Serum Creatinine, Urea and Their CD$_4^+$ T-lymphocyte Count among HIV Positive Patients before and after Initiation of HAART at St. Paul's General Specialized Hospital In Addis Ababa, Ethiopia

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Authors' contributions

This work was carried out in collaboration between all authors. Author FB had the original idea of the study. Authors MM, FB and MY designed the study, wrote the protocol and wrote the first draft of the manuscript. All authors managed the literature searches and analyses of the study performed the spectroscopy analysis. Author MM carried out the data cleaning and analysis and helped prepare the draft manuscript. Authors MW, FH and BT participated in the design of the study and guided the statistical analysis. Author MM lead on the drafting of the manuscript. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Objective: To describe the serum level of urea and creatinine, and as well as CD$_4$+ T cell count of blood among HIV positive patients before and after initiation of HAART in St. Paulo's general specialized hospital.
Methods: A retrospective follow up study was conducted among HIV infected individuals who take HAART drug combination regimens such as (TDF/3TC/EFV), (TDF/3TC/NVP), (AZT/3TC/NVP), (D4T/3TC/EFV) and (D4T/3TC/NVP) and visit St. Paulo's generalized hospital laboratory for renal

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function testing from 2007-2009G.C.

Results: A total of 2026 HIV positive patients started HAART between 2007-2009G.C in St. Paulo's ART clinic. Among them 380 HIV patients, with two and three visits for CD4+ and renal function test (creatinine & urea), were recruited to the study. Of whom 240 (63.2%) were female and 140(36.8%) male. Out of 380 patients, 104(27.4%) were taking 1b30, 94(24.7%) were using 1a30, 77(20.3%) were taking 1d, 57(15%) 1c, 14(3.7%) tdf/3tc/efv, 12(3.2%) use tdf/3tc/nvp and 22(5.7%) were taking other drug types. The statuses of CD4+ T cell count of patients become improved as they are using HAART drug through visit. These were 115, 266 and 298 out of 380 have greater than 200 CD4+ T cell count on 6th, 12th, 18th months time difference respectively. But the numbers of patients who have renal dysfunction were increased as they were using HAART drug as treatment through visits. These might indicate that, use of HAART drug combination may improve the immune status HIV positive patients even though some renal side effects are there. Therefore, patients (HAART drug user) should have a follow up on renal function to monitor side effects of drug.

Conclusion: HAART resulted in improved Immune status of HIV patients with remarkable increase in CD4 T lymphocyte count but at the same time there was an increase in Azotemia after the introduction part of HAART which suggests the impact of drug in renal function. This is especially true for TDF containing drug regimens (TDF/3TC/NVP) which dramatically improve CD4 T lymphocyte count and show significant Azotemia over times.

1. INTRODUCTION

Kidneys are bean-shaped organs, each about the size of a fist containing the uriniferous tubules, which consists of nephrons and a system of collecting ducts. The two kidneys produce about 125 ml of filtrate per minute; of this amount, 124 ml is absorbed in the organ, and only 1 ml is released in to the ureters as urine. About 1500 ml of urine is formed every 24 hr [1].

If these normal function of kidney failed, the plasma concentrations of the waste substances such as creatinine (Cr), urea (U), and as well as electrolytes (E), are increased in the blood. As a result, they are used to determine renal function. These measures are adequate to determine whether a patient is suffering from kidney disease [1].

In a condition of chronic renal dysfunction, the kidneys function begins to decrease over time gradually. As a result of kidney diseases getting worse, the wastes substances start to build up to high levels in our blood and make us feel sick. Thus, early detection and treatment can often keep chronic kidney disease from getting worse [2].

According to WHO comprehensive and integrated action of the means to prevent and control chronic disease in developing countries, renal chronic disease is a growing problem like many other chronic diseases [3]. The incidence of renal chronic disease is rising because of increased risk factors such as high blood pressure, diabetes, HIV and HAART [3-5].

Presently, this renal disease become the commonest problem in human immunodeficiency virus (HIV) infected patients [2]. The problems of kidney function in these people may be due to medications or HIV itself [6-8].

A wide clinical spectrum of renal disease exist in the course of HIV infection, which includes potentially reversible acute renal failure (ARF),electrolyte and acid-base disturbances and a group of HIV associated glomeruli-nephropathies that may present with acute or chronic renal failure [8,9].

