CASE STUDIES – HIV AND THE KIDNEYS

THE RISKS OF CONCURRENT TREATMENT WITH TENOFOVIR AND AMINOGLYCOSIDES IN PATIENTS WITH HIV-ASSOCIATED TUBERCULOSIS

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The South African public sector antiretroviral treatment (ART) guidelines have recently been changed to include tenofovir in the first-line regimen.[1] Injectable drugs from the aminoglycoside class are part of the intensive phase of regimen 2 tuberculosis (TB) treatment and the multidrug-resistant (MDR) TB treatment regimen in the South African TB programme. We wish to draw the attention of clinicians managing patients with HIV-associated TB to the potential dangers of concurrent administration of these drugs. We present two illustrative cases.

CASE 1

We recently admitted a 47-year-old man with a background of hypertension who had a serum creatinine level of 131 µmol/l prior to ART. He was diagnosed with pulmonary tuberculosis (*Mycobacterium tuberculosis* was cultured from his sputum). Because he had had a fully treated episode of pulmonary tuberculosis in 2007, he was commenced on regimen 2 TB treatment (including streptomycin during the intensive phase) in March 2010. At this time he tested HIV positive, and because he had a CD4 count of 61 cells/µl he was commenced on tenofovir, lamivudine and efavirenz in May 2010, while still receiving streptomycin. He was referred to our hospital 3 weeks later with a 1-week history of weakness, vomiting and confusion. The creatinine level was now 1 902 µmol/l and the urea level 59 mmol/l. He was admitted, tenofovir was switched to stavudine, streptomycin was stopped, and he received intravenous rehydration and a broad-spectrum antibiotic. His blood culture was negative and urine microscopy showed no evidence of urinary tract infection. His creatinine level steadily decreased and within 3 weeks was 160 µmol/l.

CASE 2

A 28-year-old HIV-infected man was on a tenofovir-based ART regimen when he was diagnosed with MDR TB. He was started on MDR TB treatment including kanamycin and remained on tenofovir. His creatinine level rose from 64 µmol/l to 180 µmol/l within 1 month of starting MDR treatment. He was then referred to our hospital. Tenofovir was changed to stavudine and the kanamycin was stopped, yet his creatinine remained elevated 3 months later (125 µmol/l), suggesting that chronic renal damage may have resulted. He will continue to be followed up.

DISCUSSION

The aminoglycosides are potent nephrotoxins, in part because of the high concentrations they attain in the proximal tubular cells (PTCs) – up to 10% of the total parenteral dose may be concentrated in these cells.[2] Here they undergo retrograde transport through the endoplasmic reticulum, where they can interfere with protein sorting and synthesis,[3] and are then transported into the nucleus and mitochondria where they can inhibit mitochondrial ribosomes[4] (in a way that is analogous to their bactericidal effect on the small ribosomal unit of bacteria). It is thought that one mechanism through which they cause acute tubular necrosis (and Fanconi's syndrome) is tubular mitochondrial toxicity.

Like the aminoglycosides, tenofovir attains high concentrations in the PTCs as a result of active uptake into these cells. A substantial proportion of patients taking tenofovir may develop certain of the features of Fanconi's syndrome (a proximal tubular wasting syndrome) as a result of PTC dysfunction. One study reported that 22% of patients on tenofovir developed at least 2 out of 6 features of proximal tubular dysfunction such as hyperaminoaciduria, glycosuria in the presence of normoglycaemia, and hyperphosphaturia.[5] Tenofovir may also cause renal failure. There is evidence to suggest that tenofovir's nephrotoxicity is related to tubular mitochondrial toxicity with abnormal mitochondria

having been observed on electron microscopy of tubular cells in renal biopsies of patients on tenofovir.[6] Acute tubular necrosis has been observed in patients who have had a renal biopsy after developing tenofovir-related acute renal failure.[7]

When tenofovir was developed there were concerns that it would be nephrotoxic because other nucleotide reverse transcriptase inhibitors (adefovir used to treat hepatitis B and cidofovir used to treat herpes virus infections) are nephrotoxic.[7] However, early clinical trials failed to demonstrate any excess risk of renal adverse events in participants receiving tenofovir.[8,9,10] These clinical trials did, however, exclude patients with impaired renal function and those on other nephrotoxic drugs. Subsequent reports from HIV treatment cohorts showed that tenofovir is associated with mild decreases in glomerular filtration rate when compared with patients on other antiretrovirals.[11,12] More importantly, a minority of patients on tenofovir develop acute or chronic renal failure. In a review of studies from developed world settings it was estimated that <1% will develop clinically significant renal impairment.[7] In 2006, Zimmermann *et al.* published 5 cases of acute renal failure related to tenofovir and reviewed a further 22 cases that had been reported in the literature to that date.[13] In 5 of these 27 patients the renal impairment did not fully resolve after stopping tenofovir. In a recent analysis of the EuroSIDA cohort, increasing exposure to tenofovir was associated with a higher incidence of chronic kidney disease.[14] A recently published systematic review and meta-analysis found that there was a modest but statistically significant increase in the risk of acute renal failure in patients on tenofovir compared with other antiretrovirals (risk difference 0.7%, 95% confidence interval (CI) 0.2 - 1.2). Importantly, in 11 of the 17 studies in the meta-analysis patients with abnormal renal function at baseline were excluded, and the majority of the studies reviewed were clinical trials from which patients on other nephrotoxic medications were likely to have been excluded.[15] These studies may therefore have underestimated the risk of tenofovir nephrotoxicity by excluding patients at higher risk.

