

**AIDS**

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**Risks and benefits of HIV pre exposure prophylaxis with tenofovir/emtricitabine in an older man with co-morbidities.**

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Running title: PrEP guidelines and tenofovir toxicity

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## **ABSTRACT**

Renal toxicity in a 73 year old man using tenofovir/emtricitabine (TDF/FTC) as pre-exposure prophylaxis (PrEP) is described. Reduced renal reserve, a higher exposure to co-medications and co-morbidities can present a challenge when assessing the risks and benefits of tenofovir based PrEP in the ageing population.

**Keywords:** PrEP, tenofovir, renal toxicity

Pre-exposure prophylaxis (PrEP) with tenofovir/emtricitabine (TDF/FTC) available as the fixed drug combination Truvada, is highly effective in preventing HIV transmission [1-3] and is used increasingly as part of a combination prevention strategy in individuals at risk of acquiring HIV. A recent mathematical model showed the importance of PrEP as a single intervention able to outperform other isolated prevention strategies [4]. Tenofovir and emtricitabine were generally well tolerated although drug-related gastrointestinal side-effects were reported more frequently in the first 12 weeks by those receiving active PrEP [1-3]. A significant decline in creatinine clearance (CrCl) was observed in 3-18% of individuals [1-3,5], with a more significant drop of CrCl (below 60mL/min) reported in 1% of patients. Following cessation of therapy, CrCl normalized [5]. In PROUD, 3/275 (1.1%) of the participants randomized to the immediate TDF/FTC arm interrupted drug due to elevated serum creatinine. Two had documented co-morbidities which may have influenced renal

function; however, a relationship to TDF/FTC exposure could not be excluded. Renal dysfunction in the third case was attributed to recreational drug use [1].

We describe the challenge of managing a 73 year old homosexual man with pre-existing comorbidities, receiving daily TDF/FTC as PrEP and subsequently developing renal dysfunction requiring two isolated hospital admissions during follow-up. This man had a history of Crohn's disease well controlled on mesalazine, and was randomized to immediate PrEP as part of the PROUD study in August 2014, following normal baseline serum creatinine level (78 $\mu$ mol/L), with an estimated CrCl of 90mL/min (Cockcroft-Gault). No side-effects and full adherence to the medication were reported over the first 12 months following study entry although, after six months, a decline in MDRD estimated glomerular filtration rate (eGFR) was observed along with low level of proteinuria ( $\leq 1+$ ) detected by urine dipstick. Serum creatinine and urine testing were increased in frequency to monitor for early signs of possible TDF-induced tubulopathy [6]. During the first 18 months, an eGFR  $< 50$ mL/min was reported on two occasions (see full details in table 1). In October 2015 the patient experienced a suspected flare of his Crohn's, manifested as profuse diarrhea and fatigue and resulting in significant dehydration and acute kidney injury (AKI). A rise in serum creatinine from 120 to 195 $\mu$ mol/L and resultant drop in CrCl from 52 to 30mL/min were noted, along with severe hypokalemia (2.1mmol/L) without hypophosphataemia (0.94mmol/L). Following cessation of TDF/FTC, fluid resuscitation and treatment with intravenous antibiotics and potassium supplementation, renal function returned to baseline. Secondary tests were performed to investigate further the possible causes for renal dysfunction. A kidney ultrasound scan was unremarkable, whilst repeated urinary fractional excretion of electrolytes, showed normal values of fractional excretion of sodium, which fell below 1% during episode of AKI, suggesting dehydration as mechanism of renal failure.

During trial management group meetings it was agreed that the risk for the user to catch HIV outweighed the risk to his renal function, hence the clinicians concurred with the participant preference to continue on PrEP. Nevertheless, following a reoccurrence of AKI, triggered by another episode of persisting diarrhea, in December 2015 the clinical team decided not to prescribe any more PrEP. On this occasion creatinine levels rose again to 1.5 times their normal value and eGFR dropped down to 32 mL/min. After intravenous fluids correction the renal function returned to pre-AKI levels.

This case describes an example of renal dysfunction in an older man with pre-existing comorbidities and co-medications on PrEP. It is known that people over 50 living with HIV are at a higher risk of clinical progression [7] and in 2014, approximately 6% of MSM newly diagnosed with HIV in the UK were over 50 years of age [8]. This data reinforce the validity of using PrEP in this selected population. Only 9% (83/900) individuals in this age group were included in IperGAY and PROUD studies. As a result, there are no solid data on the long term impact of PrEP in a HIV-negative population which is more prone to multiple comorbidities, polypharmacy and reduced renal function at baseline compared to younger counterparts. Also, onset of TDF-induced tubular dysfunction seems to correlate with older age in HIV positive patients [9]. UK national guidelines for PrEP are not yet available, but renal monitoring is advised in a position statement [10]. It is possible that cases similar to this one will become more frequent with wider availability of PrEP, suggesting the urgent need for additional PrEP options that are less renally toxic. Further data on the long term on renal monitoring of individuals with co-morbidities and aged >50 years is needed to establish the optimal frequency of testing.

We encourage research on additional options for PrEP that are less renally toxic. A combination with tenofovir alafenamide and emtricitabine (TAF/FTC) has recently been licensed for treatment, and may shortly be evaluated for PrEP [11]. TAF showed less

detrimental effects on the kidneys and bones compared with TDF in HIV-positive patients [12]. Cabotegravir, a new long-acting injectable antiretroviral agent, showed significant protection in macaques [13], and there are plans to evaluate the efficacy in a non-inferiority design compared to TDF/FTC. Due to favourable pharmacokinetics and promising preliminary in-vitro studies, maraviroc/lamivudine or raltegravir/lamivudine regimens [14] could be possible future options.

In an ideal world, potential PrEP users would have a choice of agents to select and this choice could be individualized depending on age, co-morbidities and preference. For now options are limited. Subjects in the deferred arm of the PROUD study had a particularly high risk of catching HIV infection (HIV incidence = 9.0/100 person-years). With this in mind, the balance of renal risk from daily tenofovir against a lifetime of infection with a nephrotoxic virus and need for lifelong medication favoured PrEP at baseline. With the emergence of repeated AKI, the risk-benefit balance in this participant shifted towards interruption and discontinuation of tenofovir based PrEP. This needs to be clearly explained to individuals so that they can make an informed decision about the risks, up to the point that a drug becomes clinically contraindicated.

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**TABLE 1.** Markers of renal function and kalemia over time

Time (months)	Baseline <sup>o</sup>	6	12	18	24	25 <sup>†</sup>	26	27	28 <sup>†</sup>	30
Event	PrEP start					AKI followed by PrEP suspension	PrEP restarted on Ipergay scheme		AKI followed by final PrEP suspension	Post PrEP suspension
<b>Creatinine</b> (mmol/L)	78	99	130	108	120	195	116	112	180	105
<b>eGFR*</b> (mL/min)	90	65	47	59	52	30	54	56	32	60
<b>K+</b> (mEq/L)	4.1	3.4	4.3	4.2	3.8	2.1	4.7	3.5	2.1	4.4

<sup>o</sup>. 12/08/2014

<sup>†</sup>. Hospital admission

\*. Calculated calculated by the abbreviated MDRD equation