# Variation in renal parameter values after a change in antiretroviral therapy from elvitegravir/cobicistat/emtricitabine/ tenofovir-alafenamide to bictegravir/ emtricitabine/tenofovir-alafenamide

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**SUMMARY**

Switching of EVG/COBI/FTC/TAF to BIC/FTC/TAF is a valid strategy for antiretroviral therapy optimization. Our aim was to analize how the variation of analytical parameters for renal function estimation after the change of their treatment. Secondary objectives were to determine if age and sex of the patients and the time they have previously taken cobicistat conditions the possible variation in renal parameters. An observational, descriptive and ambispective pilot study was performed. The renal laboratory parameters were obtained from the previous laboratory tests closest in time to the change (this value being considered the baseline) and after 12, 24 weeks and 12 months after a change in treatment with BIC/FTC/TAF. 60 patients were included. Regarding serum creatinine levels, a change in serum creatine levels was observed at 24 weeks (mean increase of 0.06 mg/dL, p=0.025) and at 12 months (mean increase of 0.03 mg/dL, p=0.05). Considering glomerular filtration (CKD-EPI), there was downward trend in the 3 periods analyzed, but statistical significance was not reached. There was no influence of sex, age and the length of time that the patients had taken cobicistat before the change.

Key words: **HIV, treatment, antiretroviral, renal, cobicistat, pharmacist.**

## *Variación de los valores de los parámetros renales tras un cambio en la terapia antirretroviral de elvitegravir/cobicistat/emtricitabina/ tenofoviralafenamida a bictegravir/emtricitabina/ tenofovir-alafenamida*

**RESUMEN**

El cambio de EVG/COBI/FTC/TAF a BIC/FTC/TAF es una estrategia para optimizar la terapia antirretroviral. Nuestro objetivo fue analizar cómo variaban los parámetros analíticos renales tras cambiar tratamiento. Los objetivos secundarios fueron determinar si edad y sexo de los pacientes y el tiempo que habían tomado cobicistat previamente condicionaba la posible variación de los parámetros renales. Se realizó un estudio piloto observacional, descriptivo y ambispectivo. Los parámetros renales se obtuvieron de las analíticas previas más cercanas al cambio (considerándose este valor el basal) y después de 12, 24 semanas y 12 meses tras cambiar tratamiento. Se incluyeron 60 pacientes. En los niveles de creatinina sérica, se observó cambio a las 24 semanas (aumento medio de 0,06 mg/dL, p=0,025) y a los 12 meses (aumento medio de 0,03 mg/dL, p=0,05). Considerando la tasa de filtración glomerular (CKD-EPI), hubo bajada en los 3 períodos analizados, pero sin significación estadística. No hubo influencia del sexo, edad ni tiempo que los pacientes habían tomado cobicistat previamente.

Palabras clave: **VIH, tratamiento, antirretroviral, renal, cobicistat, farmacéutico.**

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## INTRODUCTION

The survival of patients infected with the HIV virus has increased in recent years, and this has meant that these patients have reached older ages, increasing comorbidities and the need to take concomitant medication. Once high rates of effectiveness have been achieved, the development of new therapeutic alternatives aims to minimize the toxicity and potential interactions produced by antiretroviral treatment[1].

For some years now, one of the most common therapies in the treatment of human immunodeficiency virus (HIV) infection has been that which includes two nucleoside reverse transcriptase inhibitors and an integrase inhibitor, in accordance with current treatment guidelines. This is the case for both the combinations elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide (EVG/COBI/FTC/TAF) and bictegravir, emtricitabine and tenofovir alafenamide (BIC/FTC/TAF)[2].

Cobicistat is a selective inhibitor of the cytochrome P450-based mechanism and is also an inhibitor of the following transporters: P-glycoprotein (P gp), breast cancer resistance protein (BCRP), organic anion transporter polypeptide (OATP) 1B1 and OATP1B3. Concomitant administration with other products that are substrates of these transporters can lead to an increase in their plasma concentrations, leading to an increased risk of interactions in polymedicated patients[3,4].

For these reasons, switching treatment in patients receiving EVG/COBI/FTC/TAF to the recently marketed BIC/FTC/TAF is a currently accepted strategy as it is a similar combination with high potency and genetic barrier, well tolerated and with few interactions.

On the other hand, cobicistat produces a decrease in creatinine clearance (with no effect on renal glomerular function in patients with normal renal function), and an increase in serum creatinine, and may even trigger a decrease in estimated function due to inhibition of tubular creatinine secretion[5].

## OBJECTIVES

The primary objective is to determine how analytical parameters measuring renal function vary in patients on antiretroviral therapy who switch from EVG/COBI/FTC/TAF to BIC/FTC/TAF, when the potential effect on these parameters of cobicistat is eliminated. As secondary objectives we aim to determine whether the age and sex of the patients condition the possible variation in renal parameters, as well as the length of time patients had been on previous cobicistat treatment.

