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RENAL FUNCTION OUTCOMES IN PATIENTS RECEIVING TDF - CONTAINING ANTIRETROVIRAL THERAPY: A RETROSPECTIVE PILOT STUDY IN NAMIBIA

Francis Kalemeera [1], Carla Oberholster [2], Innocent Segamwenge [3], Dan Kibuule [1], Ester Naikaku [1], Mwangana Mubita [1] and Brian Godman [4, 5, * 6]

School of Pharmacy [1], School of Medicine [2], Faculty of Health Sciences, University of Namibia, Windhoek, Namibia.
Department of Internal Medicine [3], Oshakati Intermediate Hospital, Oshakati, Oshana, Namibia.
Department of Laboratory Medicine [4], Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden.
Health Economics Centre [5], University of Liverpool Management School, Liverpool, United Kingdom.
Strathclyde Institute of Pharmacy and Biomedical Sciences [6], University of Strathclyde, Glasgow, United Kingdom.

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Correspondence to Author:
Brian Godman

Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom.

E-mail: brian.godman@strath.ac.uk

ABSTRACT: Introduction and Aims: Combination antiretroviral therapy (cART) has improved morbidity and mortality in patients with HIV across countries including countries in sub-Sahara Africa. However, cART is associated with renal impairment. The lack of pre-cART data in a recently published study limited the discussion on renal-based treatment outcomes with cART, which could have important clinical implications. Consequently, the aim of this paper is to correct this. **Methods:** Longitudinal retrospective study, with renal function assessed pre-cART and at various time points on cART using the Cockcroft-Gault method. The data source was the patients' care booklets. **Results:** 71 patients were included. The majority were adults and female. Before cART initiation, 70.4% and 29.6% had abnormal and normal CrCl, respectively. CrCl was normalised in 24% of patients, while abnormal in the remainder. The mean (median) time to normalisation was 47.4 (33.7) months, observed more in paediatric than adult patients (p = 0.014). However, in paediatric patients, normalisation took longer than in adult patients. The reduction in CrCl, was observed at variable time points. 9/16 patients experienced a decline during first-line cART and 7 of these were receiving TDF. 7/16 experienced this during second-line cART and 6 were receiving TDF. **Conclusion:** HIV is typically the cause of renal impairment prior to cART, with TDF likely to be the cause of renal impairment during cART. Consequently, co-administration of TDF with other nephrotoxic drugs should be undertaken with caution if unavoidable. Overall, improvement in renal impairment was faster in adults.

INTRODUCTION: Combination antiretroviral therapy (cART) has resulted in considerable improvements in both the quality and length of life of HIV infected patients, especially in sub-Sahara Africa, the region worst hit by the human immuno-deficiency virus (HIV) [1, 2, 3].

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HIV infection has been associated with HIV associated nephropathy (HIVAN), which is known to affect African patients, or patients of African descent, more than others [4, 5, 6]. HIVAN is associated with marked increases in serum creatinine (SeCr) due to reduced creatinine clearance (CrCl), a surrogate marker of renal impairment during cART.

The widespread use of cART before the immune system is severely depressed has reversed the incidence of HIVAN, and has resulted in resolution of renal function in affected patients [6].

Notwithstanding the benefits of cART, it is associated with adverse drug reactions, including renal impairment, occurring at various times and to different degrees [3, 6, 7]. In a recent publication, we outlined the possible effects that tenofovir disoproxil fumarate (TDF) and ritonavir containing second-line cART may have had on the renal function of patients in this study [3].

However, we lacked data on the renal function before cART initiation and renal function data for the larger period of first line cART, which limited our discussion. The current study benefited from the availability of data on CrCl at three period points: before cART initiation; during first line cART; and during second-line cART.

Consequently, in this paper, we present our findings on CrCl over time per patient, and provide plausible explanations for the observations seen. In addition, discuss the implications for the future management of HIV patients in Namibia and wider. This is particularly important in Namibia with its high prevalence of HIV as well as high prevalence of HIV among women [8], similar to other Africa countries, but not to Western countries [9]. This has important pharmacogenetic consequences.

