Renal profile of patients treated with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate and dolutegravir/abacavir/lamivudine: 120-week results from a real-world cohort

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Abstract

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/c/FTC/TAF) and dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) are currently available for HIV patients.

Objectives This study evaluated modifications in the renal safety profile in a large real-world cohort of patients who had received EVG/c/FTC/TAF or DTG/ABC/3TC.

Methods A retrospective observational study of HIV-infected patients who received EVG/c/FTC/TAF or DTG/ABC/3TC between March 2015 and June 2019 at a reference hospital in north-western Spain was conducted. Epidemiological, clinical, immunovirological data and information regarding antiretroviral therapy were recorded. The statistical differences between treatments were calculated.

Results A total of 457 patients were evaluated, 266 using EVG/c/FTC/TAF and 191 using DTG/ABC/3TC. Up to week 120, serum creatinine improved in both study groups among

experienced patients (EVG/c/FTC/TAF 1.01±0.24 vs 0.91±0.19, p<0.001; DTG/ABC/3TC 1.08±0.24 vs 1.02±0.31, p<0.001), while in naïve patients serum creatinine remained stable compared with baseline. Statistically significant differences were found in serum creatinine when comparing both treatments at week 48 in experienced (0.94±0.21 vs 1.09±0.28, p<0.001) and naïve patients (0.89±0.16 vs 1.06±0.20, p=0.001), and among experienced patients at week 120 (0.91±0.19 vs 1.02±0.31, p=0.015) for the EVG/c/FTC/TAF and DTG/ABC/3TC groups, respectively. During the follow-up, 39 patients in EVG/c/FTC/TAF and 33 in DTG/ABC/3TC (p=0.449) discontinued treatment. The main reason for stopping treatment was adverse events, which were similar in both groups.

Conclusions During the follow-up, patients experienced changes that were not clinically relevant in both treatment groups. Differences in renal events were not found.

INTRODUCTION

Antiretroviral therapy (ART) has largely transformed HIV infection into a chronic disease condition, reducing morbidity, mortality and HIV transmission.[1,2] However, this has led to an ageing population that has an increased incidence of age-related comorbidities, such as cardiovascular, bone or kidney diseases, in people living with HIV.3 The possible adverse events (AEs) derived from the continued use of antiretroviral drugs need to be considered. Nonetheless, research has focused on the production of safer drugs that maintain efficacy while avoiding effects on the renal functions of HIV patients.[4,5]

Current national and international guidelines recommend starting ART soon after diagnosis. A multitude of drugs are available, and the choice of treatment is personalised, depending on comorbidities, potential side effects, concomitant medication interactions, resistance test, and convenience.[6,7]

Two antiretroviral regimens are currently the most widely used in HIV-infected patients: dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/c/FTC/TAF).

Renal parameter variations in pivotal clinical trials of EVG/c/FTC/TAF and DTG/ABC/3TC were minimal but statistically significant.[8–13] Furthermore, no real-life study has been published that compares the safety profiles of EVG/c/FTC/TDF and DTG/ABC/3TC. The aim of this study was to evaluate modifications in the renal safety profile in a large real‐world cohort of naïve and treatmentexperienced HIV patients who had received EVG/c/FTC/TAF or DTG/ABC/3TC.

METHODS

This was a retrospective observational study in adult HIV-infected patients who have been treated with EVG/c/FTC/TAF or DTG/ABC/3TC conducted between March 2015 and June 2019 at a reference hospital in north-western Spain. The selection of antiretroviral treatments was made based on clinical criteria and recommendations from the annual national clinical practice guidelines, and considering the individual characteristics of each patient: comorbidities, medical and herbal interactions, contraindications for use (positive result of HLA-B*5701 and ABC regimens) and drug resistance testing.[14] All patients who had provided signed informed consent and with at least one follow-up visit were included, regardless of baseline creatinine values, viral load, and hepatitis B and C virus coinfection, in contrast to the selection criteria for clinical trials. Patients who had changed from one treatment to another in the study were considered in the two scenarios according to the treatment they received and the specific data at the time. Only those patients participating in clinical trials or transferred from other centres (hospitals or penitentiaries) were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki on Good Clinical Practice.

