

Preventing long-term tenofovir renal toxicity by pharmacokinetic assessment

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AIDS 2016, **30**:665–666

Keywords: HIV, kidney, pharmacokinetics, tenofovir

Tenofovir is the active metabolite of tenofovir disoproxil fumarate (TDF), a commonly used antiretroviral agent in HIV treatment and in HIV preexposure prophylaxis. After a long-term exposure, TDF is associated with kidney impairment. In the D:A:D study cohort of HIV-infected patients (22 603 HIV-infected patients with baseline estimated glomerular filtration rate (eGFR) ≥ 90 ml/min per 1.73 m^2), tenofovir exposure was associated after adjustment with an increased relative risk (1.18 a year) of developing chronic kidney disease (CKD) defined by the occurrence of an eGFR below 70 ml/min per 1.73 m^2 [1]. Recent studies also suggested that tenofovir use in preexposure prophylaxis might also be associated with a weak decline in eGFR, a mean decrease in eGFR after 60 months of treatment was 6 ml/min in the Bangkok Tenofovir study [2], and around 2 ml/min per 1.73 m^2 during a median follow-up of 18 months in Partners Prep Study [3]. The decline in eGFR associated with tenofovir use is not always reversible after treatment cessation [4]. Tenofovir has a mitochondrial toxicity in tubular cells, leading to kidney tubular dysfunction (KTD) [5]. KTD affects 10.6–19% of the patients receiving tenofovir [6,7]. Tubular tenofovir toxicity is probably dose dependent. Indeed, an association between high-trough tenofovir plasma concentrations and KTD (defined by hypophosphatemia, hypouricemia, nondiabetic glucosuria, β -2 microglobulinuria, or α -1 microglobulinuria) was previously observed [6,7]. However, a decrease in eGFR may be observed without evidence for KTD. It is crucial to identify mechanisms and risk factors of tenofovir renal toxicity. Tenofovir penetrates in tubular cells by several tubular transporters. Polymorphisms in genes encoding for tubular transporters organic cationic transporter 1, multi-drug resistant protein 2 (MRP-2) and 4 (MRP-4) were associated with increased tenofovir plasma concentrations and increased risk of KTD or of decrease in eGFR [8–11].

Pharmacogenetics analysis appears as an attractive approach to improve renal safety of tenofovir, by drug dosing adjustment in patients with genotypes associated with higher plasma tenofovir concentrations. However, the cost of pharmacogenetic analysis limits the spread of these methods to improve TDF renal safety. Moreover, some scores to predict the risk of decline in eGFR or of developing CKD were developed [12,13], integrating age, medical history of hypertension, diabetes mellitus, and CD4^+ positive lymphocytes counts. Interestingly, score derived from the D:A:D study cohort, integrates the associated antiretroviral agents [13]. Association combining TDF, atazanavir and ritonavir is associated with a dramatic increase in the risk of CKD. For a 65-year-old man, with a history of diabetes mellitus, hypertension, a nadir of CD4^+ lymphocytes at $120/\text{mm}^3$ and an eGFR at 80 ml/min per 1.73 m^2 , the 5-year risk of developing CKD is 100% when TDF is associated with ritonavir/atazanavir. However, predicting is not preventing and TDF remains a useful antiretroviral agent.

In this issue, Baxi *et al.* [14] demonstrated in a cohort of 105 women that highest tenofovir areas-under-the-time-concentration-curves (AUC) were associated with a greater decline in eGFR. Higher tenofovir AUCs were associated with an increased risk of CKD defined as an eGFR under 70 ml/min per 1.73 m^2 . A pharmacokinetic study was conducted once and patients were followed during a 7-year period. A unique AUC determination would predict a long-term decline in eGFR. Their observation is in the same line as Poizot-Martin *et al.* [15] who demonstrated in a cohort of 163 HIV-infected patients that higher trough tenofovir concentrations were associated with a decline in eGFR in the following 12 months. In a previous study, Baxi *et al.* [16] observed that low BMI, older age, ritonavir use, and a decreased eGFR were associated with an increase in tenofovir plasma concentrations. Consequently, tenofovir kidney

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Received: 16 November 2015; revised: 8 December 2015; accepted: 9 December 2015.

DOI:10.1097/QAD.0000000000001004

toxicity might be expected in older patients, in patients with low BMI, and in patients receiving ritonavir. Tenofovir alafenamide (TAF), another prodrug of tenofovir, is associated with lower tenofovir plasma concentration [17]. No tubular toxicity is expected as TAF is not a substrate for MRP-2 and MRP-4 [18]. In phase 3 trials, in week 48, TAF was associated with lower levels of low molecular weight proteinuria than TDF [19]. Moreover, TAF combined to emtricitabine, elvitegravir, and cobicistat may be used in patients with renal impairment (eGFR 30–69 ml/min) without dose adjustment [20]. However, data are missing to exclude long-term toxicity. Before TAF commercialization in the near future or in patients receiving generic formulation of TDF, an interesting alternative to TDF cessation would be pharmacokinetic assessment, at least with tenofovir trough concentration measurements, and drug dosing adjustment in patients at risk of decline in kidney function. Although no studies evaluated HIV-1 viral load after TDF dosing adjustment, to our point of view, it seems unlikely that we will observe virological failure after adjustment. Clinicians must bear in mind that HIV infection increases the risk of CKD, even without TDF [21]. Anyway, TAF will not completely eliminate the problem of CKD in HIV infected patients. Moreover, for instance TAF will only be available in STR associated with emtricitabine, cobicistat, and elvitegravir. In conclusion, we suggest to identify at-risk patients of developing CKD using score available at www.hivpv.org [13], and to assess tenofovir concentrations and to adjust dosing, for these patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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