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Research Article

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Comparative Renal Function Tests between HIV Patients on and not on Antiretrovirals and HIV Negative individuals at Nyeri Provincial General Hospital, Nyeri County, Kenya.

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Keywords

Renal toxicity, Antiretrovirals, HIV negative, Proteinuria.

Abstract

Background: Renal toxicity has been identified as a major challenge resulting from long exposure to antiretroviral treatment. The complications associated with antiretrovirals usage may be life threatening leading to substituting antiretroviralsor stopping the treatment. However data on comparative analysis of renal function parameters among HIV patients on and not on Antiretrovirals and the HIV negative individuals in Kenya is generally lacking.
Objective: To establish and disseminate the report of how renal profile of HIV positive patients on and not on Antiretrovirals compares with HIV negative patients at Nyeri Provincial General Hospital.
Design: Comparative cross sectional study.
Setting: Nyeri Provincial General Hospital.
Subjects: One hundred and fifty three (51 HIV positive on ARVs, 51 HIV positive off ARVs and 51 HIV negative) were enrolled in the study.
Results: The prevalence of renal toxicity based on proteinuria was 28% for HIV patients off ARVs compared to 14% for HIV patients on ARVs and HIV negative individuals. Based on urea and creatinine levels, prevalence of renal toxicity was 8% and 2% respectively above the upper reference limit for HIV patients off ARVs compared to 0% for HIV patients on ARVs and HIV negative individuals. There was no significant relationship between renal function and HIV status, ARVs treatment status or ARVs treatment duration.
Conclusion: Findings in the current study support that there is substantial improvement in renal function after initiation of ARV therapy as found in other studies carried out among HIV positive patients in Tanzania, Uganda and elsewhere.

Introduction

Renal impairment as a result of chronic viral infections and toxicity of drugs used in treatment of these conditions has been a source of increased morbidity and mortality of HIV infected patients. Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome is a known systemic disease which affects

many body organs including the kidney functions. Most renal diseases remain asymptomatic until 50-75% of the kidney's glomerular apparatus are destroyed (1). Many drugs including ARVs are cleared by the kidneys and decreased renal clearance will result in toxicity. Dose adjustment of these drugs is based on renal function tests results outcome. Kidney diseases are a common phenomenon in HIV positive patients, many of them resulting to chronic kidney disease that affects 15-20% of people with HIV (2). Kidney disease can result from HIV if not treated or Antiretroviral used in HIV treatment and the two types of kidney impairment are of concern as even minor kidney failure is an indicator of heart complication which can lead to death because of heart disease (2). Kidney disease remains as one of the major complications of HIV infection and ARVs toxicity (3). The other causes of renal impairment related to ARVs and its complications, or other related conditions seem to be getting more important as the HIV infection natural history unfolds and life span of HIV positive individuals is prolonged due to ARVs treatment (4). Kidney complications are experienced in all the stages of HIV infection ranging from electrolyte and fluid imbalance which is common in inpatients to end-stage kidney disease (ESRD) (4). Although ARVs seem to reduce the decline of renal function, patients who achieve substantial viral load suppression continue to show increased loss of estimated Glomerular Filtration Rate (eGFR) (4).

Africa has a high burden of both renal disease and HIV. In Zambia, nearly 33% of the 26,000 persons initiating antiretroviral therapy between 2004 and 2007 had renal disease at baseline. This points to the need to include simple screening and treatment algorithms for renal disease in antiretroviral treatment programs, particularly in settings where tenofovir use is widespread (5).

Use of ARVs is associated with reduction of disease burden related to HIV/AIDS but, prolonged exposure to these ARVs may cause significance renal toxicity. However data on comparative analysis on how renal function is affected by the presence of virus and resultant treatments are generally lacking in comparison to the general population. The number of studies conducted to determine the contribution of antiretroviral agents to renal function is minimal and despite the continued scaling of ARV therapy in Kenya, documented evidence on the effect of ARVs on renal function is lacking particularly in Nyeri County. It is on this background, that this study sought to establish how renal function parameters vary between HIV patients on Antiretroviral, those off Antiretroviral and HIV negative individuals at Nyeri Provincial General Hospital (NPGH).

