Effect of TDF-containing regimens on creatinine clearance in HIV patients in Namibia with a baseline CrCl <60ml/min; findings and implications

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ABSTRACT
Background and aims: The advent of antiretroviral therapy (ART) and early diagnosis of the human immunodeficiency virus (HIV) has resulted in an appreciable reduction in morbidity and mortality among people infected with HIV. However, tenofovir disoproxil fumarate (TDF)–containing ART regimens are associated with a reduction in creatinine clearance (CrCl). No evaluation has been conducted in Namibia to date on the relationship between TDF-containing ART and CrCl among patients with moderate to severe reductions in CrCl to guide future practice. We aimed to address this. Methodology: Retrospective longitudinal study between January 2008 to December 2016 evaluating CrCl in patients with a baseline CrCl <60ml/min who were receiving TDF-containing ART in a leading hospital in Namibia. We identified patients who had experienced an improvement in CrCl and compared their characteristics with those whose CrCl did not improve. We assessed factors for an association with improvement in CrCl using binary logistic regression. Results: 389 patients were included, the majority were female (n=294). Female vs. male assessments showed no difference in age (p=0.340), weight (p=0.920), number who experienced an improvement (105 vs 39, p=0.349), or absence of improvement (189 vs. 56, p=0.349). The improvement group (male and female) had a lower baseline CrCl (45.9 vs. 55.0, p<0.001). The follow-up CrCl for the improvement and no improvement groups were 72.6 and 55.9 respectively. Multivariate analysis showed that the odds of improvement were: 0.905 (0.871 – 0.940, p<0.001) for each unit rise in the baseline CrCl, and 0.904(0.880 – 0.923) for each year of follow-up. Conclusion: More improvement than decline in CrCl was observed. Improvement occurred more in patients with lower baseline CrCl, and occurred in the early period of ART with reduced odds of experiencing this with time. Our findings indicate that TDF may be used in patients with a low baseline CrCl.

1.0 INTRODUCTION

There continues to be a high prevalence of Human Immunodeficiency Virus (HIV) in sub-Saharan Africa including Namibia, with HIV/ AIDs (Acquired Immuno-Deficiency Syndrome) still having the highest disease burden in sub-Saharan Africa (1-3). Namibia is one of the sub-Saharan African countries with the highest prevalence of HIV (4, 5). The advent of
antiretroviral therapy (ART) and early diagnosis of HIV has resulted in an appreciable reduction in morbidity and mortality among people infected with HIV (6-10). However, tenofovir disoproxil fumarate (TDF) containing ART regimens, which are extensively used in sub-Saharan Africa based on the ART guidelines of the World Health Organisation (11), are associated with a reduction in creatinine clearance (CrCl) (12-17). There is conflicting evidence though regarding the effect of a low baseline CrCl on renal function. Some authors have reported that a low baseline CrCl, signified by a high serum creatinine, is a risk factor for a further decline in CrCl (18-24). As a result, the manufacturers of TDF recommend monitoring renal function, along with the adjustment of the TDF dosage, in patients with a low baseline CrCl (25). Some authors though have documented that a low baseline CrCl has no effect on CrCl, whilst others have found that a high baseline CrCl is a risk factor for the TDF-associated decline in CrCl (26-28). This conflicting evidence potentially impacts on clinician’s judgement on the use of TDF when faced with a patient with a baseline CrCl <60ml/min.

ART – including TDF-containing regimens – is expected to improve the renal function in patients with HIV-associated renal disease (14). TDF-containing ART may still be used in patients with a low baseline CrCl as it is the only option for the effective management of patients co-infected with HIV and hepatitis-B (Hep-B) virus (29). In some patients an improvement in the CrCl may not be realised possibly due to non-HIV related causes of renal impairment such as hypertension or diabetes mellitus. In others a further decline in CrCl may occur (14). TDF may contribute though to the persistently low CrCl or the worsening of renal function, both of which increase the risk of end-stage-renal-disease, cardiovascular disease, and death (30, 31).

