Received: 20 March 2020 | First decision: 2 April 2020 | Accepted: 30 May 2020

DOI: 10.1111/apt.15901

AP&T Alimentary Pharmacology & Therapeutics WILEY

Treatment with tenofovir disoproxil fumarate or entecavir in chronic hepatitis B virus-infected patients with renal impairment: results from a 7-year, multicentre retrospective cohort study

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Funding information
Gilead Sciences Europe Ltd

Summary

Background: Limited data exist regarding tenofovir disoproxil fumarate (TDF) safety and effectiveness in chronic hepatitis B virus–infected (CHB) patients with renal impairment (RI).

Aims: To compare real-world data on renal safety and effectiveness of TDF vs entecavir (ETV) in CHB patients with moderate-to-severe RI.

Methods: Retrospective, non-interventional, cohort study analysing medical records for TDF/ETV-treated CHB patients (54 European centres). Included patients experienced moderate-to-severe RI (creatinine clearance 20-60 mL/min [Cockcroft-Gault]) either before TDF/ETV initiation ('before' subgroup [baseline = treatment initiation]) or after TDF/ETV initiation ('after' subgroup [baseline = first RI occurrence]). The primary objective was TDF safety, particularly renal-related adverse events of special interest (AESI). TDF and ETV safety and effectiveness were compared and multivariate analyses were performed using inverse probability treatment weighting.

Results: 'Before' subgroup included 107 TDF- and 91 ETV-treated patients; 'after' subgroup included 212 TDF- and 77 ETV-treated patients. Mean baseline creatinine clearance was higher for TDF- vs ETV-treated patients (both subgroups). Median follow-up was 3.1 years (both treatments). AESI were more frequent with TDF vs ETV ('before': 18.7% vs 8.8%; 'after': 9.9% vs 3.9%); however, differences were not significant by multivariate analysis. Only TDF-treated patients experienced renal tubular dysfunction (6.5% 'before'; 1.9% 'after') as well as renal adverse events leading to treatment discontinuation (8.4% 'before'; 7.1% 'after'). Effectiveness was similar between treatments.

The Handling Editor for this article was Professor Grace Wong, and it was accepted for publication after full peer-review.

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Conclusions: Overall safety was similar for TDF vs ETV (both subgroups). Given that renal tubular dysfunction occurred with TDF and not with ETV, renal safety concerns may be greater with TDF in CHB patients with RI.

1 | INTRODUCTION

Hepatitis B virus (HBV) affects around 257 million people worldwide, with chronic HBV infection (CHB) leading to a significant number of deaths due to cirrhosis and hepatocellular carcinoma.[1] Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue prodrug of tenofovir diphosphate, which inhibits HBV polymerase and exerts potent anti-HBV activity.[2,3] The efficacy and safety of TDF were maintained over 7 years of treatment in pivotal Phase III trials, with no resistance detected.[4,5] Furthermore, TDF treatment over 5 years was associated with regression of liver fibrosis and cirrhosis.[6] TDF is authorised for treatment of CHB in adult and paediatric patients (≥2 years of age), including those with pre-existing renal impairment (with dose adjustment),[7,8] and is a preferred first-line treatment for adult CHB patients.[9-11]

Despite its favourable safety profile, some tenofovir-exposed patients experience renal toxicity,[5,12] since tenofovir is primarily excreted via glomerular filtration and active tubular transport.[7,13] Long-term follow-up of CHB patients enrolled in TDF registrational studies with adequate renal function at baseline showed a low incidence of renal events.[5,6] However, several real-world observational studies reported an increased risk of nephrotoxicity with TDF, manifesting as proximal tubular dysfunction with/without decreased glomerular filtration rates.[12,14,15] A recent review highlighted conflicting evidence regarding nephrotoxicity,[12] with several studies subsequently reporting a lack of significant renal safety findings.[16-21]

CHB patients, particularly those with advanced age or comorbidities (eg hypertension/diabetes mellitus), have a relatively high prevalence of kidney disease,[22] even in the absence of anti-viral treatment.[23] Despite this, limited data exist regarding the safety and effectiveness of TDF in CHB patients with renal insufficiency: patients with pre-existing renal impairment were excluded from most Phase III trials, which required creatinine clearance ≥70 mL/min for inclusion.[4] However, a Phase III study evaluating TDF in patients with lamivudine resistance enrolled CHB patients with creatinine clearance ≥50 mL/min and included 74 patients with mild renal impairment.[24] Six of the nine patients who experienced a reduction in creatinine clearance below 50 mL/min were managed by dose modification, and there were no severe renal adverse events (AEs).[24] Furthermore, a non-interventional, prospective cohort study found a favourable safety profile among a small number of patients with pre-existing renal impairment.[16] However, retrospective/retrospective-prospective studies have linked pre-existing renal impairment to further decline in renal function with TDF.[25-27] The limited number of HBV-infected patients in these studies means that they may not be generalisable for a broader renally impaired CHB population. TDF treatment has also been associated with Fanconi syndrome in rare instances.[12]

Current TDF labelling reflects the risk of renal toxicity, recommending that creatinine clearance is evaluated prior to treatment and renal function is monitored regularly (and more frequently in patients with renal impairment risk factors).[7] The requirement for periodic renal monitoring for all TDF-treated patients is reflected in current guidelines.[9,10] EU labelling indicates that TDF should only be used in adult patients with pre-existing renal impairment 'if the potential benefits of treatment are considered to outweigh the potential risks'.[7] Additionally, dose adjustment or extended-interval dosing is recommended for patients with creatinine clearance <50 mL/min.[7]

Entecavir (ETV), a guanosine nucleoside analogue inhibitor of HBV polymerase,[28] is a first-line treatment option for CHB.[9,10] ETV is effective and well tolerated.[12,29,30] As it is eliminated renally,[31] dose adjustment is recommended in patients with renal impairment (creatinine clearance <50 mL/min).[28] Despite renal safety findings being similar for TDF and ETV in several retrospective studies,[29,30,32,33] ETV has been associated with a lower risk of proximal tubular toxicity than TDF, independent of pre-existing renal impairment.[34,35] A retrospective study evaluated ETV in HBV-infected patients, including 40 with renal dysfunction (estimated glomerular filtration rate ≤59 mL/min or receiving haemodialysis).[36] While outcomes were similar between groups, estimated glomerular filtration rates declined over 5 years in patients without renal dysfunction at baseline (who had Grade 1-2 chronic kidney disease), but this was not observed in those with baseline renal dysfunction.[36] Nonetheless, guidelines recommend renal monitoring for all patients at risk of renal disease, regardless of the nucleoside analogue received.[10]

