

Renal safety of tenofovir and/or entecavir in patients with chronic HBV mono-infection

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Background: Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) are recommended as the first-line therapy for chronic hepatitis B (CHB) due to their genetic barrier to resistance and effectiveness of virological suppression. TDF and ETV may cause renal toxicity through various mechanisms such as renal tubular injury, apoptosis, and mitochondrial toxicity. The aims of the current review were to assess the potential renal toxicity associated with the use of TDF and ETV in patients infected with chronic hepatitis B virus (HBV) and to provide clinical perspectives on these two agents in the treatment of CHB.

Methods: A literature search of clinical studies published in PubMed and posted on ClinicalTrials.gov website was implemented to find studies evaluating the potential renal toxicity of TDF and ETV.

Results: Twenty-one studies were examined in this review. The TDF dose used in the studies was 245 or 300 mg/day and that of ETV was 0.5 or 1 mg/day. Based on the markers of renal function, patients treated with TDF were not more likely to show changes in renal function than those treated with ETV; however, the estimated glomerular filtration rates (eGFRs) of patients receiving TDF tended to be more clearly reduced than those of patients receiving ETV. The eGFRs of patients treated with TDF decreased in a time-dependent manner, whereas those of patients treated with ETV increased or decreased across various time points.

Conclusion: The data shown in this study suggest that use of TDF and ETV could be at least associated with reductions in renal function in patients with chronic HBV infection. However, various risk factors, such as pre-existing renal failure and comorbidities, are also associated with decreased renal function during the treatment of TDF and ETV. Thus, studies of management strategies for HBV-infected patients with these risk factors are necessary in the near future.

Keywords: hepatitis B, tenofovir, entecavir, renal safety

Introduction

Hepatitis B virus (HBV) infection is considered as one of the most important global public health concerns; this potentially life-threatening infection damages the liver and can contribute to acute and chronic diseases. An estimated 240 million individuals are chronically infected with HBV worldwide, and over 686,000 individuals die annually because of end-stage chronic hepatitis B (CHB) and CHB-associated complications such as decompensated cirrhosis and hepatocellular carcinoma.¹

Currently, two therapeutic options (ie, interferons [IFNs] and oral nucleos(t)ide analogs [NUCs]) are used to treat CHB; however, oral NUCs have been preferred for the treatment of CHB owing to their convenient regimen.² In particular, the second-generation NUCs, such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF), are recommended as the first-line therapy for CHB because of their high genetic barrier to resistance and effectiveness of virological suppression.^{3,4} The efficacy and safety

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of both these drugs were demonstrated through previous clinical trials.³ Safety should be particularly considered, since long-term treatment for CHB is usually required with ETV or TDF, although its ideal duration of treatment is not well determined.⁵

ETV and TDF may cause renal toxicity via various mechanisms such as renal tubular injury, apoptosis, and mitochondrial toxicity.^{5,6} Previous studies also reported an association between CHB and chronic kidney disease (CKD).⁷⁻¹¹ Specifically, it was reported that glomerular diseases, such as membranous nephropathy and mesangio-capillary glomerulonephritis, might be the underlying causes of renal dysfunction in patients with CHB.^{12,13} Moreover, drug history except for NUCs, disease status of diabetes and/or hypertension (HTN), and baseline (BL) kidney function before starting NUCs may affect the potential nephrotoxicity caused by ETV and/or TDF. Consequently, renal safety is an important factor in choosing appropriate NUCs for the treatment of CHB because they are renally eliminated in an unchanged form, and this is particularly important in patients who have already had renal impairment or are at risk for it.^{7,14}

The current review aimed to assess the potential renal toxicity associated with the use of ETV and TDF in patients infected with chronic HBV and to provide clinical perspectives on these two agents in the treatment of CHB.

Methods

A literature search was conducted to identify clinical studies in patients with HBV mono-infection, which assessed the safety of ETV and/or TDF. PubMed was searched from the inception of the database to March 2017, using “hepatitis B,” “entecavir,” and “tenofovir” as the search terms to find clinical trials written only in English. The reference lists of the selected articles and related reviews were utilized to find additional relevant articles. The data posted on ClinicalTrials.gov website were also used to identify the unpublished clinical outcomes. Two reviewers independently scanned the article titles and abstracts and identified relevant studies that met the following criteria: 1) retrospective or prospective clinical studies, 2) studies involving patients only with HBV infection, 3) studies in which ETV and/or TDF had to be administered for the treatment of HBV infection, and 4) studies whose results contained renal parameters, such as estimated glomerular filtration rate (eGFR), serum creatinine, and serum phosphorus, in order to evaluate the changes in renal function.

Results

Study characteristics

The literature search (Figure 1) identified 21 eligible studies that met the predetermined inclusion criteria. The main characteristics of the selected studies are presented in Table 1.

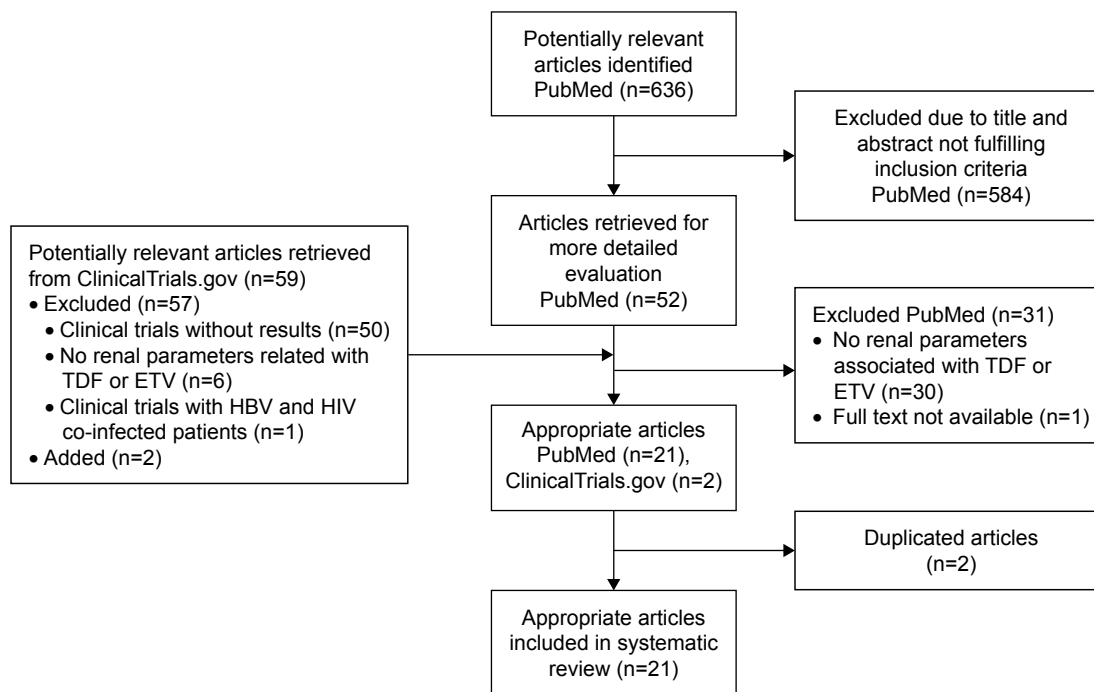


Figure 1 Flowchart of the study selection process.

