

Research Letters

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Tenofovir-associated proteinuria

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Proteinuria was observed in 27% of 153 patients taking tenofovir for more than 1 year. Concomitant protease inhibitor therapy and cumulative tenofovir exposure were independently associated with proteinuria in this cohort. Proteinuria was reversible in 11 of 12 patients who ceased tenofovir because of proteinuria without altering other medications. Clinicians should be aware that tenofovir can cause reversible proteinuria in patients with HIV.

Chronic kidney disease (CKD) is associated with increased mortality and cardiovascular disease in patients with HIV [1,2]. Cumulative exposure to tenofovir and some protease inhibitors has been associated with CKD defined according to reductions in estimates of glomerular filtration rate (GFR) [3]. Proteinuria can precede reductions in GFR and represents significant renal disease, including proximal tubular dysfunction. Proteinuria has been shown to predict all-cause mortality in individuals with untreated and treated HIV [4]. Proteinuria has been associated with tenofovir therapy, although the prevalence, predictors, and outcomes of persons who develop proteinuria in association with tenofovir therapy are not well described [5].

All patients undergo annual proteinuria screening in our clinic. This is performed by calculating the protein:creatinine ratio on a random urine specimen. The medical records of patients who received tenofovir for more than 1 year were retrospectively reviewed. Age, sex, HIV viral load, current CD4 cell count, antiretroviral status at time of initiation of tenofovir (naïve or experienced), concomitant antiretroviral therapy, duration of tenofovir therapy, estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease equation (values over 90 ml/min/1.73m² reported as >90), nonfasting serum phosphate (PO₄), and urine protein:creatinine ratio (UPCR) were collated. Proteinuria was defined as a UPCR more than 15 g/mol on repeat testing having excluded urinary tract infection. Hypertension, diabetes, and BMI were not well recorded and have not been included in this analysis. Factors associated with proteinuria were examined using univariate (Student's *t*-test for continuous variables and χ^2 test for categorical variables) and multivariate analyses. Changes in UPCR were compared

in patients who ceased tenofovir because of proteinuria with those of patients who continued tenofovir despite proteinuria.

One hundred and fifty-three patients were identified and all were included in this analysis. The characteristics of the patients are shown in Table 1. All patients had a viral load below the limit of detection of 40 copies/ml. Forty-two (27%) patients had proteinuria (mean UPCR 38, SD 34). Multivariate analyses indicated that longer duration of tenofovir use [$P=0.006$, odds ratio (OR), 1.29 per year, 95% confidence interval (CI), 1.08–1.54] and concomitant protease inhibitor therapy ($P=0.004$, OR, 7.36, 95% CI, 1.88–28.9) were associated with proteinuria. Age, sex, current CD4 cell count, or treatment status at the time of initiation of tenofovir did not predict proteinuria in multivariate analyses. Proteinuria was associated with lower eGFR (median 80.5 versus >90 ml/min/1.73m², approximate OR, 0.91 per ml/min/1.73m², approximate 95% CI, 0.87–0.95) and lower nonfasting serum PO₄ (mean 0.99 versus 1.06 mmol/l $P=0.009$, OR, 0.70 per 0.1 mmol/l increment, 95% CI, 0.53–0.91). However, the differences in these parameters between patients with and without proteinuria were small and may not be considered to be significant by the clinician.

Twelve patients ceased tenofovir and commenced an alternative nucleoside reverse transcriptase inhibitor because of proteinuria. These patients did not alter other medication. In particular, they did not commence angiotensin-converting enzyme inhibitor therapy, other antihypertensive agents, diabetic therapy, or alter protease inhibitor therapy. Patients who ceased tenofovir because of proteinuria had higher mean UPCR prior to ceasing tenofovir than patients with proteinuria who continued tenofovir (64 versus 28; $P=0.03$). Proteinuria significantly reduced over a 6-month period in 11 of 12 patients ceasing tenofovir (64–14; $P=0.001$), whereas UPCR did not significantly change over a similar period in 30 patients continuing tenofovir despite proteinuria. UPCR increased from 71 to 123 in one patient despite cessation of tenofovir. This patient was also taking ritonavir-boosted darunavir. He was normotensive and had a normal fasting blood glucose level and eGFR more than 90. His urinary albumin creatinine ratio was also increased (87, cf normal less than 1). No cause has yet been identified for this patient's proteinuria.

