linear mixed-effects model for repeated measures was used to evaluate the correlation between baseline information and eGFR changes 48 weeks following treatment initiation. The model considered sex, baseline age, viral load, aminotransferases, renal function, and treatment group as fixed effects, and incorporated random effects for individual subjects.

**Results:** There were no significant differences in UA or Cr levels during therapy over time. The eGFR level was elevated in ETV-treated patients (117.5 ± 16.65 mL/min/1.7m$^2$ vs 109.8 ± 15.69 mL/min/1.7m$^2$, $P$=0.027), whereas it did not change significantly in TDF- (123.6 ± 28.54 mL/min/1.7m$^2$ vs 115.5 ± 20.44 mL/min/1.7m$^2$, $P$=0.070) and TAF-treated (121.6 ± 23.44 mL/min/1.7m$^2$ vs 113.4 ± 16.90 mL/min/1.7m$^2$, $P$=0.053) patients. Younger patients (<30 years) and those with higher HBV DNA (> 7 $\log_{10}$IU/mL) and lower alanine aminotransferase levels (<5 × upper limit of normal) showed a significant improvement in eGFR elevation during NUCs therapy. The linear mixed-effects model showed that the baseline HBV DNA level was an important positive predictor of eGFR elevation at 48 weeks following treatment initiation (estimate was 1.437 and 2.449, $P$<0.001).

**Conclusion:** In real-life experience, ETV, TDF, and TAF therapy may not be associated with eGFR changes in NUC-experienced CHB patients without baseline renal impairment.

**Keywords:** chronic hepatitis B, nucleos(t)ide analogs, antiviral, renal function, linear mixed-effects model

## Introduction

Hepatitis B virus (HBV) infection is a major global health problem that causes a wide spectrum of liver diseases and high mortality all over the world.[1] According to 2019 global estimates, 296 million patients had chronic hepatitis B (CHB) and 820,00 people had died, mostly from decompensated liver cirrhosis and hepatocellular carcinoma (HCC).[2] In China, deaths from total liver disease due to HBV infection decreased by 29.13%, from 229,000 in 2016 to 162,000 in 2019, and the age-standardized mortality rate decreased by 4.92% per year during this period.[3] However, China still faces challenges in achieving the World Health Organization's goal of eliminating viral hepatitis as a public threat by 2030.[4]

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Oral nucleos(t)ide analogs (NUCs) are preferred for CHB treatment, contributing to the suppression of viral replication and reduction in the risk of end-stage liver diseases.[5,6] Three first-line NUCs include entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF), as recommended by the several major guidelines,[7–9] owing to the effectiveness of virological inhibition and the high genetic barrier to resistance.[10] For CHB patients who did not received first-line NUCs therapy, HBV DNA should be regularly monitored for detecting virological breakthroughs, low viremia, poor response, or resistant to provide rescue treatment as soon as possible.[8]

Hepatitis virus infection always has extrahepatic manifestations such as nephropathy.[11] CHB is closely related to chronic kidney disease (CKD).[12,13] Membranous nephropathy and mesangiocapillary glomerulonephritis have been reported as potential underlying causes of renal dysfunction in CHB patients.[14,15] Administration of antiviral drugs could improve HBV-mediated renal disease, probably through inhibition of viral replication and elimination of immune complex deposition in the kidney.[16] Renal excretion of unchanged drugs is the primary route for NUC elimination.[17] NUCs can induce renal tubular injury, apoptosis, and mitochondrial toxicity, leading to kidney toxicity.[18] History of diabetes, hypertension, and baseline renal dysfunction are considered as the risk factors for nephrotoxicity during NUC treatment.[19] Thus, the renal safety profile is an important factor in choosing appropriate NUCs for the treatment of CHB, particularly in patients who have a high risk of renal dysfunction or have already suffered kidney impairment.[13,17,19]

The present study aimed to assess the potential renal safety profiles associated with the administration of ETV, TDF, and TAF, and provide clinical perspectives on these first-line antiviral drugs in the treatment of NUC-experienced CHB patients.