Abbreviations: ETV, entecavir; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

Table 1 Main characteristics of included studies

Study	Sites	Study design	Sample size, n (M/F)	Gender, n (M/F)	Age, mean (SD) or median (range), years	Duration of follow-up, mean (SD) or median (range), months	HBV DNA at baseline, mean (SD or IQR) or median (range)	HBeAg-positive, n (%)	Status	Treatment regimens
Rivero-Barciela et al, 2017 ¹⁵	Spain	Observational study	611	Total: 444/167; TDF-containing: 305/119; ETV: 139/48	Total: 50 (13); TDF-containing: 50 (13); ETV: 50 (13)	TDF-containing: 49 (29); ETV: 55 (22)	Total: 4.0 (2.4) log ₁₀ IU/mL; TDF-containing: 3.8 (2.3) log ₁₀ IU/mL; ETV: 4.9 (2.4) log ₁₀ IU/mL	Total: 101 (16.5); TDF-containing: 67 (15.8); ETV: 34 (18.2)	TN, TE, cirrhosis	TDF: 245 mg/day; ETV: 0.5 or 1 mg/day
Koksal et al, 2016 ¹⁶	Turkey	Prospective cohort study	120	TDF: 19/25; ETV: 17/15; control: 21/23	TDF: 36 (29–43.7); ETV: 40 (27.2–46.5); control: 37.5 (29–42.2)	48	TDF: 6.8 (1.0) log ₁₀ IU/mL; ETV: 7.0 (1.2) log ₁₀ IU/mL; control: NR	TDF: 7 (15.9); ETV: 8 (25); control: NR	TN	NR
López Centeno et al, 2016 ¹⁷	Spain	Retrospective cohort study	64	TDF-containing: 25/7; ETV: 23/9	TDF-containing: 50.15 (16.17); ETV: 49.22 (15.26)	12	TDF-containing: 1,127.4 (19–2,463,121.4) copies/mL; ETV: 29,311.4 (376.2–4,660,135.2) copies/mL	TDF-containing: 13 (40.6); ETV: 5 (15.6)	TN, TE	NR
Rodríguez-Nóvoa et al, 2016 ³	Spain	Cross-sectional study	280	TDF: 38/31; ETV: 70/19; control: 58/64	TDF: 48 (12); ETV: 49 (12); control: 47 (10)	TDF: 35 (9); ETV: 43 (13)	NR	TDF: 6 (8.8); ETV: 11 (12.5); control: 2 (1.7)	TN	NR
Zoulim et al, 2016 ¹⁸	Poland, Germany, France, Italy, the Netherlands, Romania	Prospective clinical trial	92	TDF/ETV: 69/23	TDF/ETV: 43.6 (1.55) ^a	24	TDF/ETV: 4.4 (0.23) ^a log ₁₀ IU/mL	TDF/ETV: 56 (62.2)	TE	NR
Sripayoon et al, 2017 ¹⁹	Thailand	Randomized controlled trial	400	TDF: 113/87; ETV: 121/79	TDF: 41.2 (11.6); ETV: 41.6 (11.5)	36	TDF – HBeAg (+): 7.0 (1.4) log ₁₀ IU/mL – HBeAg (–): 5.0 (1.3) log ₁₀ IU/mL ETV – HBeAg (+): 7.1 (1.5) log ₁₀ IU/mL – HBeAg (–): 4.9 (1.3) log ₁₀ IU/mL	TDF: 92 (46.0); ETV: 95 (47.5)	TN	TDF: 300 mg/day; ETV: 0.5 mg/day
Tsai et al, 2016 ²⁰	Taiwan	Retrospective-prospective cohort study	141	Total: 108/33; TDF: 32/5; ETV: 46/16; LdT: 30/12	Total: 55.2 (12.2); TDF: 53.6 (12.6); ETV: 55.2 (11.5); LdT: 56.6 (12.9)	NR	Total: 6.3 (1.3) log ₁₀ copies/mL; TDF: 6.3 (1.3) log ₁₀ copies/mL; ETV: 6.4 (1.2) log ₁₀ copies/mL; LdT: 6.0 (1.4) log ₁₀ copies/mL	Total: 37 (26); TDF: 10 (27); ETV: 18 (29); LdT: 9 (21)	Cirrhosis	NR

(Continued)

Table 1 (Continued)