Materials and Methods

Following approval by Mount Kenya University Ethics Review Committee (Ref. NO.MKU/ERC/0076), Research Authorization by Nyeri County Director of Health (Ref. CP/CIRC/21/96) and Research Clearance Permit by National Commission for Science Technology and Innovation (NACOSTI/P/16/76264/13810) 153 respondents 15 years and above were recruited for the study using systematic sampling procedure. Sample size was determined using the Daniel Formula (1999). Inclusion/Exclusion Criteria were: HIV patients and HIV negative individuals both male and female 15 years and above with no prior History of a kidney disease, no diagnosed congenital anomaly of renal system, not previously diagnosed with diabetes or marked hypertension. Those who met the inclusion criteria were requested to give consent for their blood and urine samples to be used in the study. A questionnaire was administered to consenting study subjects.Data collection sheet was used to collect laboratory information on Renal Function Tests (RFTs) parameters namely Creatinine, Urea, Sodium, Potassium, Chloride and Urine protein levels for the three study groups.

***Sample Collection and Laboratory Analysis*:** 5ml of venous blood was drawn aseptically in plain vacutainer tubes and centrifuged at 3000 revolutions per minute for 3 minutes after standing for one hour at room temperature. Serum samples were used for analysis of urea, creatinine and electrolytes. Urine containers were given to recruited participants to collect their urine samples which were used to determine proteinuria using urine dip stick method. Renal functions tests were carried out on serum samples based on standard operating procedures (SOPs) in clinical chemistry section at Nyeri Provincial General Hospital Laboratory. Electrolytes which included sodium, potassium and chloride levels were analysed using Roche 9180 ISE analyser, while creatinine and urea were analysed using Roche Cobas C111 Automated Chemistry Analyser and Roche Diagnostic Reagents (German). Analytical methods used were kinetic colorimetric assay based on Jeffe Method for creatinine and kinetic test method using glutamate dehydrogenase and urease enzyme for urea. Analytical reagents from Roche Diagnostics were used in the analysis. Proteinuria was determined by urine dipstick method using Insight Expert Urinalysis Reagent Strips and Insight Expert U120 urine strip Reader.

***Quality Control*:** To ensure that quality results were produced, ISETROL Electrolyte Control material was used for electrolytes. Control tests were carried out using three levels of control material anytime SnapPak reagent was replaced and when the equipment was switched on daily. COBAS Precinorm U Plus and COBAS Precipath U Plus control material were used in Cobas C111 analyser daily in the estimation of urea and creatinine samples.

***Data management and statistical analysis*:** Data for kidney analytes collected were entered into Microsoft excel database, checked and corrected for data entry errors. They were evaluated to determine the prevalence of renal insufficiency based on kidney analytes markers. Renal derangements were classified as renal insufficiency based on elevated levels of urea and creatinine above the upper reference range and proteinuria of 1+ and above based on a urine dipstick. The levels of kidney analytes obtained were compared with published reference ranges obtained from a normalized population in Kenya (6). Data for kidney function were profiled based on HIV status, ARVs treatment status, patients' duration on ARVs, sex and age and imported into SPSS version 20.0 software. Age was grouped into seven categories, 10-20, 21-30, 31-40, 41-50, 51-60, 61-70 and 71-80 years. Duration of ARVs treatment was grouped into three categories of 1-3, 4-6, and >7 years. Variability in data was tested based on mean± SD (standard deviation) with the alpha level of significance set at 0.05. Descriptive statistics was used to clean the data. Chi-square tests were applied to test the level of significance between variables and a p-value of 0.05 was considered significant at 95% confidence interval. The results were then presented in form of graphs, charts and discussion and conclusion was inferred from the findings.

Results

Ninety four percent (94%) of HIV positive participants on ARVs had normal levels of sodium and urea, 90% had normal levels of potassium and 88% had normal chloride levels while 86% were negative for urine protein (Table 1).