Even if HAART has revolutionized the management of HIV/AIDS and is effective in reducing morbidity and mortality in HIV-positive individuals [10], it also has shifted the health concern toward chronic morbidities including renal dysfunction [11-13]. Renal damage caused by antiretroviral drugs can result in a variety of toxic drug effects presenting as acute renal failure, tubular necrosis, kidney stones, or chronic renal disease [14].

The Nephrotoxic effects by antiretroviral drugs which are accounted for 14% for late onset acute kidney injury (AKI) episode are occurring after 3 months of initiating HAART. The major proposed drugs that are implicated with chronic kidney diseases are indinavir, atazanavir and tenofovir [15,16].

1.1 Significance of the Study

Assessing the overall status of HIV infected patients is essential component to monitor response to antiretroviral therapy (HAART) which mainly measures the impact of HAART to different organs, like kidney. Some investigator's research in sub-Saharan Africa has reported effects of HAART on kidney outcomes that were comparable to those observed in resource-rich settings [17,18]. However, few data exist in resource-limited settings, like Ethiopia. So, this study was conducted to describe the rate of HAART related renal complication among patients who attend ART clinic at St. Paul Hospital from 2007 -2009 GC.

2. METHODS AND MATERIALS

A retrospective follow up study was conducted to describe the renal profile of HIV patients before and after starting therapy (HAART) in those Who attended St Paul's specialized Hospital from 2007-2009 G.C. This data was collected from HIV positive individuals who started HAART and who have two and three visit for renal function test since January 01 to April 30, 2012.

Urea, creatinine and CD_4^+ T cell test results were collected on HIV positive patient card who take HAART at least 12 month and 18 month visit in the meantime sex, age of patient and time of visits were taken.

2.1 Inclusion and Exclusion Criteria

All female and male adults who have at least two and above test of creatinine, urea and CD_4^+ T cell count were included in the study. But pregnant women, children, diabetic patients and hypertensive patients were excluded from the study.

2.1.1 Co-morbidities

Co-morbidities of renal function such as diarrhea and vomiting are likely to have deranged renal function if it is severe enough. But, this would be diagnosed and treated as early as possible and no longer could affect the value of urea and creatinine.

2.2 Planning and Data Collection

2.2.1 Data collection procedure

A standardized data extraction format was filled with the appropriate dependent and independent variables from the patient card for each patient by the principal investigators.

2.2.2 Serum level of urea, creatinine and CD4+ T cell count of blood

Appropriate kits were used to determine serum level of Urea according to the principle of Berthelot11 and serum level of creatinine according to the principle of Jaffe reaction [19]. CD4+ T cell count were performed by using flowcytometry (FACS calibur) machine according to the principle of Nicholson et al. [20]. The ration of blood urea nitrogen and creatinine was calculated and interpreted according to Uchino et al. [21].

2.2.2.1 Quality assurance

> ➢ The data extraction format was checked for consistency by the principal investigators.
> ➢ All variables were filled on the data extraction format daily.
> ➢ We had also checked whether quality control was run daily for the clinical chemistry machine.

2.3 Data Processing and Analysis

Data was collected through standard collecting format and entered into Excel. Statistical analyses were performed using SPSS version 16.0. Different variables were tested including Odds ratio (OR) determination, paired T test and Pearson's χ^2 tests were used when appropriate. $P < 0.05$ was regarded as statistically significant.

2.4 Ethical Consideration

Formal ethical clearance letter was obtained from Addis Ababa University medical Faculty School of medical laboratory science's ethical committee and from St. Paul general specialized hospital's ethical committee. The whole objective of the study was briefly explained to the laboratory head, to the assigned ART coordinator and as well as to the patients. The data was used only for the purpose of this research and during the study no personal identifier was used. After a brief explanation, Patients are asked for their permission and they signed on the consent form.

3. RESULTS

A total of 2026 HIV positive patients started HAART between 2007-2009G.C in St. Paulo's ART clinic. Among them 380 patients, with two and three visits for CD_4^+ and renal function test (creatinine & urea), were recruited to the study. After 18 month of follow up, 50 patients were dropped out or lost either because of death or they didn't came to hospital at all.

