EDITORIAL COMMENT

Preventing long-term tenofovir renal toxicity by pharmacokinetic assessment

Amandine Gagneux-Brunon, Elisabeth Botelho-Nevers, Anne Frésard and Frédéric Lucht

See related paper on page 609

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, multidrug 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/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

Department of Infectious and Tropical Diseases, University Hospital of Saint-Etienne, Saint-Etienne, France.
Correspondence to Amandine Gagneux-Brunon, CHU de Saint-Etienne, Saint-Etienne, France.
E-mail: amandinebrunon@yahoo.fr
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 alefanamide (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.

References

1. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, *et al*. **Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study.** *J Infect Dis* 2013; **207**:1359–1369.
2. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Gvetadze RJ, *et al*. **Renal function of participants in the Bangkok Tenofovir Study – Thailand, 2005–2012.** *Clin Infect Dis* 2014; **59**:716–724.
3. Mugwanya KK, Wyatt C, Celum C, Donnell D, Mugo NR, Tappero J, *et al*. **Changes in glomerular kidney function among HIV-1-uninfected men and women receiving emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis: a randomized clinical trial.** *JAMA Intern Med* 2015; **175**:246–254.
4. Jose S, Hamzah L, Campbell LJ, Hill T, Fisher M, Leen C, *et al*. **Incomplete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure.** *J Infect Dis* 2014; **210**:363–373.
5. Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D'Agati VD, Markowitz GS. **Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities.** *Kidney Int* 2010; **78**:1171–1177.
6. Rodríguez-Nóvoa S, Labarga P, D'avolio A, Barreiro P, Albalate M, Vispo E, *et al*. **Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations.** *AIDS Lond Engl* 2010; **24**:1064–1066.
7. Ezinga M, Wetzels JFM, Bosch MEW, van der Ven AJAM, Burger DM. **Long-term treatment with tenofovir: prevalence of kidney tubular dysfunction and its association with tenofovir plasma concentration.** *Antivir Ther* 2014; **19**:765–771.
8. Izzedine H, Hulot J-S, Villard E, Goyenvalle C, Dominguez S, Ghosn J, *et al*. **Association between ABCC2 gene haplotypes and tenofovir-induced proximal tubulopathy.** *J Infect Dis* 2006; **194**:1481–1491.
9. Kohler JJ, Hosseini SH, Green E, Abuin A, Ludaway T, Russ R, *et al*. **Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters.** *Lab Investig J Tech Methods Pathol* 2011; **91**:852–858.
10. Nishijima T, Komatsu H, Higasa K, Takano M, Tsuchiya K, Hayashida T, *et al*. **Single nucleotide polymorphisms in ABCC2 associate with tenofovir-induced kidney tubular dysfunction in Japanese patients with HIV-1 infection: A Pharmacogenetic Study.** *Clin Infect Dis* 2012; **55**:1558–1567.
11. Manosuthi W, Sukasem C, Thongyen S, Nilkamhang S, Sungkanuparph S. **ABCC2∗1C and plasma tenofovir concentration are correlated to decreased glomerular filtration rate in patients receiving a tenofovir-containing antiretroviral regimen.** *J Antimicrob Chemother* 2014; **69**:2195–2201.
12. Scherzer R, Gandhi M, Estrella MM, Tien PC, Deeks SG, Grunfeld C, *et al*. **A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans.** *AIDS* 2014; **28**:1289–1295.
13. Mocroft A, Lundgren JD, Ross M, Law M, Reiss P, Kirk O, *et al*. **Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D Study.** *PLoS Med* 2015; **12**:e1001809.
14. Baxi SM, Scherzer R, Greenblatt RM, Minkoff H, Sharma A, Cohen M, *et al*., for the Women's Interagency HIV Study (WIHS). **Higher tenofovir exposure is associated with longitudinal declines in kidney function in women living with HIV.** *AIDS* 2016; **30**:609–617.
15. Makinson A, Eymard-Duvernay S, Raffi F, Abgrall S, Bommart S, Zucman D, *et al*., for the ANRS EP48 HIV CHEST study Team. **Feasibility and efficacy of early lung cancer diagnosis with chest computed tomography in HIV-infected smokers.** *AIDS* 2016; **30**:573–581.
16. Baxi SM, Greenblatt RM, Bacchetti P, Scherzer R, Minkoff H, Huang Y, *et al*. **Common clinical conditions – age, low BMI, ritonavir use, mild renal impairment – affect tenofovir pharmacokinetics in a large cohort of HIV-infected women.** *AIDS Lond Engl* 2014; **28**:59–66.
17. Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F, *et al*. **Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial hiv-1 therapy: a randomized phase 2 study.** *J Acquir Immune Defic Syndr* 2014; **67**:52–58.
18. Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F, *et al*. **Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study.** *J Acquir Immune Defic Syndr* 2014; **1999**:2014; **67**:52–58.
19. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, *et al*. **Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, noninferiority trials.** *Lancet Lond Engl* 2015; **385**:2606–2615.
20. Pozniak A, Arribas JR, Gathe J, Gupta SK, Post FA, Bloch M, *et al*. **Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48 week results from a single-arm, multicenter, open-label, Phase 3 study.** *J Acquir Immune Defic Syndr* 1999Published Online First: 30 November 2015. doi:10.1097/QAI.0000000000000908.
21. Schouten J, Wit FW, Stolte IG, Kootstra NA, van der Valk M, Geerlings SE, *et al*. **Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study.** *Clin Infect Dis* 2014; **59**:1787–1797.