This retrospective, observational study was undertaken at the request of the European Medicines Agency to provide real-world data on the renal safety and effectiveness of TDF and ETV in CHB patients with moderate or severe renal impairment.[37] We report findings for the subgroups of patients with pre-existing renal impairment before treatment initiation, or renal impairment that was first experienced after treatment initiation.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multicentre, retrospective, non-interventional, cohort study that included patients with chronic HBV infection undergoing treatment between 23 April 2008 (date of European marketing authorisation for the HBV indication for TDF tablets) and 31 December 2015. De-identified data were retrospectively collected from routine

medical records at 54 centres in five European countries (France, Germany, Italy, Spain and the UK). Electronic case report forms employing unique patient identifiers and automatic checks for data completeness and inconsistencies were utilised. Patients had to fulfil two criteria to be included in the study and for data collection to commence, irrespective of which came first: (a) treatment with TDF or ETV and (b) moderate-to-severe renal impairment, defined by a creatinine clearance of 20-60 mL/min inclusive (based on the Cockcroft-Gault formula; hereafter referred to as renal impairment). Baseline was either: the date of treatment initiation (for the subgroup with renal impairment *before* treatment initiation); or the date of first occurrence of renal impairment if treatment had already been initiated (for the subgroup experiencing first renal impairment *after* treatment initiation). Data were collected during the post-baseline treatment period and for 12 weeks following drug discontinuation and/or replacement with another HBV medication, or 31 December 2015, whichever occurred first. The post-treatment observation period was extended to 6 months or 31 December 2015 (whichever occurred first), when discontinuation was due to decreasing renal function.

The study was conducted in accordance with the International Conference on Harmonisation E2E guidelines, the Guidelines for Good Pharmacoepidemiology Practices and EU Good Pharmacovigilance Practices. Participating centres adhered to any additional local ethical approval requirements. Since patient information was de-identified, informed consent was not obtained unless required by local ethics committees or by country National Data Protection Laws for participating centres. The study is registered with the EU PAS Register: EUPAS12897.

2.2 | Study participants

Participants were adults (≥18 years) with CHB who had experienced renal impairment as previously described. Patients had received monotherapy with either TDF (tablets [once-daily or extended-interval dosing for renal impairment] and/or oral granules [once-daily and reduced dose for renal impairment]), or ETV (tablets [once-daily] and/or oral solution). Patients were excluded if they had human immunodeficiency virus (HIV), hepatitis C virus or hepatitis D virus coinfection or received anti-HBV combination treatment during the renal impairment episode. If a patient received both drugs but without temporal overlap, the patient was allocated to the group corresponding to the drug received at the first occurrence of renal impairment. Concomitant nephrotoxic medications were recorded as an indicator variable ('yes/no').

2.3 | Study objectives and variables

The primary objective was to evaluate the safety of TDF in CHB patients with renal impairment—focusing on AEs of special interest, defined as: 'renal tubular dysfunction AEs', 'renal AEs leading to treatment discontinuation', 'renal AEs leading to initiation of haemodialysis (or other forms of renal support)', 'renal serious AEs (SAEs) including those leading to death' and 'decline in renal function' (if reported as an AE by the investigator). 'Renal tubular dysfunction AEs' were defined by combining reports of renal tubulopathy, including proximal renal tubulopathy, Fanconi syndrome and renal tubular necrosis. Renal AEs included AEs coded to the renal and urinary disorder System Organ Class as well as AEs reflecting renal concepts that were coded to the investigations or metabolism and nutrition disorders System Organ Classes per the Medical Dictionary for Regulatory Affairs version 20.0.

The secondary objective was to describe the effectiveness of TDF in this patient population; the tertiary objective was to compare the safety and effectiveness of TDF and ETV. Response to therapy was defined as achievement and/or maintenance of HBV DNA <69 IU/mL (400 copies/mL). Table S1 details baseline, safety, laboratory and effectiveness variables. Subgroup analyses (see Supplementary Methods) were conducted to further evaluate AEs of special interest and effectiveness. Time-to-event analyses were carried out to compare time to renal impairment and time to further aggravation of renal impairment (see Supplementary Methods). Results are presented herein for the pre-defined subgroups of patients with pre-existing renal impairment and patients with renal impairment after treatment initiation.

2.4 | Statistical analyses

The study size was based on the primary objective only and was determined based on a 3.4% cumulative incidence of renal AEs leading to dose reduction, treatment interruption or discontinuation in patients receiving TDF during the open-label period of Phase III studies.[38,39] Using this value as the expected incidence rate and accounting for 80% statistical power, a one proportion test determined that a sample size of 300 patients in the TDF group would detect an effect size of 3.1%. Since the study size was based on the primary objective, no estimates were made for the size of the ETV group.

Data were first summarised descriptively. Baseline characteristics were compared between overall TDF/ETV groups using a backward selection logistic regression model, with the ETV group as the referent. Differences between groups for some variables, including relevant comorbidities (ie hyperlipidaemia, hypertension or diabetes), required implementation of an inverse probability treatment weighted approach to compare safety and effectiveness between drugs, maximising homogeneity between groups and reducing the impact of treatment-selection bias. All statistical tests were two-tailed considering a 5% significance level. For the primary objective, the incidence rate of TDF-treated patients experiencing AEs of special interest at each 48-week (±12 week) visit window (from baseline) was calculated. Person-time for denominators of rates was calculated as the date of the first instance of the AE of special interest minus the date of treatment initiation +1 day, or date of last observation minus date of treatment initiation +1 day, whichever came first. To compare the incidence of AEs of special interest between groups,

incidence rate ratios were calculated with ETV as the reference. All statistical analyses used SAS software (SAS Institute). Statistical analyses are further detailed in Supplementary Methods.

3 | RESULTS

3.1 | Patient disposition

Of 515 patients with renal impairment examined for eligibility, 487 were included in the analysis (319 TDF, 168 ETV; Figure 1). Most of the 28 patients who were excluded had important protocol deviations including the first episode of renal impairment occurring under a previous therapy or the first available confirmatory creatinine clearance laboratory values not matching the definition of renal impairment used in the study. The median (interquartile range [minimum-maximum] duration of follow-up was 3.1 (1.3-4.8 [0-7.7]) and 3.1 (1.4-5.6 [0.1-7.7]) years in the TDF and ETV groups respectively, with a total respective follow-up person-time of 1015.4 and 594.0 years given differences in sample size between treatment groups. Of 198 patients with renal impairment before treatment initiation, 107 and 91 were TDF- and ETV-treated respectively (Figure 1). Overall, 289 patients experienced their first episode of renal impairment after treatment initiation (212 TDF, 77 ETV). Baseline patient disposition and disease characteristics are shown per renal impairment subgroup in Table 1 (Table S2 shows number of patients with missing data for each variable). Age (Figure 2) and sex (Table 1) distributions were similar between groups.