# Methods

## Patients and Study Design

This was a retrospective, observational cohort study. The community-based population study in China showed that the overall prevalence of CKD was 11.3% with at least one indicator of kidney damage.[20] The incidence of renal impairment in CHB patients who receiving NUCs therapy was 34.7%.[21,22] The two-sided confidence level was set as 95%, while the power was set as 80%. The sample size should be 43 cases in each group using PASS11.0 software calculation. The study conformed to the guidelines of the Declaration of Helsinki and principles of good clinical practice. The protocol was reviewed and approved by the Ethics Committee of Shaanxi Provincial People's Hospital (No. 2017019). The Ethics Committee of Shaanxi Provincial People's Hospital waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this was a retrospective study, and only characteristics and laboratory indicators were collected. We used an anonymized database for all analyses, and all potentially identifying variables were removed. Clinical data were collected in July 2022. Consecutive patients with newly diagnosed CHB were recruited for the study. The inclusion criteria were: (1) a diagnosis of CHB according to the Chinese National Program for Prevention and Treatment of Viral Hepatitis standard; (2) being positive for HBsAg for more than 6 months; (3) an HBV DNA level of >2000 IU/mL; (4) an elevated ALT level of more than twice the upper limit of normal (ULN); and (5) being treatment-naïve for NUCs or IFNs for at least six months before enrollment but previously treated with lamivudine (LAM), adefovir (ADV), or telbivudine (LdT) for more than six months. The exclusion criteria were as follows: (1) co-infection with other hepatitis viruses or human immunodeficiency virus (HIV); (2) concurrent decompensated liver cirrhosis (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, etc), liver failure, or HCC; (3) concurrent autoimmune diseases, solid cancer, or leukemia; and (4) concurrent alcoholism or drug addiction. Patients received ETV (0.5 mg) orally once daily, TDF (300 mg, orally once daily), or TAF (25 mg, orally once daily) monotherapy at a single unit in the Shaanxi Provincial People's Hospital based on preference and economic condition. All patients enrolled in this cohort underwent follow-up evaluations at baseline and at 12, 24, and 48 weeks of therapy. Virological and biochemical assessments were performed during the routine examination at every visit.

## Virological and Biochemical Assessment

Serum HBV DNA was quantified using a real-time polymerase chain reaction kit (Roche COBAS TaqMan; Roche Molecular Systems, Branchburg, NJ, USA), with a detection limit threshold of 20 IU/mL. Hepatitis B surface antigen (HBsAg), hepatitis Be antigen (HBeAg), and anti-HBe were quantified by the HBsAg, HBeAg, and anti-HBe reagent kit (Roche Molecular Systems, Branchburg, NJ, USA). Serum biochemical assessments, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), UREA, uric acid (UA), and creatinine (Cr), were performed using a biochemical auto-analyzer (Roche Cobas 8000; Roche Diagnostics GmbH, Mannheim, Germany) in the Department of Laboratory Medicine, Shaanxi Provincial People's Hospital. Virological response (VR) was defined as an undetectable serum HBV DNA level at 48 weeks of therapy. Biochemical response (BR) was defined as the normalization of the ALT level at 48 weeks of therapy.

## Renal Function Evaluation

The estimated glomerular filtration rate (eGFR) was estimated by either modification of diet in renal disease (MDRD) calculation[23] or chronic kidney disease epidemiology collaboration (CKD EPI)[24] based on age, sex, and Cr level.

## Statistical Analysis

SPSS software (version 23.0) was used to generate randomized subject sequences. Categorical data are presented as n (%), and statistical significance was determined using the chi-square test. Continuous data with normal distributions were presented as mean ± standard deviation, and statistical significance was determined using one-way analysis of variance (ANOVA) followed by Tukey's test. Continuous data with skewed distributions were presented as medians (interquartile range: first and third quartiles), and statistical significance was determined using the Kruskal–Wallis *H*-test. To evaluate the association between several variables and eGFR changes over time, a linear mixed-effects model for repeated measures was used in SAS 9.4, using the MIXED procedure. The model considered sex, age, history of type 2 diabetes mellitus (T2DM), HBV DNA, ALT, AST, UREA, UA, Cr, and treatment groups as fixed effects and incorporated random effects for individual subjects.

# Results

## Demographic and Baseline Characteristics of Enrolled Patients

A total of 154 patients with CHB were enrolled in this study, including 45 who had received ETV therapy, 62 who had received TDF therapy, and 47 who had received TAF therapy. The baseline demographic and clinical characteristics of the three groups were similar and are summarized in Table 1. There were no significant differences in age, sex ratio, or virological and biochemical baseline characteristics among the three groups. Seventeen patients (11.04%) had a history of T2DM and had undergone insulin therapy (Table 1). Based on the MDRD formula, ten patients (five in the ETV treatment group, four in the TDF treatment group, and one in the TAF treatment group) showed an eGFR level of less than 90 mL/min/1.73m$^2$. Based on the CKD EPI formula, three patients in the ETV treatment group had an eGFR level of less than 90 mL/min/1.73m$^2$. None of the patients had a baseline eGFR level of less than 60 mL/min/1.73m$^2$.