The prevalence of proteinuria among those patients taking tenofovir in our cohort was 27%. We found an

Table 1. Characteristics of patients with and without proteinuria while taking tenofovir.

	Patient group Mean (SD) or n (%)			Analysis			
	Total group	With proteinuria	Without proteinuria	Univariate P	P	Multivariate OR	95% CI
n	153	42 (27%)	111 (73%)				
Age (years)	47.7 (9.9)	51.2 (10.5)	46.3 (9.4)	0.01			
Men	134 (87.6)	38 (90.5)	96 (86.5)				
ART-naïve at time of initiation of tenofovir	55 (35.9)	14 (33)	41 (36.9)				
CD4/ μ l	612 (236)	629 (231)	606 (238)				
eGFR ^a	88	80.5	>90	<0.001 ^b	<0.001 ^b	0.91 per ml/min/1.73m ²	0.87–0.95
ml/min/1.73m ²	(77–>90)	(64.8–>90)	(79–>90)				
eGFR > 90	75 (49)	15 (36)	60 (54)	0.043 ^c			
PO ₄	1.04 (0.18)	0.99 (0.18)	1.06 (0.17)	<0.001	0.009	0.03 per mmol/l	0.00–0.40
mmol/l						0.70 per 0.1 mmol/l	0.53–0.91
Duration of tenofovir (months)	62.0 (27.7)	74.6 (26.9)	57.2 (26.6)	<0.001	0.006	1.02 per month	1.01–1.04
Concomitant protease inhibitors	115 (75)	37 (88)	78 (70)	0.002	0.004	1.29 per year	1.08–1.54
							1.88–28.9

ART, antiretroviral therapy; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

^aMedian (interquartile range).

^bApproximate results (treating '>90' values as equal to 90).

^cNot included in multivariate analysis.

association between duration of tenofovir therapy and proteinuria and estimated that the odds of proteinuria increased by 2% for every month of tenofovir therapy (29% per year). These findings are consistent with other studies. The risk of proteinuria increased by 30% per year of exposure to tenofovir in one study [6]. Another study reported that the incidence of proteinuria in patients taking tenofovir was 19% over 2 years [5]. The co-administration of protease inhibitor therapy with tenofovir increased the odds of proteinuria by seven times in our study. This is consistent with another study [5]. Possible causes of this association include ritonavir inhibition of enzymes involved in tenofovir elimination from the kidney.

Tenofovir-associated proteinuria was reversible in the majority (11/12) of patients who ceased the drug in our cohort. Other studies have not demonstrated such reversibility in renal abnormalities in patients who cease tenofovir [5,6]. Renal parameters did not improve following tenofovir cessation in 42% of patients in one study [5]. The mean eGFR of the patients who ceased tenofovir in that study was 51 ml/min/1.73m² compared with 76.3 ml/min/1.73m² in our study. It is interesting to speculate that proteinuria may be an early and reversible effect of tenofovir-associated renal damage. As hypertension and diabetes were not well documented in this cohort, we cannot exclude the possibility that the management of these conditions impacted upon the improvements of proteinuria in patients ceasing tenofovir because of proteinuria; however, this seems unlikely. This retrospective study was also limited by its inability to provide information regarding the timing of the onset of proteinuria in patients taking tenofovir.