Currently, little is known about the effects of TDF-containing ART on the CrCl of HIV infected patients in Namibia who have a baseline CrCl of <60ml/min. This is important given the high prevalence of HIV in Namibia and the recommended use of TDF containing regimens. In addition, there are considerable genetic differences between patients with HIV/AIDS found in sub-Saharan Africa versus Western countries with a greater predominance of women with HIV in sub-Saharan Africa (5, 10). Consequently, we conducted this study in order to estimate the number and proportion of patients receiving TDF-containing ART who experienced an improvement, no change, or a decline in CrCl, including those who newly acquired the state of severe renal insufficiency. Additionally, we assessed the factors associated with changes in renal function. We believe these findings will help improve the management of patients who receive TDF-containing regimens in Namibia and wider.

2.0 METHODOLOGY

2.1 STUDY DESIGN AND SETTING
This was a retrospective longitudinal study conducted for the period from January 2008 to December 2016. We evaluated the CrCl in HIV patients who were receiving TDF-containing ART. This study was based on data from the HIV clinic in Oshakati Intermediate Hospital (OIH), a public referral hospital in northern Namibia, with a 750 bed capacity. Oshakati Intermediate Hospital was chosen because it was selected by the Ministry of Health and Social Services, Namibia, to be a sentinel site for pharmacovigilance studies in patients with HIV and other diseases due to its high patient numbers.

2.2 STUDY POPULATION AND INCLUSION CRITERIA
Our target population was HIV infected patients who were 16 years of age and older when they received TDF-containing ART, and had a baseline CrCl <60ml/min. Patients were included if they had three or more recorded values of CrCl in their health records.

2.3 DATA SOURCE
The study data were acquired from the Research Monitoring and Evaluation (RM & E) unit of the Ministry of Health and Social Services (MoHSS). This data is normally collected during routine care, Each HIV infected patient receiving care at a particular health facility is given a file – referred to as the patient care booklet. The patient’s health facility-based identification number is written on this booklet. The baseline and follow-up medical and clinical data are recorded in this booklet. The data from the booklets are entered into the electronic patient
management system (ePMS) by data clerks on a regular basis. The ePMS is a computer based database at each health facility providing information on HIV care and treatment. This data is electronically transmitted regularly to the RM & E unit which stores it in the national ePMS.

2.4 DATA ANALYSIS
2.4.1 Descriptive Statistic
We estimated the means and standard deviations (SD) of continuous variables, namely age (in years), weight (in Kg), follow-up duration (in years), and CrCl (ml/min). Numbers and proportions of patients are reported according to gender and outcome groups. The definitions for the outcome groups are provided in Box 1.

2.4.2 Metrics for changes in CrCl
We calculated the difference between the baseline and the last recorded CrCl, and used this to estimate the percentage change in CrCl. Based on the definitions in Box 1, we identified patients who had experienced an improvement in CrCl, those who did not experience a clinically significant change in CrCl, those who experienced a ≥25% decline in their CrCl, and those who ended up with severe renal insufficiency. We divided the patients into two groups: (a) the improvement group, and (b) the no improvement group. We also identified patients who had experienced a change in CrCl, which according to the definitions neither improved nor declined in their CrCl. Those who had a significant decline in CrCl were few, so for analysis purposes we grouped them together with those who did not experience any improvement.

2.4.3 Statistical analysis
We tested the differences in the mean age, weight, follow-up duration, and baseline CrCl between the two groups, using the Student’s T-test. To assess the differences between females and males we used the Pearson Chi-square test. To test the changes in stages of CrCl based on the baseline and the last CrCl we used the McNemar-Bowker test. The baseline was the first recorded CrCl. The time the patient had been receiving ART prior to this date was not used in the analysis. To identify factors that were associated with improvement in CrCl, we used univariate and multivariate methods in the binary logistic regression method. The confidence interval was set at 95%, and the significance at a p-value <.05. The analysis was conducted using SPSS.

