Comparison of the effectiveness and renal safety of tenofovir versus entecavir in patients with chronic hepatitis B

Beatriz López Centeno¹, Roberto Collado Borrell¹, Montserrat Pérez Encinas¹, María Luisa Gutiérrez García² and Patricia Sanmartín Fenollera¹

¹Servicio de Farmacia, Hospital Universitario Fundación Alcorcón, Madrid. ²Servicio de Aparato Digestivo, Hospital Universitario Fundación Alcorcón, Madrid. España.

Abstract
Objective: To compare the effectiveness and renal safety of treatment with tenofovir versus entecavir in patients with chronic hepatitis-B.

Methods: Retrospective study in hepatitis-B patients who initiated treatment with tenofovir or entecavir since January 1998 until 2013. The primary effectiveness variable was defined as viral DNA < 20 UI/ml (HBV-DNA) and the variable for renal safety was variations in glomerular filtration rate (eGFR) after 48 weeks of treatment.

Results: The analysis was conducted in 64 patients (1:1), with similar characteristics except for the prevalence of naive patients (p=0.036), comorbidities (p=0.077) and nephrotoxic drugs (p=0.088) in the entecavir arm, while the tenofovir arm presented a prevalence of patients with HBV-DNA < 20 UI/ml (p=0.032) and HBeAg-positive (p=0.050). Statistical univariate analysis and adjustment for confounding variables was conducted through the Propensity Score (PS). The outcomes for the primary effectiveness variable showed tenofovir superiority after PS adjustment, with an OR adj = 6.7 (95% CI:1.2-35.3; p=0.028). Three patients on tenofovir experienced seroconversion (p=0.148). The outcomes for the primary safety variable (eGFR < 60 ml/min/1.73m²) showed no difference between both arms after adjustment, achieving an OR adj = 0.6 (95% CI:0.1-2.8; p=0.521). The tenofovir arm registered two cases of treatment interruption due to renal toxicity, with subsequent recovery, including one Fanconi Syndrome.

Comparación entre la efectividad y la seguridad renal del tenofovir y el entecavir en pacientes con hepatitis B crónica

Resumen
Objetivo: Comparar la efectividad y seguridad renal del tratamiento con tenofovir frente al entecavir en pacientes con hepatitis B crónica.

Métodos: Estudio retrospectivo en pacientes con hepatitis B que iniciaron tratamiento con tenofovir o entecavir entre enero 1998-2013. La variable principal de la efectividad fue definida como DNA viral < 20 UI/ml (HBV-DNA) y la de la seguridad renal como variaciones en el filtrado glomerular (eGFR) tras 48 semanas de tratamiento.

Resultados: Se analizaron un total de 64 pacientes (1:1), con características semejantes excepto por el predominio de pacientes sin tratamiento previo (p=0,036), comorbilidades (p=0,077) y fármacos nefrotóxicos (p=0,088) en el grupo-entecavir, y de pacientes con HBV-DNA < 20 UI/ml (p=0,032) y HBeAg-positivo (p=0,050) en el grupo-tenofovir. Se realizaron análisis estadísticos univariantes y se ajustaron las variables confusoras mediante Propensity score (PS). Los resultados para la variable principal de efectividad (HBV-DNA < 20 UI/ml) denotan una superioridad del tenofovir tras el ajuste por PS con una OR adj = 6,7 (IC95%: 1,2-35,3; p=0,028). Tres pacientes con tenofovir sufrieron seroconversión (p=0,148). Los resultados para la variable principal de seguridad (eGFR < 60 ml/min/1.73m²) no mostraron diferencias entre ambas ramas tras el ajuste, obteniendo una OR adj = 0,6 (IC95%: 0,1-2,8; p=0,521). El grupo-tenofovir registró dos casos de suspensión por toxicidad renal, con posterior recuperación, entre ellos un síndrome de Fanconi.

* Autor para correspondencia.
Correo electrónico: blopezcenteno@gmail.com (Beatriz López Centeno).

