

# Differences in nephrotoxicity risk and renal effects among anti-viral therapies against hepatitis B

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## SUMMARY

### Background

Results are conflicting with respect to the renal effects of anti-viral agents used for hepatitis B virus infection.

### Aim

To compare short and long-term renal effects in real-life settings and to determine risk factors for renal impairment during treatment.

### Methods

2221 treatment-naïve patients were enrolled. Among these, 895 (302 lamivudine, 27 telbivudine, 282 entecavir, 273 tenofovir and 11 adefovir initiated patients) had 'repeated measures' of creatinine (baseline, 1st, 6th, 12th and 24th month of treatment). Telbivudine and adefovir groups were excluded from further analysis because of the low number of patients. We calculated the glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) formula at each time point. Hypophosphataemia was also recorded. Risk factors for renal impairment were analysed.

### Results

Tenofovir caused a decline in GFR at each time point when compared to baseline levels. However, lamivudine and entecavir did not change GFR. GFR-shifting from  $\geq 90$  to 60–89 mL/min/1.73 m<sup>2</sup> was comparable among groups. The proportion of patients whose baseline creatinine increased more than 25% was comparable among all anti-virals. GFR showed a decline in patients who switched from entecavir to tenofovir. One patient with compensated cirrhosis needed to change from tenofovir because of renal safety. Seven and three patients developed transient hypophosphataemia in the tenofovir and lamivudine groups, respectively.

### Conclusions

Although tenofovir caused a decline in GFR, differences between the anti-viral agents do not appear to be so impressive. In patients with and without renal risk factors at baseline, there is no impact of anti-virals, including tenofovir.

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## INTRODUCTION

For treatment of chronic hepatitis B, anti-viral agents are usually safe and well-tolerated. However, their main limitation is the need for indefinite treatment duration. They display anti-viral activity through blocking of viral DNA polymerase. Host DNA polymerase is also affected, which may lead to a mitochondrial functional deficiency. Clinically, mitochondrial deficiency is responsible for adverse effects including lactic acidosis, myopathy, neuropathy and nephrotoxicity. All anti-viral agents [nucleos (t)ide analogues (NA)] used in chronic hepatitis B infection are cleared by the kidney and nephrotoxicity is among the potential adverse events. Nucleotide analogues (adefovir and tenofovir) have received the most attention with respect to renal toxicity,<sup>1–6</sup> whereas improvement of GFR has been reported with telbivudine.<sup>7</sup> Renal toxicity of adefovir is mostly dose-dependent and adverse events occur rarely at the approved dose of 10 mg daily. Some studies have reported worsened renal functions during tenofovir treatment.<sup>6, 8</sup> However, most of the tenofovir-related renal toxicities were in patients with HIV coinfection<sup>8, 9</sup> and have been less studied in patients with chronic HBV infection. Some studies demonstrated minor renal deterioration that was attributed to tenofovir treatment in HBV patients.<sup>10–12</sup> Fanconi syndrome is a rare disease of the proximal renal tubules and to date, a few cases of tenofovir-associated Fanconi syndrome have been reported in HBV monoinfected patients.<sup>13, 14</sup> Similar to nucleotide analogues, entecavir, telbivudine and lamivudine show their anti-viral effect by inhibiting DNA polymerase. However, there is no evidence for renal adverse effects attributed to these three agents. In contrast, several studies have reported a beneficial effect of telbivudine on renal functions with an unclear mechanism.<sup>7, 15</sup>

Renal impairment during the course of anti-viral treatment of hepatitis B still needs to be clarified whether it is related to anti-viral nephrotoxicity or pre-existing risk factors for renal disease. The available studies mostly examine the decline rather than an improvement in renal function in patients receiving anti-viral agents for hepatitis B.<sup>16</sup> In this community-based, real-life cohort study we examined the renal effects of the available anti-viral agents in a large number of patient groups with hepatitis B. To our knowledge, this study includes the highest number of HBV treated patients regarding the renal impact of short and long term use of anti-viral treatment. Our aim was also to assess the renal risk factors in these patients.