Study	Sites	Study design	Sample size, n (M/F)	Gender	Age, mean (SD) or median (range), years	Duration of follow-up, mean (SD) or median (range), months	HBV DNA at baseline, mean (SD or IQR) or median (range)	HBsAg positive, n (%)	Status	Treatment regimens
Park et al, 2016 ²¹	Korea	Prospective clinical trial	64	TDF/ETV: 52/12	TDF/ETV: 47 (9.8)	12	TDF/ETV: 4.29 (1.23) log ₁₀ IU/mL	TDF/ETV: 57 (89.1)	TE, MDR CHB	TDF: 300 mg/day; ETV: 1.0mg/day
Wang et al, 2016 ²²	Taiwan	Retrospective clinical trial	236	TDF - TN: 100/31 - TE: 83/22	TDF - TN: 48.9 (12.9) - TE: 48.9 (13.4)	38.5 (13-49)	TDF - TN: 6.9 (1.5) log ₁₀ copies/mL - TE: 6.2 (1.9) log ₁₀ copies/mL	TDF - TN: 42 (32.1) - TE: 51 (48.6)	TN, TE, cirrhosis	NR
Tsai et al, 2016 ²³	Taiwan	Retrospective cohort study	587	TDF: 121/49; ETV: 168/65; LdT: 132/52	TDF: 51.8 (11.9); ETV: 52.8 (12.4); LdT: 54.2 (14.6)	TDF: 12 (12-24); ETV: 36 (12-84); LdT: 36 (12-60)	TDF: 6.4 (1.9) log ₁₀ copies/mL; ETV: 6.2 (1.5) log ₁₀ copies/mL; LdT: 5.7 (1.8) log ₁₀ copies/mL	TDF: 39 (22.9); ETV: 61 (26.2); LdT: 33 (17.9)	TN, cirrhosis	NR
Koklu et al, 2015 ²⁴	Turkey	NR	857	TDF: 183/90; ETV: 197/85; LAM: 185/117	TDF: 47.74 (12.45); ETV: 49.86 (13.35); LAM: 49.21 (13.17)	24	TDF: 6.69 (1.79) log ₁₀ copies/mL; ETV: 6.54 (1.74) log ₁₀ copies/mL; LAM: 5.27 (1.63) log ₁₀ copies/mL	TDF: 68 (27.8); ETV: 68 (27.1); LAM: 33 (11.5)	TN, cirrhosis	NR
Kim et al, 2015 ²⁵	Korea	NR	52	Total: 38/14; TDF/ETV: 22/5; TDF/LAM: 16/9	Total: 53.5 (9.9); TDF/ETV: 52.6 (9.6); TDF/LAM: 54.4 (10.3)	Total: 16 (8-22); TDF/ETV: 16 (10-22); TDF/LAM: 16 (8-17)	Total: 3.69 (1.57) log ₁₀ IU/mL; TDF/ETV: 4.14 (1.64) log ₁₀ IU/mL; TDF/LAM: 3.22 (1.38) log ₁₀ IU/mL	Total: 48 (92.3); TDF/ETV: 24 (88.9); TDF/LAM: 24 (96.0)	TE, cirrhosis	TDF: NR; ETV: 1 mg/day; LAM: 100 mg/day
Ha et al, 2015 ²⁶	USA (all Asians)	Matched case-cohort study	206	TDF: 65/38; ETV: 65/38	TDF: 43.5 (10.4); ETV: 43.8 (10.7)	TDF: 24 (6-66); ETV: 18 (6-54)	TDF: 5.3 (1.5) log ₁₀ IU/mL; ETV: 6.15 (1.9) log ₁₀ IU/mL	TDF: 34 (35.4); ETV: 46 (44.7)	TN, cirrhosis	TDF: 300 mg/day; ETV: 0.5 or 1.0 mg/day
Lim et al, 2016 ²⁷	Korea	Randomized open-label trial	102	Total: 88/14; TDF→TDF: 42/8; TDF/ETV→TDF: 46/6	Total: 50 (26-70); TDF→TDF: 49 (28-68); TDF/ETV→TDF: 50 (26-70)	24 (TDF or TDF/ETV for 12, then TDF for 12)	Total: 3.38 (1.78-9.00) log ₁₀ IU/mL; TDF→TDF: 3.27 (1.78-9.00) log ₁₀ IU/mL; TDF/ETV→TDF: 3.50 (2.04-8.79) log ₁₀ IU/mL	Total: 90 (88.2); TDF→TDF: 44 (88); TDF/ETV→TDF: 46 (88.5)	TE, cirrhosis, ADV-resistant	TDF: 300 mg/day; ETV: 1 mg/day
Hung et al, 2015 ²⁸	Taiwan	NR	189	TDF: 30/11; ETV: 106/42	TDF: 49.8 (13.1); ETV: 50.6 (14.7)	6	TDF: 7.0 (1.9) log ₁₀ copies/mL; ETV: 6.5 (1.9) log ₁₀ copies/mL	TDF: 14 (34); ETV: 42 (28)	TN, cirrhosis, severe acute exacerbation	TDF: 300 mg/day; ETV: 0.5 mg/day

Lim et al, 2016 ²⁹	Korea	Randomized open-label trial	90	Total: 68/22; TDF: 32/13; TDF/ETV: 36/9	Total: 51 (9); TDF: 51 (9); TDF/ETV: 52 (10)	12	Total: 4.02 (3.08–5.24) ^b log ₁₀ IU/mL; TDF: 4.09 (3.07–5.47) ^b log ₁₀ IU/mL; TDF/ETV: 3.74 (3.10–4.95) ^b log ₁₀ IU/mL	Total: 80 (88.9); TDF: 40 (88.9); TDF/ETV: 40 (88.9)	TE, cirrhosis; ETV-resistant	TDF: 300 mg/day; ETV: 1 mg/day
Qi et al, 2015 ³⁰	China	Prospective cohort study	275	Untreated: 27/9; LAM: 25/25; ADV: 49/11; LdT: 54/14; ETV: 46/15	Untreated: 31 (21–59); LAM: 53.5 (23–66); ADV: 49 (24–70); LdT: 33.5 (21–64); ETV: 42 (19–64)	Untreated: 23 (12–46); LAM: 24 (11–36); ADV: 24 (8–47); LdT: 23 (12–45); ETV: 24 (11–47)	Untreated: 5.5 (2.9–8.1) log ₁₀ copies/mL; LAM: 6.1 (4.2–8.9) log ₁₀ copies/mL; ADV: 6.4 (3.8–9.9) log ₁₀ copies/mL; LdT: 7.4 (3.2–9.8) log ₁₀ copies/mL; ETV: 6.7 (4.1–8.9) log ₁₀ copies/mL	Untreated: 18 (50); LAM: 24 (48); ADV: 31 (52); LdT: 59 (87); ETV: 46 (75)	TN, TE, cirrhosis	LAM: 100 mg/day; ADV: 10 mg/day; LdT: 600 mg/day; ETV: 0.5 mg/day
Tien et al, 2015 ³¹	USA (all Asians)	Cross-sectional study	146	Total: 78/68; untreated: 24/36; TDF: 29/13; ETV: 25/19	Total: 48 (11); untreated: 46 (12); TDF: 49 (12); ETV: 51 (9)	Total: 29 (19); untreated: NR; TDF: 26 (13); ETV: 32 (24)	NR	Total: 27 (18); untreated: 8 (13); TDF: 11 (26); ETV: 8 (18)	TN, TE, cirrhosis	NR
Lok et al, 2012 ³²	USA, Argentina, Australia, Brazil, Canada, France, India, Italy, Mexico, Poland, Russian Federation, South Africa, Turkey	Randomized open-label trial	379	TDF/ETV: 146/51; ETV: 116/66	TDF/ETV: 39 (1.0) ^a ; ETV: 40 (1.1) ^a	25	TDF/ETV: 7.5 (0.10) ^a log ₁₀ IU/mL; 7.5 (0.11) ^a log ₁₀ IU/mL	TDF/ETV: 138 (70.1); ETV: 126 (69.2)	TN	TDF: 300 mg/day; ETV: 0.5 mg/day
Gish et al, 2012 ³³	USA	Retrospective cohort study	160	TDF: 52/28; ETV: 52/28	TDF: 54.5 (13); ETV: 55.1 (12)	TDF: 19.8 (2.1–45.5); ETV: 29.3 (1.1–55.1)	TDF: 6.99 log ₁₀ IU/mL; ETV: 7.36 log ₁₀ IU/mL	NR	NR	TDF: 300 mg/day; ETV: 0.5 or 1 mg/day
Liau et al, 2011 ³⁴	Taiwan	Randomized double-blind trial	112	TDF: 37/8; TDF/FTC: 40/5; ETV: 17/5	TDF: 52 (48–57) ^b ; TDF/FTC: 50 (42–58) ^b ; ETV: 54 (47–58) ^b	12	TDF: 5.70 (4.9–6.6) ^b log ₁₀ copies/mL; TDF/FTC: 6.28 (4.5–7.3) ^b log ₁₀ copies/mL; ETV: 5.93 (4.2–7.4) ^b log ₁₀ copies/mL	TDF: 14 (31.1); TDF/FTC: 18 (40.0); ETV: 7 (31.8)	TN, TE (but, excluded for prior TDF or ETV and ADV ≥24 months)	TDF: 300 mg/day; ETV: 0.5 or 1 mg/day; FTC: 200 mg/day