Epidemiological, clinical, immunovirological data and information regarding ART were recorded. The basal renal profile was compared with that at weeks 48 and 120 after receiving the study ART. Those patients who did not reach study week 120 at the time of cut-off were only included in the study week 48 for laboratory determinations. Otherwise, they remained in the safety analysis until the end of the study. Creatinine clearance (CrCl) and serum creatinine (SCr) were recorded. CrCl was calculated using the CKD-EPI formula, and was classified into four groups as follows: normal (>60 mL/min/1.73 m^2), mild (59–30 mL/min/1.73 m^2), moderate (29–15 mL/min/1.73 m^2) and severe (<15

mL/min/1.73 m^2). Furthermore, renal events (including dialysis, Fanconi syndrome, chronic kidney disease, renal colic or other events) during or before the study drug initiation were recorded. The "Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.1" was considered for assessing the severity of laboratory abnormalities. The presence of the following cardiovascular risk factors was recorded: dyslipidaemia (total cholesterol (TC) ≥200 mg/dL, triglycerides (TG) ≥150 mg/dL, low-density lipoprotein colesterol (LDL-C) ≥130 mg/dL and/or treatment with lipid‐lowering agents registered in the medical records), arterial hypertension (recorded in the medical records and/or antihypertensive treatment), diabetes mellitus (registered in the medical records and/or treatment with oral glucose‐lowering agents or insulin) and smoking (current smoker, ex‐smoker or non‐smoker).

The time of follow-up was defined as the day of EVG/c/FTC/TAF or DTG/ABC/3TC initiation until the day of discontinuation, the last visit to the pharmacy service, or death. Statistical analysis was performed using SPSS v.24. software. Group differences were compared using the Pearson chi-square or Fisher's exact test and Student's *t*-test or the Mann–Whitney U-test, respectively, for categorical and continuous variables. Repeated measurements were compared using paired Student's *t*-test or Wilcoxon signed-rank test. Univariate analyses were performed with all the covariates. Cox regression analysis was performed to identify the risk of discontinuation because of Aes by treatment. P values of 0.05 or less were considered statistically significant.

RESULTS

Baseline characteristics of the study population

A total of 457 patients started study treatments in the study period, 266 EVG/c/FTC/TAF and 191 DTG/ABC/3TC. Most patients were men (75.7%) with a median age of 49.2±10.7 years and 84.0% were treatment-experienced. The main reasons for switching previous ART in treatment-experienced patients were 38.0% for simplification, 31.3% to prevent AEs and 18.2% for AEs (6.1%, 28 patients, related to impaired renal function). The previous treatments which caused renal disorders in 28 patients before starting EVG/c/FTC/TAF were: 4/19 FTC/TDF+efavirenz; 3/19 FTC/TDF+rilpivirine; 3/19

EVG/c/FTC/TDF; 2/19 FTC/TDF+raltegravir; 2/19 FTC/TDF+atazanavir; 1/19 ABC/3TC+DTG; 1/19 FTC/TDF+etravirine; 1/19 ABC/3TC+lopinavir; 1/19 FTC/TAF+rilpivirine and 1/19 FTC/TDF+darunavir; and before DTG/ABC/3TC were: 5/9 FTC/TDF+efavirenz; 2/9 EVG/c/FTC/TDF; 1/9 FTC/TDF+fosamprenavir and 1/9 ABC/3TC+zidovudine. For both groups, the most common acquisition risk factor for HIV infection was related to sexual activity (65.2%) followed by intravenous drug use (28.2%). Baseline characteristics are depicted in table 1. There was a higher rate of naïve patients in the EVG/c/FTC/TAF group and with fewer basal RNA-HIV log copies/mL. The EVG/c/FTC/TAF group was more likely to be younger. Among experienced patients, those in the EVG/c/FTC/TAF group had better renal function. The acquisition risk factor for HIV infection was different between the two groups.