## METHODS

This study enrolled treatment-naïve adult patients with chronic hepatitis B who were initiated with anti-viral agents. The study protocol was approved by the Ethics Committee of Hacettepe University School of Medicine. To be eligible, patients needed to be treatment-naïve and exposed to NA for at least 6 months. Patients were required to have at least 6 months of follow-up and serum creatinine measurements before and during anti-viral therapy (at least one measurement at the 1st, 6th, 12th or 24th month). Exclusion criteria were as follows: absence of or insufficient renal safety data, patients coinfecting with HIV, hepatitis C or D; accompanying hepatocellular or any other carcinoma and history of organ transplantation, acute hepatitis B or liver failure at admission.

Sociodemographic data and grade of liver fibrosis were recorded and the groups were further subdivided as cirrhotics (compensated or decompensated) and noncirrhotics.

### Selection of anti-viral therapy

Almost all of the patients had health insurance and according to health budget laws in Turkey during the study period (August 2009–July 2014), selection of anti-viral agent depended upon pre-treatment HBV DNA levels and presence or absence of cirrhosis. For cirrhotics, any NA could be preferred. For noncirrhotics with low pre-treatment HBV DNA ( $\leq 10^7$  copy/mL), only lamivudine or telbivudine could be selected. Noncirrhotics with high pre-treatment HBV DNA ( $> 10^7$  copy/mL) could begin with any NA, including tenofovir and entecavir. Another important factor for anti-viral selection was based on the time of market entrance of each NA. Lamivudine is the oldest and telbivudine is the youngest (available for 3 years) NA on the market.

### Assessment of renal function

Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) calculation [GFR (mL/min/1.73 m<sup>2</sup>):  $186 \times \text{Serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times \text{Gender} \times \text{Race}$ ].

GFR was calculated before and at the 1st, 6th, 12th and 24th month of initial NA treatment ('repeated measures'). Also, 12th month GFR was calculated in patients who changed initial NA. GFR was categorised into three subgroups: (i)  $< 60$  mL/min/1.73 m<sup>2</sup>, (ii) 60–89 mL/min/1.73 m<sup>2</sup> and (iii)  $\geq 90$  mL/min/1.73 m<sup>2</sup>.

Serum calcium and phosphate levels were also recorded at the GFR estimated months.

### Assessment of patients

To further study the impact of NA on renal function, results of patients with ‘repeated measures’ [serum creatinine measurements at the beginning (baseline) and at the 1st, 6th, 12th and 24th month of treatment] were obtained with details in this study. Patients who had ‘repeated measures’ and continued initial NA therapy for at least 24 months were compared with respect to renal effects of each NA. Patients who changed initial NA after 24 months were further followed up for at least 12 months. In those patients, baseline creatinine and GFR were considered at the time of initiating the new drug and further comparisons were performed accordingly. Analyses were performed separately for patients with decompensated cirrhosis.

### Statistical analysis

All statistical analyses were done using SPSS 16.0 (SPSS software; SPSS Inc., Chicago, IL, USA).  $\chi^2$  test was used for comparison of categorical variables. For continuous variables, one-way analysis of variance and Student’s *t*-test were used to analyse the variance among groups if