Notes: ^aThis indicates standard error (SE). ^bThis indicates median (IQR).

Abbreviations: ADV, adefovir dipivoxil; CHB, chronic hepatitis B; ETV, entecavir; FTC, emtricitabine; F, female; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IQR, interquartile range; LAM, lamivudine; LdT, telbivudine; M, male; MDR, multidrug-resistant; NR, not reported; SD, standard deviation; TDF, tenofovir disoproxil fumarate; TN, treatment-naïve; TE, treatment-experienced.

The final eligible studies included in this review were conducted in the United States, Europe, Thailand, Taiwan, Korea, and China.^{3,15–34} In particular, 13 studies were conducted on Asian individuals.^{19–23,25–31,34} Most of the studies (61.9%), excluding five randomized clinical studies^{19,27,29,32,34} and three studies that did not accurately report study designs,^{24,25,28} were observational studies. Most studies were published in the last 2 years, although the articles dated back to 2011. Overall, 95.2% (20/21) of the studies were conducted on patients with mixed hepatitis B e antigen (HBeAg) status whereas only one study³³ did not report HBeAg status. The TDF dose used in the studies was 245 or 300 mg/day and that of ETV was 0.5 or 1 mg/day.

Evaluation of renal safety of TDF and ETV

Information bias that may result from broad heterogeneity in the methodology among different studies was the major issue hindering meta-analyses. As presented in Table 2, various parameters were utilized in order to measure renal functions after administering TDF and ETV. The most common parameter used was eGFR calculated using modification of diet in renal disease (MDRD) and Cockcroft–Gault (CG) formulae.

An observational study comparing long-term renal functions reported eGFR in 424 patients with TDF-containing regimens and 187 patients with ETV according to the MDRD method.¹⁵ In the patients with TDF-containing regimens, the mean eGFR decreased from 90.8 mL/min at BL to 85.1 mL/min at 60 months. However, in the patients with ETV, the mean eGFR increased from 81.2 mL/min at BL to 90.7 mL/min at 60 months. A retrospective–prospective cohort study conducted in Taiwan determined a change in eGFR in 37 patients with TDF and 62 patients with ETV based on the MDRD method.²⁰ In the patients with TDF, the mean eGFR changed from 78.3 mL/min/1.73 m² at BL to 73.0 mL/min/1.73 m² at 24 months, whereas in the patients with ETV, the mean eGFR increased from 75.6 mL/min/1.73 m² at BL to 79.3 mL/min/1.73 m² at 24 months. A similar change in eGFR calculated using the MDRD method was also observed in a retrospective cohort study conducted in Taiwan.²³ The mean eGFR in 170 patients with TDF changed from 92 mL/min/1.73 m² at BL to 86.3 mL/min/1.73 m² at 24 months; however, in 233 patients with ETV, the mean eGFR changed from 86.1 mL/min/1.73 m² at BL to 94.4 mL/min/1.73 m² at 24 months.

A prospective cohort study conducted in Turkey reported a change in eGFR in 44 patients with TDF and 32 patients with ETV according to the Chronic Kidney Disease Epidemiology

Collaboration and cystatin C (CKD-EPI-CysC) method.¹⁶ The mean eGFR in the patients with TDF decreased from 84.7 mL/min/1.73 m² at BL to 76.9 mL/min/1.73 m² at 24 months ($p=0.004$) and that in the patients with ETV decreased from 90.0 mL/min/1.73 m² at BL to 84.5 mL/min/1.73 m² at 24 months ($p=0.46$). However, the mean values of eGFR in both groups were different when the Chronic Kidney Disease Epidemiology Collaboration and creatinine plus cystatin C (CKD-EPI-Cr-CysC) method was used. The mean eGFR in the patients with TDF changed from 90.6 mL/min/1.73 m² at BL to 73.6 mL/min/1.73 m² at 24 months ($p=0.05$), and the mean eGFR in the patients with ETV changed from 93.5 mL/min/1.73 m² at BL to 82.3 mL/min/1.73 m² at 24 months ($p=0.17$). A study conducted by Koklu et al²⁴ in Turkey reported eGFR calculated using the MDRD method. The mean eGFR in 273 patients with TDF changed from 100.72 mL/min/1.73 m² at BL to 96.72 mL/min/1.73 m² at 24 months ($p=0.001$), whereas the mean eGFR in 282 patients with ETV changed from 96.20 mL/min/1.73 m² at BL to 95.94 mL/min/1.73 m² at 24 months ($p=0.535$). In a study conducted by Hung et al²⁸ in Taiwan, TDF and ETV showed decreased mean eGFR calculated using the MDRD method. The mean eGFR in 41 patients with TDF changed from 108 to 87 mL/min/1.73 m² at 6 months ($p=0.001$), and the mean eGFR in 148 patients with ETV changed from 92 to 84 mL/min/1.73 m² at 6 months ($p=0.001$).