## MATERIAL AND METHODS

An observational, descriptive and ambispective pilot study was conducted, including patients with HIV infection on antiretroviral treatment who changed their treatment with EVG/COBI/FTC/TAF to BIC/FTC/TAF.

The inclusion criteria were: patients over 18 years of age who came to pick up their antiretroviral therapy, who had signed an informed consent form designed for this study, and who had laboratory tests performed at the center with data estimating their baseline renal function with glomerular filtration rate (CKD-EPI)[6].

The variables were obtained from the clinical history based on analyses programmed by the Internal Medicine Department to monitor the patients before and after the change, including the following variables: age, sex, weight and height, baseline viral load and CD4 count, serum creatinine and glomerular filtration rate estimated by the CKD-EPI equation.

The renal analytical parameters were obtained from the previous analysis closest to the change (this value being considered the baseline) and after 12, 24 weeks and 12 months after change of treatment with BIC/FTC/TAF.

Statistical analysis was performed using the PSPP statistical program. To analyze quantitative data (serum creatinine levels and glomerular filtration rate), the Wilcoxon W test for paired nonparametric samples was used. For qualitative data, Pearson's Chi-square test was used. A $p<0.05$ was considered statistically significant.

The study was approved by the Drug Research Ethics Committee (CEIm).

## RESULTS

Sixty adult patients with HIV infection were included, 42 (70%) males, age (mean±SD) 51.6±10.4 years, CD4 count 530±351/mcl. Ninety-five percent had undetectable viral load (<20 copies/mL).

Regarding serum creatinine levels, a change in serum creatinine levels was observed at 24 weeks, with an increase in 26 of the patients, mean increase of 0.06 mg/dL, CI=95% [0.01;0.11]; p=0.025. At 12 months an increase in serum creatinine concentration was also observed in 29 patients, with a mean increase of 0.03 mg/dL, CI=95% [0.00;0.07]; p=0.05 In the case of the analysis at 12 weeks the increase was not significant (p=0.145), with a creatinine increase of 0.03mg/dL, CI=95%, [-0.01;0.07].

Regarding glomerular filtration rate calculated with CKD-EPI, a worsening trend was observed in the 3 periods analyzed, but in none of the cases was it significant. At 12 weeks, there was a decrease in filtration rate of 1.89 mL/min, CI=95%, [-4.85;+1.07]; p=0.205. At week 24, the decrease in glomerular filtration rate was 2.97 mL/min, CI=95%, [-6;+0.07]; p=0.055. While at 12 months, the mean decrease was 1.55 ml/min, CI=95%, [-3.74;+0.64]; p=0.162.

When analyzing the relationship between renal parameters with sex, [-0.20;+0.42], p=0.13, and age of patients, [-0.31;+0.28], p=0.85; it was observed that there were no significant differences. We examined whether the length of time patients had been taking cobicistat prior to switching antiretroviral therapy had an influence, but likewise found no difference [-0.20; +0.37], p=0.31.

## DISCUSSION

Clinical trials with EVG/COBI/FTC/TAF, demonstrated increases in serum creatinine from week 2 of treatment that remained stable over 144 weeks. In patients who had never received treatment, a mean change from baseline of 0.04±0.12 mg/dL was observed after 144 weeks of treatment[7]. In our study, despite the fact that patients switched to a cobicistat-free treatment regimen, an increase in plasma creatinine levels was observed in the 3 periods analyzed, being only significant at 24 weeks and at 12 months with no significant impact on glomerular filtration rate calculated using the CKD-EPI formula.

Initiation of treatment with bictegravir has been shown to increase serum creatinine due to inhibition of tubular creatinine secretion; however, these changes are not considered clinically relevant since they do not reflect a change in glomerular filtration rate. Increases in serum creatinine occu-

rred at week 4 of treatment and remained stable until week 144[8]. In the same vein, Ragmopal *et al.* based on the analysis of 4 clinical trials, found similarly to our study that after switching to BIC/FTC/TAF, glomerular filtration showed a decrease of 2.9 ml/min at week 12 and remained stable with a decrease of 2.7 ml/min at week 48[9]. Despite the fact that in this study the patients started from combinations with different types of regimens, 56% changed from EVG/COBI/FTC/TAF. 9 on the other hand, a study in women, in which 53% of participants switched from combinations containing EVG/COBI to BIC/FTC/TAF also concluded that there was a decrease in glomerular filtration rate, corroborating the results of our study[10].

## CONCLUSIONS

Increased serum creatinine was observed after treatment change at both week 24 and 12 months. Regarding glomerular filtration rate estimation, the change was not significant in any of the analyzed periods. There was no relationship with sex, age or previous time on cobicistat.

*Conflict of interests: The authors declare that they do not present a conflict of interest.*

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