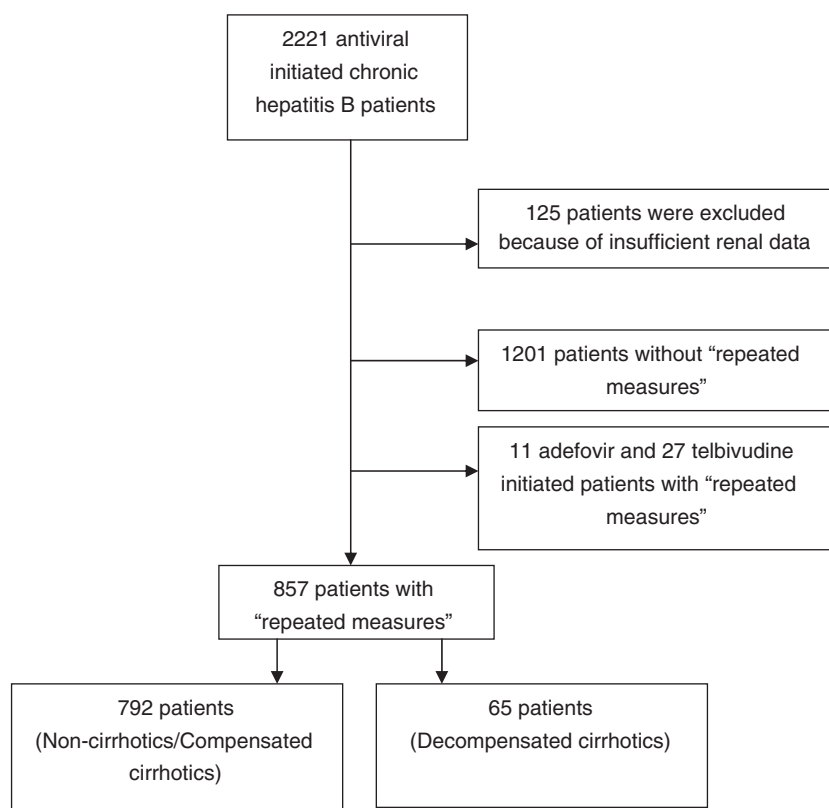
appropriate. Repeated measures analysis of variance (rANOVA) was used to compare ‘repeated measures’ of GFR and creatinine. Logistic regression analysis was used to identify independent factors related with ‘Shift from 60–89 to  $\geq 90$ ’. A *P*-value of 0.05 and below was considered statistically significant.

## RESULTS

### Baseline demographics

We included 2221 treatment-naive chronic hepatitis B patients from 22 centres throughout Turkey. One hundred and twenty-five patients were excluded because of incomplete data. Among the remaining 2096 patients, lamivudine, entecavir, tenofovir, telbivudine and adefovir were initiated in 749, 568, 589, 165 and 25 individuals, respectively.

There were 895 patients who used initial NA for at least 24 months and had ‘repeated measures’ at the beginning, and at the 1st, 6th, 12th and 24th month of follow-up (Figure 1). Those patients with ‘repeated measures’ were included in further statistical analysis. Considering the patients with and without ‘repeated measures’, there was no difference regarding baseline features, including demographics, stage of liver disease and



**Figure 1** | Flow of patient selection for the study analysis.

renal function tests in each NA group. Since the number of patients with 'repeated measures' was low in the telbivudine and adefovir groups, we excluded them from further statistical analysis. With respect to ethnic composition, all patients were white. Demographic data and baseline laboratory test results of patients with 'repeated measures' according to initiated NAs are summarised in Table 1.

Among patients with 'repeated measures', 239 (27.9%) had cirrhosis and 65 had decompensated cirrhosis. More than 85% of the noncirrhotic patients had a liver biopsy at the beginning. There were differences among groups with respect to baseline ALT, AST, HBV DNA and HBeAg because of the anti-viral policy in Turkey as stated in the methods section.

#### Evaluation of GFR with 'repeated measures' and serum calcium and phosphate

In noncirrhotics/compensated cirrhotics, GFR was significantly decreased with time in the tenofovir group ( $P = 0.001$ ), whereas GFRs were unchanged in the other groups (Figure 2). Similarly, serum creatinine increased with time in the tenofovir group ( $P = 0.001$ ) but was unchanged in the other groups (Figure 3). Serum calcium and phosphate were unchanged in all NA groups

(Table 2). Five and three patients developed transient hypophosphataemia ( $<2$  g/dL) in the tenofovir and lamivudine groups, respectively.

In patients with decompensated cirrhosis, GFR decreased significantly in the tenofovir group ( $P = 0.001$ ) but was unchanged in the lamivudine and entecavir groups. Serum creatinine was unchanged with time in the lamivudine and entecavir groups, whereas it increased in the tenofovir group ( $P = 0.001$ ) (Table 3). Since few patients with decompensated cirrhosis had repeated measures of calcium and phosphate, statistical analysis was not performed.

#### Comparison of "GFR-difference" among anti-viral groups

GFR-difference was significantly higher in the tenofovir group compared to other groups at the 1st month. All groups had comparable GFR-differences at the other months (Table 4).

