3 Agence française de sécurité sanitaire des produits de santé (AFSSAPS). [*Professional Letter*]. http://www.infectiologie.com/site/medias/_documents/consensus/lp-110311-nitrofurantoine.pdf (28 May 2013, date last accessed).

4 WHO Collaborating Centre for Drug Statistics Methodology. *Anatomic Therapeutic Chemical (ATC) Classification Index With Defined Daily Doses (DDDs)*. Oslo, Norway: Norwegian Institute of Public Health, 2001.

5 Direction de l'évaluation des médicaments et des produits biologiques département de pharmacovigilance, Agence française de sécurité sanitaire des produits de santé (AFSSAPS). [*National Commission for Pharmacovigilance. Minutes of the Meeting of Tuesday, May 24, 2011*]. http://ansm.sante.fr/var/ansm_site/storage/original/application/99a60cf5689464353d7567fe7c079892.pdf (28 May 2013, date last accessed).

6 Mullard A. Mediator scandal rocks French medical community. *Lancet* 2011; **377**: 890–2.

7 ESAC-Net. *Antimicrobial Consumption Rates by Country*. http://ecdc.europa.eu/en/activities/surveillance/ESAC-Net/database/Pages/consumption-rates-by-country.aspx (28 May 2013, date last accessed).

8 Gupta K, Hooton TM, Naber KG *et al*. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011; **52**: e103–20.

9 Shehab N, Patel PR, Srinivasan A *et al*. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis* 2008; **47**: 735–43.

10 Gbaguidi-Haore H, Dumartin C, L'Heriteau F *et al*. Antibiotics involved in the occurrence of antibiotic-resistant bacteria: a nationwide multilevel study suggests differences within antibiotic classes. *J Antimicrob Chemother* 2013; **68**: 461–70.

J Antimicrob Chemother 2014
doi:10.1093/jac/dkt306
Advance Access publication 9 August 2013

Urolithiasis associated with atazanavir may mask a metabolic 'channelling' bias

Giovanni Guaraldi[1]*, Giovanni Dolci[1] and Antonio Bellasi[2]

[1]*Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy;* [2]*UOC Nefrologia e Dialisi, Azienda Ospedaliera Sant'Anna, Como, Italy*

*Corresponding author. Tel: +39-059-4225318; Fax: +39 059-4223710; E-mail: giovanni.guaraldi@unimore.it

Keywords: metabolic syndrome, protease inhibitors, chronic kidney disease

Sir,

Chronic kidney disease (CKD) is an emerging clinical issue in HIV, particularly in ageing infected patients. Nephrotoxicity is a major issue and a frequent cause of drug switching owing to glomerular or tubular damage and the fear of progressive CKD.[1,2] However, the incidence and impact of urolithiasis as an independent contributor to CKD are not known in HIV-infected patients.

Historically, antiretroviral-induced urolithiasis has been common in patients treated with indinavir, probably due to drug crystallization and precipitation in the kidneys.[3]

At present, with regards to the risk of urolithiasis, the use of boosted or unboosted atazanavir as preferred protease inhibitor (PI) is of concern. In a large retrospective study of 1240 HIV-infected individuals, Hamada *et al*.[4] reported a urolithiasis incidence of 23.7 cases per 1000 patient-years among atazanavir-treated patients. Notably, the authors postulated that atazanavir/ritonavir can promote kidney stones via similar mechanisms to indinavir-induced urolithiasis.[4] This single-centre study,[4] as the authors pointed out, had several limitations owing to its observational and retrospective nature and because of the absence of renal stone composition analyses. In particular, the hypothesized pathogenetic mechanism – atazanavir-supersaturated urine inducing crystalluria – is difficult to test in consideration of the lack of association between serum bilirubin levels, surrogate markers of plasma atazanavir concentration and the risk of kidney stones.

By contrast, baseline data showed significantly higher uric acid concentrations in patients treated with atazanavir/ritonavir compared with patients treated with other PIs. Even though uric acid levels did not affect the Cox proportional hazard regression model results, and atazanavir/ritonavir exposure was associated with a 10-fold increased risk for kidney stones, these results may have been distorted by a 'channelling' bias. Atazanavir/ritonavir is preferentially prescribed to patients with higher metabolic risk profiles (European AIDS Clinical Society; Version 6.1; November 2012; http://www.europeanaidsclinicalsociety.org/index.php?option=com_content&view=article&id=59&Itemid=41).

An expanding body of evidence supports the notion that kidney stones are not always a separate entity but in some instances represent an epiphenomenon of a systemic metabolic disorder, being associated with insulin resistance and metabolic syndrome.[5,6] In keeping with the study by Hamada *et al*.,[4] it is plausible that at least some of the reported effects of atazanavir/ritonavir could be confounded by physician prescription.

Interestingly, the prevalence of nephrolithiasis seems higher among HIV-infected individuals than the general population (0.8%).[2] Raheem *et al*.[7] described 46 cases of nephrolithiasis in a cohort of 436 HIV-positive subjects, corresponding to an overall 11% prevalence: similar to what is expected in the general population. Unfortunately, stone analysis was only available in seven subjects and documented four cases of calcium oxalate monohydrate crystals and only one case each of cystine, uric acid and atazanavir crystals. A similar prevalence of kidney stones was described in the Castle study, the largest randomized clinical trial on atazanavir/ritonavir ever performed in naive patients.[3]

Though evidence in HIV-infected individuals is far from being conclusive, the study by Hamada *et al*.[4] suggests a thorough metabolic evaluation for nephrolithiasis in HIV-infected patients with recurrent episodes of kidney stones, a family history of nephrolithiasis or evidence of multiple kidney stones at imaging.

However, we suggest caution in interpreting the epidemiological data linking atazanavir exposure and kidney stones owing to a potential 'channelling' bias. Indeed, an excess number of patients

with metabolic disturbance may be prescribed the atazanavir/ritonavir regimen in light of its favourable lipid profile, but these patients are in fact at higher risk for urolithiasis. This situation significantly resembles our observation regarding the spurious association between abacavir and cardiovascular disease, which in fact was mediated by CKD, which was in turn the comorbidity that prompted healthcare workers to prefer abacavir to tenofovir.

New observational studies and randomized clinical trials are needed to prove this hypothesis.

Funding

No funding of any kind has been received to prepare this letter.

Transparency declarations

None to declare.

References

1 Del Palacio M, Romero S, Casado JL. Proximal tubular renal dysfunction or damage in HIV-infected patients. *AIDS Rev* 2012; **14**: 179–87.

2 Alexander RT, Hemmelgarn BR, Wiebe N *et al*. Kidney stones and kidney function loss: a cohort study. *BMJ* 2012; **345**: e5287.

3 Rockwood N, Mandalia S, Bower M *et al*. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. *AIDS* 2011; **25**: 1671–3.

4 Hamada Y, Nishijima T, Watanabe K *et al*. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. *Clin Infect Dis* 2012; **55**: 1262–9.

5 Sakhaee K. Recent advances in the pathophysiology of nephrolithiasis. *Kidney Int* 2009; **75**: 585–95.

6 Maalouf NM, Cameron MA, Moe OW *et al*. Novel insights into the pathogenesis of uric acid nephrolithiasis. *Curr Opin Nephrol Hypertens* 2004; **13**: 181–9.

7 Raheem OA, Mirheydar HS, Palazzi K *et al*. Prevalence of nephrolithiasis in human immunodeficiency virus infected patients on the highly active antiretroviral therapy. *J Endourol* 2012; **26**: 1095–8.