MATERIALS AND METHODS: This was a retrospective longitudinal study that adopted qualitative and quantitative methods of analysis. The study site was an HIV clinic, hosted in a leading hospital in Namibia, treating these patients.

The study population were patients who were receiving second-line cART. To evaluate the patients' renal function, we calculated CrCl by the Cockcroft-Gault (C-G) method [7] before and at various time points after initiation of first-line cART. The C-G method was used because it is the one recommended by the Ministry of Health and Social Services (MoHSS) in Namibia for assessing renal function in HIV infected patients [10].

Renal function was considered to have declined if the last CrCl was less than the CrCl prior to cART initiation by ≥25%. The patients were placed in renal function categories based on their estimated CrCl as follows: stage I was ≥90; stage II was 60 – <90; stage III was 30 – <60; stage IV was 15-<30 and Stage V <15 ml/min [11].

The data source was the patients' care booklets. SPSS was used for statistical analysis. We used Chi-square test to compare renal function between groups, and McNemar's test to assess changes in renal function. Renal function was considered to have changed significantly if the magnitude of the change was ≥ or ≤ 25% [12].

We set the confidence level at 95% and the statistical significance at a p-value of <0.05. The study received ethical approval from the Faculty of Health Sciences, University of Namibia, and from the MoHSS in Namibia.

RESULTS:

Summary of Patients' Characteristics: A total of 81 patients were initially included in the study; however, 10 were subsequently excluded because they had only one SeCr test performed making 71 in all for analysis. The majority of the included patients were adults [76.1% (n = 54)] and female, [59.2% (n = 42)]. **Table 1** documents the patient characteristics, immune status, cART regimens, period spent on cART, and other clinical data.

CrCl before Initiation of cART: Prior to initiation of cART, 70.4% (n = 50) and 29.6% (n = 21) of patients had abnormal and normal CrCl, respectively. In the following sections, these are presented with regards to the state of CrCl the patient had before and during cART.

CrCl during cART in Patients who had Normal CrCl Prior to cART: Patients who had normal CrCl were initiated on first-line cART regimens as follows: AZT-based regimens, n = 6; d4T - based regimens, n = 5; and TDF- based regimens, n = 10. At the time of data collection, 76.2% (n = 16) had changed from normal to abnormal CrCl status, leaving 23.8% (n = 5) with normal CrCl values.

The abnormal CrCl was detected after approximately six months of cART for 37.5% (n = 6) of the patients, while for the remaining 62.5% (n = 10) the decline was detected at widely variable time points, all of which were beyond one year of cART **Table 2**, **Fig. 1**. The mean (medium) time that had elapsed from cART initiation to the detection of renal impairment was 36.7 (17.7) months **Table 3**.