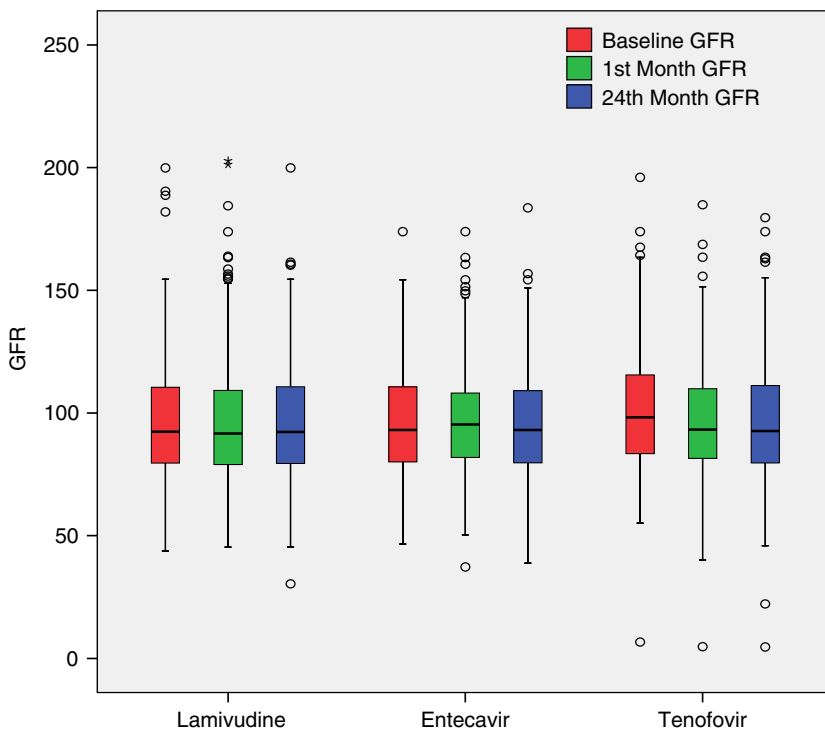
#### GFR changes in groups according to baseline GFR ranges

Baseline GFR ranges were comparable among lamivudine, tenofovir and entecavir groups. Proportions of patients shifted from  $\geq 90$  mL/min/1.73 m<sup>2</sup> GFR to

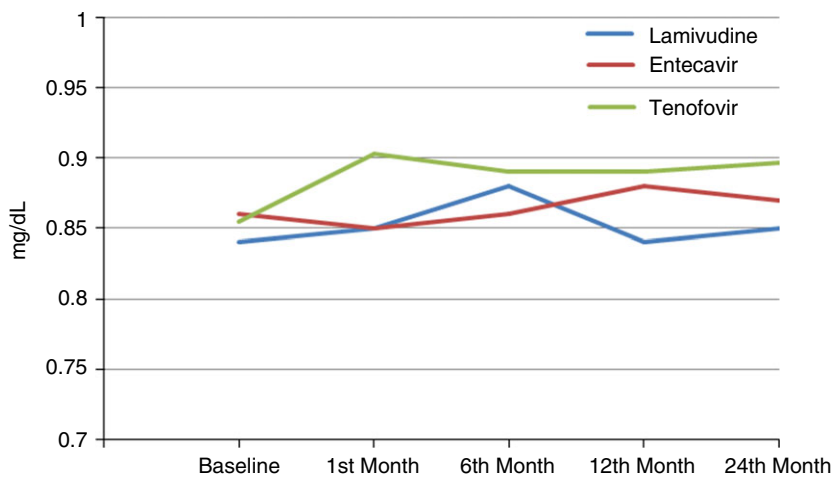
**Table 1** | Demographic features and pre-treatment laboratory tests of treatment groups

