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This is a non-final version of an article published in final form in AIDS: 28 January 2013 - Volume 27 - Issue 3 - p 479–481 doi: 10.1097/QAD.0b013e32835883bf

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[http://dx.doi.org/10.1097/QAD.0b013e32835883bf](http://dx.doi.org/10.1097/QAD.0b013e32835883bf)
Tenofovir Associated Proteinuria

Kelly M D¹, Gibson A¹, Bartlett H², Rowling D¹, Patten J¹

¹Brisbane Sexual Health and HIV Service – clinic 2, 270 Roma St Brisbane, Queensland Australia;

²Queensland University of Technology

Abstract

Proteinuria was observed in 27% of 153 patients taking tenofovir for more than one 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.

Keywords

Proteinuria, Chronic Kidney Disease, Tenofovir
Chronic Kidney Disease (CKD) is associated with increased mortality and cardiovascular disease in patients with HIV. Cumulative exposure to tenofovir and some protease inhibitors has been associated with CKD defined according to reductions in estimates of glomerular filtration rate (GFR). Proteinuria can precede reductions in GFR and represents significant renal pathology including proximal tubular dysfunction. Proteinuria has been shown to predict all cause mortality in subjects with untreated and treated HIV. 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.

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 one year were retrospectively reviewed. Age, gender, HIV viral load, current CD4 count, antiretroviral status at time of initiation of tenofovir (naïve or experienced); concomitant antiretroviral therapy (ART), 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), non-fasting serum phosphate (PO₄), and urine protein:creatinine ratio (UPCR) were collated. Proteinuria was defined as a UPCR >15 g/mol on repeat testing having excluded urinary tract infection. Hypertension, diabetes and body mass index were not well recorded and have not been included in this analysis. Factors associated with proteinuria were examined using univariate (student t test for continuous variables and chi square 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, OR 1.29 per year, 95% confidence interval 1.08-1.54) and concomitant protease inhibitor therapy (p=0.004, OR 7.36, 95% confidence interval 1.88-28.9) were associated with proteinuria. Age, gender, current CD4 count or treatment status at the time initiation of tenofovir did not predict proteinuria in multivariate analyses.
Proteinuria was associated with lower eGFR (median 80.5 v >90 mL/min/1.73m², approximate OR 0.91 per mL/min/1.73m², approximate 95% confidence interval 0.87-0.95) and lower non-fasting serum PO₄ (mean 0.99 v 1.06 mmol/L p=0.009, OR 0.70 per 0.1 mmol/L increment, 95% confidence interval 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 v 28 p=0.03). Proteinuria significantly reduced over a six month period in 11 of 12 patients ceasing tenofovir (64 to 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 > 90. His urinary albumin creatinine ratio was also increased (87, cf normal <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 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. Another study reported that the incidence of proteinuria in patients taking tenofovir was 9% per year. 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. 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. The reasons for this disparity are unclear however it is likely that patients in other
studies had more pronounced renal dysfunction at the time of tenofovir cessation. The mean eGFR of
the patients who ceased tenofovir in one study was 51 mL/min/1.73m$^2$ compared with 76.3
mL/min/1.73m$^2$ in our study. Renal parameters did not improve following tenofovir cessation in 42% of
patients in this 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.

Proteinuria was commonly detected in patients taking tenofovir for more than one year in this cohort.
The risk of proteinuria increased with 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.
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Analysis</th>
</tr>
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<tbody>
<tr>
<td>Mean (SD) or Number (%)</td>
<td>Univariate</td>
</tr>
<tr>
<td><strong>Total group</strong></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>153</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.7 (9.9)</td>
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<tr>
<td>Male</td>
<td>134 (87.6)</td>
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<tr>
<td>Proteinuria</td>
<td></td>
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<tr>
<td>ART naïve at time of initiation of tenofovir</td>
<td>55 (35.9)</td>
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<tr>
<td>CD4/µL</td>
<td>612 (236)</td>
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<tr>
<td>eGFR* mL/min/1.73m²</td>
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<tr>
<td>eGFR &gt; 90</td>
<td>88 (77-90)</td>
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<tr>
<td>PO₄ mmol/L</td>
<td>1.04 (0.18)</td>
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<tr>
<td>Duration of tenofovir (months)</td>
<td>62.0 (27.7)</td>
</tr>
<tr>
<td>Concomitant protease inhibitors</td>
<td>115 (75)</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of patients with and without proteinuria whilst taking tenofovir.
* Median (interquartile range)
** approximate results (treating ‘>90’ values as equal to 90)
*** not included in multivariate analysis