**Box 1: Definitions**

**The baseline CrCl:** The first CrCl was considered as the baseline, irrespective of the time the patient had been on antiretroviral therapy. **Consequently,** the duration of follow up was the difference in time between the first recorded CrCl and the time when the change in CrCl changed significantly, or the time when the last CrCl was recorded. NB: The Namibia ART guidelines currently recommend use of the Cockcroft-Gault method for assessing renal function. The formula recommended is:

\[
CrCl = \frac{(140 - \text{age (years)}) \times \text{weight (Kg)}}{\text{serum creatinine (umole per L)}} \times 1.22
\]

For females, the answer is multiplied by 0.85 (29)

**Categories of renal function:** Renal function was categorised as follows: stage I - ≥90ml/min (normal); Stage II – 60 to 89ml/min (mildly); Stage III – 30 to 59ml/min (moderate); and Stage IV - <29ml/min (severe), as used by Michels et al (32).

**Improvement in CrCl:** An improvement in CrCl was classified to have occurred when the patient had two or more consecutive records of CrCl ≥60ml/min, including the most recent one. In addition, when the last CrCl was greater than the baseline value by ≥25%, improvement was said to have occurred. A patient was said to have experienced a further decline in CrCl when their last CrCl was lower than the baseline CrCl by ≥25%. Those patients who experienced the ≥25% decline were grouped together in the analysis with those whose last CrCl was <60ml/min despite the fact that they had experienced an increase in CrCl that was <25%.
2.5 ETHICS
The study was approved by the research committee at the University of Namibia Faculty of Health Sciences and the centre of post-graduate studies at the University of Namibia, and the Research and Ethics Committee of the MoHSS: Namibia (Ref 17/3/3). Patient anonymity was ensured by obtaining data without patient names. Furthermore, the data was stored on a password protected computer, which was only accessed by the data collector.

3.0 RESULTS
A total of 1771 patient records were assessed. Of these, 22.0% (n=389) had a baseline CrCl <60ml/min, and were therefore included in the study (Figure 1).

Figure 1 - Flow diagram of patients

6.7% of patients (26/389) had severe renal insufficiency at baseline. Of the 389 included patients, the majority were female (75.6%: 294/389) (Table 1) and no difference in gender amongst those with severe renal insufficiency was observed (6.1%: 18/294 vs. 8.4%: 8/95; p=0.435). There was no difference in age, weight and follow-up duration, between the females and males who had moderate renal insufficiency (Table 2).

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients, n (%)</td>
<td>389</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.2(10.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.2(14.6)</td>
</tr>
<tr>
<td>Baseline CrCl (ml/min)</td>
<td>50.5(9.9)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>294(75.6)</td>
</tr>
<tr>
<td>Male</td>
<td>95(24.4)</td>
</tr>
<tr>
<td>Renal function proportions at baseline, n (%)</td>
<td></td>
</tr>
<tr>
<td>Moderate (30 – 59 ml/min)</td>
<td>363(93.3)</td>
</tr>
<tr>
<td>Severe (&lt;30 ml/min)</td>
<td>26(6.7)</td>
</tr>
</tbody>
</table>

Improvements in CrCl were observed in 37.0% (144/389) of the cohort. The proportion of females who experienced an improvement in CrCl was not significantly different from that of males: 35.7% (105/294) vs. 41.5% (39/95), p=0.349. This specific group of patients (n=144)
had a mean baseline CrCl of 45.9 ±15.9 ml/min, which increased to 72.6±16.6 ml/min over a period of 1.9±0.8 years. The mean increase in CrCl was statistically significant - 26.7 (23.0 – 30.5) ml/min; p<.001 (Table 2).