Discussion

Close attention should be paid to the safety and efficacy of TDF and ETV for the long-term treatment of chronic HBV infection, because they are currently the most potent antiviral agents for treating HBV infection.^{3,5} TDF and ETV are likely to cause renal toxicity through various mechanisms including renal tubular injury, apoptosis, and mitochondrial toxicity.^{5,6} The present study reviewed the literature and provided a comprehensive summary of the renal safety of TDF and ETV for the treatment of patients with chronic HBV infection. The results based on the studies reviewed in this article indicated that TDF and ETV could be responsible at least for reduced kidney function in patients with chronic HBV infection.

In this study, the effects of TDF and ETV on renal function were assessed. Based on the markers of renal function, compared to patients treated with ETV, those treated with TDF were not more likely to show changes in renal function, although the eGFR of patients treated with TDF tended to be more clearly reduced than that of patients receiving ETV. The eGFRs of patients treated with TDF decreased in a time-dependent manner, whereas those of patients

Table 2 Summary of renal safety evaluation provided by included studies

Study	Renal safety evaluation	Summary	
Riveiro-Barciela et al, 2017 ¹⁵	Mean eGFR by MDRD, mL/min	TDF-containing ETV BL: 90.8, 12th MO: 90.3, 36th MO: 88.9, 60th MO: 85.1 BL: 81.2, 12th MO: 79.0, 36th MO: 84.8, 60th MO: 90.7	
	Mean creatinine, mg/dL	TDF-containing ETV BL: 0.9, 12th MO: 0.9, 36th MO: 0.91, 60th MO: 0.95 BL: 0.99, 12th MO: 1.0, 36th MO: 1.0, 60th MO: 0.9	
Koksal et al, 2016 ¹⁶	eGFR by CKD-EPI-CysC, mean (SD), mL/min/1.73 m ²	TDF BL: 84.7 (29.6), 3rd MO: 82.8 (45.9), 12th MO: 79.7 (36.3), 24th MO: 76.9 (30.8); p=0.004 ETV BL: 90.0 (24.1), 3rd MO: 96.6 (81.6), 12th MO: 92.9 (43.3), 24th MO: 84.5 (29.5); p=0.46	
	eGFR by CKD-EPI-Cr-CysC, mean (SD), mL/min/1.73 m ²	TDF BL: 90.6 (22.5), 3rd MO: 82.7 (31.2), 12th MO: 83.1 (32.2), 24th MO: 73.6 (34.7); p=0.05 ETV BL: 93.5 (19.6), 3rd MO: 95.6 (41.1), 12th MO: 88.7 (31.2), 24th MO: 82.3 (23.7); p=0.17	
	Creatinine, mean (SD), mg/dL	TDF BL: 0.76 (0.16), 3rd MO: 0.86 (0.19), 12th MO: 0.81 (0.24), 24th MO: 0.85 (0.26); p=0.08 ETV BL: 0.83 (0.18), 3rd MO: 0.84 (0.14), 12th MO: 0.82 (0.13), 24th MO: 0.80 (0.16); p=0.16	
López Centeno et al, 2016 ¹⁷	eGFR <60 mL/min/1.73 m ² , n (%)	TDF-containing ETV BL: 4 (12.5), 12th MO: 6 (19.4) BL: 5 (15.6), 12th MO: 5 (15.6)	
	Creatinine ≥1.4 mg/dL, n (%)	TDF-containing ETV BL: 3 (9.4), 12th MO: 4 (12.9) BL: 2 (6.3), 12th MO: 2 (6.3)	
Rodríguez-Nóvoa et al, 2016 ³	Creatinine, median (SD), mg/dL	TDF 0.95 (0.15) ETV 1.02 (0.20) Control 0.93 (0.16)	
		Phosphate, median (SD), mg/dL	TDF 3.18 (0.55) ETV 3.19 (0.54) Control 3.28 (0.45)
			eGFR by MDRD4, median (SD), mL/min
	Ratio protein/creatinine, median (SD), mg/g		
		Ratio retinol-binding protein/creatinine, median (SD), µg/mL	
	Creatinine increase from BL ≥0.3 mg/dL, n (%)		TDF/ETV 24th MO: 1 (1.1)
			Creatinine increase from BL ≥0.5 mg/dL, n (%)
		Creatinine clearance <50 mL/min, n (%)	
Phosphate <2.0 mg/dL, n (%)	TDF/ETV 24th MO: 2 (2.2)		
	Phosphate <2.3 mg/dL, n (%)	TDF/ETV 24th MO: 8 (8.9)	
Sriprayoon et al, 2017 ¹⁹		eGFR at BL, mean (SD), mL/min/1.73 m ²	TDF 106.7 (20.6) ETV 105.3 (22.3)
	eGFR decrease ≥20%, n (%)	TDF 12th MO: 18 (9.4), 24th MO: 33 (17.3), 36th MO: 32 (16.8) ETV 12th MO: 6 (3.1), 24th MO: 13 (6.7), 36th MO: 29 (14.9)	
		Phosphorus <2.0 mg/dL, n (%)	TDF 12th MO: 0 (0.0), 24th MO: 0 (0.0), 36th MO: 0 (0.0) ETV 12th MO: 0 (0.0), 24th MO: 0 (0.0), 36th MO: 0 (0.0)
	Fractional excretion of phosphate, mean (SD)		TDF 24th MO: 9.4 (3.7), 36th MO: 9.6 (3.8) ETV 24th MO: 8.9 (3.6), 36th MO: 8.7 (3.5)
Tsai et al, 2016 ²⁰		eGFR by MDRD, mean (SD), mL/min/1.73 m ²	TDF Prior 12th MO: 80.1 (13.3), BL: 78.3 (11.6), 24th MO: 73.0 (13.1) ETV Prior 12th MO: 76.2 (11.3), BL: 75.6 (9.5), 24th MO: 79.3 (14.2)
	Rise in CKD category with ≥25% increase in eGFR, n (%)	TDF 0 (0.0) ETV 0 (0.0)	
	Rise in CKD category with <25% rise in eGFR, n (%)	TDF 1 (2.7) ETV 1 (1.6)	

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Table 2 (Continued)