Proteinuria was commonly detected in patients taking tenofovir for more than 1 year in this cohort. The risk of proteinuria increased with a longer duration of tenofovir therapy and was greater in persons also taking protease inhibitor therapy. Proteinuria was generally observed in the absence of marked decreases in either serum phosphate or eGFR. Tenofovir-associated proteinuria generally resolved upon cessation of the drug. Larger studies are warranted to confirm these initial findings; to describe the natural history of tenofovir-associated proteinuria; to determine the value of regular proteinuria screening in persons taking tenofovir; and to address the impact of tenofovir-associated nephrotoxicity on bone disease.

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Conflicts of interest

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No impact of rifamycin selection on tuberculosis treatment outcome in HIV coinfected patients

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Rifabutin has been substituted for rifampicin when treating tuberculosis (TB)/HIV coinfection. However, despite reports of anti-TB treatment failure and acquired rifamycin resistance, long-term clinical outcome data are lacking. Observational analyses performed in a UK TB/HIV cohort demonstrated no difference in severe adverse events, anti-TB treatment completion, relapse frequency or subsequent rifamycin resistance when rifampicin and rifabutin were compared, using different combinations of antiretroviral therapy. Our data support the wider use of rifabutin in TB/HIV coinfection.

Drug sensitive tuberculosis (TB) is generally treated with a rifamycin-containing regimen, typically rifampicin (RMP) [1]. This potent inducer of the hepatic cytochrome P450 (CYP) enzyme has significant drug interactions with combination antiretroviral therapy (ART) such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). An alternative rifamycin, rifabutin (RFB), has less effect

on CYP and can be substituted for RMP when ART is co-prescribed [2].

RFB has been used successfully to treat non-HIV-infected individuals [3]. However, there is little long-term outcome data on HIV coinfection [4]. Systematic reviews suggest that despite its high cost, RFB may be cost saving in patients taking PIs [5].

When RFB is used with ritonavir-boosted PIs, it is generally given in low dose, intermittent regimen to compensate for both the increased drug concentration of RFB associated with concomitant PI use and the drug's long half-life. However, this has resulted in anti-TB treatment failure and relapse with acquired rifamycin resistance [6]. A pharmacokinetic study demonstrated subtherapeutic concentrations of RFB and its active metabolite when combined with ritonavir-boosted PIs and given at current recommended dosages in HIV-infected subjects, with subsequent acquired rifamycin resistance [7].

Our centre has been using RFB as part of its anti-TB treatment strategy for several years. In view of these reports, we undertook a review of outcomes of our TB/HIV coinfected population who received rifamycin during their treatment for active TB.

We identified all adult HIV-infected individuals receiving a rifamycin between January 1997 and December 2008 at our HIV centre. TB was diagnosed if the patient was culture positive for *Mycobacterium tuberculosis*, or culture negative but nucleic acid amplification assay positive with clinico-radiological features and treatment response consistent with TB, or had histological findings and treatment response consistent with TB. Patients with known rifamycin resistance were excluded from assessment.

The duration of anti-TB treatment, whether the senior supervising clinician considered treatment was successfully completed, the occurrence of severe (grade III/IV) adverse drug reactions causing functional disability or requiring medical intervention [8] and the frequency of TB recurrence was identified using retrospective case note review.

Prescription of anti-TB medication and ART was at the discretion of individual physician using local treatment protocols. Drug dosage was in line with current British HIV Association guidance [2]; prescribed as self-administered treatment using dosette boxes and pill counts when required. RMP was used at a weight-based dosage of 450–600 mg once daily with concurrent NNRTIs and single agent ritonavir. RFB was prescribed at 450 mg once daily with efavirenz and 300 mg once daily with nevirapine NNRTIs and was given at a standard dosage of 150 mg thrice weekly with boosted

PIs. Other anti-TB drugs were taken daily. As this was a clinical service evaluation, ethical approval was not required.

Subgroup analysis of population characteristics by rifamycin and ART use was undertaken using χ^2 -test and Fisher's exact test.