Out of 380 patients, 104(27.4%) were taking D4T/3TC/EFV, 94(24.7%) were using D4T/3TC/NVP, 77(20.3%) were taking TDF/3TC/NVP, 57(15%) AZT/3TC/NVP, 14(3.7%) TDF/3TC/EFV, 12(3.2%) use TDF/3TC/NVP and 22(5.7%) were taking other drug types.

3.1 Demographic Data

From 380 HIV positive study participant, 240 (63.2%) were female and 140(36.8%) male. The mean age of the participants was 36.84, minimum age 19 and the maximum age 68.

Association between sex and renal profile reveals the prevalence of renal dysfunction before initiation of HAART for female participants was (68)28.3% while for males it was (28)20%. After initiation of HAART this number had increased for female participants than their male counterparts in all (6th, 12th& 18th month) visits but there was no significant association between sex and renal abnormality (p>0.05). And highest number prevalence was seen in the age group from 34-38, with prevalence before initiation of HAART (5.5%) and after initiation, with prevalence of 7.6%, 10.3%, &10.4% in the 6th, 12th& 18th month visits respectively. But it doesn't have significant association with this specific age group (p>0.005) (Table 3).

3.2 Immune Status of HIV Patient

Before initiations of HAART 265 out of 380(69.7%) of patients had CD_4^+ count below 200 cells/µl, this number after six month treatment of HAART CD4 count of patients was become 114 out of 380(30%). After 12 months of treatment the count was 139 out of 380(36.6%). Finally, after 18 months of HAART treatment from initial, the result becomes 50 out of 330(15.2%) (Table 1). Mean values of CD_4^+ cell count on HIV positive patients before initiation of HAART was 179 which is below 200 cells/µl , after 6 month treatment of HAART this number changed into 287 cells/ µl, after 12 month HAART treatment it become 359 cells / µl and after 18 month treatment the number of CD4+ cell count become 395 cells /µl.

3.3 Renal Profile

Before initiations of HAART 96 out of 380(25.3%) of the participants had creatinine result out of normal range (<0.5 and >1.1 mg/dl). This figure, after six month treatment or initiation of HAART was becomes 100(26.3%). After 12 months of treatment the result was 147(38.7%). Finally, after 18 months from initial treatment the number was become 123 out of 330(37.7%). The mean value of creatinine before HAART treatment was 0.9105±0.48 (X±SD), after 6 month treatment the mean value changed into 0.9425±0.46 (X±SD), after 12 month it become 0.9527±0.30 (X±SD), and finally after 18 month it become 0.9923±0.48 (X±SD).

Before initiations of HAART 120 from 380(31.6%) had Urea result out of normal range (<10 and >50). This number, after six month initiation of HAART was becomes 143 out of 380(37.6%). After 12 months of HAART treatment the result was becomes 82 out of 380(21.6%). Finally, after 18 months from initial treatment the result showed 130 out of 330(40.3%). By using paired *t*-test between visit have significant association (p<0.005) for both creatinine and urea. The mean value of urea before HAART treatment was 19.831±11.6 (X±SD), after 6 month of HAART it become 23.013±15.5 (X±SD), after 12 month of HAART treatment it become 22.863±11.4 (X±SD), and finally after 18 month of HAART treatment it become 23.738±27.6 (X±SD).

Table 1. CD_4^+ T cell count of HIV patients before and after initiation of HAART at St. Paul Generalized Hospital from 2007-2009 G.C

CD 4+ T-cell count	Before HAART		After 6 month of HAART		After 12 Month of HAART		After 18 month of HAART	
	#	%	#	%	#	%	#	%
< 200 CD4+Tcell	265	69.7	114	30	82	21.6	280	84.8
>200 CD4+ T cell	115	30.3	266	70	298	78.4	50	15.2
Total	380	100	380	100	380	100	330	100

Table 2. Renal profile of HIV patients before and after initiation of HAART at St. Paul Generalized Hospital from 2007-2009 G.C

Type of test	Result(mg/dl)	Before HAART	After 6 months	After 12 months	After 18 months
Creatinine	0.5-1.1	284(74.7%)	280(73.7%)	241(63.4%)	203(62.3%)
	<0.5 and >1.1	96(25.3%)	100(26.3%)	139(36.6%)	123(37.7)
Urea	10-50	260(68.4%)	237(62.4%)	233(61%)	193(59.7%)
	<10 and >50	120(31.6%)	143(37.6%)	147(38.7%)	130(40.3%)