63.0% (245/389) of the patients did not experience an improvement in CrCl. The proportion of females in this group was not significantly different from that of the males: 64.3% (189/294) vs. 58.9% (56/95), p=0.349. These patients received ART for a mean period of 1.8±0.8 years. The mean difference between the baseline and follow-up CrCl values was not significant: 9.4±8.6, p=0.91. Five of the patients in this group experienced a ≥25% decline in CrCl. Their baseline and follow-up CrCl were 53.3±5.6 and 14.2±8.7 ml/min, respectively. The mean decrease in CrCl in the five patients was statistically significant: 48.6 (36.5 – 60.6, p<.001). The decline occurred over a mean period of 1.7±0.9 years.

Table 2: Changes in renal function during follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement in CrCl</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n, %)</td>
<td>No (n, %)</td>
</tr>
<tr>
<td><strong>Total number of patients, n (%)</strong></td>
<td>144(37.0)</td>
<td>245(63%)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any improvement in CrCl</td>
<td>144</td>
<td>129</td>
</tr>
<tr>
<td>Any decline in CrCl</td>
<td>-</td>
<td>96</td>
</tr>
<tr>
<td>No change in CrCl</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.7(10.6)</td>
<td>38.6(10.20)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>62.3(13.7)</td>
<td>62.1(15.5)</td>
</tr>
<tr>
<td>Follow-up duration (Years)</td>
<td>1.9(8.8)</td>
<td>1.8(8.8)</td>
</tr>
<tr>
<td>Baseline CrCl (ml/min)</td>
<td>45.9(15.8)</td>
<td>55.0(3.9)</td>
</tr>
<tr>
<td>Follow-up CrCl (ml/min)</td>
<td>72.6(16.6)</td>
<td>55.9(8.6)</td>
</tr>
<tr>
<td><strong>Decline in CrCl, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>105(27.0)</td>
<td>189(48.6)</td>
</tr>
<tr>
<td>Male</td>
<td>39(10.0)</td>
<td>56(14.4)</td>
</tr>
<tr>
<td>Renal function at baseline, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (30 – 59 ml/min)</td>
<td>118(30.3)</td>
<td>245(63.0)</td>
</tr>
<tr>
<td>Severe (&lt;30 ml/min)</td>
<td>26(6.7)</td>
<td>-</td>
</tr>
<tr>
<td>Renal function, during follow-up, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (≥90 ml/min)</td>
<td>16(4.1)</td>
<td>-</td>
</tr>
<tr>
<td>Mild (60 – 89 ml/min)</td>
<td>114(29.3)</td>
<td>63(16.2)*</td>
</tr>
<tr>
<td>Moderate (30 – 59 ml/min)</td>
<td>14(3.6)</td>
<td>177(45.5)</td>
</tr>
<tr>
<td>Severe (&lt;30 ml/min)</td>
<td>-</td>
<td>5(1.3)</td>
</tr>
</tbody>
</table>

*No. of Patients had some improvement but which was <25% increase in CrCl
* No of patients who had any decline (this includes the five who had a significant decline in CrCl)
* No. of patients who no change in their CrCl
* Based on the criteria used for the identification of improvement,
* Signifies change in the number and proportion of patients in stages I and II, by McNemar-Bowker Test.

Between the group of patients who experienced a statistically significant improvement in CrCl and the group that did not experience an improvement in CrCl there was no difference in age, weight, length of follow-up, and baseline CrCl (Table 2). In addition, there was no difference by gender in the proportion who experienced an improvement in CrCl (Table 3).

A higher baseline CrCl was associated with lesser odds of experiencing an improvement in CrCl: 0.905 (0.871 – 0.940), p<.001. The duration of ART follow-up increasing the odds of
experiencing an improvement in CrCl were reduced: by 0.904 (0.880 - 0.929), p<.001. Patients’ age, weight, and sex did not significantly affect improvement (Table 3).