Renal profile variations in the EVG/c/FTC/TAF group

When we compared the baseline profile with those at 48 and 120 weeks, statistically significant differences were found among experienced patients in SCr (1.01±0.24 vs 0.94±0.21, $p<0.001$ and 1.01±0.24 vs 0.91±0.19, $p<0.001$, respectively). The rate of naïve patients with CrCl values in the normal rango (>60 mL/min) was 100% at 48 and 120 weeks after prescription of EVG/c/FTC/TAF, higher than basal values (98.1%). In experienced patients, the rate of patients with CrCl <60 mL/min decreased at 48 weeks (6.4%) and 120 weeks (1.9%, $p=0.007$) compared with baseline (11.3%) (table 2).

Renal profile variations in the DTG/ABC/3TC group

In experienced patients, a statistically significant difference was observed in SCr between baseline and 120 weeks (1.08±0.24 vs 1.02±0.31, $p=0.015$). The rate of naïve patients with normal CrCl values at 48 and 120 weeks after prescription of DTG/ABC/3TC was 94.4% and 100%, respectively, compared with basal values (100%). In experienced patients, the CrCl <60 mL/min rate increased at 48 weeks (23.2%) then decreased at 120 weeks (10.4%) with respect to baseline (18.9%) (table 3).

Renal profile variations between groups

Similar baseline values were found in SCr and CrCl, except when we considered experienced patients (1.01±0.24 vs 1.08±0.24; p=0.004 for SCr and 88.7% vs 81.1%, p=0.035 for CrCl >60 mL/min). Statistically significant differences were seen in SCr when comparing both treatments at week 48 (0.94±0.21 vs 1.09±0.28, p<0.001) and at week 120 (0.91±0.19 vs 1.02±0.31, p=0.015) among experienced patients, and at 48 weeks (0.89±0.16 vs 1.06±0.20, p=0.001) for naïve patients for the EVG/c/FTC/TAF and DTG/ABC/3TC groups, respectively (table 4).

No differences were found in the number of patients who suffered renal events (5.6% in the EVG/c/FTC/TAF group vs 5.8% in the DTG/ABC/3TC group, p=0.956).

A total of 17 patients died, 6 in the EVG/c/FTC/TAF group and 11 in the DTG/ABC/3TC group, without a relationship being seen with renal events.

During follow-up, 72 patients (15.8%) discontinued treatment, 39 in EVG/c/FTC/TAF and 33 n DTG/ABC/3TC (p=0.449). The main reason for EVG/c/FTC/TAF discontinuation was Aes (41%, 16 patients): hypercholesterolaemia (43.8%), central nervous system disorders (CNSd) (18.8%), gastrointestinal disorders (GI) (12.5%), renal function alteration (6.3%), rash (6.3%), weight gain (6.3%) and arthralgia (6.3%). Also, AEs were the main reason for therapy discontinuation in patients taking DTG/ABC/3TC (63.6%, 21 patients): CNSd (68.2%), GI (22.7%) and renal function alteration (9.1%). The risk of discontinuation due to AEs was similar in both groups (HR 1.77, 95% CI 0.92–3.39, p=0.087).

Only 2 patients (one in each group) discontinued therapy due to renal toxicity. In fact, both patients already had chronic kidney disease. Patient 1, DTG/ABC/3TC group, baseline SCr 1.67 mg/dL, reached week 120 with SCr 2.07 mg/dL, and then treatment was interrupted. Patient 2: EVG/c/FTC/TAF group, baseline SCr 1.43 mg/dL, reached week 48 with SCr 1.84 mg/dL and then treatment was suspended.

DISCUSSION

To our knowledge, this is the first study comparing renal variations from basal values to 120 weeks after starting EVG/c/FTC/TAF and DTG/ABC/3TC in a real-world cohort.

During the follow-up, the patients in both treatment groups experienced changes that were not clinically relevant.