Table 3. Renal profile verses age of HIV patients before and after initiation of HAART, at St. Paul General Hospital from 2007-2009 G.C

Age (Yrs.)	Test	Normal range	Term of visit			
			0(initial)	6-month	12-month	18-month
19-23	Creatinine	0.5-1.1	4(1.05%)	6(1.6%)	3(0.8%)	3(.8%)
		<0.5 and >1.1	2(0.5%)	0(0%)	3(0.8%)	3(0.8%)
	Urea	10-50	4(1.05%)	5(1.3%)	2(0.53%)	4(1.1%)
		<10 and >50	2(0.53%)	1(0.3%)	4(1.1%)	1(0.3%)
24-28	Creatinine	0.5-1.1	51(13.4%)	50(13.2%).	38(10%)	34(9.4)
		<0.5 and >1.1	17(4.5%)	18(4.7%)	30(7.9%)	17(4.7%)
	Urea	10-50	51(13.4%)	46(12.1%)	43(11.3%)	37(9.7%)
		<10 and >50	17(4.5%)	22(5.8%)	25(6.6%)	16(4.2%)
29-33	Creatinine	0.5-1.1	58(15.3%)	59(15.5%)	47(12.4%)	32(8.6)
		<0.5 and >1.1	14(3.7%)	13(3.4%)	25(6.6%)	32(8.6%)
	Urea	10-50	46(12.1%)	54(14.2%)	51(13.4%)	34(9%)
		<10 and >50	26(6.8%)	18(4.7%)	21(5.5%)	27(7.1%)
34-38	Creatinine	0.5-1.1	84(22.1%)	76(20%)	66(17.4)	54(14.7%)
		<0.5 and >1.1	21(5.5%)	29(7.6%)	39(10.3%)	37(10.4%)
	Urea	10-50	78(20.5%)	68(17.9%)	72(19%)	56(14.7%)
		<10 and >50	27(7.1%)	37(9.7%)	33(8.7%)	36(9.5%)
39-43	Creatinine	0.5-1.1	34(8.9%)	35(9.2%)	33(8.7%)	25(6.6%)
		<0.5 and >1.1	11(2.9%)	10(2.6)	12(3.2%)	17(4.5%)
	Urea	10-50	29(7.6%)	26(6.8%)	25(6.6%)	17(4.5%)
		<10 and >50	16(4.2%)	19(5%)	20(5.3%)	25(6.6%)
44-48	Creatinine	0.5-1.1	27(7.1%)	27(7.1%)	27(7.1%0	25(6.7%)
		<0.5 and >1.1	11(2.9%)	11(2.9%)	11(2.9%)	7(1.9%)
	Urea	10-50	20(5.3%)	21(5.5%)	21(5.5%)	18(4.7%)
		<10 and >50	18(4.7%)	17(4.5%)	17(4.5%)	14(3.7%)

The Association between renal profile (urea and creatinine) and time of visits within drug type's use was analyzed by using paired *t*-test. Results of paired *t*-test showed that there was a significant association between renal profile and term of visits use within each drug type (P<0.005). Moreover, the association between renal profile in each term of visits with HAART drug use showed that there was no significant association (P>0.005) (Tables 4 and 5). On the other hand, odds ratio of some HAART drug have value of greater than one, this means HAART drug has risk on renal function even if some of HAART drug had Odds ratio value with inverse relation to renal function test (the detail is on Tables 4 and 5).

The association between renal profiles (urea and creatinine) with CD_4^+ T-cell count was assessed, there was no a significant association (P>0.05) (Graph 1).
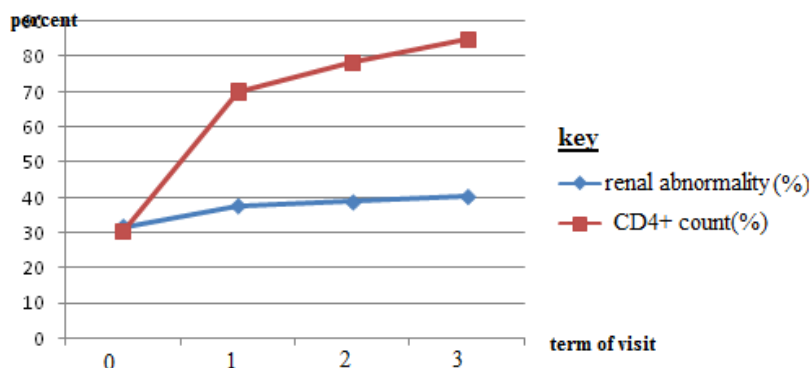
Based on the BUN Creatinine ratio the renal profile of the participant showed that 8.95%, 10.5%, 9% and 5% indicates pre renal abnormality and 1.05%, 1.15%, 0.5% and 1% renal abnormality in each visit respectively (Table 6).

