CASE REPORT

Irreversible acute kidney injury following efavirenz/tenofovir disoproxil fumarate/emtricitabine overdose

Jason Ensor1,2, Shumani Malaka3, Benita Barton4, John Black5,6, Robert Freercks1,2
1Renal Unit, Livingstone Hospital, Port Elizabeth, South Africa; 2Division of Nephrology and Hypertension, University of Cape Town, South Africa; 3PathCare, Port Elizabeth, South Africa; 4Nelson Mandela University, Port Elizabeth, South Africa; 5Division of Infectious Diseases, Livingstone Hospital, Port Elizabeth; 6Division of Infectious Disease, University of Cape Town, South Africa.

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Correspondence: Robert Freercks, robert.freercks@uct.ac.za.
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CASE PRESENTATION

A 42-year-old HIV-positive white male presented to a secondary hospital in February 2017, three days after attempting suicide by overdosing on his fixed-dose combination antiretroviral tablets (Odimune; Cipla) containing TDF 300 mg, emtricitabine 200 mg (FTC) and efavirenz 600 mg (EFV). He had been taking TDF/FTC/EFV treatment daily since starting HIV treatment in 2014 and had a suppressed viral load. He reported ingesting 90 tablets, comprising 54 g EFV, 18 g FTC and 27 g TDF (or 450 mg/kg). Since the overdose, he had been nauseous and vomiting at home and had been confused and drowsy. He was, however, able to call for help after two days. He reported no abdominal pain but was tremulous and dehydrated and had noticed that he was no longer passing urine. His serum creatinine at presentation was 641 μmol/L compared to 69 μmol/L three months earlier. He was admitted and rehydrated over the next 72 hours but remained anuric and was therefore referred to our hospital for evaluation and further treatment. On admission to our unit, he was oedematous and in pulmonary oedema with respiratory distress. The serum creatinine was now 1264 μmol/L and he was started on haemodialysis three times per week. Despite beginning to pass normal volumes of urine within a week, he remained dialysis-dependent at six weeks. A renal biopsy was performed six weeks after admission, to exclude an associated interstitial nephritis. The biopsy confirmed acute tubular necrosis (ATN) with normal glomeruli and only mild interstitial changes, but also demonstrated a brownish-green pigment present in the cytoplasm of some tubular epithelial cells. The

INTRODUCTION

Nephrotoxicity due to chronic use of tenofovir disoproxil fumarate (TDF) is well-described in the literature; risk factors for toxicity include older age, low body weight and CD4 count, concomitant use of nephrotoxic agents, male sex, hepatitis C co-infection and advanced HIV disease [1]. Very little is known or published about the effects of acute toxicity or the clinical management of this condition. We present here a case of acute and irreversible renal failure that followed an intentional overdose of fixed dose combination antiretroviral therapy containing efavirenz, TDF and emtricitabine. The renal histology findings are discussed and a rationale for the use of emergency haemodialysis in the management of TDF overdose is presented.

Keywords: Africa; AKI; tenofovir overdose; HIV; dialysis.

ABSTRACT

Nephrotoxicity due to chronic use of tenofovir disoproxil fumarate (TDF) is well described, but very little is known or published about the effects of acute toxicity or the clinical management of this condition. We present here a case of acute and irreversible renal failure that followed an intentional overdose of fixed dose combination antiretroviral therapy containing efavirenz, TDF and emtricitabine. The renal histology findings are discussed and a rationale for the use of emergency haemodialysis in the management of TDF overdose is presented.
pigment was associated with indentations and pyknosis of the nuclei that appeared to precede cell necrosis and loss of nuclear detail. In addition, patchy areas of anuclear proximal tubules containing pigment were also present. The pigment did not stain with periodic acid–Shiff, Masson’s trichrome or Perl’s Prussian blue stains (Figure 1a–c). Electron microscopy of the tubular epithelium revealed degenerate epithelial cells and reduced numbers of mitochondria. In addition, there were areas of osmiophilic degenerate material which were thought to represent degenerate mitochondria and correlated with the deposits observed on light microscopy (Figure 2a–d). Unfortunately, our patient did not recover sufficient renal function and was therefore transitioned onto continuous ambulatory peritoneal dialysis on which he is doing well. The serum creatinine six months after the initial overdose was 473 μmol/L.

DISCUSSION
Toxicity with chronic use of TDF results in proximal tubular dysfunction and can manifest as a full or partial Fanconi syndrome and/or progressive renal dysfunction. The proposed mechanism is due to drug accumulation in proximal tubular cells with resultant mitochondrial toxicity through inhibition of mitochondrial gamma polymerase and consequent oxidative stress and impaired cellular protective responses. Histologically, apart from the usual non-specific manifestations of acute tubular necrosis, this may be associated with pigmented inclusions in proximal tubular cells seen on haematoxylin and eosin staining on light microscopy and seen as abnormal and giant mitochondria on electron microscopy [2]. Genetic polymorphisms in proximal tubular transporters are also thought to contribute to the risk of intracellular accumulation in individuals [1,3].