TABLE 1: PATIENT DATA SUMMARY

Item	All	Female	Male
Number (%) of patients	71 (100)	42 (59.2)	29 (40.8)
Paediatric Patients	17 (23.9)	9 (12.7)	8 (11.2)
Adult Patients: No (%)	54 (76.1)	34 (47.9)	20 (28.2)
Age			
Mean Age (years) Paediatric Patients (confidence limits)	12.4 (3.5 – 8.9)	12 (7.9 – 16.1)	12.7 (9.6 – 15.7)
Mean Age (years) Adult Patients (confidence limits)	36 (25.8 – 46.2)	32.5 (23.6 – 41.4)	42 (32.4 – 51.6)
Weight (kg)			
Mean weight before initiating cART (Paediatric)	39 (18 – 60)	-	-
Mean weight before initiating cART (Adults)	57 (45 – 69)	56 (44 – 57)	58 (47 – 70)
SeCr tests			
Mean no. of tests per patient (confidence limits)	3.8 (4.0 – 6.0)	5 (3.8 – 6.0)	5 (3.7 – 6.5)
Immune Status			
Adults			
Average CD4 count before initiating ART	171 (31 – 303)	169 (23 – 315)	171 (42 – 296)
Average CD4 count at switching	319 (61 – 577)	262 (50 – 473)	274 (3 – 545)
Paediatrics			
Average CD4 count before initiating ART	177 (65 – 290)	-	-
Average CD4 count at switching	488 (221 -754)	-	-
cART			
First-line Regimen Received: No (%)			
AZT/3TC/EFV	3 (4.2)	1 (1.4)	2 (2.8)
AZT/3TC/NVP	27 (38.0)	16 (22.5)	11 (15.5)
AZT/ddI/LPV	1 (1.4)	-	1 (1.4)
D4T/3TC/NVP	15 (21.1)	9 (12.7)	6 (8.5)
D4T/3TC/EFV	1 (1.4)	-	1 (1.4)
TDF/3TC/EFV	5 (7.0)	3 (4.2)	2 (2.8)
TDF/3TC/NVP	17 (23.9)	11 (15.5)	6 (8.5)
TDF/FTC/EFV	1 (1.4)	1 (1.4)	-
TDF/FTC/NVP	1 (1.4)	1 (1.4)	-
Second-line Regimen: No (%)			
TDF/3TC/AZT/LPV/r	71 (100)	42 (59.2)	29 (40.8)
Period on ART(Years)			
First-line ART (n=71)	2.8 (0.6 – 5.0)	2.7 (0.6 – 4.8)	3.0 (0.7 – 5.3)
Second-line ART (n=47)	1.7 (0.4 – 3.0)	1.8 (0.3 – 3.3)	1.6 (0.7 – 2.6)
Chronic Disease [Number (%)]			
Peripheral Neuropathy	1 (1.4)	1 (1.4)	-
Anaemia	1 (1.4)	1 (1.4)	-
Syphylis	3 (4.2)	1 (1.4)	2 (2.8)
Tuberculosis	3 (4.2)	1 (1.4)	2 (2.8)
Hepatitis B	11 (15.4)	7 (9.9)	4 (4.6)
Co-Medication			
Before initiating ART			
RHZE	3 (4.2)		
During ART	No records		

TABLE 2: NUMBER OF PATIENTS AND TIME POINTS AT WHICH CHANGES FROM NORMAL TO ABNORMAL CrCl OCCURRED

Renal function Before cART		During cART (both first- and second-line regimen)	Mean (confidence limits) period spent on cART (in Months)	Number with abnormal renal function detected within this period (in Months)					Totals (after initiation of cART)
				0-6	7-12	13-18	19-24	>24	
No. with normal CrCl	21	5*	43.9 (6.2 - 81.7)	n/a	n/a	n/a	n/a		5
No. with abnormal CrCl	0	16#	40.1 (3.8 - 76.4)	2	4	3	-	7	16

*Of these, 2 were receiving TDF-containing cART during first-line; # of these, 7 received TDF during first line, and 6 during second line.

This abnormality in CrCl was detected during first-line cART for 42.9% (n = 9) and during second-line cART for 33.3% (n = 7) of the patients. Of the 9 patients, seven had received TDF-containing first line cART, while 2 (9.5%) had received AZT- and d4T- based cART regimens. Of the 7 patients on second-line cART, six (n = 6) were exposed to TDF only during second-line cART. Of the 23.8% who still had a normal CrCl at the time of data collection, three had received TDF-containing cART for 12.5, 14.5, and 60.4 months, and two had received AZT-based cART for 82.3 and 93.8 months.

CrCl during cART in Patients who had Abnormal CrCl Prior to cART: The patients who had abnormal renal function (n = 50) prior to initiation of cART received their initial cART regimens as follows: AZT-based regimens n = 25; d4T - based regimens, n = 11; and TDF-based regimens, n = 14). Twelve of the 50 (24.0%) patients experienced normalisation in CrCl **Table 4**.