Study	Renal safety evaluation	Summary
Park et al, 2016 ²¹	No change in CKD category, n (%)	TDF 34 (91.9) ETV 57 (91.9)
	Drop in CKD category with <25% decrease in eGFR, n (%)	TDF 1 (2.7) ETV 4 (6.5)
	Drop in CKD category with ≥25% decrease in eGFR, n (%)	TDF 1 (2.7) ETV 0 (0.0)
	Creatinine, median (range), mg/dL	TDF/ETV BL: 0.87 (0.38–1.30), 12th MO: 0.90 (0.57–1.28)
	Creatinine increase from BL >0.5 mg/dL, n (%)	TDF/ETV 1 (1.56) (BL: 0.60 mg/dL, 9th MO: 1.36 mg/dL, 12th MO: 0.58 mg/dL)
	eGFR, mean (SD), mL/min/1.73 m ²	TDF (TN) BL: 98.9, 6th MO: 94.5, 12th MO: 90.5, 24th MO: 90.5, 36th MO: 90.9 TDF (TE) BL: 92.2, 6th MO: 87.3, 12th MO: 86.7, 24th MO: 85.3, 36th MO: 84.3
Wang et al, 2016 ²²	eGFR decrease >20%, n (%)	TDF (TN, TE) 38 (16.89)
	Creatinine increase from BL ≥0.5 mg/dL, n (%)	TDF (TN, TE) 8 (3.56)
	Phosphate <2.5 mg/dL, n (%)	TDF (TN, TE) 14 (8.28)
	eGFR by MDRD, mean (SD), mL/min/1.73 m ²	TDF BL: 92, 12th MO: 85.6, 24th MO: 86.3 ETV BL: 86.1, 12th MO: 92.6, 24th MO: 94.4, 36th MO: 97, 48th MO: 100.8, 60th MO: 100.4 LdT BL: 81.1, 12th MO: 81.8, 24th MO: 79.3, 36th MO: 81.1, 48th MO: 84.7, 60th MO: 87.6
	Phosphate <2.5 mg/dL, n (%)	TDF 4 (8.2) ETV 1 (1.8) LdT 1 (5.3)
	eGFR by MDRD, mean (SD), mL/min/1.73 m ²	TDF BL: 100.72 (25.19), 1st MO: 96.44 (24.27), 6th MO: 97.13 (23.95), 12th MO: 96.11 (24.42), 24th MO: 96.72 (25.67); p=0.001 ETV BL: 96.20 (22.53), 1st MO: 96.37 (21.01), 6th MO: 95.87 (21.84), 12th MO: 94.30 (23.80), 24th MO: 95.94 (23.85); p=0.535 LAM BL: 96.91 (25.17), 1st MO: 96.00 (25.28), 6th MO: 95.34 (26.78), 12th MO: 97.50 (25.39), 24th MO: 96.23 (24.07); p=0.490
Koklu et al, 2015 ²⁴	Creatinine, mean (SD), mg/dL	TDF BL: 0.85 (0.42), 1st MO: 0.90 (0.56), 6th MO: 0.89 (0.51), 12th MO: 0.89 (0.42), 24th MO: 0.90 (0.58); p=0.001 ETV BL: 0.86 (0.19), 1st MO: 0.85 (0.18), 6th MO: 0.86 (0.19), 12th MO: 0.88 (0.21), 24th MO: 0.87 (0.22); p=0.500 LAM BL: 0.84 (0.17), 1st MO: 0.85 (0.18), 6th MO: 0.88 (0.42), 12th MO: 0.84 (0.19), 24th MO: 0.85 (0.21); p=0.111
	Phosphate, mean (SD), mg/dL	TDF BL: 3.23 (0.45), 1st MO: 3.21 (0.49), 6th MO: 3.21 (0.46), 12th MO: 3.15 (0.53), 24th MO: 3.23 (0.62); p=0.810 ETV BL: 3.38 (0.36), 1st MO: 3.47 (0.36), 6th MO: 3.39 (0.38), 12th MO: 3.39 (0.36), 24th MO: 3.45 (0.43); p=0.358 LAM BL: 3.08 (0.81), 1st MO: 3.17 (0.89), 6th MO: 3.28 (1.04), 12th MO: 3.22 (0.98), 24th MO: 2.98 (0.70); p=0.121
	Creatinine increase from BL >0.5 mg/dL, n (%)	TDF/ETV 0 (0.0) TDF/LAM 0 (0.0)
	Creatinine increase from BL >0.3 mg/dL, n (%)	TDF/ETV 5 (18.52) TDF/LAM 5 (20.00)
	Creatinine clearance <50 mL/min, n (%)	TDF/ETV 0 (0.0) TDF/LAM 0 (0.0)
	Phosphate <2.0 mg/dL, n (%)	TDF/ETV 0 (0.0) TDF/LAM 0 (0.0)
Kim et al, 2015 ²⁵	Phosphate <2.7 mg/dL, n (%)	TDF/ETV 2 (7.41) TDF/LAM 3 (12.00)
	Change in creatinine, mean (IQR), mg/dL	TDF/ETV 6th MO: -0.03 (-0.25 to 0.23), 12th MO: 0.11 (-0.11 to 0.38), 18th MO: 0.21 (-0.08 to 0.42) TDF/LAM 6th MO: -0.04 (-0.21 to 0.24), 12th MO: 0.08 (-0.28 to 0.25), 18th MO: 0.19 (-0.02 to 0.43)

(Continued)

Table 2 (Continued)