It is known that nucleoside analogue reverse transcriptase inhibitors (NRTIs) combinations ABC/3TC and TAF/FTC can cause kidney disorders according to their respective technical data sheets. Both combinations have a similar renal safety profile.[15] As for the integrase strand transfer inhibitor (INSTI), few renal effects have been described with the use of EVG. However, cobicistat (an enhancer that must accompany EVG) and DTG increase SCr due to alterations in the renal tubule without causing renal toxicity or modification of the glomerular filtration rate.[16,17]

Although experienced patients in both groups achieved improved renal function compared with baseline, our results were more remarkable in the EVG/c/FTC/TAF group, as patients achieved a better renal profile at week 120. It is worth noting that these patients had a better baseline renal profile and that the difference between the two groups was not considered clinically relevant.

In EVG/c/FTC/TAF pivotal trials in naïve patients, there was less decrease in CrCl in patients with TAF than TDF and fewer patients with the TAF-regimen experienced a decrease of ≥25% from baseline to week 144 ($p<0.001$).[8,9] We found that 100% of naïve patients in the EVG/c/FTC/TAF group achieved a normal CrCl at 48 and 120 weeks. The rate of experienced patients with mild CrCl decreased during the follow-up, achieving a higher percentage of patients with normal renal function compared with baseline. Gupta *et al*, in their meta-analysis of 26 trials, demonstrated in both naïve and experienced patients improvements in CrCl and in proximal tubule function in the TAF-containing-regimen group at 96 weeks.[18] The findings from our study confirm those from the clinical trials, as switching to a TAF-based regimen allowed an improvement in renal function at week 48.[10] There are several studies in patients with impaired renal function, evaluating the renal profile after switching to EVG/c/FTC/TAF. Pozniak *et al* did not find significant changes in CrCl in patients switching to EVG/c/FTC/TAF at week 48. Otherwise they observed an improvement in clinical changes in other renal parameters (proteinuria, albuminuria, proximal renal tubular function and bone mineral density).[19]

Considering the DTG/ABC/3TC group, our data showed increases in SCr and small decreases in CrCl at week 48 among naïve patients, without this becoming a clinically significant difference. While at week 120, we observed an improvement in both

parameters, achieving 100% of patients with a normal CrCl. This small and predictable increase in SCr was also found in pivotal trials, owing to DTG's inhibition of creatinine secretion, but it was not considered clinically significant.[12] Experienced patients also showed a decrease in CrCl at 48 weeks. Even though almost 90% of patients acquired normal renal function at week 120, the rate of patients with moderate CrCl increased from baseline. As found in this study, the same decrease in CrCl was observed in a pivotal trial of patients switching to DTG/ABC/3TC.[13] Baldin *et al* compared patients switching to DTG/ABC/3TC or DTG/3TC, and they also observed at week 48 a significant reduction in CrCl in both groups, but this was higher in the dual therapy. Comparing both groups, this difference was statistically significant.[20]

In our study when we compared both treatment groups, nave patients reached normal renal function at week 120. We only observed significant differences in SCr at week 48, as described in the Results. In experienced patients, differences in SCr were observed at 48 and 120 weeks, but it must be considered that basal differences were present for SCr. For both groups, it can be concluded that more patients had a normal CrCl by week 120 compared with basal rates. Furthermore, no differences were found in the number of patients who suffered renal events between both treatments. Winston *et al* compared patients switching to TAF/FTC from ABC/3TC while continuing the same third drug. Their findings related to CrCl were similar at week 48 in both groups. Winston *et al* found a similar incidence of AEs and no patient developed a tubulopathy. Two patients in the TAF/FTC group had to suspend treatment due to renal events, while in the ABC/3TC group no patients interrupted treatment for this reason.15 In our study, the incidence of treatment-related AEs and discontinuation due to renal causes were similar in both groups.

The reasons for the conflicting results observed between clinical trials and some cohorts, such as our data, remain nuclear and may be related to the heterogeneity of the study populations, time of follow-up, and the observational research design partially explaining these findings. For the present study, the main limitations were the small sample size, baseline differences in both study groups, a single-centre study, and the retrospective observational design that might have introduced uncontrolled bias. Another limitation was the consideration of only two parameters to measure the renal profile: SCr and CrCl. Future studies should analyse proteinuria, albuminuria or bone mineral density.