TABLE 3: TIME (MONTHS) TAKEN FOR CHANGE IN CrCl TO BE OBSERVED

	Mean (Months)	Confidence Interval (Months)	Median (Months)
Time taken for Decline in CrCl to be observed	36.7	-1.2 – 74.7	17.7
Time elapsed for Improvement in CrCl to be observed	47.4	19.4 – 75.3	33.7

TABLE 4: CHANGES FROM ABNORMAL TO NORMAL CrCl: TIME POINTS AT WHICH CHANGES OCCURRED

Renal function before cART		During cART (both first- and second-line regimen)	Mean (confidence limits) period spent on cART (in Months)	Number with normal renal function detected within this period (in Months)					Totals (after initiation of cART)
				0-6	7-12	13-18	19-24	>24	
No. with normal CrCl	0	12	56.8 (27.8 – 85.8)	-	-	-	-	12	12
No. with abnormal CrCl	50	38	43.1 (14.1 – 72.1)	n/a	n/a	n/a	n/a	n/a	38

NB: Thirteen (n = 13) patients experienced increases in CrCl ranging from 12% to 23%. These were not counted amongst those with improved CrCl.

Of the normalisations: 3(25%) and 9(75%) occurred during first- and second- line cART, respectively. Some patients experienced further decline in CrCl (n = 8), while for others no significant change in CrCl was observed (n = 30). The mean time that elapsed for improvement to be detected was 47.4 months, with a median of 33.7 months **Table 5**.

TABLE 5: PERIOD SPENT ON cART FOR PATIENTS WITH ≥25% AND THOSE WITH 12-23%

	Mean (months)	Confidence interval	Median (months)
Period on cART for patients with ≥25% increase in CrCl	47.4	19.4 - 75.3	33.7
Period on cART for patients with 12-23% increase in CrCl	31.2	-12.6 - 75.0	11.5

Assessment of Factors Affecting the CrCl Outcome: Of the 21 patients who had a normal CrCl pre-cART initiation, the majority (n = 18) had a baseline CD4 count <200 cells/mm^3. The baseline CD4 count did not influence CrCl (p-value = 0.09). Similarly, the age-group of the patients did not have an effect on the CrCl stage of the patient prior to initiation of cART, even though there were more adults by proportion with abnormal CrCl (Cl 95%, OR = 2.8 [0.9 – 8.9]; p = 0.076). Normalisation in CrCl was significantly lower in adults than in paediatric patients: 7/41 (17.1%) and 5/9 (55.6%); p-value = 0.014 **Table 6.**

TABLE 6: NUMBERS CHANGED FROM NORMAL TO ABNORMAL AND *VICE-VERSA*, AND TAKEN FOR ANY CHANGES TO BE OBSERVED

	Adult patients	Paediatric patients	Significance (X^2)
Number changed from normal to abnormal	7 (17.1%)	5(55.6%)	p-value = 0.014
Number unchanged- or normalised	34(82.9%)	4(44.4%)	
Time in months on ART for improvement in CrCl to be observed: mean (confidence limits)	39.8 (24.0 – 55.6)	62.2 (26.2 – 98.5)*	

*51.25 (20.9 - 81.6) for the paediatric patients after removal of the record of one patient who had spent 106.8 months on cART

Furthermore, experiencing normalisation in paediatric patients was six times greater than that in the adults: OR = 6.1. Normalisation of CrCl was observed to occur close to two years after cART initiation **Fig. 1**.