	Lamivudine, $n = 302$	Entecavir, $n = 282$	Tenofovir $n = 273$	$P$
Age	49.21 ± 13.17	49.86 ± 13.35	47.74 ± 12.45	0.145
Gender (Female/Male)	117/185	85/197	90/183	0.081
Body mass index	26.62 ± 4.38	26.88 ± 4.32	27.17 ± 4.64	0.547
Diabetes mellitus	12 (4.0%)	25 (8.9%)	13 (4.8%)	0.027
Hypertension	28 (9.3%)	29 (10.3%)	16 (5.9%)	0.148
Fibrosis stage				
Noncirrhosis	251 (83.1%)	190 (67.4%)	177 (64.8%)	0.001
Compensated cirrhosis	32 (10.6%)	65 (23.0%)	77 (28.2%)	
Decompensated cirrhosis	19 (6.3%)	27 (9.6%)	19 (7%)	
HBVDNA log	5.27 ± 1.63	6.54 ± 1.74	6.69 ± 1.79	0.001*†
HBeAg positive	33 (11.5%)	68 (27.1%)	68 (27.8%)	0.001*†
ALT	63.98 ± 6.80	104.86 ± 149.34	99.10 ± 123.65	0.001*†
AST	50.46 ± 47.41	79.33 ± 109.48	75.54 ± 86.67	0.001*†
Baseline serum creatinine (mg/dL)	0.84 ± 0.18	0.86 ± 0.20	0.85 ± 0.40	0.690
Baseline serum calcium (mg/dL)	9.26 ± 0.89	9.17 ± 0.49	9.27 ± 0.51	0.347
Baseline serum phosphate (mg/dL)	3.29 ± 0.93	3.31 ± 0.51	3.15 ± 0.50	0.236
Baseline albumin (g/dL)	4.15 ± 0.49	3.98 ± 0.55	4.04 ± 0.53	0.001†
Baseline GFR	96.90 ± 25.65	96.44 ± 23.03	101.13 ± 24.98	0.047
60	14 (4.6%)	11 (3.9%)	5 (1.8%)	
60–89	123 (40.7%)	105 (37.2%)	91 (33.3%)	
$\geq 90$	165 (54.6%)	166 (58.9%)	177 (64.8%)	

There is a significant difference between; \*Tenofovir-Lamivudine, †Entecavir-Lamivudine.



**Figure 2 |** Baseline, 1st and 24th month GFRs according to anti-viral drugs.



**Figure 3 |** 'Repeated measures' of serum creatinine in treatment groups.

60–89 mL/min/1.73 m<sup>2</sup> GFR were comparable among the groups. Hence, multivariate analysis was not performed. However, in noncirrhotics/compensated cirrhotics with baseline GFR between 60 and 89 mL/min/1.73 m<sup>2</sup>, the least improvement was detected in the tenofovir group ( $P = 0.01$ ; Table 5).

In decompensated patients, the number of patients in each group was low for further statistical comments (Table 5).

Regression analysis for shifting GFR from 60–89 mL/min/1.73 m<sup>2</sup> to  $\geq 90$  mL/min/1.73 m<sup>2</sup> demonstrated that there was no independent factor with respect to age, gender, hypertension, diabetes mellitus,

anti-viral drug, presence of HBeAg, HBV DNA level and fibrosis stage.

A greater than 25% increment of baseline serum creatinine at the 1st, 6th, 12th and 24th month was comparable among all groups in both noncirrhotics/compensated cirrhotics and decompensated cirrhotics (Table 6).

#### 'GFR-differences' in risk-free patients

When we excluded patients who had any possible renal risk factors, including  $>50$  years of age, decompensated cirrhosis, hypertension and diabetes mellitus, there was no significant difference among the groups at the end of the 24th month ( $P = 0.582$ ).

**Table 2** | Comparison of repeated measurements of GFRs and laboratory tests of noncirrhotic and compensated cirrhotic patients at follow-up