## Virological, Biochemical, and Serological Response

HBV DNA levels decrease in patients receiving antiviral therapy. The proportion of VR at 48 weeks of therapy in the ETV, TDF, and TAF treatment groups was 82.22% (37/45), 88.71% (55/62), and 91.49% (43/47), respectively. There were no significant differences in VR percentage among the groups ($P$=0.467; Figure 1A). Patients who did not achieve VR after 48 weeks of therapy showed lower levels of viremia (an HBV DNA level of <2000 IU/mL). The proportion of BR at 48 weeks of therapy in the ETV, TDF, and TAF treatment groups was 86.66% (39/45), 85.48% (53/62), and 85.10% (40/47), respectively. There were no significant differences in BR percentage among the three groups ($P$=0.919; Figure 1B). ALT levels were <2×UNL in CHB patients who did not achieve BR. However, none of the patients experienced HBsAg loss during therapy.

**Table 1** Baseline Characteristics of Enrolled Subjects

| | ETV | TDF | TAF | Statistical Value | *P* Value |
|---|---|---|---|---|---|
| Case (n) | 45 | 62 | 47 | – | – |
| Sex (Male/Female) | 32/13 | 50/12 | 36/9 | $\chi^2$=1.026 | 0.424 |
| Age (years) | 27.76 ± 8.43 | 26.81 ± 7.08 | 27.91 ± 6.91 | *F*=0.360 | 0.699 |
| History of T2DM (n, %) | 6 (13.33%) | 7 (11.29%) | 4 (8.51%) | $\chi^2$=0.873 | 0.772 |
| Previous NUCs strategy | | | | | |
| LAM (n) | 12 | 14 | 11 | – | – |
| ADV (n) | 17 | 18 | 7 | – | – |
| LdT (n) | 16 | 30 | 29 | – | – |
| HBV DNA ($log_{10}$IU/mL) | 7.86 ± 1.27 | 7.98 ± 1.12 | 7.55 ± 1.21 | *F*=1.800 | 0.169 |
| HBeAg positive (n, %) | 37 (82.22%) | 49 (79.03%) | 38 (80.85%) | $\chi^2$=0.276 | 0.782 |
| ALT (IU/L) | 137 (86, 230) | 198 (86, 275) | 123 (82, 199) | *H*=1.397 | 0.497 |
| AST (IU/L) | 93 (65, 124) | 82 (50, 141) | 70 (51, 115) | *H*=2.469 | 0.291 |
| UREA (mmol/L) | 4.48 ± 0.93 | 4.71 ± 1.15 | 4.60 ± 1.01 | *F*=0.635 | 0.531 |
| UA (μmol/L) | 282.2 ± 67.59 | 286.1 ± 82.80 | 281.1 ± 63.89 | *F*=0.071 | 0.931 |
| Cr (μmol/L) | 74.19 ± 11.28 | 73.60 ± 11.69 | 73.66 ± 10.08 | *F*=0.042 | 0.959 |
| eGFR MDRD (mL/min/1.73m$^2$) | 109.8 ± 15.69 | 115.5 ± 20.44 | 113.4 ± 16.90 | *F*=1.262 | 0.286 |
| eGFR CKD-EPI (mL/min/1.73m$^2$) | 113.7 ± 12.01 | 116.9 ± 11.47 | 115.7 ± 10.41 | *F*=1.062 | 0.348 |

## Maintenance of Renal Function in Response to Different Antiviral Therapies for CHB Patients

UREA levels increased at 24 and 48 weeks of therapy in CHB patients receiving ETV and TDF therapy ($P<0.05$, Figure 2A), but there was no significant difference in UREA levels during TAF therapy over time ($P=0.521$, Figure 2A). There were no remarkable differences in either UA or Cr levels over time ($P>0.05$, Figure 2B and C). Based on the MDRD formula, the eGFR level did not significantly change at 12 and 24 weeks of therapy in any of the treatment groups ($P>0.05$, Figure 2D). The eGFR MDRD level in ETV-treated CHB patients increased after 48 weeks of therapy (117.5 ± 16.65 mL/min/1.7m$^2$) when compared with baseline ($P=0.027$, Figure 2D). The eGFR MDRD level was also elevated in TDF-treated patients (+8.13 mL/min/1.73m$^2$) and TAF-treated patients (+8.20 mL/min/1.73m$^2$) after 48 weeks of therapy, but these differences failed to achieve statistical significance ($P=0.070$ and 0.053, respectively, Figure 2D). Four patients who had received ETV therapy had eGFR MDRD levels of less than 90 mL/min/1.73m$^2$; their baseline eGFR MDRD level was also reduced. One patient with TDF therapy, whose baseline eGFR MDRD level was normal, showed a significant eGFR MDRD reduction after 48 weeks of therapy. Based on the CKD EPI formula, the eGFR CKD EPI level was increased in ETV-treated CHB patients after 48 weeks of therapy when compared with baseline (+4.94 mL/min/1.73m$^2$), but this difference just missed statistical significance ($P=0.051$, Figure 2E). There was