One hundred and forty-one TB/HIV coinfected patients received rifamycin-based anti-TB treatment. Their median age was 36 years [interquartile range (IQR) 32–43], 52% were women and 72% black African. One hundred and three (72%) had positive culture results for *M. tuberculosis* (four with isoniazid drug resistance). Pulmonary TB was demonstrable in 58 (41%) patients. Median blood CD4 cell count prior to anti-TB therapy was 141 cells/ μ l (IQR 51–272).

One hundred and six (75%) used ART at any time during anti-TB therapy. Forty-one (29%) were already receiving ART, whereas the median ART start time for the others once established on anti-TB treatment was 2 months (IQR 1–3). RMP was given to 86 patients (60% received concomitant ART) and RFB to 79 (99% received concomitant ART). Twenty-four patients initiated treatment with RMP and then switched to RFB (in two-thirds due to the introduction of a PI-based ART regimen).

Six different ART regimens were used in 106 patients: 68 (64%) were PI-based (including one patient on PI monotherapy), 36 (34%) were NNRTI-based, 1 (1%) was NRTI-based and in one (1%) the specific ART regimen was unknown.

When RMP was used as the sole rifamycin during anti-TB treatment, 21 of 28 (75%) were prescribed NNRTI-

based ART and seven of 28 (25%) PI-based ART. In contrast, 44 of 54 (81%) patients prescribed RFB used a PI-based regimen and 10 of 54 (19%) NNRTI-based ART, $P < 0.001$. When patients switched from RMP to RFB, 17 of 24 (71%) were prescribed PI-based, five (21%) NNRTI-based and one (4%) triple NRTI-based ART.

Patients on ART + RMP or who switched rifamycin had evidence of a trend towards a longer median duration of anti-TB treatment, $P = 0.06$ (Table 1).

Severe (grade III/IV) adverse events occurred in 39 of 106 (37%) patients who did and 13 of 35 (43%) did not receive ART during anti-TB treatment, $P = 0.21$ (Table 1). There was no significant difference in the overall number of patients experiencing at least one severe adverse event according to type of rifamycin and concurrent ART usage, $P = 0.58$.

The frequency of individual severe adverse events was similar between rifamycins for all but arthralgia [present in seven of 13, 54%, receiving RMP without concurrent ART compared with RMP or RFB with ART (1/13, 8% and 2/13, 15%, respectively), $P = 0.002$] (Table 1). No patient had to modify therapy, though 11 of 141 (8%) briefly interrupted treatment due to hepatotoxicity. This was unrelated to rifamycin type or concurrent ART usage.

There was no significant difference in the proportion completing anti-TB therapy using different combinations of rifamycin and ART, $P = 0.53$ (Table 1). Six of 141 (4%) patients were lost to follow-up and two (1%) died during anti-TB therapy. The remaining 133 (94%) patients were considered cured of TB by their treating physician.

Table 1. Outcomes in 141 HIV-infected adults according to rifamycin and antiretroviral therapy use.

	No ART during TB Rx		ART during TB Rx		
	RMP, n=34	RFB, n=1	RMP, n=28	RFB, n=54	RMP+RFB, n=24
Median (IQR) duration of TB treatment (months)	6 (6–12)	6	9 (6–12)	7 (6–12)	12 (6–14)
Frequency of at least one severe (grade III/IV) adverse event	13 (38%)	1 (100%)	13 (46%)	16 (30%)	9 (38%)
Hepatotoxicity	2 (6%)	–	4 (14%)	4 (7%)	4 (17%)
Peripheral neuropathy	1 (3%)	–	4 (14%)	5 (9%)	3 (13%)
Rash	3 (9%)	–	2 (7%)	3 (6%)	2 (8%)
Persistent vomiting	–	–	1 (4%)	1 (2%)	–
Arthralgia	7 (21%)	–	1 (4%)	2 (4%)	–
Neutropaenia	2 (6%)	1 (100%)	3 (11%)	4 (7%)	5 (21%)
Other	1 (3%)	–	–	2 (4%)	3 (13%)
Deaths during TB treatment ^a	1 (3%)	–	–	1 (2%)	–
Completion of treatment	30 (88%)	1 (100%)	27 (96%)	52 (96%)	23 (96%)
Median (IQR) follow-up (months)	69 (24–99)	116	60 (24–95)	60 (24–94)	57 (26–91)
Recurrence of TB	1 (3%)	0	2 (7%)	1 (2%)	0
Deaths following completion of TB treatment ^b	4 (12%)	–	2 (7%)	3 (6%)	1 (4%)