	Lamivudine, <i>n</i> = 283	Entecavir, <i>n</i> = 255	Tenofovir, <i>n</i> = 254
<b>GFR</b>			
Baseline	96.91 ± 25.17	96.20 ± 22.53	100.72 ± 25.19
1st month	96.00 ± 25.28	96.37 ± 21.01	96.44 ± 24.27
6th month	95.34 ± 26.78	95.87 ± 21.84	97.13 ± 23.95
12th month	97.50 ± 25.39	94.30 ± 23.80	96.11 ± 24.42
24th month	96.23 ± 24.07	95.94 ± 23.85	96.72 ± 25.67
<i>P</i>	0.490	0.535	0.001
<b>Creatinine</b>			
Baseline	0.84 ± 0.17	0.86 ± 0.19	0.85 ± 0.42
1st month	0.85 ± 0.18	0.85 ± 0.18	0.90 ± 0.56
6th month	0.88 ± 0.42	0.86 ± 0.19	0.89 ± 0.51
12th month	0.84 ± 0.19	0.88 ± 0.21	0.89 ± 0.42
24th month	0.85 ± 0.21	0.87 ± 0.22	0.90 ± 0.58
<i>P</i>	0.111	0.500	0.001
<b>Phosphate</b>			
Baseline	3.08 ± 0.81	3.38 ± 0.36	3.23 ± 0.45
1st month	3.17 ± 0.89	3.47 ± 0.36	3.21 ± 0.49
6th month	3.28 ± 1.04	3.39 ± 0.38	3.21 ± 0.46
12th month	3.22 ± 0.98	3.39 ± 0.36	3.15 ± 0.53
24th month	2.98 ± 0.70	3.45 ± 0.43	3.23 ± 0.62
<i>P</i>	0.121	0.358	0.810
<b>Calcium</b>			
Baseline	9.41 ± 0.50	9.24 ± 0.34	9.30 ± 0.46
24th month	9.43 ± 0.56	9.36 ± 0.43	9.33 ± 0.55
<i>P</i>	0.751	0.011	0.452

**Table 3** | Comparison of repeated measurements of GFR and creatinine in patients with decompensated cirrhosis

	Lamivudine, <i>n</i> = 19	Entecavir, <i>n</i> = 27	Tenofovir, <i>n</i> = 19
<b>GFR</b>			
Baseline	96.77 ± 32.78	98.75 ± 27.73	106.61 ± 21.80
1st month	98.11 ± 27.65	97.57 ± 29.81	92.55 ± 21.21
6th month	98.86 ± 34.03	98.53 ± 24.31	92.01 ± 25.84
12th month	100.90 ± 36.26	92.90 ± 28.63	89.08 ± 19.25
24th month	98.72 ± 41.11	93.96 ± 29.61	95.47 ± 20.92
<i>P</i>	0.977	0.508	0.001
<b>Creatinine</b>			
Baseline	0.90 ± 0.23	0.90 ± 0.24	0.78 ± 0.14
1st month	0.88 ± 0.26	0.97 ± 0.51	0.88 ± 0.15
6th month	0.94 ± 0.48	0.89 ± 0.20	0.90 ± 0.19
12th month	0.94 ± 0.52	1.01 ± 0.57	0.91 ± 0.16
24th month	0.98 ± 0.61	1.00 ± 0.47	0.86 ± 0.16
<i>P</i>	0.653	0.380	0.001

### GFR changes and hypophosphataemia in patients switching from one anti-viral to another

During follow-up, 282 patients changed initial NA. Only one patient had to change tenofovir to entecavir at the 4th month of therapy as a result of a greater than 25% increment of baseline serum creatinine. 171 patients

changed their initial NA after 24 months as a result of viral breakthrough. All were 'switch' rather than 'add-on'. After switching medication, all patients' HBV DNA became negative at the end of 12 months. Among 171 patients, four had decompensated cirrhosis and four switched to adefovir. Those eight patients were excluded

**Table 4 | Comparison of GFR-difference among anti-viral groups**

GFR difference, mL/min/1.73 m <sup>2</sup>	Lamivudine	Entecavir	Tenofovir	P
Baseline–1st month	0.91 ± 20.30	-0.17 ± 16.34	4.27 ± 17.86	0.017
Baseline–6th month	1.57 ± 23.43	0.32 ± 19.43	3.58 ± 18.87	0.204
Baseline–12th month	-0.58 ± 22.43	1.89 ± 28.28	4.60 ± 20.89	0.026
Baseline–24th month	0.68 ± 21.76	0.25 ± 22.70	3.99 ± 16.96	0.098

