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Original Article

Nephrotoxicity during tenofovir treatment: a three-year follow-up study in a Brazilian reference clinic

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ABSTRACT

In this study, 275 patients in use of tenofovir were retrospectively followed-up for three years to evaluate risk factors involved in impaired renal function. Analysis of variance (ANOVA) and Tukey's test were used to verify any differences in creatinine levels and estimated clearance at 0, 6, 12, 24 and 36 months, adjusting for the co-variables sex, skin color, age >50 years, arterial hypertension, diabetes and the use of the ritonavir-boosted protease inhibitors (PI/r) lopinavir/r or atazanavir/r. The software package STATISTICA 10® was used for statistical analysis. The patients' mean age was 43.2 ± 10.7 years. Systemic arterial hypertension (SAH) and diabetes were found in 20.4% and 8.7% of the patients, respectively. Overall, 96.7% were on tenofovir associated with lamivudine (TDF + 3TC), 39.3% on lopinavir/r, 29.8% on efavirenz, and 17.6% on atazanavir/r. There was a statistically significant difference in estimated creatinine clearance at 24 months, when the co-variables *male* ($F = 3.95$; $p = 0.048$), *SAH* ($F = 6.964$; $p = 0.009$), and *age over 50 years* ($F = 45.81$; $p < 0.001$) were taken into consideration. Analysis of the co-variable *use of atazanavir/r* showed a tendency toward an increased risk over time ($F = 2.437$; $p = 0.063$); however, no significant time interaction was seen. At 36-month, a statistically significant difference was found for

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age over 50 years, ($F = 32.02$; $p < 0.05$) and there was a significant time-by-sex interaction ($F = 3.117$; $p = 0.0149$). TDF was discontinued in 12 patients, one because of a femoral neck fracture (0.7%) and 11 due to nephrotoxicity (4%). Of these latter cases, 9/11 patients were also using protease inhibitors. These data strongly alert that tenofovir use should be individualized with careful attention to renal function especially in male patients, over 50 years, with SAH, and probably those on ATV/r.

Introduction

For years now, antiretroviral therapy (ART) has been changing the natural history of the human immunodeficiency virus (HIV) infection by reducing its related morbidity and mortality, resulting in high survival rates among infected patients.[1,2] However, new adverse effects have arisen, with an important impact on patients' quality of life such as progressive changes in renal function apparently related to the use of tenofovir (TDF).[3] Initiating ART with TDF as a component of a dual-nucleoside analog regimen is already a consensus in the literature due to its potency, good tolerability profile and, mainly, to its low pill burden regimen and co-formulations.[4–6] These features increase in importance considering the current context of treating all patients at an early stage,[4,5] thus exposing patients to the use of antiretroviral (ARV) therapy for longer periods of time and to the consequent cumulative toxicity,[7] without, however, taking into account individual factors that may be associated with greater probability of developing side effects. Another important fact is that TDF is the approved drug for pre-exposure prophylaxis (PrEP),[4,6] thereby also generating risks for patients who are not infected with HIV. The objective of the present study was to evaluate the risk factors for developing impaired renal function in patients in use of TDF who were receiving care at an AIDS reference center in Vitória, Espírito Santo, Brazil between April 2006 and April 2013.

Material and methods

Patients infected by HIV [either mono-infected or co-infected with the hepatitis B virus (HBV) or with the hepatitis C virus (HCV)] and HBV mono-infected patients, at the outpatient HIV clinic at Santa Casa de Vitoria, ES, all of whom in use of TDF between April 2006 and April 2013, were included in the study. This outpatient clinic is an important reference center in the state of Espirito Santo, taking care of around 900 individuals. For inclusion in the study, patients' records should have information about the urine analyses, creatinine measurements and estimated clearance calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, prior to treatment and at 6 months, 1 year, 2 years, and 3 years of follow-up. A total of 275 patients were screened as they had at least one measure before initiating TDF and one measure after that. As AZT/3TC was the ART backbone recommended by National Guidelines at that time, almost 30% of the patients were using TDF. Of those on TDF, 21 patients were excluded, as no measures before use were available. The CKD-EPI was chosen because it is more frequently used to evaluate renal function in HIV patients.[8] An Excel database was created and repeated measures analysis of variance (ANOVA) was used to check for any changes in renal function at 6, 12, 24, and 36 months adjusting for the co-variables sex, skin color, diabetes, systemic arterial hypertension (SAH), age, and use of the ritonavir-boosted protease inhibitors (PI/r), atazanavir/r or lopinavir/r. Repeated-measures ANOVA is an extension of the paired-t test that is required for comparing three or more dependent means. It is used when variables are measured at multiple times in the same subject to assess changes due to an intervention. Tukey's test was used whenever any difference was found. The software STATISTICA 10® was used for statistical analysis. The significance level adopted for the study was 5%.

Results

Of the 275 participants in the study, 176 (64%) were white, 171 were male (62%). The mean age was 43.2 ± 10.7 years. Overall, 253 were HIV-mono-infected patients, while 10 were co-infected with HBV, 5 with HCV, and 7 were HBV-mono-infected. HIV risk factor was heterosexual relation in 172 cases, while 77 cases consisted of men who had sex with men (MSM), and 12 patients were injection drug users (IDU). Overall, 20.4% had SAH. Fasting glucose levels were abnormal in 14.9%, with 8.7% being diabetics (Table 1). The association of TDF with lamivudine (TDF + 3TC) was used by 96.7%. Lopinavir/r was used by 39.3% of patients, efavirenz (EFV) by 29.8%, and atazanavir/r by 17.6%, while 6.9% used another PI/r, and 4.6% of the patients were on nevirapine. At baseline, mean estimated glomerular filtration rate (eGFR) was 100.5 ± 17.66 mL/min ($n = 275$ patients). Mean eGFR decreased to 96.15 ± 23.15 mL/min at six months (measured in 244 patients, 61.5% male), 94.5 ± 20.74 mL/min at one year (measured in 247 patients, 62.3% male), 92.18 ± 22.42 mL/min at two years (measured in 227 patients, 62.6% male), and 89.80 ± 21.1 mL/min at three years of follow-up (measured in 170 patients, 63.5% male). Proteinuria was detected, using test strips, in 1.1% of patients at baseline, 2.5% at six months, in 3% at one year, and in 5% at two and three years of follow-up. At the 24-month analysis, statistically significant differences were found over time in patients' creatinine levels and clearance ($p < 0.05$). Male sex ($F = 3.95$; $p = 0.048$), presence of SAH ($F = 6.964$; $p = 0.009$), and age over 50 years ($F = 45.81$; $p < 0.001$) were statistically associated with greater decrease in estimated clearance levels. In addition, there was a trend toward renal function deterioration among those on atazanavir/r ($F = 2.437$; $p = 0.064$) (Table 2 and Fig. 1). Furthermore, the