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Conclusions: In our study, there are significant differences between both treatments regarding effectiveness, with tenofovir demonstrating superiority. In terms of renal safety, we have not found any significant differences, but two cases of treatment interruption due to renal toxicity with tenofovir lead us to the conclusion that treatment decision in patients with renal function alteration should include an individualized assessment of each case.

KEYWORDS
Tenofovir; Entecavir; Chronic hepatitis B; Renal safety; Effectiveness

Conclusions: En nuestro estudio existen diferencias significativas entre ambos tratamientos respecto a su efectividad, mostrándose el tenofovir superior. En cuanto a la seguridad renal, no hemos encontrado diferencias significativas, pero dos casos de suspensión de tratamiento por toxicidad renal con tenofovir nos llevan a concluir que la decisión de tratamiento en los pacientes con alteraciones en la función renal debería incluir un análisis individualizado de cada caso.

PALABRAS CLAVE
Tenofovir; Entecavir; Hepatitis B crónica; Seguridad renal; Efectividad

Contribution to scientific literature

This study provides a direct comparison between two drugs in patients with chronic Hepatitis B (CHB) under actual clinical practice, a comparison that has been made in several studies against other analogues used in the CHB treatment but with limited data in as for the comparison between these two agents; and it also provides a direct comparison between the renal safety of entecavir and tenofovir and analysis of additional risk factors for developing kidney disease in CHB patients.

The results of the study confirm the effectiveness and safety in clinical practice of both drugs and help improve the selection and individualization of treatment based on patient baseline characteristics; the role of hospital pharmacists is key to controlling and monitoring both the effectiveness and safety of pharmacological treatment of chronic ambulatory dispensation mainly due to its high impact on hospital costs and quality of care.

Introduction

The therapy objective in chronic Hepatitis B (CHB) is an increase in survival by preventing the progression of the hepatic lesion. This objective is achieved by a sustained suppression of viral replication. Treatment indication is based on the combination of three criteria: virus DNA and alanine aminotransferase in serum levels, and liver biopsy.

Treatment options can be divided into two classes of drugs: pegylated interferon alpha and nucleoside/nucleotide analogues (NUCs). For treatment selection, the following must be taken into account: antiviral efficacy, resistances, safety profile, way of administration, and costs. Entecavir (ETV) and tenofovir (TDF) are two potent inhibitors with a high resistance barrier, which positions them as first choice for monotherapy treatment. ETV presents high potency, a good safety profile, and a minimum rate of resistance development in naïve patients (1.2% after 5 years); however, it has a lower response rate in patients with resistance to lamivudine (LAM), as well as an increase in resistance (up to 51% at 5 years), which prevents it from being a drug of choice for these patients. TDF is a potent and selective nucleotide analogue, active both in naïve patients and in previously treated patients with resistance to LAM. It also has an indication for naïve patients with HIV infection, and its resistance profile is still to be defined (no resistances described at 5 years).

All NUCs are renally excreted unchanged; therefore, it is recommended to watch and conduct a dose adjustment when required in patients with kidney failure. ADV and TDF have been associated to nephrotoxicity, and it has been primarily described in HIV-infected patients. Some cases in CHB patients have been described in literature; however, this association has not been conclusively established in long-term clinical trials. Renal toxicity presents as a proximal tubule dysfunction, even with cases of Fanconi Syndrome (eGFR reduction, hypophosphatemia, hypouricemia, renal loss of ions).

Even though the efficacy of ETV and TDF has been demonstrated and compared vs. other analogues, there are limited data regarding the comparison between these two potent agents. Data are also limited regarding renal safety; however a potential nephrotoxicity has been more widely studied in TDF, basically in the HIV co-infected population. The objective of the present study was to compare the effectiveness and renal safety of treatment with tenofovir vs. entecavir in CHB patients after 48 weeks of treatment.