The obtained results in our real-word study were similar to those in registration trials. A better renal profile has been widely demonstrated in patients treated with TAF instead of TDF, due to the lower concentration of tenofovir in plasma. In our study we wanted to determine if the TAF-based regimen (in our case EVG/c/FTC/TAF) is comparable to another single stable regimen (DTG/ABC/3TC) from a renal safety point of view. In experienced patients, we have found that each regimen allows an improvement in renal profile from baseline to week 120. Both treatments are comparable in terms of renal safety, with no significant differences in renal events, discontinuation of treatment for renal reasons or glomerular filtration values. For future studies, it would be interesting to compare other regimens that are more widely used nowadays such as DTG/3TC. Two-drug regimens promise good results, since the current tren is towards simplifyingtreatment to fewer drugs that are as effective and safe as possible.

In summary, both study treatments showed favourable renal safety and tolerance, with similar rates of drug-related AEs or discontinuation. Furthermore, no differences in renal events were found. Therefore, this study provides further data to enable clinicians to select the best treatment option according to each individual patient.

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Acknowledgements The authors would like to thank Fundación Profesor Novoa Santos, Service of Infectious Internal Medicine and Service of Pharmacy for its contribution to this study.

Funding This work was supported in part by grants from Fundación Profesor Novoa Santos, A Coruña.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The study was conducted in accordance with the Declaration of Helsinki of Good Clinical Practices.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Table 1 Baseline characteristics of the study population

Parameter	EVG/c/FTC/TAF (n=266)	DTG/ABC/3TC (n=191)	P value
Male (%)	76.3	74.9	0.722
Ethnicity origin (%)			
White	84.6	92.7	
Latin or Hispanic	12	6.3	–
Black heritage	3.4	1	
Age (years) (mean±SD)	48.0±10.5	50.9±10.6	**0.004**
20–40 (%)	23.7	13.1	
41–60 (%)	65.8	74.3	**0.018**
>60 (%)	10.5	12.6	
Acquisition risk factor for HIV infection (%):			
MSM	36.5	26.7	
Heterosexual	32.3	33.5	**0.03**
IDU	23.3	35.1	
Vertical	1.5	0.5	
Unknown	6.4	4.2	
Naive (%)	19.5	11.0	**0.014**
Mean CD4 (cells/μL±SD)	463.1±362.8	344.1±199.7	0.314
Mean RNA-HIV (log copies/mL±SD)	4.7±0.9	5.1±0.8	**0.025**
Experienced (%)	80.5	89.0	**0.014**
Mean CD4 (cells/μL±SD)	633.7±314.0	669.6±332.2	0.274
RNA-HIV basal (%VL <50 copies/mL)	84.0	85.3	0.727
Cardiovascular risk factors (%)			
Hypertension	12.4	11.5	0.775
Dyslipidaemia	59.1	61.7	0.571
Diabetes	6.4	8.4	0.419
Obesity	4.5	4.2	0.868
Smoking history			
Former	15.8	9.9	0.539
Current	41.0	31.4	
Naïve			
Renal function			

Table 1 Baseline characteristics of the study population

Parameter	EVG/c/FTC/TAF (n=266)	DTG/ABC/3TC (n=191)	P value
CrCl			
Normal (>60 mL/min) (%)	98.1	100	1
Mild (59–30 mL/min) (%)	1.9	0	
Moderate (29–15 mL/min) (%)	0	0	
SCr (mg/dL) (mean±SD)	0.91±0.19	1.0±0.18	0.080
Experienced			
Renal function			
CrCl			
Normal (>60 mL/min) (%)	88.7	81.1	**0.035**
Mild (59–30 mL/min) (%)	11.3	18.9	
Moderate (29–15 mL/min) (%)	0	0	
SCr (mg/dL) (mean±SD)	1.01±0.24	1.08±0.24	**0.004**

Statistically significant differences are shown in bold.