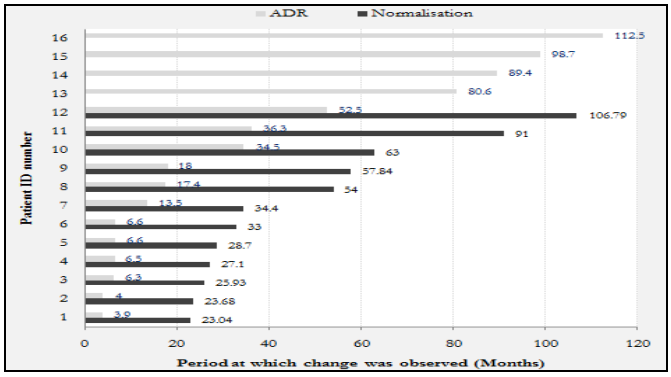

FIG. 1: ADR (RENAL IMPAIRMENT) OBSERVED AT EARLIER TIMES THAN NORMALISATION OF CrCl

DISCUSSION: Our findings present a global picture of the plausible renal function outcomes in HIV infected patients after initiation of cART, since the study participants existed in two groups: those with normal CrCl and others with abnormal CrCl before cART. As mentioned, the Acquired Immunodeficiency Syndrome (AIDS) in HIV-infected patients may be accompanied by HIVAN [13, 14]. This kidney disease is known to affect black patient populations more than others [4, 5]. Whilst cases of HIVAN have been reported in asymptomatic patients, and at the level of seroconversion, HIVAN is still generally recognised as a complication of AIDS [15]. As such, one of the risk factors for HIVAN is a low baseline CD4 count (<200 cells/mm^3) [16]. HIVAN is associated with a rapid decline in the glomerular filtration rate (GFR) coupled with moderate to nephrotic range proteinuria, which if untreated will progress to end stage renal disease (ESRD) and ultimately death [4]. Even though the majority of patients on our study were black Africans, with a baseline CD4 count <200, the data did not show any association between the observed CD4 counts and the stage of CrCl (p = 0.09); consequently, appearing to rule out HIVAN as the cause of the low CrCl before the initiation cART.

Moreover, for a number of the patients, the stage of abnormal CrCl was sustained without further decline, which is not expected to happen in patients with HIVAN since the characteristic feature of HIVAN is aggressive focal segmental glomerulo-sclerosis accompanied with rapid decline in glomerular filtration [15].

Furthermore, individual patient's ages could not explain the differences in CrCl amongst the patients before initiation of cART. In addition, assessment of CrCl by age group - adults *vs.* paediatric - did not show any influence of age on CrCl. In regards to age or age-groups, our findings are similar to those by Chaisir *et al*., who studied the risk factors for renal impairment in patients receiving TDF - containing cART, but did not include increasing patient age as one of the risk factors for TDF - associated renal impairment [17]. Against this in the study by Queseda *et al*., increasing age was listed amongst the risk factors [18]. Overall, among the possible causes of renal impairment prior to cART initiation in our study, HIV infection was the known common factor. We observed two outcomes in patients who had normal CrCl before starting cART. The first was a significant drop in CrCl, associated with a change from normal to abnormal CrCl (n = 16, 76.2%); and the second was the maintenance of normal CrCl (n = 5, 23.8%). Antiretroviral drug-associated renal impairment is a known phenomenon. Amongst these medicines, TDF is associated with the highest incidence of renal impairment as it interferes with nephrogenic proximal tubular function. This might explain why the majority of patients in this category who experienced a significant decline in CrCl during first-line cART were receiving TDF - containing cART (n = 7; 77.8%).

Furthermore, of the patients who experienced a decline in CrCl during second-line cART, the majority (n = 6, 85.7%) only became exposed to TDF during second-line cART. As such, TDF is a probable cause of the decline in CrCl. However, as Queseda *et al*., and Chaisiri *et al*., discuss, the plausible synergy between TDF and ritonavir (RTV) as a risk factor for renal impairment cannot be overlooked [17, 18]. At the time of data collection, all these patients were receiving TDF containing second line regimens, which means that they had not experienced TDF-associated acute renal impairment such as the Fanconi Syndrome. Overall, our data showed a slow decline in CrCl, which may be interpreted as one of the slow progressing drug-related renal diseases such as

arterio-nephrosclerosis [6]. The abnormal CrCl that we observed prior to initiation of cART may have been evidence of HIV-associated renal impairment - not necessarily HIVAN, although there may have been other causes. Our suspicion of HIV associated renal impairment was augmented by the fact that we observed improvement in CrCl after initiation of cART. According to the 'improvement' criteria we used, improvement was observed in 16.9% (n = 12) of the patients; of whom, five were paediatric and seven were adults.