Methods

Study Design and Setting

We performed a comparative retrospective cohort study of adult CHB patients (over 18-year-old, of both genders) who initiated treatment with TDF or ETV between January 1998 and 2013 and were followed-up during 48 weeks in a public university hospital. Patients were excluded if they had evidence of co-infected with HIV or Hepatitis-C. The patient list was obtained through the drug dispensing module for Hospital Pharmacy outpatients (Farmatools®). Clinical data were obtained from electronic clinical records (Selene®/GPC®).
The following data were collected: demographic data (age and gender), pharmacological (previous treatment and concomitant nephrotoxic drugs), comorbidities (hypertension and diabetes) and clinical (serum levels of: virus DNA (HBV-DNA)(IU/ml), alanine aminotransferase (ALT)(IU/L), creatinine (Cr)(mg/dl) and phosphate (P)(mg/dl), CHB serotype (HBeAg-positive or negative) and estimated glomerular filtration rate (eGFR)(ml/min/1.73m²) according to the CDK-EPI formula[^12], at baseline and at 48 weeks.

**Outcome Measurements**

The effectiveness variable was studied in terms of response: virological (HBV-DNA<20UI/ml), biochemical (ALT normalization), and serological (seroconversion) at 48 weeks of treatment initiation. A high HBV-DNA level was defined as values above 6log[^10]. Seroconversion is understood as HBeAg loss and anti-HBe development, confirmed in two different tests. Elevated ALT levels were those 3 times over the normal upper limit (0-41UI/L).

Regarding safety, renal toxicity was assessed. Glemorular safety variables were defined as: changes in eGFR (proportion of patients with: eGFR<60ml/min/1.73m² and eGFR reduction >25%) and increase in Cr (Cr>1.4mg/dl; normal range: 0.6-1.4mg/dl) at 48 weeks after initiating treatment. Preexisting kidney failure is understood as <60ml/min/1.73m². The magnitude of Cr increases and eGFR reductions >25% are tested in order to detect kidney failure. P level was used as tubular toxicity variable, considering: mild (2-2.5mg/dl), moderate (1-1.99mg/dl) and severe hypophosphatemia (<1mg/dl)[^13]. To assess the evolution, data were collected at baseline, 24 and 48 weeks.

Comorbidities, previous treatment and age were also analyzed; and regarding concomitant treatment, only those drugs which are nephrotoxic according to their product specifications were taken into account.

**Statistical Analysis**

All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS v.18.0). Data were described as mean ± standard deviation (SD) or absolute and relative frequencies.

In order to compare effectiveness and safety measures between treatments, Chi-Square Test was used for hypothesis contrast, and Odds Ratio (OR) was estimated, with a 95% Confidence Interval (95%C.I.). The homogeneity of both treatment arms was studied through univariate analysis, applying the Chi-Square Test for qualitative variables, and Student’s t test or Mann Whitney’s U to compare quantitative variables. A 95%C.I was determined, with p<0.05 as statistically significant differences.

The Propensity Score (PS) is used in order to reduce and control any selection and confusion bias[^14,15]. Rosenbaum and Rubin[^14] put PS forward as the conditioned propensity of being assigned to a treatment, given a set of observed co-variables (potential confounding factors) before receiving the treatment. Comparison through PS is a way to correct the estimation of a treatment effect in non-experimental designs, based on the idea that there is a reduction in bias when the comparison of outcomes is conducted using subjects as similar as possible in both treatments.

Mixed models were used for the assessment of renal function evolution over time, which allow to model unbalanced longitudinal data[^10]. These models included time as repeated measure, and the time*treatment interaction. Different structures of co-variance were modeled, and the best model was selected according to a likelihood test. A statistically significant interaction effect indicated that time evolution differs between treatments. Bonferroni Correction was used for multiple comparisons.

**Results**

The study included 64 CHB patients (1:1). A 62.5% of patients treated with TDF received the drug as monotherapy, and 37.5% received it in combination with LAM. All patients in the ETV arm were treated with monotherapy.