A lower proportion of TDF- vs ETV-treated patients had pre-existing renal impairment (33.5% vs 54.2%). At baseline, mean (95% confidence interval [CI]) creatinine clearance was 48.5 (46.3-50.7) and 43.9 (41.0-46.7) mL/min in the TDF and ETV groups respectively in patients with pre-existing renal impairment (Table 1). For patients with renal impairment after treatment initiation, the mean (95% CI) creatinine clearance at first occurrence of renal impairment (baseline) was 53.8 (52.7-54.8) and 47.8 (45.2-50.5) mL/min in the TDF and ETV groups respectively (Table 1).

For both renal impairment subgroups, a greater proportion of TDF- vs ETV-treated patients were treatment-experienced (Figure 3). Most patients received TDF or ETV as a once-daily tablet at baseline and during the observation period (Figure 4). During the observation period, 51.4% and 27.5% of patients with pre-existing renal impairment and 45.3% and 18.2% of patients with renal impairment after treatment initiation received extended-interval dosing in TDF and ETV groups respectively. Few patients received reduced-dose treatment (with the oral granules) given once-daily.

3.2 | Safety in patients with pre-existing renal impairment

Among patients with pre-existing renal impairment, 28 (26.2%) TDF-treated patients experienced 38 AEs, including 9 SAEs, while 12 (13.2%) ETV-treated patients experienced 15 AEs, including 6 SAEs (Table 2). Treatment-related AEs were experienced by 21 (19.6%) and 4 (4.4%) TDF- and ETV-treated patients respectively. TDF dosing was

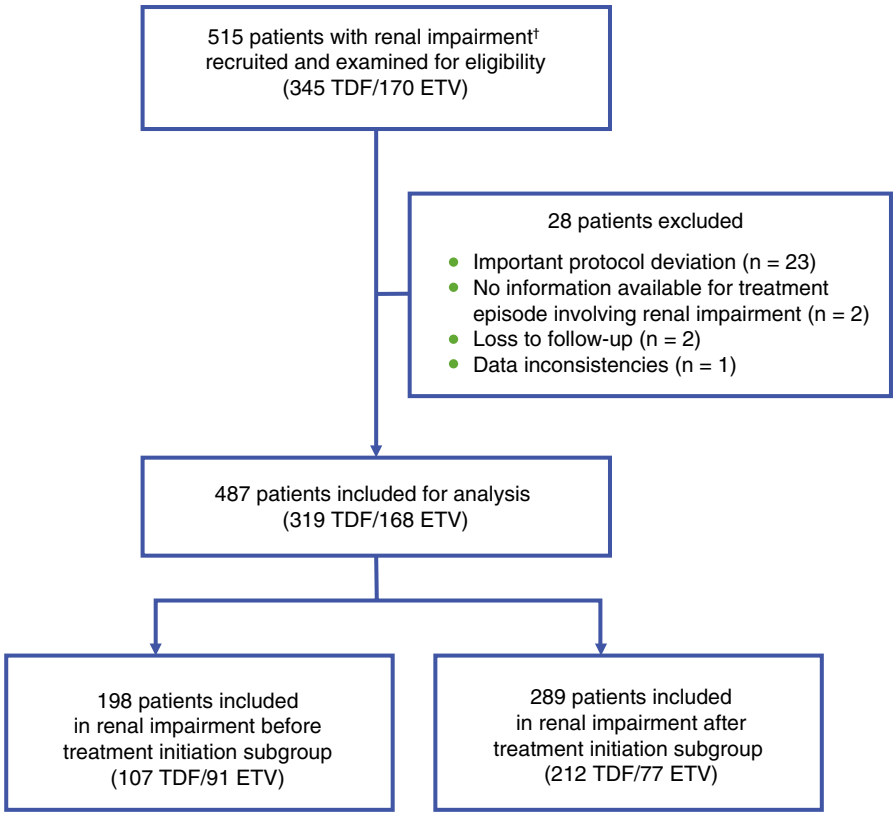

FIGURE 1 Patient flow diagram. †Moderate-to-severe renal impairment: creatinine clearance 20-60 mL/min (per Cockcroft–Gault formula). ETV, entecavir; TDF, tenofovir disoproxil fumarate

TABLE 1 Baseline patient and disease characteristics by renal impairment subgroup

Variable	Category[a] or evaluable N (TDF)|N (ETV)[b]	n (%) or median (interquartile range)[c]			
		Renal impairment before treatment initiation		Renal impairment after treatment initiation	
		TDF (N = 107)	ETV (N = 91)	TDF (N = 212)	ETV (N = 77)
Sex	Male	67 (62.6)	62 (68.1)	151 (71.2)	54 (70.1)
	Female	40 (37.4)	29 (31.9)	61 (28.8)	23 (29.9)
Clinical evidence of cirrhosis[d]	No	56 (52.3)	64 (70.3)	124 (58.5)	55 (71.4)
	Yes	31 (29.0)	18 (19.8)	86 (40.6)	18 (23.4)
	Missing	20 (18.7)	9 (9.9)	2 (0.9)	4 (5.2)
Clinical evidence of decompensated liver disease	No	85 (79.4)	72 (79.1)	199 (93.9)	65 (84.4)
	Yes	4 (3.7)	5 (5.5)	11 (5.2)	7 (9.1)
	Missing	18 (16.8)	14 (15.4)	2 (0.9)	5 (6.5)
Previous HBV treatment before TDF or ETV initiation	No	39 (36.4)	47 (51.6)	65 (30.7)	52 (67.5)
	Yes	68 (63.6)	44 (48.4)	147 (69.3)	25 (32.5)
Concomitant use of potentially nephrotoxic or NSAID drugs	No	91 (85.0)	73 (80.2)	175 (82.5)	67 (87.0)
	Yes	16 (15.0)	18 (19.8)	37 (17.5)	10 (13.0)
Presence of hyperlipidaemia, hypertension or diabetes[e]	No	56 (52.3)	25 (27.5)	107 (50.5)	24 (31.2)
	Yes	51 (47.7)	66 (72.5)	105 (49.5)	53 (68.8)
	Hyperlipidaemia	8 (7.5)	20 (22.0)	22 (10.4)	16 (20.8)
	Hypertension	47 (43.9)	54 (59.3)	92 (43.4)	48 (62.3)
	Diabetes	18 (16.8)	26 (28.6)	28 (13.2)	14 (18.2)
Duration of CHB infection, y	107|91 212|77	9.1 (0.2-19.1)	4.6 (0.8-15.2)	11.5 (5.0-20.4)	4.6 (0.8-13.2)
Duration of previous HBV treatment, y	96|91 204|74	3.3 (0.0-9.7)	0.0 (0.0-6.1)	4.9 (0.0-10.7)	0.0 (0.0-1.0)
Serum albumin, g/L	45|35 151|46	45.0 (40.0-46.0)	42.0 (37.0-45.0)	44.7 (41.0-47.0)	40.9 (35.0-43.0)
Alanine aminotransferase, μkat/L	63|46 200|68	0.4 (0.2-0.6)	0.6 (0.4-1.0)	0.4 (0.4-0.6)	0.4 (0.2-0.6)
Aspartate aminotransferase, μkat/L	63|45 190|67	0.4 (0.4-0.6)	0.4 (0.4-1.0)	0.4 (0.4-0.6)	0.4 (0.4-0.6)
Serum bilirubin, μmol/L	61|45 151|65	10.3 (7.5-15.6)	10.4 (7.0-15.9)	10.0 (6.8-15.0)	10.6 (8.6-15.9)
BMI	102|83 187|72	23.4 (21.1-26.3)	24.6 (22.4-27.4)	25.1 (22.8-27.4)	26.2 (23.3-28.5)
Creatinine clearance, mL/min (mean [95% CI])[f]	70|51 212|77	48.5 (46.3-50.7)	43.9 (41.0-46.7)	53.8 (52.7-54.8)	47.8 (45.2-50.5)
Serum HBV DNA, $\log_{10}$ IU/mL	62|44 186|58	2.6 (1.6-7.7)	4.6 (2.2-15.6)	0.0 (0.0-2.9)	2.9 (1.4-4.2)
International normalised ratio	52|41 159|51	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (1.0-1.2)
Platelet count, thousand/μL	67|50 198|72	187.0 (152.0-220.0)	185.0 (136.0-228.0)	181.0 (147.0-224.0)	185.5 (139.5-222.5)
Serum phosphate, mmol/L	42|25 153|38	0.8 (0.6-1.0)	1.1 (0.8-1.1)	1.0 (0.8-1.1)	1.1 (1.0-1.5)