Interestingly, the proportion of paediatric patients who experienced improvement in CrCl was significantly greater than that of adults (p = 0.014). In addition, we noted that the normalisation of CrCl in the paediatric patients occurred after long periods on cART compared to the normalisation we observed in the adult patients. This finding, albeit in a small sample size, appears to mean that HIV-associated renal damage in paediatric / adolescent patients was greater in severity than seen in adults. Evaluation of the observed improvement against the time it occurred in the five paediatric patients favours this hypothesis. However, the number of paediatric patients is too small for inferences to be made. This will be the subject of future research. Furthermore, a number of paediatric patients remained in the abnormal state even after prolonged periods of cART.

In another group of patients (n = 13), we observed sustained increases in CrCl of 12% to 23% above the baseline. Since these increases were sustained, it is possible that with continued cART, the CrCl of these patients will rise progressively to ≥25%. This supposition is based on the fact that the average period spent on cART for the 12 patients who experienced an improvement in CrCl was generally longer than the period spent on cART by those who had increases in CrCl <25%: 27.4 (11.5 - 43.4) and 17.3 (5.6 - 28.6) months, respectively. Patel *et al*., found the recovery of renal function occurred rapidly [19]. However, in our study, the time that elapsed before an improvement in CrCl was observed (50.5[33.7] months) was longer than the time taken for a decline (renal impairment) to take place (33.5[13.5] months). The shortest time for a decline to be observed in our patients was 3.9 months, while the shortest time for an improvement to be observed was 23 months.

Rapid improvement in CrCl would be observed in patients who had TDF-associated Fanconi syndrome, for whom TDF would be withdrawn. In some patients, who had an abnormal CrCl in the pre-cART initiation period there was neither improvement nor further decline in CrCl. We could not ascertain the cause or predictors of renal impairment in these patients.

Limitations: The lack of information on the other possible aetiologies for renal impairment was a major confounder. However, the observed improvements in 12 patients indicate that HIV infection may have been the sole cause of renal impairment. In addition, the sustained increases in CrCl in 13 patients may rule out other possible causes of renal impairment, with the expectation that renal function in these patients will normalise. The fact that renal function is generally not monitored in patients receiving non-TDF-containing regimens does not negate the possibility of development of renal insufficiency during first-line cART. Nevertheless, the probability of renal impairment having occurred during first-line cART in these patients is low. In any case, renal impairment would not have been detected except if the clinical presentation of the patient warranted the assessment of renal function. Other possible causes of renal impairment cannot be ruled out. Because the cART records of HIV infected patients are stored separately from other medical records in health facilities in Namibia, we were unable to ascertain the cause of the abnormal CrCl in the pre-cART initiation period. Another limitation was the low number of patients in the study. We will though be following this up with further patients. In addition, we only collected data from one hospital. However, this was a leading hospital clinic treating HIV patients in Namibia. Despite these limitations, we believe our findings are robust providing guidance for the future.

CONCLUSION: It is likely HIV infection was responsible for renal impairment in those patients who experienced renal improvement after initiating cART. This is not a new finding. However, there was diversity in the rate of recovery from renal impairment in our patients. The slow recovery we observed in paediatric patients compared to the adult patients was an interesting finding which needs further investigation.

There is also a need to gather further information on co-morbidities in these patients, especially those that are known to affect renal function such as diabetes mellitus and hypertension, which can be facilitated by the integration of HIV with other services and data in resource limited settings. Renal biopsies would also be of great value. Pre-cART renal impairment in HIV infected patients does not always preclude the use of TDF-containing cART as improvement in renal function is possible. Consequently, this makes the prediction of the occurrence of renal pathology in a patient receiving TDF-containing cART extremely challenging. In view of this, co-administration of TDF with other nephrotoxic drugs should be undertaken with caution if unavoidable. Ultimately, it is critical that patients' renal function is monitored regularly during treatment.

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CONFLICT OF INTEREST: All authors declare they have no conflicts of interest to declare.

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