Baseline patient characteristics included in the study appear in table 1. Both treatment arms appeared demographically comparable, with significant differences in basal HBV-DNA, HBeAg-positive and prior treatment. Patients were classified into the following treatment subgroups: without any previous treatment (naïve), previously treated with ADV, and treated with other drugs for CHB.

The concomitant nephrotoxic drugs collected were: trimethoprim-sulfamethoxazole, metformin, enalapril/ramipril, spirinolactone, cyclosporin-A, methotrexate, and cyclophosphamide.

In view of these data, we have identified the following as potential confounding variables in terms of effectiveness: basal HBV-DNA, HBeAg-positive and prior treatment; and in terms of safety: age, basal eGFR, prior treatment, nephrotoxic drugs, and comorbidities, which we have compared through univariate analysis in order to study treatment homogeneity. For PS development, those variables with p<0.1 were selected (basal HBV-DNA, HBeAg-positive, prior treatment, nephrotoxic drugs, and comorbidities). We assessed the discriminant validity of the model through the Under the Curve Area (ROC). With our model, we have a 0.8 area (95%C.I: 0.7-0.9), which indicates a good discriminant validity. We used PS as quantitative variable for adjustment in a multivariate logistic regression model (dependent variable is the treatment group), in order to assess treatment effect on the primary variables of effectiveness and safety, as defined in our study (Fig. 1a-b).
Effectiveness

At 48 weeks, 90.3% of patients in the TDF arm achieved virological response vs. 67.7% in the ETV arm (Fig.2); after the univariate analysis, the OR was 4.4 (95%CI:1.1-18.2; p=0.059), and after adjustment by PS, the value was OR adj =6.7 (95%CI:1.2-35.3; <p=0.028).

The percentage of patients who achieved ALT normalization was 97% in the TDF arm and 87.5% in the ETV arm, without significant differences (p=0.355). In the TDF arm, three patients (9.4%) presented seroconversion; there were no cases in the ETV arm (p=0.148).

Safety

Out of 63 patients (TDF n=31 and ETV n=32), and after 48 weeks, 19.4% of patients in the TDF arm showed eGFR<60ml/min/1.73m² vs. 15.6% in the ETV arm. After univariate analysis, we obtained an OR=0.8 (95%CI:0.2-2.8; p=0.750), and the PS-adjusted outcome was an OR adj value of 0.6 (95%CI:0.1-2.8; p=0.521). Regarding the reduction in eGFR, only one patient in the ETV arm vs. none in the TDF arm suffered a reduction over 25%.

The percentage of patients with Cr outside the normal range was 12.9% in the TDF arm vs. 6.3% in the ETV arm, without statistical significance (p=0.672).

Phosphate determination was conducted, after 24 weeks of treatment, in 53.1% of patients (62.5% TDF and 43.8% ETV); 2 cases of moderate hypophosphatemia were observed in the TDF arm only. Both cases were >60-year-old male patients, with comorbidities, nephrotoxic drugs, and one of them, who would develop Fanconi Syndrome, had preexisting kidney failure. As a result, one of the patients interrupted treatment at 24 weeks, after achieving seroconversion, and the other
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one at 48 weeks, when he developed Fanconi Syndrome, and recovered his renal parameters 12 weeks after TDF interruption, and subsequently was switched to ETV treatment (Table 2).

After 48 weeks, 71% of patients had phosphate determination (84.4% TDF and 53.1% ETV) with normal levels or mild hypophosphatemia. In the analysis with mixed models we did not find any statistically significant interaction effect ($p=0.882$); P levels were reduced by 0.256 ($p=0.051$) and 0.226 ($p=0.154$) in the TDF and ETV arm respectively. We did not find statistically signifi-
cant differences either in the evolution of Cr ($p=0.110$) or eGFR ($p=0.659$) (Table 3).