CrCl, creatinine clearance; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; EVG/c/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate; IDU, intravenous drug use; MSM, men who have sex with men; SCr, serum creatinine; VL, viral load.

Table 2 Renal profile evolution in the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/c/FTC/TAF) group

Parameter	Basal	W48	P value*	W120	P value†
Naive patients	(n=52)	(n=48)		(n=32)	
SCr (mg/dL) (mean±SD)	0.91±0.19	0.89±0.16	0.110	0.86±0.14	0.282
CrCl					
Normal (>60 mL/min) (%)	98.1	100	–	100	–
Mild (59–30 mL/min) (%)	1.9	0	0.968	0	0.805
Experienced patients	(n=213)	(n=188)		(n=106)	
SCr (mg/dL) (mean±SD)	1.01±0.24	0.94±0.21	**<0.001**	0.91±0.19	**<0.001**
CrCl					
Normal (>60 mL/min) (%)	88.7	93.6	**<0.001**	98.1	1
Mild (59–30 mL/min) (%)	11.3	6.4	0.125	1.9	**0.007**

Statistically significant differences are shown in bold.

*P value: basal renal profile vs renal profile at week 48.

†P value: basal renal profile vs renal profile at week 120.

CrCl, creatinine clearance; SCr, serum creatinine; W48, week 48; W120, week 120.

Table 3 Renal profile evolution in the dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) group

Parameter	Basal	W48	P value*	W120	P value†
Naive patients	(n=21)	(n=17)		(n=9)	
SCr (mg/dL) (mean±SD)	1.00±0.18	1.06±0.20	0.162	0.95±0.12	0.236
CrCl					
Normal (>60 mL/min) (%)	100	94.4	–	100	–
Mild (59–30 mL/min) (%)	0	5.6	0.938	0	–
Experienced patients	(n=170)	(n=142)		(n=126)	
SCr (mg/dL) (mean±SD)	1.08±0.24	1.09±0.28	0.981	1.02±0.31	**<0.001**
CrCl					
Normal (>60 mL/min) (%)	81.1	76.8	–	89.6	–
Mild (59–30 mL/min) (%)	18.9	22.5	0.430	8.8	0.060
Moderate (29–15 mL/min) (%)	0	0.7		1.6	

Statistically significant differences are shown in bold.

*P value: basal renal profile vs renal profile at week 48.

†P value: basal renal profile vs renal profile at week 120.

CrCl, creatinine clearance; SCr, serum creatinine; W48, week 48; W120, week 120.

Table 4 Renal profile evolution in the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/c/FTC/TAF) and dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) groups

	W48			W120		
Parameter	EVG/c/FTC/TAF	DTG/ABC/3TC	P value*	EVG/c/FTC/TAF	DTG/ABC/3TC	P value†
Naïve patients	(n=48)	(n=17)		(n=32)		(n=9)
CrCl						
Normal (>60 mL/min) (%)	100	94.4	0.273	100	100	–
Mild (59–30 mL/min) (%)	0	5.6		0	0	
Moderate (29–15 mL/min) (%)	0	0				
SCr (mg/dL) (mean±SD)	0.89±0.16	1.06±0.20	**0.001**	0.86±0.14	0.95±0.12	0.152
Experienced patients	(n=188)	(n=142)		(n=106)	(n=126)	
CrCl						
Normal (>60 mL/min) (%)	93.6	76.8	–	98.1	89.6	–
Mild (59–30 mL/min) (%)	6.4	22.5		1.9	8.8	
Moderate (29–15 mL/min) (%)	0	0.7		0	1.6	
SCr (mg/dL) (mean±SD)	0.94±0.21	1.09±0.28	**<0.001**	0.91±0.19	1.02±0.31	**0.015**

Statistically significant differences are shown in bold.

*P value: basal renal profile vs renal profile at week 48.

†P value: basal renal profile vs renal profile at week 120.

CrCl, creatinine clearance; SCr, serum creatinine; W48, week 48; W120, week 120.