Study	Renal safety evaluation	Summary	
Ha et al, 2015 ²⁶	Change in creatinine clearance, mean (IQR), mL/min	TDF/ETV	6th MO: 0.7 (–60.9 to 16.9), 12th MO: –12.5 (–63.2 to 7.3), 18th MO: –22.1 (–64.3 to 6.9)
		TDF/LAM	6th MO: 2.4 (–26.5 to 16.4), 12th MO: –7.5 (–31.9 to 33.4), 18th MO: –21.3 (–37.0 to –8.9)
	Patients reclassified to a higher category of renal impairment classification, n (%)	TDF	16 (15.5)
		ETV	18 (17.5)
Lim et al, 2016 ²⁷	% change in eGFR from BL in patients reclassified to a more severe renal classification on treatment, n (%)	TDF	<10%: 3 (19), 10%–19.99%: 4 (25), 20%–29.99%: 7 (44), 30%–39.99%: 2 (13), >40%: 0 (0)
		ETV	<10%: 2 (11), 10%–19.99%: 9 (50), 20%–29.99%: 6 (33), 30%–39.99%: 0 (0), >40%: 1 (6)
	Creatinine increase from BL \geq 0.5 mg/dL, n (%)	TDF→TDF	0 (0.0)
		TDF/ ETV→TDF	0 (0.0)
eGFR <50 mL/min/1.73 m ² , n (%)	TDF→TDF	0 (0.0)	
	TDF/ ETV→TDF	0 (0.0)	
	TDF→TDF	0 (0.0)	
Phosphate <2.0 mg/dL, n (%)	TDF→TDF	0 (0.0)	
	TDF/ ETV→TDF	0 (0.0)	
	TDF→TDF	0 (0.0)	
Hung et al, 2015 ²⁸	Creatinine increase from BL \geq 0.5 mg/dL at 6 MO, n (%)	TDF	2 (6.67)
		ETV	2 (2.02)
	Mean eGFR by MDRD, mL/min/1.73 m ²	TDF	BL: 108, 6th MO: 87; <i>p</i> =0.001
Lim et al, 2016 ²⁹	Creatinine increase from BL \geq 0.5 mg/dL, n (%)	TDF	0 (0.0)
		TDF/ETV	0 (0.0)
	eGFR <50 mL/min/1.73 m ² , n (%)	TDF	1 (2.22)
		TDF/ETV	0 (0.0)
Phosphate <2.0 mg/dL, n (%)	TDF	0 (0.0)	
	TDF/ETV	1 (2.22)	
	TDF/ETV	1 (2.22)	
Qi et al, 2015 ³⁰	Change in creatinine, mg/dL	Untreated	12th MO: 0.004, 24th MO: 0.012, 36th MO: 0.030
		LAM	12th MO: 0.018, 24th MO: 0.047, 36th MO: 0.082
		ADV	12th MO: 0.071, 24th MO: 0.128, 36th MO: 0.314
		LdT	12th MO: –0.066, 24th MO: –0.100, 36th MO: –0.135
		ETV	12th MO: 0.006, 24th MO: –0.023, 36th MO: 0.007
	Change in eGFR by CG, mL/min	Untreated	12th MO: –0.665, 24th MO: –0.892, 36th MO: –1.047
		LAM	12th MO: –4.530, 24th MO: –8.817, 36th MO: –11.637
		ADV	12th MO: –5.623, 24th MO: –11.260, 36th MO: –13.720
		LdT	12th MO: 8.232, 24th MO: 14.998, 36th MO: 23.619
		ETV	12th MO: –0.001, 24th MO: 1.806, 36th MO: –1.358
	Change in eGFR by MDRD, mL/min	Untreated	12th MO: –0.692, 24th MO: –1.071, 36th MO: –1.799
		LAM	12th MO: –4.715, 24th MO: –10.166, 36th MO: –12.410
		ADV	12th MO: –6.922, 24th MO: –11.637, 36th MO: –15.381
		LdT	12th MO: 9.570, 24th MO: 15.428, 36th MO: 26.236
		ETV	12th MO: –0.002, 24th MO: 1.988, 36th MO: –1.284
Tien et al, 2015 ³¹	eGFR by CG, mean (SD), mL/min	Untreated	118 (36)
		TDF	108 (29)
		ETV	103 (26)
	eGFR by MDRD, mean (SD), mL/min	Untreated	118 (28)
		TDF	103 (26)
		ETV	102 (22)
	Phosphate, mean (SD), mg/dL	Untreated	3.4 (0.5)
		TDF	3.4 (0.5)
		ETV	3.5 (0.5)

(Continued)

Table 2 (Continued)

Study	Renal safety evaluation	Summary	
Lok et al, 2012 ³²	Phosphate <2.8 mg/dL, n (%)	Untreated	5 (8)
		TDF	6 (14)
		ETV	2 (4)
	Creatinine, mean (SD), mg/dL	Untreated	0.65 (0.17)
		TDF	0.79 (0.22)
		ETV	0.76 (0.19)
	Creatinine >1.5 mg/dL, n (%)	Untreated	0 (0)
		TDF	0 (0)
		ETV	0 (0)
Creatinine increase from BL \geq 0.3 mg/dL, n (%)	TDF/ETV	4 (2.0)	
	ETV	6 (3.3)	
	TDF/ETV	0 (0.0)	
Gish et al, 2012 ³³	Creatinine increase from BL \geq 0.5 mg/dL, n (%)	ETV	3 (1.6)
		TDF	22 (27.5)
		ETV	23 (28.8)
	Creatinine increase from BL \geq 0.2 mg/dL, n (%)	TDF	3 (3.8)
		ETV	11 (13.8)
		TDF	28 (35.0)
	eGFR decrease \geq 20% (CG), n (%)	ETV	29 (36.3)
		TDF	33 (41.3)
		ETV	35 (43.8)
Liaw et al, 2011 ³⁴	Creatinine increase from BL \geq 0.5 mg/dL, n (%)	TDF	4 (8.9)
		TDF/FTC	1 (2.2)
		ETV	1 (4.5)
	Phosphate <2.0 mg/dL, n (%)	TDF	1 (2.2)
		TDF/FTC	2 (4.4)
	ETV	0 (0.0)	

Notes: The change in eGFR was calculated by (2nd year eGFR – baseline eGFR)/baseline eGFR \times 100%. Categories of CKD were defined based on eGFR: \geq 90, 60–89, 59–30, and <30 mL/min/1.73 m², respectively. Classification of eGFR is as follows: unimpaired (eGFR >80 mL/min), mildly impaired (50 mL/min \leq eGFR \leq 80 mL/min), moderately impaired (30 mL/min \leq eGFR <50 mL/min), and severely impaired (eGFR <30 mL/min).