**Discussion**

The present study, conducted under real practice conditions, the effectiveness and safety of both therapeutic options is compared after 48 weeks of treatment, in a cohort of naïve and pre-treated patients, and naïve regarding NUC treatment. Our finding is that TDF is significantly more effective than ETV to achieve HBV-

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**Figure 1.** Propensity Score results (PS). The test result variable(s): Predicted probability of being assigned to one group or another treatment group, given a set of observed co-variables (potential confounding factors) before receiving the treatment. Area Under the Curve (ROC): 0.790 (95%CI: 0.680-0.901).

**Figure 2.** Time evolution of the percentage of patients with HBV-DNA<20UI/ml.

* 1 patient discontinued treatment with TDF at 24 weeks by moderate hypophosphatemia.
and ETV were the most potent drugs in HBeAg-positive,
and 76% respectively. The authors concluded that TD F
tients, as happens in the meta-analysis by Govan et al.
while TDF was the most potent in HBeAg-negative pa-
presession and 73% ALT normalization vs. ETV with 88%
second, with a 61% viral suppression, 70% ALT normali-
zation, seroconversion; however three seroconversion
cases occurred in the TDF arm.
A retrospective study conducted by Gao et al.17 in naï-
ve patients with high HBV-DNA, finds that in HBeAg-po-
sitive patients, TDF is significantly more effective than
ETV to achieve complete viral suppression (<60UI/ml=300copies/ml). However, no significant difference was
found among HBeAg-negative patients. When compara-
ing our TDF superiority outcomes with this study, we
must take into account that in our cohort the patients
with high HBV-DNA was below 50%, and are based on
HBeAg-negative patients mainly, although we must con-
sider that these variables has been identified as confoun-
ding, and included in PS.
Our outcomes are consistent with the meta-analysis
by Woo et al.18 where 20 clinical trials to determine the
most effective therapies during the first year of treatment
in naïve patients were included. In HBeAg-positive pa-
tients, TDF was more effective at achieving viral suppres-
sion (<1000copies/ml) with an 88% probability, 66% ALT
normalization and 20% seroconversion. ETV appeared
second, with a 61% viral suppression, 70% ALT normali-
zation and 19% seroconversion. Regarding HBeAg-nega-
tive, TDF was also the most effective, with 94% viral su-
ppression and 73% ALT normalization vs. ETV with 88%
and 76% respectively. The authors concluded that TDF
and ETV were the most potent drugs in HBeAg-positive,
while TDF was the most potent in HBeAg-negative pa-
tients, as happens in the meta-analysis by Govan et al.19
Zuo et al.20 conducted a meta-analysis with the conclu-
sion that virological response (<400copies/ml) with TDF
was superior to ETV in naïve patients during their first year
of treatment, and no differences were found in ALT nor-
malization, seroconversion, or safety. Our outcomes coincide
to a great extent with this study, with the exception that
our cohort included both naïve and pre-treated patients.
On the contrary, other retrospective comparative stud-
ies conducted showed that both antivirals are similar in
terms of efficacy. Dogan et al.5 conducted a study in
 naïve and pre-treated patients with efficacy outcomes
(<400copies/ml) of 72.3% for TDF and 69% for ETV. The
authors concluded that there were no significant diffe-
rences regarding the efficacy of both drugs. We must
highlight that only one case of seroconversion with ETV
was observed in this study, unlike what happened in our
cohort. Guzelbulut et al.21 did not find any differences
in efficacy either (<400copies/ml); all patients included
were naïve and had high HBV-DNA, unlike our series.
The outcomes of these retrospective studies coincided
with a meta-analysis by Dakin et al.22 where 13 clinical
trials with naïve HBeAg-positive patients were analyzed;
it was observed that, at one year of treatment, 94% of
patients on TDF reached viral suppression (>300copies/
ml) vs. 73% on ETV; all treatments increased the proba-
bility of seroconversion, though no significant differen-
tions were found. A meta-analysis performed by Ke et al.23
considered ETV and TDF as similarly effective and safe
after 24 and 48 weeks of treatment. Finally, Maratea et
al.24 did not find any significant differences in effective-
ness, after an indirect comparison between both drugs.
Regarding renal safety, no significant differences were
found in our study between both treatment arms, for any
of the renal parameters analyzed. When we compared
our outcomes with the comparative study conducted by
Gish et al.25 who evaluated the risk of renal toxicity (Cr,
eGFR<60ml/min and renal events) with TDF (monotherapy
or combination) vs. ETV (monotherapy) in naïve patients,
we observed there was an agreement, because they did
not find any significant differences in renal parameters.
In the same line, another retrospective comparative study
conducted by Nguyen et al.26 in patients on monotherapy
studied the renal function (Cr, eGFR and P) at baseline, 6
and 12 months of treatment. The study did not find any
significant deterioration in renal function after 12 months
with TDF, but this was detected in the ETV cohort; howe-
ver, the authors concluded that this deterioration was due
to the worse basal renal function in this arm.
At the time of studying the renal toxicity of ETV and
TDF separately, our findings coincided with the informa-
tion available so far27-30; because we did not observe any
worsening in renal function over the follow-up period.
In our series, a slightly higher deterioration in renal func-
tion was observed in the TDF arm, even though there
was a lower risk factors associated than in the ETV arm;
and there was one case of treatment interruption due to
renal toxicity, vs. none in the ETV arm. However, these
differences did not achieve statistical significance.
If we analyze the patient who developed Fanconi Sy-
Dna<20UI/ml; and regarding safety, we did not find any
significant differences between both drugs. We have not
found any significant differences in biochemical respon-
se and seroconversion; however three seroconversion
cases occurred in the TDF arm.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>0 weeks</th>
<th>24 weeks</th>
<th>48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>1.49</td>
<td>1.62</td>
<td>1.94</td>
</tr>
<tr>
<td>eGFR</td>
<td>48</td>
<td>43.4</td>
<td>34</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>3.2</td>
<td>1.9</td>
<td>2</td>
</tr>
<tr>
<td>Dosage TDF (300mg)</td>
<td>every 24 hours</td>
<td>every 48 hours</td>
<td>every 72 hours</td>
</tr>
</tbody>
</table>