**Table 5 | Change in GFR at the end of the 24th month of treatment among groups.**

	Lamivudine, n (%)	Entecavir, n (%)	Tenofovir, n (%)	P
Noncirrhotics and patients with compensated cirrhosis				
Shift from ≥90 to 60–89 mL/min/1.73 m <sup>2</sup>	34 (15.0%)	35 (17.8%)	32 (14.5%)	0.628
Shift from 60–89 to ≥90 mL/min/1.73 m <sup>2</sup>	37 (16.1%)	40 (19.9%)	18 (8.7%)	0.006
Patients with decompensated cirrhosis				
Shift from ≥90 to 60–89 mL/min/1.73 m <sup>2</sup>	1 (8.3%)	2 (10.5%)	1 (5.3%)	0.835
Shift from 60–89 to ≥90 mL/min/1.73 m <sup>2</sup>	5 (31.3%)	4 (19.0%)	–	0.045

from further analysis. Among the remaining 163 non-cirrhotic/compensated cirrhotic patients, 132 and 13 switched from lamivudine to tenofovir and to entecavir, respectively. Eighteen patients changed from entecavir to tenofovir.

At the 12th month after 'switch', GFR and creatinine were unchanged in patients switched from lamivudine to entecavir. GFR showed a decrement and creatinine showed an increment but did not reach statistical significance in patients switched from lamivudine to tenofovir at the end of the 12th month (Table 7). However, those patients switched from lamivudine to tenofovir had a significant shift from 60–89 mL/min/1.73 m<sup>2</sup> to <60 mL/min/1.73 m<sup>2</sup> (Table 8).

The patients switched from entecavir to tenofovir showed significant deterioration with respect to GFR and serum creatinine at the end of the 12th month ( $P = 0.01$  for GFR and  $P = 0.007$  for creatinine; Table 7). Also, patients switched from entecavir to tenofovir had a significant shift from >90 mL/min/1.73 m<sup>2</sup> to 60–89 mL/min/1.73 m<sup>2</sup> ( $P = 0.001$ ; Table 8).

Two patients developed transient hypophosphataemia (<2 g/dL) who were switched from lamivudine to tenofovir. There was no hypophosphataemia in the other switched groups.

During follow-up, two patients with decompensated cirrhosis died due to nonrenal reasons at the 14th and 18th months of lamivudine and entecavir treatment, respectively.

**Table 6 | Patients who had >25% increased creatinine at follow-up**

	Lamivudine, n (%)	Entecavir, n (%)	Tenofovir, n (%)	P
Noncirrhotics and patients with compensated cirrhosis				
1st month	21 (7.4)	11 (4.3)	22 (8.7)	0.133
6th month	27 (9.5)	25 (9.8)	20 (7.9)	0.711
12th month	23 (8.1)	38 (14.9)	29 (11.4)	0.051
24th month	26 (9.2)	30 (11.8)	31 (12.2)	0.477
Patients with decompensated cirrhosis				
1st month	1 (5.3%)	4 (14.8%)	4 (21.1%)	0.364
6th month	3 (15.8%)	4 (14.8%)	5 (26.3%)	0.575
12th month	3 (15.8%)	4 (14.8%)	6 (31.6%)	0.324
24th month	3 (15.8%)	5 (18.5%)	4 (21.1%)	0.916

**Table 7** | Change in GFR from baseline in anti-viral switched patients at the end of the 1st year

First drug	Second (switched) drug	GFR			Creatinine		
		Baseline	12th month	P	Baseline	12th month	P
Lamivudine	Tenofovir, n = 132	95.58 ± 27.88	92.20 ± 26.00	0.105	0.84 ± 0.17	0.90 ± 0.41	0.077
	Entecavir, n = 13	107.56 ± 35.49	106.38 ± 17.32	0.885	0.80 ± 0.19	0.78 ± 0.16	0.662
Entecavir	Tenofovir, n = 18	104.40 ± 24.70	93.91 ± 25.57	0.010	0.82 ± 0.20	0.90 ± 0.20	0.007

**Table 8** | Shifting of GFR among anti-viral switched groups

	60 mL /min/1.73 m <sup>2</sup>	60–90 mL /min/1.73 m <sup>2</sup>	90 mL /min/1.73 m <sup>2</sup>	P
Lamivudine				
Tenofovir				
Baseline GFR	1	61	70	0.001
12th month GFR	10	54	68	
Entecavir				
Baseline GFR	1	2	10	0.136
12th month GFR	–	3	10	
Entecavir				
Tenofovir				
Baseline GFR	1	4	13	0.001
12th month GFR	1	8	9	

## DISCUSSION

In the present study, we clearly showed that tenofovir caused a decline in GFR in both tenofovir-initiated and tenofovir-switched patients. Lamivudine and entecavir did not change GFR and serum creatinine significantly. When all possible risk factors including diabetes mellitus, hypertension, >50 years of age and decompensated cirrhosis were excluded, all anti-virals had comparable effects on GFR.

