

## Should kidney disease risk affect antiretroviral choice?

In *The Lancet HIV*, Amanda Mocroft and colleagues<sup>1</sup> report an association between several widely used antiretroviral drugs and chronic kidney disease. Chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) lower than 60 mL/min per 1.73m<sup>2</sup> or persistent proteinuria, is more common in people living with HIV than in HIV-negative populations. Although only a small proportion of those with chronic kidney disease will eventually need renal replacement therapy, the disease is an important risk factor for cardiovascular events and death.<sup>2,3</sup> The burden of chronic kidney disease is set to increase as the HIV-positive population ages and renal risk factors such as diabetes, hypertension, and cardiovascular disease become more prevalent.<sup>4</sup> Consequently, preservation of renal function by early detection and optimised management of proteinuria and cardiometabolic risk factors is likely to become of increasing importance, and avoidance of nephrotoxic drugs is an integral part of such a strategy.

Antiretrovirals might affect renal function in several ways. Tenofovir disoproxil fumarate can cause proximal tubulopathy (Fanconi syndrome) and acute tubular injury,<sup>5,6</sup> whereas atazanavir and ritonavir can cause interstitial nephritis and kidney stones.<sup>7</sup> These toxicities, although rarely encountered in clinical practice, could partly explain the observed associations of tenofovir and atazanavir with a rapid decline in eGFR (>3–5 mL/min per 1.73m<sup>2</sup> each year)<sup>8</sup> and incident chronic kidney disease<sup>9,10</sup> (table). Antiretroviral toxicity, however, needs to be distinguished from the non-progressive reductions in eGFR that are reported with ritonavir, cobicistat, rilpivirine, raltegravir, and dolutegravir, which are explained by reversible inhibition

of creatinine transporters located on the tubular cell membrane.<sup>7</sup> These benign eGFR reductions are unaccompanied by (worsening) proteinuria, haematuria, or normoglycaemic glycosuria.

Mocroft and colleagues have extended their previous observations<sup>9</sup> and now report a significant increase in incidence of chronic kidney disease with exposure to tenofovir disoproxil fumarate, ritonavir-boosted atazanavir, and ritonavir-boosted lopinavir in patients with baseline eGFR higher than 90 mL/min per 1.73m<sup>2</sup>. For each additional year of exposure, the incidence of chronic kidney disease increased by 14% with tenofovir disoproxil fumarate, 20% with ritonavir-boosted atazanavir, and 11% with ritonavir-boosted lopinavir. No increased risk of chronic kidney disease was recorded with abacavir, which is reassuring in view of the fact that it is used more frequently than the other drugs in patients with chronic kidney disease, or with other ritonavir-boosted protease inhibitors, although the power to detect an association with darunavir was low.

The strengths of Mocroft and colleagues' study include the restriction to patients with preserved renal function at cohort entry, the size and global nature of the cohort, good availability of information about renal risk factors, and the prolonged follow-up. Limitations include the absence of data for other medications or substances that might have affected renal function, unmeasured confounding, and potential prescribing biases (analyses were not adjusted for the eGFR at which specific antiretrovirals were initiated). Moreover, because this was an observational cohort study, causality of the observed associations cannot be inferred. Urinalysis data would have allowed adjustment for any abnormalities

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	Reported renal pathology*	Acute kidney injury <sup>11</sup>	Rapid eGFR decline <sup>8</sup>	Proteinuria <sup>8</sup>	CKD (baseline eGFR >60 mL/min per 1.73 m <sup>2</sup> ) <sup>8,10</sup>	CKD (baseline eGFR >90 mL/min per 1.73 m <sup>2</sup> ) <sup>1,9</sup>
Tenofovir disoproxil fumarate	Acute tubular injury	No	Yes	Yes	Yes <sup>8</sup> /yes <sup>10</sup>	Yes
Atazanavir	Interstitial nephritis; nephrolithiasis	No	Yes	No	No <sup>8</sup> /yes <sup>10</sup>	Yes
Lopinavir	Interstitial nephritis and nephrolithiasis?	Not reported	No	No	No <sup>8</sup> /yes <sup>10</sup>	Yes
Ritonavir	Interstitial nephritis and nephrolithiasis?	Not reported	No	Yes	No <sup>8</sup> /not reported <sup>10</sup>	Not reported

CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. \*Data for tenofovir disoproxil fumarate and atazanavir come from case series, data for lopinavir and ritonavir from case reports.

**Table: Renal pathology and renal syndromes that have been reported with selected antiretrovirals**

at baseline and provided insightful information, in that eGFR decline accompanied by (worsening) proteinuria, glycosuria, or haematuria would have lent additional support to the notion that the observed associations might result from antiretroviral toxicity, especially if these abnormalities resolved or improved after discontinuation of the offending agents.

How relevant are these findings for clinical practice? First, the incidence of chronic kidney disease in the study population was very low (1.76 per 1000 person-years of follow-up; 95% CI 1.56–1.97), and the observed modest (14–20%) annual increase in chronic kidney disease risk with tenofovir disoproxil fumarate and ritonavir-boosted atazanavir should not distract clinicians from choosing antiretrovirals that have been very successful in achieving durable viral suppression. In terms of prevention of chronic kidney disease, monitoring of renal function (eGFR and urinalysis) allows the identification of individuals with progressive eGFR decline, proteinuria, haematuria, and normoglycaemic glycosuria in whom modifiable risk factors should be identified and managed before the eGFR falls to lower than 60 mL/min per 1.73m<sup>2</sup>.<sup>12</sup> In patients treated with tenofovir disoproxil fumarate whose eGFR decline or abnormal urinary findings are unresponsive to such measures, the drug should be discontinued if suitable alternatives are available, and a high degree of eGFR reversibility has been recorded in patients who discontinue tenofovir.<sup>13</sup> On the basis of the findings from Mocroft and colleagues' report and previous studies, the same should probably also apply to ritonavir-boosted atazanavir or lopinavir, although no studies so far have investigated the potential benefits of such a strategy.

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