TDF: tenofovir; eGFR: estimated glomerular filtration rate (ml/min/1.73m2); serum creatinine and phosphate (mg/dl).
diabetes on treatment with metformin, previously treated with ADV, who presented preexisting kidney failure at baseline. Therefore, he presented various risk factors, according to the multivariate analysis conducted with postmarketing clinical data, which show that advanced age (>60 years), preexisting kidney failure, comorbidities, concomitant nephrotoxic drugs, advanced HIV co-infection, and even male gender, are all risk factors to induce eGFR reductions by TDF11,37. There are limited published data about TDF-induced Fanconi Syndrome in CHB mono-infection patients, which suggests this is a rare adverse effect; by contrast, there are numerous cases published in HIV co-infected patients6,38. Several studies publish cases of Fanconi Syndrome in CHB mono-infection patients treated with TDF; in all of them the patients has associated risk factors (hypertension, preexisting kidney failure, and three of them prior treatment with ADV)32,33. Those cases described are similar to ours in terms of the coincidence of additional risk factors for renal disease, and the reversibility of the disorder; but they differ regarding the time of development, because in their case Fanconi Syndrome appeared after 3-4 years of exposure to TDF, while our patient developed it after one year of treatment.

Some of the limitations of the present study are its retrospective nature and the reduced sample size, that doesn’t allow subgroup analysis based on the presence or lack of prior treatment, the HBsAg sign, the magnitude of basal HBV-DNA, and combination treatment with LAM, which can make it difficult to extrapolate our outcomes. Regarding the follow-up period, even though sufficient to assess effectiveness, it is not enough in order to assess long-term safety. On the other hand, in order to evaluate effectiveness, we have only assessed viral suppression, ALT normalization and seroconversion, without considering other parameters such as histological improvement and loss of surface antigen. Regarding the safety study, we have used only eGFR, Cr and P, because the retrospective nature of the study did not allow an analysis of other parameters, due to the lack of records in most cases. Furthermore, we have not been able to estimate the effect of prior treatment with ADV as a risk factor, due to the small proportion of pre-treated patients in our series. We consider of interest the analysis of its potential influence in the development of nephrotoxicity in subsequent treatments with TDF and ETV; however, we have not found any published evidence on this respect.