Table 4. Odd ratio, p- value and percent of drug type versus creatinine in each visit of HIV patients before and after initiation of HAART, at St. Paul General Hospital from 2007-2009 G.C

Drug type	Term of visit	Creatinine (mg/dl)		OR	Confidence interval	p-value
		0.5-1.1	<0.5 and >1.1			
d4t/3tc/nvp	After 6 month	73(77.7%)	21(22.3%)	0.416	0.16-1.11	0.079
	After 12 month	55(58.5%)	39(41.5%)	1.591	0.68-5.27	0.223
	After 18 month	55(65.5%)	29(34.9%)	0.659	0.24-1.85	0.429
d4t/3tc/efv	After 6 month	73(77.7%)	21(22.3%)	0.416	0.16-1.11	0.079
	After 12 month	55(58.5%)	39(41.5%)	1.591	0.68-5.27	0.223
	After 18 month	55(65.5%)	29(34.9%)	0.659	0.24-1.85	0.429
azt/3tc/nvp	After 6 month	44(77.2%)	13(22.8%)	0.427	0.15-1.22	0.112
	After 12 month	33(57.9%)	24(42.1%)	1.939	0.66-5.67	0.227
	After 18 month	27(54%)	23(46%)	1.065	0.36-3.15	0.910
(Tdf/3tc/nvp)	After 6 month	55(71.4%)	22(28.6%)	0.576	0.22-1.54	0.274
	After 12 month	50(64.9%)	27(35.1%)	1.440	0.51-4.11	0.495
	After 18 month	41(65%)	22(35%)	0.671	0.23-1.94	0.642
Tdf/3tc/efv	After 6 month	9(64.3%)	5(35.7%)	0.802	0.20-3.21	0.755
	After 12 month	10(71.4%)	4(28.6%)	1.067	0.24-4.74	0.932
	After 18 month	9(81.8%)	2(18.2%)	0.278	0.05-1.67	0.167

Table 5. Odd ratio, p- value and percent of drug type versus Urea in each visit of HIV patients before and after initiation of HAART, at St. Paul General Hospital from 2007-2009 G.C

Drug type	Term of visit	Urea (mg dl)		OR	Confidence interval	p-value
		10-50	<10 and >50			
D4t/3tc/nvp	After 6 month	62(66%)	32(34%)	1.106	0.41-2.99	0.842
	After 12 month	54(57.4%)	40(42.6%)	1.296	0.50-3.39	0.596
	After 18 month	45(53.6%)	39(46.4%)	2.6	0.78-8.72	0.122
D4t/3tc/efv	After 6 month	61(58.7%)	43(41.3%)	1.511	0.59-4.02	0.409
	After 12 month	65(62.5%)	39(37.5%)	1.050	0.40-2.73	0.92
	After 18 month	53(60.2%)	35(39.8%)	1.981	0.59-6.64	0.268
Azt/3tc/nvp	After 6 month	36(63.2%)	21(36.8%)	1.25	0.44-3.56	0.676
	After 12 month	39(66.7%)	19(33.7%)	0.875	0.31-2.45	0.799
	After 18 month	32(62.7%)	19(37.3%)	1.781	0.50-6.32	0.371
(Tdf/3tc/nvp)	After 6 month	44(57.1%)	33(42.9%)	1.607	0.59-4.39	0.354
	After 12 month	41(53.2%)	36(46.8%)	1.537	0.58-4.08	0.389
	After 18 month	38(62.3%)	23(37.7%)	1.816	0.52-6.30	0.347
Tdf/3tc/efv	After 6 month	11(78.6%)	3(21.4%)	0.584	0.12-2.78	0.5
	After 12 month	12(85.7%)	2(14.3%)	0.292	0.05-1.65	0.163
	After 18 month	9(81.8%)	2(18.2%)	0.667	0.10-4.48	0.677