The mechanism of acute toxicity is unclear, although it is conceivable that it would be similar to that of chronic toxicity described above. We could find only one report describing acute toxicology in rats, which defined the animal toxic dose as more than 30 mg/kg. Interestingly, pigment accumulation in the proximal tubules of all rats exposed to TDF was noted at 43 weeks after dosing [4]. Little is known about acute toxicity due to overdose in humans and the only information available is limited to a handful of case reports. Havenith et al. [5] have recently reported a case where acute kidney injury complicated EFV/FTC/TDF (Atripla, MSD) overdose, with partial recovery of renal function; the ingested TDF dose was 21 g. In their case, dialysis was initiated on day nine after initial expectant management and was required for a total of six weeks before partial renal recovery to an estimated

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**Figure 1.** (a) Renal cortex with brownish-green pigment present in the cytoplasm of some tubular epithelial cells (haematoxylin and eosin stain, original magnification x400). (b) Highlighted area, from fig 1(a), showing pigment with loss of nuclear detail. (c) The pigment indents the nucleus and is negative on a periodic acid–Schiff stain (periodic acid-Schiff stain, original magnification x400).
glomerular filtration rate of 35 mL/min. In their report, the authors justify why earlier use of haemodialysis would be expected to result in a rapid reduction of plasma TDF levels. TDF is a prodrug of the acyclic nucleotide reverse transcriptase inhibitor tenofovir and is eliminated exclusively in the urine with no extra-renal route of elimination. Peak serum levels (Cmax) are achieved within 0.5–4 hours after dosing in healthy volunteers. High-flux haemodialysis, started at Cmax and continued for 4 hours, removes TDF with a clearance rate of 134 mL/min and an extraction ratio of 54%, resulting in the removal of approximately 50% of the bioavailable ingested dose. Serum levels rebound somewhat after discontinuation of dialysis, reflecting redistribution from the tissues [6]. Therefore, early initiation of high-intensity and prolonged or repeated haemodialysis would be expected to markedly reduce plasma levels of TDF in patients presenting with an overdose, although it is uncertain whether this would translate into clinical benefit and prevention of AKI.

Lee et al. have also recently described a case of dolutegravir, FTC and TDF overdose, which was associated with mild and reversible AKI and where dialysis was not performed. However, as Havenith et al. point out, the total ingested dose was far lower at 4.9 g [7]. In our case, the ingested dose of 27 g is much higher, and similar to that reported by Havenith et al., where there was only partial recovery of renal function.

The renal histology in our case demonstrated severe proximal tubular necrosis, which would be in keeping with a toxic insult to the kidney. Proximal tubular cells demonstrated cellular swelling and the presence of a green-brown pigment in cells which were anuclear. This is notable given the description of pigmented deposits being present in animal toxicology studies of tenofovir [4]. Electron microscopy of the tubular epithelium in this case confirmed a toxic acute tubular necrosis with a decrease in the number of normal mitochondria and a large amount of material thought to represent degenerate mitochondria. The mitochondria were not found to be dysmorphic as in prior reports [2], but this may be because of the acute nature of the insult in this case compared to the chronic toxicity previously described. Our patient had no clinical evidence to suggest chronic toxicity given that he had a normal baseline serum creatinine just a few months prior to presentation. No urine testing had been done prior to his overdose and since he was anuric at presentation, it was not possible to assess for other markers of tubular toxicity.
It is not known whether earlier haemodialysis could have ameliorated the severe renal injury in our patient, although as described above, it is possible to rapidly lower serum levels of TDF with appropriate haemodialysis. What is also not clear is why there have been so few reports of renal injury following antiretroviral therapy overdose and we speculate that factors such as genetic susceptibility to TDF accumulation could also play a role in the genesis of tubular injury in acute exposure as for those in chronic exposure. Other factors such as chronic use as well as accompanying vomiting and hypovolaemia, as in this patient, could also increase individual susceptibility to renal injury.

Tenofovir alafenamide (TAF) is a prodrug of tenofovir, which is metabolised intracellularly to its active metabolite, tenofovir diphosphate. Compared to TDF, this allows for lower dosing, lower plasma tenofovir concentrations and lower toxicity, while retaining similar antiviral efficacy [8]. Replacement of TDF by TAF would, one hopes, see a reduction in the risk of developing renal disease. Presumed TAF-related nephrotoxicity has, however, been reported in a patient with significant renal co-morbidity, so although TAF is generally associated with improved renal outcomes, clinicians should remain vigilant when using TAF in high risk patients [9].

CONCLUSIONS

In summary, we have presented a case of acute and irreversible renal failure following intentional overdose of TDF/FTC/EFV combination antiretroviral tablets. Clinicians need to be aware of the potential for severe AKI in such instances and of the role of emergency haemodialysis in lowering serum TDF levels. It is uncertain, though, whether this strategy will ameliorate or prevent associated AKI and this requires further study.

Ethical considerations

Consent for publication was obtained from the patient.

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REFERENCES