As our study was non-randomized, we have adjusted outcomes by using PS, in order to reduce the influence of confounding factors. This index shows the probability that a patient will fall into one arm of the study or the other, when there has been no randomization. When outcomes are adjusted using PS, even though with certain limitations, it can be assumed that the characteristics of the study patients which could have any influence in outcomes will be distributed in an “almost-random” manner. This adjustment offers some robustness to our outcomes; therefore, our study is relevant, because there are only a few studies to this date with a direct comparison between ETV and TDF in CHB patients under real practice conditions.

In summary, we have found that TDF performs as the more potent option vs. ETV during the first year of treatment in CHB patients, both naïve and pre-treated. On the contrary, both drugs are equivalent in term of renal safety in patients with preserved renal function. Given that it is still to be determined if ETV and TDF are equivalent therapeutic options or not, we believe it is necessary to conduct direct comparisons of a prospective nature with a larger population, allowing analysis by subgroups, and to determine in terms of effectiveness which is the NUC to choose based on the basal characteristics of patients. On the other hand, studies on safety are required, both in naïve and pre-treated patients, with long follow-up periods, focused on the renal profile, in

### Table 3. Initial and 48 weeks later antiviral drugs-based renal function parameters

<table>
<thead>
<tr>
<th>Antiviral Drug</th>
<th>Parameters</th>
<th>0 weeks</th>
<th>48 weeks</th>
<th>95% CI</th>
<th>Value p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF (n=32)</td>
<td>Serum creatinine</td>
<td>1.09 (SE: 0.04)</td>
<td>1.12 (SE: 0.04)</td>
<td>-0.03 (-0.08;0.02)</td>
<td>0.173</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>78.99 (SE: 3.48)</td>
<td>78.15 (SE: 3.9)</td>
<td>0.85 (-9.5;11.19)</td>
<td>0.872</td>
</tr>
<tr>
<td></td>
<td>Serum phosphate (n=25)</td>
<td>3.465 (SE: 0.13)</td>
<td>3.209 (SE: 0.12)</td>
<td>0.256 (-0.002;0.514)</td>
<td>0.051</td>
</tr>
<tr>
<td>Dosage TDF (300mg)</td>
<td>Serum creatinine</td>
<td>1.05 (SE: 0.04)</td>
<td>1.03 (SE: 0.04)</td>
<td>0.02 (-0.03;0.07)</td>
<td>0.364</td>
</tr>
<tr>
<td></td>
<td>eGFR</td>
<td>81.54 (SE: 3.48)</td>
<td>83.95 (SE: 3.84)</td>
<td>-2.41 (-12.67;7.84)</td>
<td>0.642</td>
</tr>
<tr>
<td></td>
<td>Serum phosphate (n=20)</td>
<td>3.280 (SE: 0.14)</td>
<td>3.054 (SE: 0.15)</td>
<td>0.226 (-0.088;0.541)</td>
<td>0.154</td>
</tr>
</tbody>
</table>

TDF: tenofovir; ETV: entecavir; eGFR: estimated glomerular filtration rate (ml/min/1.73m²); serum creatinine and phosphate (mg/dl); SE: standard error.
order to obtain more conclusive outcomes. Meanwhile, while waiting for new evidence, the decision of treatment in patients with renal function alteration should include an individualized assessment, and it would be advisable to monitor glomerular and tubular function during TDF treatments.

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Conflict of interest

The authors declare that they have no conflict of interest.

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