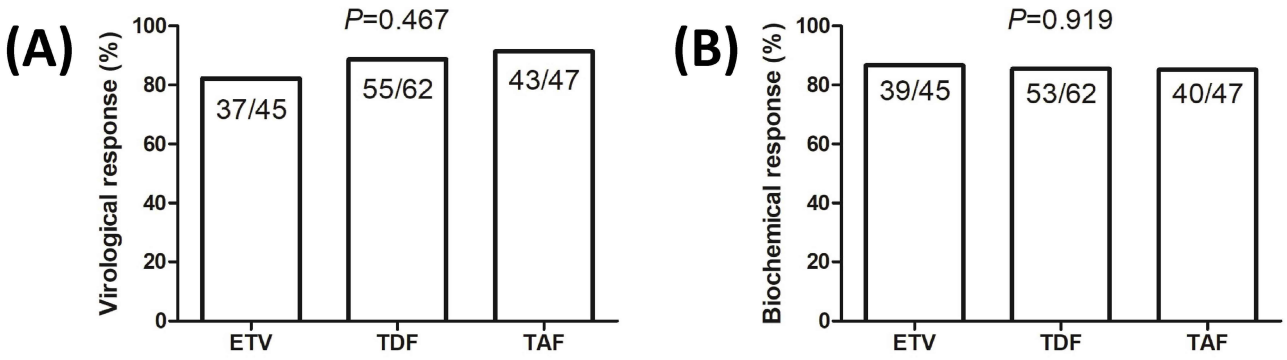


**Figure 1** The rates of virological and biochemical response to antiviral therapy at 48 weeks of therapy. (**A**) Rate of virological response (undetectable HBV DNA) at 48 weeks of therapy. (**B**) Rate of biochemical response (ALT normalization) at 48 weeks of therapy. Statistical analysis was performed using Chi-squared test.