Tenofovir is one of the most potent NA. However, its potential renal toxicity is still being questioned. Actually, renal adverse events have been reported mostly in tenofovir-exposed HIV patients.<sup>17, 18</sup> However, the results are conflicting in hepatitis B patients. In a study with 737 tenofovir-treated hepatitis B patients, 6% of patients had to reduce tenofovir dosage because of worsened GFR.<sup>19</sup> On the other hand, in a long-term follow-up study (144 weeks) with 542 chronic hepatitis B patients, deterioration of serum creatinine was detected in less than 1% of patients.<sup>20</sup> Another study has also reported such a low percentage of renal toxicity.<sup>21</sup> A study comparing entecavir with tenofovir indicated that there was no difference in changes in markers of renal function.<sup>22</sup> Our findings demonstrated that tenofovir caused a decline in GFR in both treatment-naïve and tenofovir-switched patients in almost all subgroup analyses.

However, all NAs had comparable effects in renal risk-free patients. Anti-viral groups were also comparable with respect to a greater than 25% increment from baseline creatinine. Hence, a tenofovir-associated decline in GFR seems to have minor clinical relevance in the present study.

Actually, minimal decline of creatinine clearance has been reported for all available drugs other than for telbivudine in long-term follow-up.<sup>21–23</sup> It is not clear whether this is due to the anti-viral's own effect or accompanying diseases. Gane *et al.* reported a cumulative analysis of renal function in the telbivudine clinical trial database.<sup>7</sup> They showed the superiority of telbivudine over lamivudine with respect to renal function. However, the mechanism of the renal protective effect of telbivudine has not yet been clarified and needs further explanation.

The most important factor for renal toxicity of anti-viral agents, especially nucleotide analogues, is pre-existing risk factors for renal disease.<sup>22, 24</sup> Risk factors include diabetes, coinfection with HIV, decompensated cirrhosis, poorly controlled hypertension, proteinuria, active glomerulonephritis, concomitant nephrotoxic drugs and solid organ transplantation.<sup>4, 24</sup> In our study, none of the analysed factors, including exposed-anti-viral drug were found to be an independent risk



factor for renal dysfunction. When we excluded patients with any risk factors, the disadvantage of tenofovir regarding GFR became decreased but did not disappear.

Hypophosphataemia is among the rare adverse events of nucleotide analogues. It is not clear whether hypophosphataemia occurs as a result of nephropathy in the proximal renal tubules or vitamin D deficiency.<sup>25</sup> Most of the tenofovir-related hypophosphataemia and Fanconi's syndrome reports are from HIV patients.<sup>13,14,26</sup> In the present study, only 7 of 423 patients (tenofovir initiated and switched patients) developed transient hypophosphataemia and none had to change tenofovir treatment. Also, two lamivudine-initiated patients had transient hypophosphataemia. Moreover, all anti-viral groups were comparable with respect to serum phosphate levels at follow-up.

As a limitation of our study, baseline characteristics did not match well. The number of patients was also low in the telbivudine and adefovir groups. However, this is a real life cohort and the patients used initial NA for similar durations. Also, duration of NA therapy was long

enough to evaluate the short and long-term renal effects under optimal conditions.

In conclusion, tenofovir caused a decline in GFR at both short and long-term follow-ups. However, that decline was mild and seemed to give a minimal clinical effect. Continuous renal monitoring, including GFR and serum creatinine and phosphate, is necessary while using any anti-viral drug against chronic hepatitis B.

## AUTHORSHIP

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*Author contributions:* Seyfettin Koklu planned the study and wrote the text, Hayrettin Koklu and Nimet Koklu collected the data, Osman Yuksel performed the statistical analysis, and Selman Unverdi consulted in the renal aspects of the study. The remaining authors contributed to the study by providing patient data. All authors approved the final version of the manuscript.

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