Abbreviations: BMI, body mass index; CHB, chronic hepatitis B virus infection; CI, confidence interval; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; NSAID, nonsteroidal anti-inflammatory drug; TDF, tenofovir disoproxil fumarate.

[a]For categorical variables, category is shown.

[b]For continuous variables, the number of evaluable patients in each treatment group is indicated: the evaluable N for the renal impairment before treatment initiation subgroup is shown in the first row and the evaluable N for the renal impairment after treatment initiation subgroup is shown in the second row. Note that the number of participants with missing data are shown in Table S2 and age is presented in Figure 2.

[c]n (%) and median (interquartile range) are shown for categorical and continuous variables respectively, unless otherwise stated.

[d]Evidence indicated by the site investigator.

[e]Patients could have multiple comorbidities.

[f]Creatinine clearance was 20-60 mL/min for all patients.

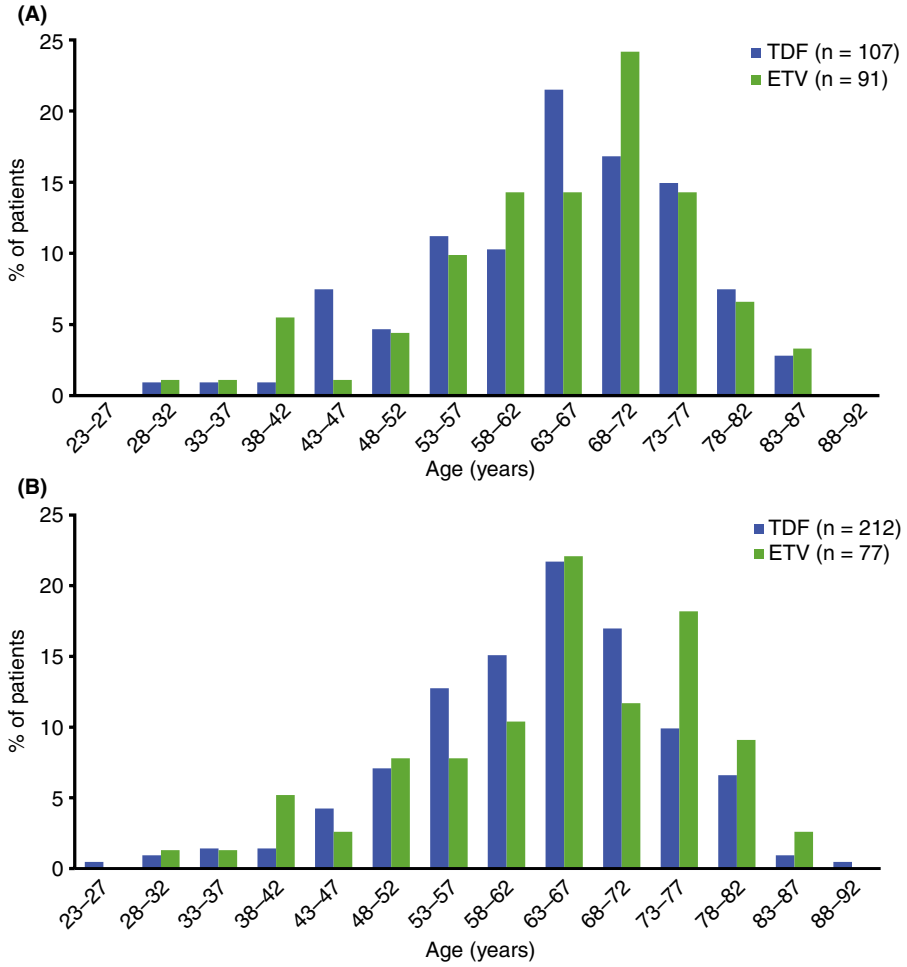

FIGURE 2 Age distribution of TDF- and ETV-treated patients. Patients with renal impairment before (A) and after (B) treatment initiation. Age was collected in 5-year groups. ETV, entecavir; TDF, tenofovir disoproxil fumarate

altered following AEs in 18 patients (64.3% of the 28 patients who experienced AEs). Twenty (18.7%) TDF-treated patients experienced 21 AEs of special interest, while 8 (8.8%) ETV-treated patients experienced 9 AEs of special interest (Table 3). For TDF-treated patients, the most frequent AE of special interest was renal AEs leading to treatment discontinuation, experienced by 8.4% of patients, while 7.5%, 6.5% and 3.7% of patients experienced a decline in renal function (reported as an AE), renal tubular dysfunction AEs and renal SAEs respectively. Decline in renal function and renal SAEs were reported by 7.7% and 2.2% of ETV-treated patients. There were no incidences of renal tubular dysfunction AEs or renal AEs leading to treatment discontinuation in ETV-treated patients. Frequencies of AEs of special interest were numerically higher in the TDF compared with the ETV group but, given the relatively small number of events, the incidence rate ratio for AEs of special interest did not achieve statistical significance (2.05 [95% CI: 0.89-4.75]; $P = 0.094$). In addition, there was no statistical difference in incidence rate ratio between treatments when evaluated by subgroups (Table S3). No renal SAEs leading to death (Table 3) or renal AEs leading to dialysis (or other forms of renal support) were reported for either treatment group. Mean creatinine clearance remained relatively stable over time in TDF-treated patients, while it tended to increase slightly in ETV-treated patients (Figure S1). However, it should be noted that the creatinine clearance values are not directly comparable between treatment groups due to the differences at baseline. Interpretation is further challenged by the low number of evaluable patients at later time points. Modelling of time to development of renal impairment, controlling for baseline characteristics and prior adefovir treatment, was not statistically different between TDF and ETV, nor was modelling of further aggravation of renal impairment (see Supplementary Results).