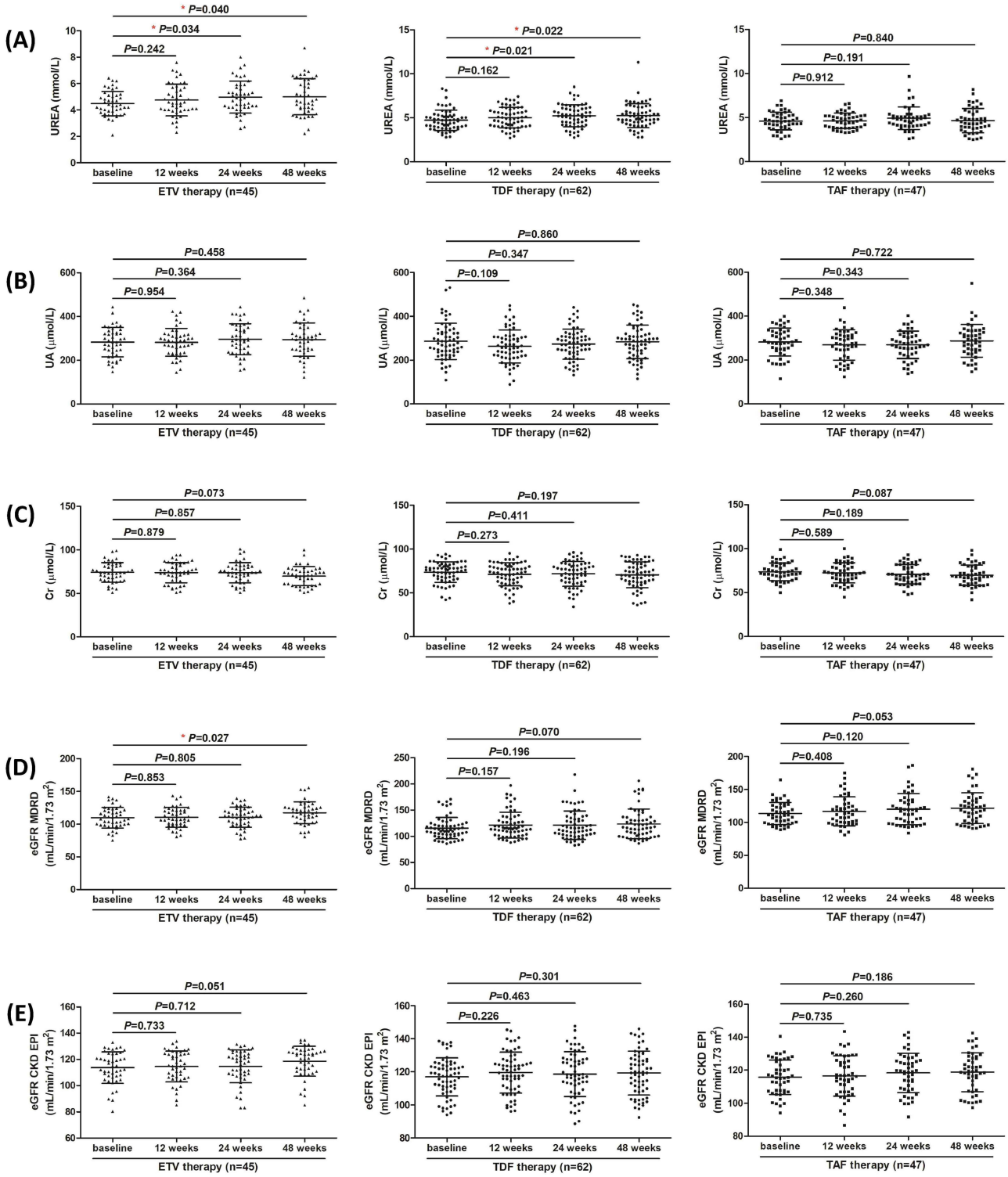


**Figure 2** Evolution of renal function by antiviral therapy over 48 weeks. (**A**) Change of UREA in ETV, TDF, and TAF therapy. (**B**) Change of UA in ETV, TDF, and TAF therapy. (**C**) Change of Cr in ETV, TDF, and TAF therapy. (**D**) Change of eGFR MDRD in ETV, TDF, and TAF therapy. (**E**) Change of eGFR CKD PEI in ETV, TDF, and TAF therapy. Individual level for each value was shown. Statistical analysis was performed using one-way ANOVA followed by Tukey's test. * indicated $P<0.05$ between two groups.

no remarkable difference in eGFR CKD EPI levels between the TDF and TAF therapy groups over time ($P>0.05$, Figure 2E). One patient who had received ETV therapy, whose baseline eGFR CKD EPI level was less than 90 mL/min/1.73m$^2$, revealed a reduction in eGFR CKD EPI level after 48 weeks of therapy.


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## Predictors of Significant eGFR Change

UREA levels were significantly elevated at 24 and 48 weeks of therapy in male patients aged<30 years, with baseline HBV DNA levels of>7 $log_{10}$IU/mL, baseline ALT levels of >5×ULN, and no history of T2DM ($P$<0.05, Figure 3A). The UA levels did not change significantly among the different groups ($P$>0.05, Figure 3B). Cr levels were reduced at 48 weeks of therapy in male patients aged<30 years, with baseline HBV DNA levels of >7 $log_{10}$IU/mL, baseline ALT levels of <5×ULN, and no history of T2DM ($P$<0.05, Figure 3C). Importantly, eGFR levels were strongly increased after 48 weeks of therapy in patients aged<30 years, with baseline HBV DNA levels of >7 $log_{10}$IU/mL, baseline ALT levels of <5×ULN, and no history of T2DM based on both the MDRD and CKD EPI formulas ($P$<0.05, Figure 3D and E).

Moreover, we entered all variables as fixed effects and incorporated random effects into the linear mixed model to account for repeated measures. Although we found that eGFR increased at 48 weeks after ETV therapy, previous studies have demonstrated that ETV treatment was not associated with either improvement or deterioration of renal function in CHB patients.[25,26] Thus, ETV therapy was used as the reference for this model. The results from the MDRD and CKD EPI equations showed similar eGFR changes at 48 weeks of therapy. Changes in eGFR over time were not significantly associated with age, history of T2DM, or baseline ALT, AST, UREA, or UA levels ($P$>0.05, Table 2). Interestingly, baseline HBV DNA levels had a statistically significant positive influence on eGFR values over time ($P$<0.001, Table 2). Although male sex and baseline Cr levels were also shown to positively affect eGFR CKD EPI values over time ($P$<0.05,