Table 3: Analysis of factors for an association with improvement in CrCl

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta coefficient</th>
<th>Crude OR (95% CI)</th>
<th>p-value</th>
<th>Beta coefficient</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CrCl</td>
<td>-.109</td>
<td>.897 (.865 - .930)</td>
<td>&lt;.001</td>
<td>-.100</td>
<td>.905 (.871 – .940)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>-.105</td>
<td>.900 (.878 – .923)</td>
<td>&lt;.001</td>
<td>-.101</td>
<td>.904 (.880 – .923)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>.010</td>
<td>1.010 (.990 – 1.030)</td>
<td>.339</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td>-.226</td>
<td>.798 (.497 – 1.281)</td>
<td>.349</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weight</td>
<td>.001</td>
<td>1.001 (.987 – 1.015)</td>
<td>.919</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

4.0 DISCUSSION

To the best of our knowledge, this is the first evaluation conducted in Namibia on the relationship between TDF-containing ART and CrCl among patients with moderate to severe reductions in CrCl. With regard to patient outcomes, we observed cases of improvement in CrCl when a TDF-containing ART was initiated in patients with moderate to severe reductions in CrCl. We also observed cases of a further decline in CrCl. Importantly, with regard to the factors associated with the outcomes, our findings indicated that firstly a lower baseline CrCl was associated with an improvement in CrCl. Secondly, the improvement or significant decline in CrCl did not increase with time; and thirdly, age, weight, and gender had no significant association with the CrCl.

The improvement in CrCl that we observed was an expected finding based on previous findings (33, 34). We believe that a number of these patients were experiencing HIV-associated renal impairment as HIV directly infects the renal tubular cells leading to a reduction in CrCl (35). Effective ART is expected to improve CrCl in such cases. In the pre-ART era, HIV-associated renal diseases were a frequent sign of AIDS, the incidence of which appreciably reduced following the advent of highly active ART (36, 37). In the ART-era, HIV-associated renal disease may well be due to late diagnosis of HIV infection and/or the late presentation of patients to health facilities for therapy (38). Consequently, our suspicion of HIV-associated renal impairment, which resolved following initiation of TDF-containing ART, is clinically rational. Furthermore, we noted that the CrCl increased for a number of patients, but because the increase was <25% of the baseline these patients were not considered to have experienced an improvement in CrCl due to the criteria that were used to assign improvement.

There are a number of possible reasons as to why some patients’ CrCl did not improve according to our definition. Firstly, some patients may have had pre-existing non-HIV related renal disease. Patients with NSAID-, diabetes- and hypertension-related renal impairment are examples in this category (16, 39-41). However, data on co-morbidities and co-medications were lacking in the patients’ notes; consequently, we could not investigate this further. This will be the subject of future research projects. Secondly, some of our patients may have had HIV-associated renal impairment, which resolved due to ART, but the resolution was blunted by TDF-associated proximal tubulopathy (42). Thirdly, some of the criteria we used to identify an improvement excluded a number of patients because their last CrCl was not greater than the baseline CrCl by 25% of more. Nevertheless, we did not alter the criteria because a ≥25% change in CrCl has been regarded as clinically significant (43, 44). Some patients also had a progressive reduction in CrCl; however, these were not identified as experiencers of the decline in CrCl because the last CrCl was less than the first by <25%. It is noteworthy that the reductions in CrCl increased the risk of severe renal
insufficiency or end-stage-renal-disease as seen in a few patients in our study who ended up in the severe renal insufficiency group. Prescribing TDF for patients with a low baseline CrCl can lead to severe renal failure or end-stage-renal-disease, but there is evidence that such outcomes have occurred in patients who had normal or mildly reduced renal function at baseline. Consequently, TDF-containing ART may be prescribed for patients with a low baseline CrCl. This is important for cases with HIV/Hep-B coinfection (16, 29).

With regard to the duration of follow-up, we found that the likelihood of an improvement in CrCl to occur reduced with time. Considering that the improvement in CrCl is secondary to viral suppression, which is expected to happen within the first six months of ART (11, 29, 45), it could be argued that the CrCl improves with viral suppression. However, there is contrasting evidence that the resolution of HIV-associated decline in CrCl may still be observed long after viral suppression (46, 47). In concurrence with this, our findings suggest that the improvement in CrCl usually occurs within the first one to two years of ART with a reducing likelihood of improvement after this. Since the use of TDF-containing ART has been shown to significantly reduce CrCl with time, the reduced chance for improving with time may be related to the worsening in renal function. However, our cohort of patients had been receiving TDF containing ART for a relatively short period for a significant reduction in CrCl to be observed. We will though be investigating this further in the future.