Note: ART during TB Rx and no ART during TB Rx indicate whether or not antiretroviral therapy was given concurrently with antituberculosis treatment, respectively. ART, antiretroviral therapy; RFB, rifabutin; RMP, rifampicin; RMP+RFB, rifampicin and rifabutin given serially during antituberculosis treatment; TB, tuberculosis.

^aOne patient died due to a cerebrovascular accident and the second due to TB.

^bFive patients died due to HIV-related illnesses: two due to carcinoma and the cause of death was not available for three.

After a median follow-up from TB treatment completion of 64 months (IQR 29–98), four of 133 (3%) patients relapsed – all with a drug-sensitive organism. Of these, only one had received RFB as part of anti-TB therapy (Table 1).

In our retrospective cohort study, at the current recommended dosing, when compared with RMP, RFB does not appear to be associated with an excess of severe adverse events or an increased risk of relapse or subsequent acquired rifamycin resistance. Other data have suggested that acquired rifamycin resistance is more likely with intermittent RFB dosing. However, Burman *et al.* [6] used a variety of treatment regimens, including a less frequent rifamycin schedule than reported here, and, in fact, found the use of ART to be protective. The carefully performed study by Boulanger *et al.* [7] in predominantly African–Americans, noted that RFB, and its metabolite, levels were low using intermittent dosing. Of the 10 patients, one (weight 118 kg, BMI 34.3 kg/m²) developed acquired rifamycin resistance. Although the numbers were small and follow-up was not reported (all were regarded as cured at treatment completion), it is possible that therapeutic failure reflected the patient's high BMI and would be less likely in average-sized individuals. Also, other anti-TB drugs appear to have been given thrice weekly, rather than daily, which is our practice.

In our study, almost all patients using RFB were on ART (predominantly PI). Yet, severe adverse events were no more frequent – implying that these agents can be safely combined in routine clinical practice.

Although our dataset is retrospective, reasonably small in size, and drug levels were not measured, we believe that it lends support to the wider use of RFB in TB/HIV-coinfected patients. It is hoped that its recent price reduction will improve access to this promising therapeutic option in resource-poor areas with high rates of co-existent TB and HIV (<http://www.clintonhealthaccess.org/news-and-information/arv-price-reductions-faqs-august-2009>).

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The safety of flucloxacillin in HIV-infected patients with positive HLA-B*5701 genotype

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Positive HLA-B*5701 genotype has recently been identified as the main genetic risk factor for flucloxacillin drug-induced liver injury (DILI). Testing for HLA-B*5701 is routine in many HIV clinics to identify those at risk of hypersensitivity reaction (HSR) to abacavir. Considering the high prevalence of soft-tissue infections in HIV patients, we conducted a retrospective study to investigate whether flucloxacillin use was associated with adverse events in HIV patients known to be HLA-B*5701 positive.

Flucloxacillin is a semi-synthetic penicillin, widely used for the management of soft-tissue infections. Although generally perceived as having little serious toxicity, flucloxacillin has been associated with drug-induced liver injury (DILI) [1–3]. A recent study of 51 well defined cases of flucloxacillin DILI and 282 controls matched for sex and ancestry used genome-wide association (GWA) methods identifies any association peaks in the major histocompatibility complex region (MHC) [4]. In particular, the GWA revealed the presence of the HLA-B*5701 allele to be associated with a high risk of DILI (odds ratio = 80.6, $P = 8.7 \times 10^{-33}$) with the conclusion that HLA-B*5701 may be the main genetic risk factor for flucloxacillin-induced liver injury.