Graph 1. The renal profile verses CD4+ count (%) of HIV positive patients before and after initiation of HAART, at St. Paul General Hospital from 2007-2009 G.C

Table 6. The BUN Creatinine ratio versus term of visit in number and percent HIV patients before and after initiation of HAART, at St. Paul General Hospital from 2007-2009 G.C

BUN/creatinine ratio	Site of abnormality	Term of visit							
		0 (initial)		After 6 month		after12 month		After 18 month	
		#	%	#	%	#	%	#	%
<10[a]	Others	201	52.90%	171	45%	171	45%	168	51.50%
10-20	Normal	141	37.10%	165	43.40%	173	45.50%	138	42.30%
>20[b]	Pre-renal	34	8.95%	40	10.50%	34	9%	16	5%
	Renal	4	1.05%	4	1.10%	2	0.50%	4	1%
Total		380	100%	380	100%	380	100%	326	100%

[a]*abnormal result below the reference range, b abnormal result above the reference range*

4. DISCUSSION

In this study we used evaluating criteria for renal abnormality only creatinine and urea even if different criteria for evaluation and classification of renal function and abnormalities were used in different studies.

According to our study the more HIV drug users were female than male and also the renal abnormality was higher in female than male but there was no significant association (p>0.05). Even if more abnormality was seen between the ages of 34-38, there was no significant association between renal abnormality and age group. These disagree with other studies done before that had significant association between renal abnormality and older age [15].

HAART dramatically improve the Immune status (CD4+ count) of HIV patients especially after 6 months of treatment which also had significant association (p=0.042) with TDF containing drug regimen, which is supported by other studies results too [11,18,22].

Even though other studies result showed beneficent effect of HAART on improvement of HIV related renal complication [23,24], our study analysis result showed that HAART had no impact on improvement of renal abnormalities, rather it increases the prevalence of renal abnormality in every visit though it was statistically insignificant. This is may be because we were merely interested in HAART associated renal complication and we didn't assess the pre HAART HIV related renal complication [10].

The level of renal abnormality was also correlated with drug type and the result showed tenofovir (TDF) containing combination (TDF/3TC/NVP) induced renal abnormalities after 18 month treatment that was indicated by increased urea associated azotemia. These had significant association (p=0.033, OR=6, CI (1.153-31.228)). And these were supported by other study [15,25].

5. CONCLUSION

HAART resulted in improved Immune status of HIV positive patients with remarkable increase in CD_4^+ T lymphocyte count for about 12 month but after 18 month of treatment the CD_4^+ T cell count start to decrease. Besides, HAART drug use or treatment resulted in an increased in Azotemia. This suggests that the impact of drug in renal function as the time frame is increased is bad to renal function. This is especially true for TDF containing drug regimens which dramatically improved CD_4^+ T lymphocyte count and showed significant Azotemia over times. In addition to this pre-renal abnormality is more prevalent than renal abnormality in the study participants in all visits.

The number patients in table two who have higher value of urea and creatinine were increased over time on visits and by using paired *t*- test there was strong association between renal function and term of visits which is p-value less than 0.05. This may indicate that the function of renal become decline and worse on period of HAART drug use.

The mean value of CD4 +cell count is increase through over time of HAART treatment this can tell us HAART can improve the immunity of patients whereas the mean value of creatinine and urea are increase over the period of HAART treatment this means as patients have HAART treatment for HIV virus, the function renal become worse.

Therefore, physician should focus and select the drug regimen with minimal renal toxicity before

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initiation of HAART. And patients should have a continuous assessment test for renal function, whether it function properly or not.

6. RECOMMENDATION

Intensive renal function test has to be performed for HIV patients who are taking HAART to detect early renal abnormality and immediate measure has to be taken.

We recommended further study to be performed for renal profile with liver function tests, electrolyte measurement along with nephrotoxicity with taking in to consideration other confounding variables.

7. LIMITATION OF THE STUDY

We couldn't do a test of creatinine clearance for our study participant which is a better indicator of renal dysfunction.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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