With regard to age, it is known that the progressive decline in CrCl occurs with increasing age due to the declining number of functional nephrons (48). The current literature suggests that the risk of TDF-associated renal impairment increases with age. Consequently, not observing an improvement with increasing age was expected. In addition, the mean age of the cohort showed that many patients had not reached the age at which the number of nephrons would reduce. Weight too did not have an association with the CrCl in our cohort. Some studies have shown that a low body weight is associated with a decline in CrCl due to the high TDF concentrations in plasma (28, 44, 49). Others have shown though that a heavier body weight is associated with a decline in CrCl; however, this may be due to weight associated comorbidities such as hypertension and diabetes mellitus (50).

Normally males have higher CrCl than females (51). In HIV infected patients the opposite is true, and the gap between males’ and females’ CrCl is likely larger than normally observed due to HIV-associated hypoestrogenemia in females (52). The protective effect that estrogen has on the nephrons is diminished, which may explain why the risk of TDF-associated decline in CrCl in females is several times that in males (52). However, in our cohort of patients there was no difference in the baseline CrCl between the males and females. Similarly, there was no difference in the proportion of patients that experienced an improvement in CrCl. We suspect that male patients may have experienced a more severe disease that led to greater damage to their kidneys (51). However, we could not verify this. We will though research this further in future studies.

We are aware that there were a number of limitations in this study. Firstly, some increases in CrCl were of such a small magnitude but were identified as improvements because of the persistent measurements of the CrCl ≥60ml/min. For these, the change in serum creatinine was very low. Consequently, the definition of improvement in these patients may need revision. Secondly, some patients had sustained increases in CrCl but because the increases were <25% of the baseline CrCl they were not recognised as improvements. Similarly, the patients who experienced a drop in CrCl that was <25% of the baseline were not considered to have experienced a significant decline in CrCl. Again, this may mean that the definitions need to be revised. Thirdly, the patients who experienced a significant decline in CrCl were few, and for that reason no analysis was performed on possible factors associated with a significant decline. Fourthly, the baseline CrCl was the first recorded measurement. For some patients, this CrCl was available after one or more years of receiving ART meaning that the baseline may not have been a true baseline. The absence of CrCl records was likely due to the use of a non-TDF containing regimen since CrCl is only estimated for patients receiving TDF-containing regimens. The duration of follow-up was the time between the first CrCl measurement and the last or the time of the first significant drop in CrCl. Fifthly, the study was based on data collected during routine clinical care and so lacked the benefit of having data that had been collected at uniform intervals. The time
between tests was also relatively long for some patients, which made the estimated time to experience a drop in CrCl longer. In addition, data regarding the CrCl of patients receiving non-TDF containing regimens could not be fully assessed with this dataset. Finally, we lacked data on co-morbidities and co-medications that are normally associated with a decline in CrCl and could not investigate these further within the available datasets. Despite these limitations, we believe our findings are robust providing direction for the future.

5.0 CONCLUSION

The improvement in CrCl following the initiation of TDF-containing ART was an expected finding among patients who have HIV-associated renal disease. It appears that the improvement in renal function as estimated by CrCl occurs within one to two years. Improvements in CrCl may still occur after more than two years; however, the odds of experiencing an improvement significantly reduce with time. We observed further declines in CrCl in these patients although this occurred in very few patients. Our findings indicate that TDF use was associated with more improvement than decline in CrCl, and therefore should not be withheld from patients with a baseline CrCl <60ml/min. We will be following this up in the future.

Conflicts of interest

There were no conflicts of interest and this study was self funded.

References