Abbreviations: BL, baseline; CKD-EPI-CysC, Chronic Kidney Disease Epidemiology Collaboration and cystatin C; CKD-EPI-Cr-CysC, Chronic Kidney Disease Epidemiology Collaboration and creatinine plus cystatin C; CG, Cockcroft–Gault; eGFR, estimated glomerular filtration rate; ETV, entecavir; FTC, emtricitabine; IQR, interquartile range; LAM, lamivudine; LdT, telbivudine; MDRD, modification of diet in renal disease; MDRD4, modification of diet in renal disease 4-variable version; MO, month; SD, standard deviation; TDF, tenofovir disoproxil fumarate; TN, treatment-naïve; TE, treatment-experienced.

treated with ETV increased or decreased across various time points.^{15,16,20,23,24,28} Similar percentage of patients in both the treatment groups showed \geq 20% decrease in eGFR during the treatment (based on CG, TDF 35.0% vs ETV 36.3%; based on MDRD, TDF 41.3% vs ETV 43.8%).³³ A similar tendency was also observed in a recent clinical trial conducted in Thailand.¹⁹ After 36 months, 16.8% and 14.9% of patients receiving TDF and ETV, respectively, experienced \geq 20% decrease in eGFR; however, the decrease was observed in more patients receiving TDF than in those receiving ETV at 12 and 24 months.¹⁹ Around 30% of patients in both TDF and ETV groups experienced a \geq 0.2 mg/dL increase in creatinine from BL; however, creatinine increase of \geq 0.5 mg/dL from BL occurred in more patients receiving ETV than in those receiving TDF (13.8% vs 3.8%; $p=0.025$).³³ The frequencies of creatinine elevation by \geq 0.3 mg/dL were similar in both groups (TDF/ETV 2.0% vs ETV 3.3%); however, creatinine elevation by \geq 0.5 mg/dL was more frequent in patients treated with ETV alone (TDF/ETV 0.0% vs ETV 1.6%).³²

These heterogeneous results may be partially attributed to different characteristics, such as comorbidities and co-administered drugs, of the study subjects.

According to multivariate analyses, various risk factors, such as advanced age, preexisting renal failure, comorbidities, history of transplant, concomitant nephrotoxic drugs, advanced HIV coinfection, and male gender, were associated with eGFR reductions by TDF or ETV.^{23,26,33,35,36} Especially, preexisting renal insufficiency was a major independent risk factor for deterioration of renal function during the treatment of chronic HBV infection.^{23,26,33} Moreover, previous studies have reported an association of CHB with CKD, and ~15%–30% of patients with CHB showed BL renal insufficiency or comorbidities that were likely to cause CKD, such as diabetes mellitus (DM) and HTN.^{7–11} However, TDF therapy was not significantly associated with changes in renal function when compared with ETV therapy.^{26,33} Large proportions of TDF and ETV are also renally excreted in their unchanged forms.^{37,38} Thus, NUCs

other than TDF and ETV may be considered to prevent the progression of renal decline in patients with CHB and decreased renal functions.

Compared with TDF, tenofovir alafenamide (TAF), a novel prodrug of tenofovir, led to approximately four times higher intracellular concentrations of tenofovir diphosphate, an active metabolite, which may result in much lower doses of TAF than those of TDF.^{39,40} Consequently, ~90% lower systemic exposure of tenofovir was expected in patients treated with TAF than in those treated with TDF.⁴⁰ This is likely to reduce the risk for tenofovir-associated renal toxicity. According to a clinical trial conducted in patients infected with HIV-1, decreases or slight increases from BL to Week 48 in total urinary protein, albumin, retinol-binding protein, and β_2 -microglobulin to urine creatinine ratios were observed in the TAF group; however, increases from BL to Week 48 in the protein to urine creatinine ratios were reported in the TDF group.⁴⁰ Two recent randomized clinical trials conducted in patients with HBeAg-negative or -positive chronic HBV infection reported that TAF not only was non-inferior to TDF but also improved the negative effect of tenofovir on renal function.^{41,42} In patients with HBeAg-negative chronic HBV infection, a small mean increase in creatinine from BL to Week 48 was reported in both TAF and TDF groups, and at Week 48, a median decrease in eGFR by CG was lower in patients treated with TAF than in those treated with TDF.⁴¹ Significantly smaller increases from BL to Week 48 in the markers of proximal tubular dysfunction, retinol-binding protein, and β_2 -microglobulin to urine creatinine ratios were noted in the TAF group than in the TDF group.⁴¹ Similar tendencies were observed in patients with HBeAg-positive chronic HBV infection.⁴² A network meta-analysis conducted by Chan et al⁷ reported that telbivudine (LdT) consistently improved renal functions measured by eGFR independent of measuring methods. In particular, tenofovir monotherapy caused decreases in eGFR, but combinational therapy of tenofovir with LdT improved renal functions.⁷

According to the WHO guidelines for the treatment of CHB in 2015, measuring BL renal function and assessing BL risks for renal dysfunction are recommended before commencing antiviral therapy.⁴³ In cases where BL patients have eGFR <50 mL/min or risk factors for renal insufficiency, such as long-term DM, uncontrolled HTN, and severe bone-related diseases, tenofovir should be avoided, its dose should be adjusted, or ETV should be used.⁴³ Thus, as shown in previous randomized clinical studies,^{40,41} TAF could be considered as the first drug of choice for the treatment of CHB in patients with reduced renal function or in those with risk

factors for renal dysfunction. In addition, LdT monotherapy or combinational therapy with TAF could be another option for these patients; however, well-organized, randomized clinical trials are necessary to prove renal safety when TAF + LdT or LdT alone is administered to these patients.

This study had some limitations that should be addressed. Two electronic databases (ie, PubMed and ClinicalTrials.gov website) were utilized to search relevant clinical trials, although various databases are available. This limited database utilization also likely limited our opportunities to search additional valuable and relevant clinical trials. Almost all of the selected clinical trials mentioned that TDF and ETV were not likely to have significantly negative effects on renal functions. However, consistent results were not shown partially owing to the different characteristics of study subjects and various markers used to measure renal functions, which made the conducting of further meta-analysis difficult.

Conclusion

The data reported in this study suggest that use of TDF and ETV could be associated with reductions in kidney function in patients with chronic HBV infection. The eGFRs of patients treated with TDF were reduced in a time-dependent manner, whereas the eGFRs of patients treated with ETV increased or decreased across various time points. TAF as the first drug of choice for the treatment of chronic HBV infection could be used in patients with decreased renal function or in those with risk factors for renal dysfunction, and TAF + LdT or LdT alone could also be considered for these patients. However, well-organized, prospective, large-scale, randomized clinical trials are necessary to determine the renal safety of TAF + LdT or LdT alone for the treatment of such patients. In addition, studies on management strategies for HBV-infected patients with various risk factors (eg, advanced age, pre-existing renal failure, comorbidities, history of transplant, and concomitant nephrotoxic drugs) associated with reduction in eGFR are warranted in the near future.

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Disclosure

The authors report no conflicts of interest in this work.

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