3.3 | Safety in patients with renal impairment after treatment initiation

Of the patients with renal impairment occurring after treatment initiation, 38 (17.9%) TDF-treated patients experienced 51 AEs, including 19 SAEs, while 7 (9.1%) ETV-treated patients experienced 9 AEs, including 7 SAEs (Table 2). Treatment-related AEs were experienced by 24 (11.3%) and 4 (5.2%) of TDF- and ETV-treated patients respectively. TDF dosing was altered following AEs in 20 patients (52.6% of the 38 patients who experienced AEs). Twenty-one (9.9%) TDF-treated patients experienced 27 AEs of special interest, while 3 (3.9%) ETV-treated patients experienced 3 AEs of special interest

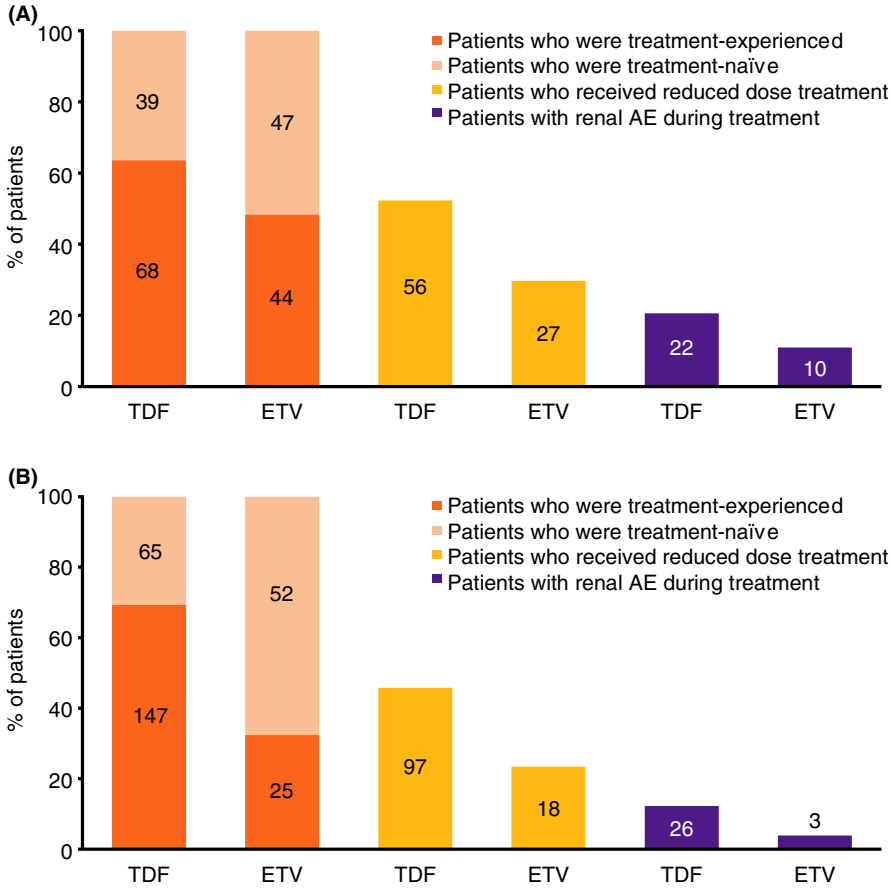

FIGURE 3 Distribution of patients in each subgroup according to prior treatment and renal AE. Patients with renal impairment before (A) and after (B) treatment initiation. Annotated numbers show the number of patients in each subgroup. AE, adverse event; ETV, entecavir; TDF, tenofovir disoproxil fumarate

(Table 3). For TDF-treated patients, the most frequent AE of special interest was renal AEs leading to treatment discontinuation, experienced by 7.1% of patients, while 4.2%, 2.4% and 1.9% of patients experienced a decline in renal function, renal SAEs, and renal tubular dysfunction AEs respectively. Decline in renal function and renal SAEs were experienced by 2.6% and 1.3% of ETV-treated patients; none experienced renal tubular dysfunction AEs or renal AEs leading to treatment discontinuation. Although numerically higher proportions of TDF-treated patients experienced these AEs, the incidence rate ratio for AEs of special interest did not differ between treatment groups overall (2.30 [95% CI: 0.27-19.84]; P = 0.447) or in further subgroup analyses (Table S3). There were no renal SAEs leading to death (Table 3) or renal AEs leading to dialysis (or other forms of renal support) in either treatment group. In both treatment groups, mean creatinine clearance tended to slightly decrease over time (Figure S1), although these data should be interpreted with caution given the few observations at later time points, as noted previously. Modelling of time to further aggravation of renal impairment was not statistically different between TDF and ETV (see Supplementary Results).

3.4 | Effectiveness of TDF and ETV

In patients with pre-existing renal impairment and in those with renal impairment after treatment initiation, there were no differences between the TDF and ETV treatment groups in the likelihood of achieving HBV DNA levels <69 IU/mL (Table S4). The hazard ratio (95% CI) of TDF- vs ETV-treated patients for achieving and/or maintaining viral suppression was 1.1 (0.61-1.8) in the subgroup of patients with pre-existing renal impairment and 0.99 (0.44-2.22) in the subgroup of patients with renal impairment after treatment initiation. Findings were similar among further patient subgroups.

4 | DISCUSSION

This retrospective, non-interventional cohort study was undertaken to address the paucity of data regarding the safety and effectiveness of TDF and ETV in CHB patients with moderate or severe renal impairment (creatinine clearance 20-60 mL/min): an issue despite the fact that these two first-line treatments have been approved for use for over 12 years.[28,40-42] The study evaluated patients receiving TDF or ETV who had pre-existing renal impairment, as well as those who developed renal impairment after treatment with either of the agents was initiated. To our knowledge, this is the largest evaluation to date of TDF in CHB patients with this degree of renal impairment, providing insight into these two important patient populations.