There is concern that in sub-Saharan Africa the risks of tenofovir nephrotoxicity may be greater because of the high background prevalence of renal disease, including HIV-associated nephropathy, and lack of capacity to monitor renal function regularly. An analysis of renal outcomes of the DART study, conducted in Uganda and Zimbabwe, showed no difference in the incidence of severe reductions in estimated glomerular filtration rate in patients started on tenofovir-based regimens compared with other regimens, but all the patients who died of renal failure (*N*=11) were on tenofovir. Contributing co-morbidities were identified in most of these 11 patients. In one of these patients it was thought that the combination of gentamicin and tenofovir was responsible.[16] An additional issue to consider in our setting is that if patients do develop severe renal failure, access to dialysis facilities, especially in rural areas, is limited.

It is biologically plausible that the toxicities of aminoglycosides and tenofovir may be additive in the mitochondria of PTCs. Analysis of data from the tenofovir expanded-access programme revealed that being on concomitant nephrotoxic medications was an independent risk factor for elevations in serum creatinine during follow-up.[17] In a case-control study conducted in a US HIV clinic, concurrent nephrotoxic medication (such as high-dose or chronic non-steroidal anti-inflammatory drugs (NSAIDs), amphotericin B and aminoglycosides) was shown to independently increase the risk of tenofovir-associated nephrotoxicity (odds ratio 6.4, 95% CI 2.2 - 18.4).[18] Indeed, the package insert for tenofovir states that it 'should be avoided with concurrent or recent use of a nephrotoxic agent'.[19]

A particular concern is that aminoglycosides for treating TB are prescribed for between 2 and 6 months. It is likely that the risk of nephrotoxicity with tenofovir and aminoglycoside will be greater if co-administered for this long duration. One approach that has been suggested is that the combination could be used, but with close monitoring of serum creatinine. However, given that drug-induced nephrotoxicity may result in acute renal failure within 1 - 2 weeks this would necessitate a frequency of monitoring and follow-up of results that is not practical in busy HIV and TB programmes.

While the new national ART guidelines do not address the risks of co-administration of tenofovir and aminoglycosides,[1] we think that there is sufficient evidence to concur with a recent recommendation to avoid the co-administration of tenofovir and aminoglycosides whenever possible.[20] When considering what to do in the light of this co-toxicity, it is important to recall that the aminoglycosides (kanamycin or amikacin) used in the treatment of MDR TB and the cyclic polypeptide, capreomycin, used in the treatment of extensively drug-resistant (XDR) TB, are essential components of these treatment regimens. On the other hand, streptomycin is not a critical component of regimen 2 TB treatment, particularly now that rapid drug susceptibility testing is available to appropriately direct therapy in patients being retreated for TB. We therefore recommend the following:

- During the intensive phase of MDR TB treatment (while the patient is on amikacin or kanamycin), do not prescribe tenofovir. In place of tenofovir use zidovudine, stavudine or abacavir. After completing the aminoglycoside component of MDR TB treatment, patients could be switched to tenofovir provided the estimated creatinine clearance is >50 ml/min. This switch to tenofovir is particularly important in patients with hepatitis B co-infection.

- The same approach should be used in patients on capreomycin during the intensive phase of XDR TB treatment. Capreomycin is also nephrotoxic.

- In patients on tenofovir who require regimen 2 TB treatment, omit streptomycin from regimen 2. In

How to calculate creatinine clearance (modified Cockroft and Gault formula)

$$eGFR = \frac{(140 - age) \times weight\ (kg)}{serum\ creatinine\ (\mu mol/l)}$$

For females multiply the GFR by 0.85.
eGFR = estimated glomerular filtration rate.

patients starting tenofovir-containing ART while on regimen 2 TB treatment, omit the streptomycin from regimen 2 from when they start the tenofovir. In all other respects regimen 2 TB treatment should remain unchanged.

Our first case highlights another important point: that it is critically important to calculate the estimated creatinine clearance in patients before starting tenofovir, and if it is <50 ml/min, tenofovir should not be used.[1] This patient had an estimated clearance of 32 ml/min prior to ART (this was probably related to HIV-associated nephropathy and/or hypertensive nephropathy). This patient should therefore not have received tenofovir or streptomycin. It is likely that in this case underlying renal impairment and treatment with two nephrotoxins all contributed to the development of severe acute renal failure.

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