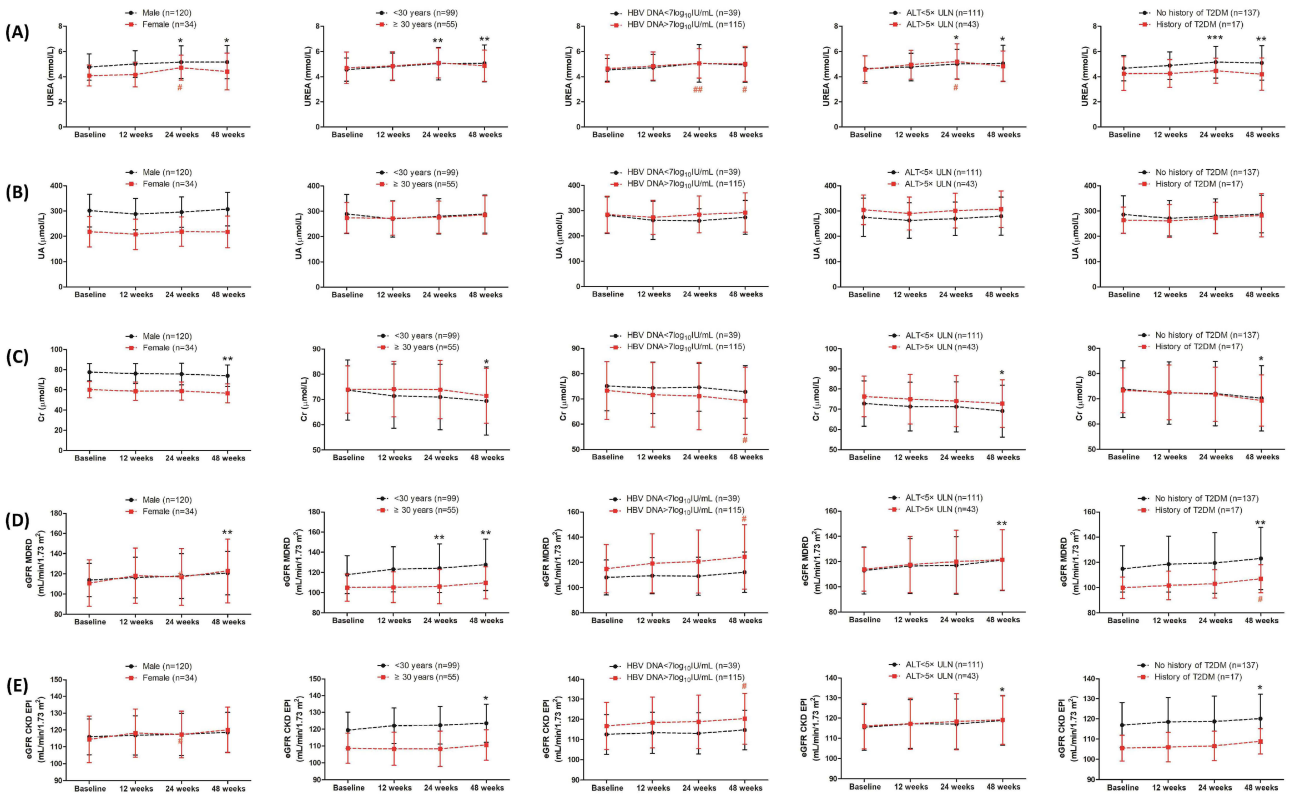


**Figure 3** Evolution of renal function by antiviral therapy over 48 weeks under different factors. (**A**) Changes of UREA between different sex, between different age (<30 years and ≥30 years), between different baseline HBV DNA (< 7$log_{10}$IU/mL and > 7$log_{10}$IU/mL), between baseline ALT (<5×ULN and>5×ULN), and between the history of T2DM (no history of T2DM and history of T2DM). (**B**) Changes of UA between different sex, between different age (<30 years and ≥30 years), between different baseline HBV DNA (< 7$log_{10}$IU/mL and > 7$log_{10}$IU/mL), between baseline ALT (<5×ULN and >5×ULN), and between the history of T2DM (no history of T2DM and history of T2DM). (**C**) Changes of Cr between different sex, between different age (<30 years and ≥30 years), between different baseline HBV DNA (< 7$log_{10}$IU/mL and > 7$log_{10}$IU/mL), between baseline ALT (<5×ULN and >5×ULN), and between the history of T2DM (no history of T2DM and history of T2DM). (**D**) Changes of eGFR MDRD between different sex, between different age (<30 years and ≥30 years), between different baseline HBV DNA (< 7$log_{10}$IU/mL and > 7$log_{10}$IU/mL), between baseline ALT (<5×ULN and >5×ULN), and between the history of T2DM (no history of T2DM and history of T2DM). (**E**) Changes of eGFR CKD EPI between different sex, between different age (<30 years and ≥30 years), between different baseline HBV DNA (< 7$log_{10}$IU/mL and > 7$log_{10}$IU/mL), and between baseline ALT (<5×ULN and >5×ULN), and between the history of T2DM (no history of T2DM and history of T2DM). Statistical analysis was performed using one-way ANOVA followed by Tukey's test. * and # indicated $P$<0.05 compared with baseline. ** and ## indicated $P$<0.01 compared with baseline. *** indicated $P$<0.001 compared with baseline.