HLA-B*5701 screening is routinely performed to identify HIV-infected individuals at risk of hypersensitivity reaction (HSR) to the antiretroviral drug, abacavir [5]. As a result, HLA-B*5701 testing is now a routine part of care in many HIV clinics [6]. With a population prevalence of approximately 5% (depending on the ethnic mix in local populations), many clinics now have sizeable cohorts of patients known to be carriers of the HLA-B*5701 allele. Given the high prevalence of soft-tissue infections in HIV-1 positive patients, we investigated whether flucloxacillin use was associated with adverse events in HIV-infected individuals known to be HLA-B*5701 positive.

We identified 79 individuals from a single London-based clinic who had tested positive for the HLA-B*5701 allele using a commercial polymerase chain reaction assay (Lab21 Ltd., Cambridge, UK) since 2008. Using our

prospective clinical and pharmacy databases, we assessed clinical and laboratory parameters in patients receiving flucloxacillin between January 2008 and July 2012.

In total 10 of 79 (12.7%) had received flucloxacillin during this period (median age 51 years (range 47–56 years) and 9 of 10 (90%) were men). In all cases, flucloxacillin was prescribed for uncomplicated soft-tissue infections. The median total dose and duration of treatment were 20 g (range 10–28 g) and 10 days (range 5–14 days), respectively. Of those given flucloxacillin, one patient had chronic hepatitis C virus (HCV) infection. After reviewing all available clinical and laboratory information, no case of suspected or confirmed clinical or biochemical toxicities within 1–90 days after prescription of flucloxacillin were identified.

During this period of study, all patients had liver function tests including alanine aminotransferase (ALT), bilirubin and alkaline phosphatase (Alk Phos) assessed.

Liver function tests were within normal limits apart from in the one case with HCV infection, in which ALT before and after the 90 days of observation remained above 60 (IU/l). The interval of 1–90 days after prescription was chosen because of the characteristic clinical picture of flucloxacillin-DILI described in clinical reports of liver disease associated with flucloxacillin [1,2].

The strength of the association between HLA-B*5071 and flucloxacillin DILI suggests that genetic screening might be able to prevent adverse events in those HIV-1 positive patients carrying this allele. However, we failed to find evidence of toxicity in a small sample of patients treated with flucloxacillin and carrying both the HLA-B*5701 allele and receiving flucloxacillin. Although these data suggest that there may not be a major risk to HIV patients in routine practice, a note of caution needs to be added. In previous work, age over 55 years old, female sex and a treatment duration longer than 14 days have been proposed as risk factors for flucloxacillin DILI [1,7,8]. In this study, all patients were below the age of 55 years, only one was a woman and none had more than 14 days of flucloxacillin therapy. For this reason it is not possible to conclude that for all HIV-1 positive individuals, having a HLA-B*5071 genotype is not associated with flucloxacillin DILI. It remains crucial for clinicians to be aware of the association of HLA-B*5701 with DILI, particularly in elderly patients, those with underlying liver disease and those requiring prolonged antibiotic therapy. Data to inform recommendations in those groups will require studies in larger populations. In differing healthcare settings, other antibiotics may be used more frequently than flucloxacillin for soft-tissue infections (e.g. nafcillin or oxacillin) and these data cannot be generalized to those groups.

For HLA-B*5701 positive individuals in whom other risk factors are present, alternative antibiotics to flucloxacillin could be considered. However, given that most clinicians are comfortable and confident using flucloxacillin, careful monitoring of liver function parameters would seem to be a prudent alternative based on these initial data.

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