In this study, the overall safety profile was similar between TDF and ETV for both renal impairment subgroups. A higher proportion of AEs of special interest was observed in TDF- compared with ETV-treated patients for both subgroups. However, incidence rate ratios did not significantly differ between treatments following

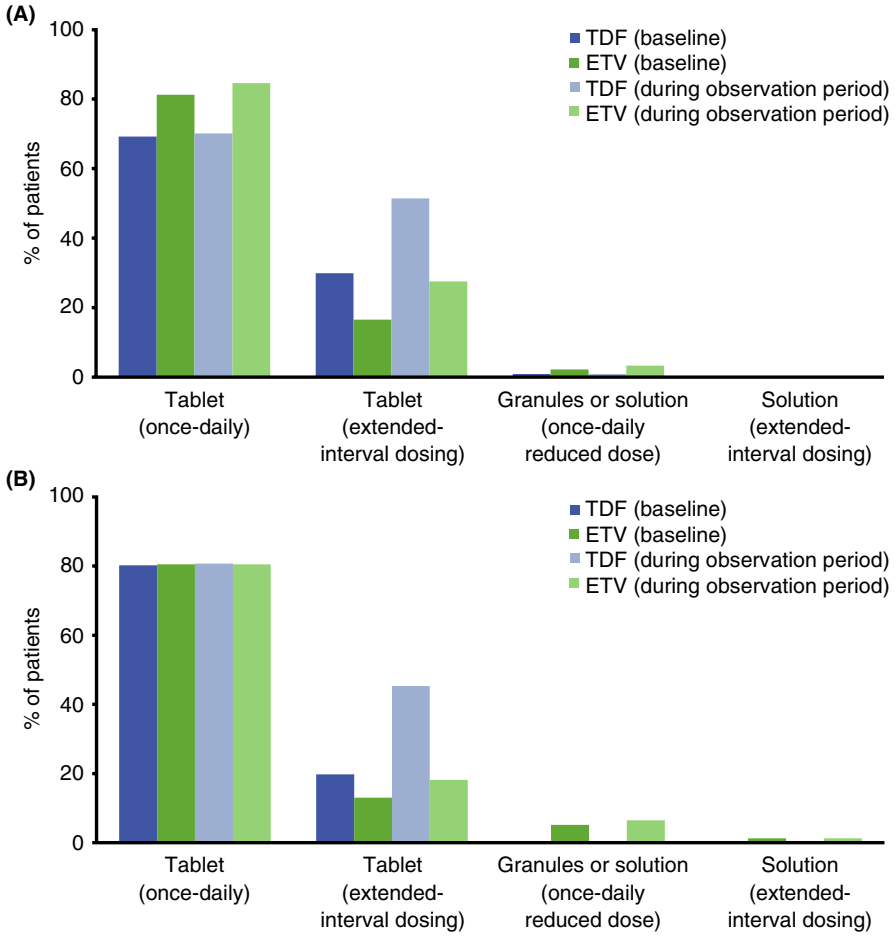

FIGURE 4 Dosage forms and schedules at baseline and during the observation period. Patients with renal impairment before (A) and after (B) treatment initiation. Some patients switched between dosing forms during the observation period. ETV, entecavir; TDF, tenofovir disoproxil fumarate

implementation of an inverse probability treatment-weighted approach, which enables comparison of the treatment groups given the differences in baseline characteristics. The one exception to this was the significant difference in incidence rate ratio between TDF- and ETV-treated patients with pre-existing renal impairment for treatment-related AEs, which is in keeping with the well-understood safety profile for TDF. However, renal tubular dysfunction AEs and renal AEs leading to drug discontinuation were only reported in TDF-treated patients. Not unexpectedly, there was also no observed difference in effectiveness (HBV DNA suppression) between TDF and ETV, regardless of renal impairment subgroup.

Chronic hepatitis B virus–infected patients with renal impairment are predisposed to experience further decline in renal function once anti-HBV treatment is initiated.[26,29,35,43] In this analysis, baseline creatinine clearance was lower in ETV- vs TDF-treated patients with pre-existing renal impairment, suggesting that clinicians might prefer to prescribe ETV for individuals with diminished renal function, per treatment guidelines.[9,10] A greater proportion of patients with pre-existing renal impairment experienced AEs of special interest compared with those who experienced renal impairment after treatment initiation, emphasising the importance of this risk factor in treatment selection. The safety findings in this real-world cohort study are consistent with the known safety profiles of TDF and ETV, and underscore the importance of regular renal function monitoring and dose adjustment, where appropriate, in clinical practice, as described in current product labelling and recommended in current international clinical practice guidelines.[7,9,10,28]

Our observation of renal tubular dysfunction AEs and renal AEs leading to treatment discontinuation in TDF-treated patients, but not in those who received ETV, is in keeping with the established renal safety concerns with TDF treatment. While TDF has an established role in the treatment of CHB patients, new options are becoming available that may offer an improved renal safety profile: tenofovir alafenamide (TAF) has received authorisation for the treatment of CHB in over 75 countries worldwide (data on file—Gilead Sciences, Inc), including the USA[44] and members of the EU.[45] In head-to-head trials in CHB patients with baseline creatinine clearance ≥50 mL/min, TAF demonstrated non-inferiority to TDF at Weeks 48 and 96 in terms of efficacy.[46-48] Importantly, treatment with TAF was associated with lower rates of renal and bone abnormalities compared with TDF.[46-48] Switching from TDF to TAF was also associated with improvements in renal and bone parameters (with non-inferior efficacy), in a study evaluating this switch in 243 patients with CHB.[49] Some markers of renal tubular function also improved in another study of 75 CHB patients (including 8 patients with creatinine clearance <60 mL/min), following a switch from TDF to TAF.[50] In addition, renal function was improved in CHB patients with renal impairment 24 weeks after switching from TDF to TAF, including in those with end-stage renal disease on chronic haemodialysis.[51] No dose adjustment is required for TAF in

TABLE 2 Incidence rate ratios of TDF- and ETV-treated patients experiencing an AE by renal impairment subgroup