**Table 2** Predictors for eGFR Changes from Baseline at 48 weeks of Therapy

| | eGFR MDRD | | | eGFR CKD EPI | | |
|---|---|---|---|---|---|---|
| | **Estimate** | **Standard Error** | ***P* Value** | **Estimate** | **Standard Error** | ***P* Value** |
| Male sex | 3.961 | 4.198 | 0.346 | 6.037 | 2.320 | 0.009 |
| Age | 0.204 | 0.142 | 0.151 | 0.100 | 0.087 | 0.251 |
| History of T2DM | 0.107 | 0.012 | 0.278 | 0.105 | 0.016 | 0.179 |
| HBV DNA (baseline) | 1.437 | 1.103 | 0.0002 | 2.449 | 1.731 | <0.0001 |
| ALT (baseline) | 0.013 | 0.013 | 0.331 | 0.006 | 0.008 | 0.501 |
| AST (baseline) | −0.016 | 0.013 | 0.233 | −0.008 | 0.009 | 0.380 |
| UREA (baseline) | −0.654 | 1.058 | 0.537 | −0.387 | 0.526 | 0.462 |
| UA (baseline) | 0.011 | 0.016 | 0.485 | 0.005 | 0.009 | 0.580 |
| Cr (baseline) | −0.020 | 0.121 | 0.869 | −0.263 | 0.077 | 0.0007 |
| TDF therapy | −2.076 | 2.905 | 0.475 | 1.881 | 1.405 | 0.181 |
| TAF therapy | −1.129 | 2.710 | 0.677 | 0.577 | 1.577 | 0.714 |

**Notes**: ETV therapy was set as reference.

Table 2), these predictors failed to achieve statistically significant differences in eGFR MDRD values ($P>0.05$, Table 2). Importantly, neither TDF nor TAF therapy were robustly related to eGFR changes over time ($P>0.05$; Table 2).

## Discussion

We conducted this retrospective cohort study to compare the influence of ETV, TDF, and TAF on the treatment of NUC-experienced CHB by assessing UREA, UA, Cr, and eGFR. We found that the efficacy of ETV, TDF, and TAF was similar during the 48 weeks of therapy in patients with CHB. It is well accepted that fluctuations in eGFR level (± 10 mL/min/1.73m$^2$) within the normal range are not clinically significant. Only ten patients had a lower baseline eGFR level based on the MDRD formula. eGFR level was significantly elevated in ETV-treated CHB patients but not in TDF- or TAF-treated patients. Younger patients and those with a higher baseline viral load and lower liver inflammation showed a remarkable improvement in eGFR elevation during therapy. The linear mixed-effects model demonstrated that the baseline HBV DNA level was an important positive predictor of eGFR elevation after 48 weeks of NUC therapy. The probable mechanism is that NUCs can not only rapidly inhibit viral replication, which is directly associated with chronic pathological injury in the kidney, but also eliminate the deposition of HBV antigen–antibody complexes in the kidneys of patients with higher baseline HBV DNA. However, neither TDF nor TAF therapy contributed to the eGFR changes over time. The current data indicate that first-line NUC antiviral therapy might not be associated with renoprotective or nephrotoxic effects in the treatment of NUC-treated CHB patients.

Treatment with CHB, irrespective of medication (including LAM, ADV, ETV, or TDF), seemed to result in a milder decrease in renal function.[27] In contrast, LdT therapy was associated with a sustained improvement in renal function in CHB patients and liver transplant recipients with HBV-related cirrhosis, particularly among patients with an increased risk of renal impairment.[28,29] However, the potential benefit of LdT on renal function does not outweigh its high rate of drug resistance or other adverse effects.[30] Thus, LAM, ADV, and LdT are not recommended as first-line anti-HBV agents. The first-line antiviral drugs ETV, TDF, and TAF showed similar effects for suppression of HBV replication and reduction of hepatitis B core-related antigen in CHB patients and HBV-associated acute-on-chronic liver failure.[31–33] The effects of ETV, TDF, and TAF in terms of the risk of cirrhosis-related complications, HCC, and orthotopic liver transplantation or mortality were statistically similar in treatment-naïve CHB patients.[31,34] Herein, we revealed similar results: ETV, TDF, and TAF showed comparable VR and BR rates after 48 weeks of therapy, indicating that the efficacy of the three first-line NUCs was similar during therapy in NUC-treated CHB patients. However, the renal safety profiles of ETV, TDF, and TAF are not fully understood.