Subgroup	Treatment	Number of AEs, n (%)[a]	Number of patients, n (%)	Total person-time, y	Rate per 1000 person-years (95% CI)[b]	Incidence rate ratio (95% CI)[c]	*P* value
Renal impairment before treatment initiation							
Patients experiencing any AE	ETV	15	12 (13.2)	314.9	38.1 (19.7-66.6)	Reference	—
	TDF	38	28 (26.2)	375.3	74.6 (49.6-107.8)	1.73 (0.87-3.41)	0.116
Treatment-related AEs	ETV	4 (26.7)	4 (4.4)	327.1	12.2 (3.3-31.3)	Reference	—
	TDF	27 (71.1)	21 (19.6)	385.4	54.5 (33.7-83.3)	4.76 (1.52-14.91)	0.007
AE leading to death[d,e]	ETV	4 (26.7)	3 (3.3)	337.2	8.9 (1.8-26.0)	Reference	—
	TDF	5 (13.2)	3 (2.8)	417.5	7.2 (1.5-21.0)	1.08 (0.16-7.10)	0.936
Renal AEs	ETV	11 (73.3)	10 (11.0)	312.5	32.0 (15.3-58.9)	Reference	—
	TDF	24 (63.2)	22 (20.6)	380.7	57.8 (36.2-87.5)	1.50 (0.72-3.14)	0.277
SAEs	ETV	6 (40.0)	5 (5.5)	331.6	15.1 (4.9-35.2)	Reference	—
	TDF	9 (23.7)	7 (6.5)	409.2	17.1 (6.9-35.2)	1.15 (0.34-3.85)	0.820
Renal SAEs	ETV	2 (13.3)	2 (2.2)	329.7	6.1 (0.7-21.9)	Reference	—
	TDF	4 (10.5)	4 (3.7)	410.9	9.7 (2.7-24.9)	1.12 (0.23-5.52)	0.887
Renal impairment after treatment initiation							
Patients experiencing any AE	ETV	9	7 (9.1)	370.6	18.9 (7.6-38.9)	Reference	—
	TDF	51	38 (17.9)	1000.1	38.0 (26.9-52.2)	2.03 (0.62-6.61)	0.239
Treatment-related AEs	ETV	4 (44.4)	4 (5.2)	373.2	10.7 (2.9-27.4)	Reference	—
	TDF	29 (56.9)	24 (11.3)	1005.7	23.9 (15.3-35.5)	1.91 (0.45-8.07)	0.381
AE leading to death[d,f]	ETV	6 (66.7)	4 (5.2)	376.7	10.6 (2.9-27.2)	Reference	—
	TDF	12 (23.5)	8 (3.8)	1029.1	7.8 (3.4-15.3)	0.89 (0.17-4.59)	0.887
Renal AEs	ETV	3 (33.3)	3 (3.9)	370.4	8.1 (1.7-23.7)	Reference	—
	TDF	33 (64.7)	26 (12.3)	1009.3	25.8 (16.8-37.7)	3.49 (0.42-28.70)	0.245
SAEs	ETV	7 (77.8)	5 (6.5)	374.0	13.4 (4.3-31.2)	Reference	—
	TDF	19 (37.3)	13 (6.1)	1025.9	12.7 (6.7-21.7)	0.88 (0.20-3.81)	0.860
Renal SAEs	ETV	1 (11.1)	1 (1.3)	373.9	2.7 (0.1-14.9)	Reference	—
	TDF	9 (17.6)	5 (2.4)	1025.3	4.9 (1.6-11.4)	1.61 (0.03-81.81)	0.812

Abbreviations; AE, adverse event; CI, confidence interval; ETV, entecavir; SAE, serious adverse event; TDF, tenofovir disoproxil fumarate.

[a]Multiple AEs could occur in a single patient.

[b]Based on time to first experienced AE.

[c]Incidence rate ratio was calculated using multiple imputation and an inverse probability treatment weighted approach.

[d]For patients with multiple AEs leading to death, only one AE was counted. One TDF-treated patient with renal impairment before treatment initiation experienced three AEs leading to death and one TDF-treated patient with renal impairment after treatment initiation experienced two AEs leading to death.

[e]Three TDF-treated patients died due to malignancy (n = 2) and haemorrhagic shock (n = 1). Three ETV-treated patients died due to chronic lymphocytic leukaemia (n = 1), sepsis (n = 1) and unknown cause (n = 1).

[f]Eight TDF-treated patients died, due to malignancy (n = 2), cardiac failure and multiple organ dysfunction (n = 1), cardiogenic shock (n = 1), cerebral haemorrhage (n = 1), sepsis (n = 1) and unknown cause (n = 2). Four ETV-treated patients died, due to pneumonia and multiple organ dysfunction (n = 1) and unknown cause (n = 3).

CHB patients with creatinine clearance ≥15 mL/min (or <15 mL/min in patients receiving haemodialysis),[52] thus TAF represents an important new treatment option for CHB patients with renal impairment. In accordance with this, TAF, along with ETV, is preferred over TDF in current treatment guidelines for certain at-risk CHB patients, including those with renal impairment or bone disease.[9,10] Studies evaluating TAF are ongoing and long-term data are awaited.

Regardless of renal impairment subgroup, there was no evidence for a difference in effectiveness between TDF and ETV, in agreement with the equivalent long-term efficacy of TDF and ETV described previously.[53-55] However, data from patients with more than 48 weeks of continuous treatment were limited, and accurate retrospective assessment of effectiveness can be challenging due to differences in HBV DNA monitoring frequency and assay cut-offs between study centres.

TABLE 3 Incidence rate ratios of TDF- and ETV-treated patients experiencing an AE of special interest[a] by renal impairment subgroup

Subgroup	Treatment	Number of AESIs, n (%)	Number of patients, n (%)	Total person-time, y	Rate per 1000 person-years (95% CI)[b]	Incidence rate ratio (95% CI)[c]	*P* value
Renal impairment before treatment initiation							
Patients experiencing any AE of special interest	ETV	9	8 (8.8)	318.2	25.1 (10.9-49.5)	Reference	—
	TDF	21	20 (18.7)	384.5	52.0 (31.8-80.3)	2.05 (0.89-4.75)	0.094
Presence of a renal tubular dysfunction AE	ETV	0	0	—	—	—	—
	TDF[d]	7 (33.3)	7 (6.5)	413.1	16.9 (6.8-34.9)	NE	—
Renal AEs leading to drug discontinuation	ETV	0	0	—	—	—	—
	TDF	9 (42.9)	9 (8.4)	413.3	21.8 (10.0-41.3)	NE	—
Renal SAEs including those leading to death[e]	ETV	2 (22.2)	2 (2.2)	329.7	6.1 (0.7-21.9)	Reference	—
	TDF	4 (19.0)	4 (3.7)	410.9	9.7 (2.7-24.9)	1.12 (0.23-5.52)	0.887
Decline in renal function reported as AE	ETV	7 (77.8)	7 (7.7)	323.6	21.6 (8.7-44.6)	Reference	—
	TDF	8 (38.1)	8 (7.5)	397.1	20.1 (8.7-39.7)	1.19 (0.42-3.34)	0.745
Renal impairment after treatment initiation							
Patients experiencing any AE of special interest	ETV	3	3 (3.9)	370.4	8.1 (1.7-23.7)	Reference	—
	TDF	27	21 (9.9)	1019.1	20.6 (12.8-31.5)	2.30 (0.27-19.84)	0.447
Presence of a renal tubular dysfunction AE	ETV	0	0	—	—	—	—
	TDF[f]	4 (14.8)	4 (1.9)	1025.6	3.9 (1.1-10.0)	NE	—
Renal AEs leading to drug discontinuation	ETV	0	0	—	—	—	—
	TDF[g]	17 (63.0)	15 (7.1)	1024.9	14.6 (8.2-24.1)	NE	—
Renal SAEs including those leading to death[e]	ETV	1 (33.3)	1 (1.3)	373.9	2.7 (0.1-14.9)	Reference	—
	TDF[h]	9 (33.3)	5 (2.4)	1025.3	4.9 (1.6-11.4)	1.61 (0.03-81.81)	0.812
Decline in renal function reported as AE	ETV	2 (66.7)	2 (2.6)	373.1	5.4 (0.6-19.4)	Reference	—
	TDF	9 (33.3)	9 (4.2)	1026.8	8.8 (4.0-16.6)	1.35 (0.09-19.31)	0.824

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; ETV, entecavir; NE, not estimable; SAE, serious adverse event; TDF, tenofovir disoproxil fumarate.

[a]No patients experienced renal AEs leading to initiation of dialysis.

[b]Based on time to first experienced AE of special interest.

[c]Incidence rate ratio was calculated using multiple imputation and an inverse probability treatment weighted approach.

[d]The reported Preferred Terms were renal tubular disorder (n = 6) and Fanconi syndrome acquired (n = 1).

[e]No renal SAEs leading to death were reported.

[f]The reported Preferred Terms were renal tubular disorder (n = 3) and renal tubular necrosis (n = 1).

[g]One patient experienced three AEs of this category.

[h]Two patients experienced the same type of SAE multiple times (two and four times respectively).

The retrospective design of this study confers important limitations. While the data capture process was designed to minimise potential bias, the high proportion of missing data limits the analysis and there was potential for measurement error. In addition, data capture wording may have been misinterpreted, which was of particular concern for determining the relationship between the occurrence of renal impairment and drug initiation, leading to a lack of exact renal laboratory data at baseline for 77 patients (all with pre-existing renal impairment: 37 TDF; 40 ETV). However, findings did not differ between the multiple imputation approach used and complete case analyses (data not shown), indicating that overall conclusions were unaffected. Differences in the number of visits and follow-up investigations between patients may introduce imprecision, while subgroup analyses risk type I or II errors since the study was statistically powered based on the primary objective. There is the potential for imbalances in baseline characteristics; for example, ETV may have been preferentially selected for use in older patients with comorbidities, although we used propensity score weighting to balance comorbidities as much as possible. However, this real-world, multicentre study analysed a large group of CHB patients with either pre-existing renal impairment or renal impairment after treatment initiation, including patients with cirrhosis and relevant comorbidities. Thus, it provides valuable insights into the safety and effectiveness of TDF and ETV in two different contexts of renal impairment important for clinical practice.

In conclusion, in this large multinational, real-world study, the overall safety profile was similar between TDF and ETV for CHB patients who experienced either moderate or severe pre-existing

renal impairment or renal impairment beginning after treatment initiation. However, higher proportions of AEs of special interest, including renal tubular dysfunction, were observed in TDF- vs ETV-treated patients in both renal impairment subgroups. Effectiveness was similar between TDF and ETV for both renal impairment subgroups. Our findings support the current prescribing information and renal function assessment recommendations for both therapies.

ACKNOWLEDGEMENTS

We thank all patients and the full ReCoRd investigator group involved in the study. Participating investigators were: in France, M. Bourlière, V. De Ledinghen, G. Riachi, F. Zoulim, V. Loustaud-Ratti, A. Tran, D. Larrey, J. Dumortier, V. Leroy, S. Metivier, P. Sellier; in Germany, S. Mauss, J. Peterson, T. Berg, I. Schiefke, C. Niederau, G. Teuber, T. Goeser, M. C. Jung, A. Grambihler, A. Pathil-Warth, K. Sprinzl, M. Von der Ohe, C. Antoni, K. Weigand; in Italy, P. Andreone, P. Lampertico, V. Di Marco, S. Madonia, M. Puoti, T. Santantonio, M. Vigano, A. Ciancio, G. D'Offizi, M. Pirisi; in Spain, M. Buti, E. Suarez Garcia, J. M. Pascasio Acevedo, R. Andrade, F. Gea, M. A. Serra Desfilis, E. Molina Perez, M. Manzano Alonso, J. A. Carrion, S. Aoufi Rabih, M. M. Planas; in the UK, S. Ryder, K. Agarwal, A. Ustianowski, R. Aspinall, P. Kennedy, A. M. Geretti, R. McCorry, M. Foxton, B. Healy. Medical writing support, including development of drafts in consultation with the authors, assembling tables and figures, collating author comments, copyediting, fact checking and referencing, was provided by Beatrice Tyrrell, DPhil at Aspire Scientific (Bollington, UK) and funded by Gilead Sciences Europe Ltd (Uxbridge, UK). Gilead Sciences Europe Ltd (Uxbridge, UK) designed and funded the study and was involved in the collection, analysis and interpretation of data, as well as reviewing drafts and the final manuscript. The final decision to submit the article for publication was solely that of the authors.

Declaration of personal interests: PL has participated in advisory boards/speaker bureaux for AbbVie, Alnylam, Arrowhead, Bristol-Myers Squibb, Eiger, Gilead Sciences, Janssen, MYR Pharmaceuticals, MSD and Roche. TB has received research support from AbbVie, Bristol-Myers Squibb, Gilead, Intercept, Janssen, Merck/MSD, Novartis, Pfizer, Roche and Sequana Medical; and provided consultancy, and participated in speakers bureaux and advisory boards for AbbVie, Alexion, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Intercept, Janssen, Merck/MSD, Merz, Novartis, Sequana Medical and Roche. MB has received grants from Gilead Sciences and lecture sponsorship from AbbVie, Gilead Sciences and Merck. AP has acted as a consultant for AbbVie and received lecture sponsorship from AbbVie, Bristol-Myers Squibb and Gilead Sciences. JP has received grants or research support from Bristol-Myers Squibb, Novartis and Roche; acted as a consultant/advisor for Abbott, AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Janssen, Kedrion, Merck, MSD, Novartis and Roche; and acted as a speaker for Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, Janssen, Kedrion, MSD, Novartis and Roche. SDR has participated in advisory boards and acted as a paid speaker for AbbVie, Gilead and MSD. FZ has received grants from Evotec and Roche, and acted as a consultant for AbbVie, Arbutus, Gilead, Janssen, MYR Pharma, Roche, Springbank, Transgene, and Vir Biotech. IB, JFF, BJ, MOB, AvT and HR are employees and stockholders of Gilead Sciences.

AUTHORSHIP

Guarantor of the article: HR.

Author contributions: All authors made substantial contributions to the study, critically revised the manuscript for important intellectual content, approved the final version of the article (including the authorship list) and agreed to be accountable for all aspects of the work. PL, TB, MB, AP, JP, FZ, IB, JFF, AvT and HR contributed to the conception, design and conduct of the study and the analysis or interpretation of the data. SDR conducted the study and analysed or interpreted the data. BJ and MOB contributed to the conception and design of the study and the analysis and interpretation of the data.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Lampertico P, Berg T, Buti M, et al; the ReCoRd (Retrospective, Cohort, Renal, Viread) Investigators' Group. Treatment with tenofovir disoproxil fumarate or entecavir in chronic hepatitis B virus-infected patients with renal impairment: results from a 7-year, multicentre retrospective cohort study. *Aliment Pharmacol Ther*. 2020;52:500–512. https://doi.org/10.1111/apt.15901

APPENDIX 1

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