Controversy remained regarding the influence of renal function in HBV-infected patients receiving ETV or TDF therapy. Zhang et al showed that eGFR remained stable in treatment-naïve CHB patients given ETV.[35] ETV treatment for HBV-infected patients with severe renal dysfunction, including those undergoing hemodialysis, was also effective and

did not affect renal function.[26] However, meta-analysis results revealed that both ETV and TDF therapy slightly reduced eGFR levels, but that TDF therapy might have a higher risk of renal damage in CHB and HBV-related cirrhosis.[19,36] Furthermore, CHB patients receiving TDF treatment experienced a more rapid decline in eGFR and a higher incidence of kidney dysfunction compared with those receiving ETV treatment.[37,38] TDF administration was also closely related to an increased risk of renal dysfunction compared with ETV in a Korean nationwide study.[39] In contrast, there was no evidence of a difference in rats or incidence of renal impairment during follow-up of TDF-treated and untreated CHB patients in a retrospective longitudinal study conducted in the UK.[40] Similarly, TDF was not associated with a higher risk of worsening renal function during short- or intermediate-term follow-up periods in patients without significant renal impairment in aUS cohort,[41] but a significant renal decline was found in TDF-treated patients with baseline renal impairment.[41,42] The present study included Chinese CHB patients who did not have severe renal dysfunction. We showed that, although UREA levels increased in CHB patients treated with ETV and TDF during the short-term (24-week) and intermediate-term (48-week) treatment periods, UA and Cr levels were not significantly affected by ETV or TDF treatment over time. Furthermore, eGFR level was elevated after 48 weeks of ETV therapy but did not change remarkably during TDF therapy. The linear mixed-effects model also showed that TDF is superfluous in relation to renal impairment during therapy. Thus, ETV and TDF may not be associated with nephrotoxicity in NUC-treated CHB patients without baseline kidney impairment. Rodriguez-Novoa et al found that TDF therapy was independently associated with altered retinol-binding protein levels, which serves as an important early biomarker for subclinical renal tubular damage.[43] Further investigation of retinol-binding protein levels during first-line antiviral therapy may be pivotal for the assessment of early renal impairment in CHB patients.

In this study, we analyzed the effect of TAF therapy on NUC-treated CHB patients without baseline renal impairment. TAF seemed to have less impact on renal function during intermediate-term therapy because there were no significant differences in all renal function indices (UREA, UA, Cr, and eGFR) between the visiting time points and baseline. The linear mixed-effects model also revealed that TAF is superfluous in relation to eGFR changes during therapy. Thus, TAF may not be associated with renoprotection or nephrotoxicity in NUC-treated CHB patients without baseline renal impairment.

Several factors contribute to the increased risk of renal dysfunction during antiviral therapy. Age and UEAR were significant negative predictive factors for eGFR changes in CHB patients irrespective of medication (adefovir, telbivudine, ETV, or IFNs).[35] Age, hypertension, diabetes mellitus, bilirubin level, pre-existing renal failure, and comorbidities were associated with decreased renal function during ETV and TDF treatment.[19,44,45] Pre-switch baseline eGFR was a significant predictor of changes in eGFR in HIV-infected patients after switching from TDF to TAF.[46,47] We also analyzed potential predictors of renal function improvement during ETV, TDF, and TAF therapy. We found that CHB patients aged<30 years, with a baseline HBV DNA level of>7 $\log_{10}$IU/mL, a baseline ALT level of<5×ULN, and no history of T2DMshowed remarkable improvement in eGFR during ETV, TDF, and TAF therapy. In contrast, the linear mixed-effects model revealed that a higher baseline viral load predicted eGFR elevation at 48 weeks of therapy. Collectively, baseline HBV DNA level might be the most important positive predictor of eGFR change during first-line NUC treatment in NUC-experienced CHB patients without baseline renal dysfunction.

The current study had several limitations. Firstly, this was a retrospective study with a limited sample size in a real-world setting. Necroinflammatory or fibrotic findings were not recorded, although these patients did not have decompensated liver cirrhosis. Secondly, we also did not record other parameters that are important in the evaluation of renal function, such as proteinurine, proteinuria, urinary N-acetyl-β-glucosaminidase, retinol-binding protein, serum phosphate, or comorbidities. A large-scale prospective cohort study is required to confirm these findings. Thirdly, longer follow-up periods are needed because CHB treatment with NUCs is generally long-term or lifelong.

## Conclusion

In summary, our current findings provide evidence that ETV, TDF, and TAF therapy may not be associated with eGFR changes in NUC-experienced CHB patients without baseline renal impairment. Other factors, such as potential drug resistance sites and pharmacoeconomic evaluations, should be considered when selecting drugs for NUC-treated CHB patients.

## Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethical Approval

The study was reviewed and approved by the Ethics Committee of Shaanxi Provincial People's Hospital (No. 2017019) and was performed in compliance with the Declaration of Helsinki. Clinical data were collected in July 2022.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript.

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## Disclosure

The authors have no conflicts of interest to declare in this work.

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