Table1: Renal Profile for HIV+ Participants on ARVs

	Sodium	**Potassium**	**Chloride**	**Creatinine**	**urea**		**Urine protein**
Lowered	6%		4%	41%	6%	Positive	14%
Normal	94%	90%	88%	59%	94%	Negative	86%
Elevated		10%	8%				
Total	100%	100%	100%	100%	100%		100%

The findings in this study corresponds to a study that established that reduction in HIV viral load by antiretrovirals (ARVs) can prevent the progress of proteinuria resulting in improved clinical outcome of HIV-infected individuals (7). The findings were also in line with(8) who found out that suppression of viral load was associated with improved renal function in those patients who began ARVs and CD4 cell count was low with grade 2 or higher kidney disease in a subset of participants enrolled in US AIDS Clinical Trial Group studies. The findings in the current study are similar to those found by (9) with a prevalence of 3.7% renal insufficiency of HIV positive patients off ARVs and majority of HIV positive patients on ARVs had normal renal function. The findings in this study concur with a study conducted in Tanzania which revealed a considerable renal improvement in the majority of HIV positive patients after initiating ARVs for an average of two years (10).

Ninety percent (90%) of HIV positive participants not on ARVs had normal urea levels, 94% had normal levels of potassium while 88% had normal levels of chloride. Majority (72%) were negative for urine protein (Table 2).

Table 2: Renal profile for HIV+ Participants not on ARVs

	Sodium	**Potassium**	**Chloride**	**Creatinine**	**Urea**		**Urine protein**
Lowered	14%		10%	43%	2%	Positive	28%
Normal	86%	94%	88%	55%	90%	Negative	72%
Elevated		6%	2%	2%	8%		
Total	100%	100%	100%	100%	100%		100%

The finding of proteinuria in HIV positive respondents not on ARVs at 28% was lower than that of a similar study in Uganda (11) with a prevalence of 52.4% among newly diagnosed HIV positive adults. The findings in this study are also lower than those indicated by (12) who reported a prevalence of 30% proteinuria in HIV-infected children at Kenyatta National Hospital. In the current study, prevalence of proteinuria was14% in HIV patients on ARVs and HIV negative individuals, which are higher than that of proteinuria among general adult population in USA which ranges from 6–10% (7), but lower than that of other studies in the same country that established a higher prevalence of proteinuria in adults infected by HIV ranging from 17–45% and 21–33% in children (7).

The findings are also in agreement with another study carried out in a rural Ugandan population with advanced HIV disease and marked renal dysfunction which greatly improved after two years of ARVs initiation (13).This study found a higher prevalence of renal insufficiency in HIV positive patients not on ARVs than in HIV treated patients and HIV negative individuals. This could be associated with HIV replication effect on the kidneys as indicated by(14) who reported that HIV causes kidney injury leading to loss of function and elevated levels of creatinine.

All HIV negative participants had normal levels of potassium and Urea while majority (86%) were negative for urine protein (Table 3)

Table 3*: *Renal Profile of HIV- Patients

	Sodium	**Potassium**	**Chloride**	**Creatinine**	**Urea**		**Urine protein**
Lowered	2%		4%	35%		Positive	14%
Normal	98%	100%	88%	65%	100%	Negative	86%
Elevated			8%				
Total	100%	100%	100%	100%	100%		100%

Two percent (2%) of the HIV positive patients not on Antiretrovirals had an elevated creatinine levels which is the main marker for diagnosis of renal diseases and 8% with abnormal urea levels another key marker of renal abnormalities. The percentages of renal abnormalities in most of the kidney analytes except for potassium and chloride for HIV positive not on Antiretrovirals were higher than those of HIV positive on Antiretrovirals. The percentage of proteinuria was twice higher in HIV positive patients not on Antiretrovirals as compared to HIV positive on Antiretrovirals and HIV negative individuals which is an early indicator of renal abnormalities (Table 4).

Table 4: Abnormal Renal Profile for all Participants

Analytes (RR Units)	% HIV + on ARVs (N=51)	% HIV+ not on ARVs (N=51)	% HIV – (N=51)
Creatinine (59-127 umol/l)	0% elevated	2% elevated	0% elevated
Urea (1.5-5.9 mmol/l)	0% elevated	8% elevated	0% elevated
Sodium (Na^+) (134-153 mmol/l)	6% lowered	14% lowered	2% lowered
Potassium (K^+) (3.o-5.3 mmol/l)	10% elevated	6% Elevated	0% elevated
Chloride (Cl^-) (101-110 mmol/l)	8% elevated	2% elevated	8% elevated
Protein in urine	14% positive	28% positive	14% positive

Reference ranges adopted from (6)

The prevalence of abnormal renal analytes of urea, creatinine and proteinuria which are key markers for diagnosing drug-induced toxicities affecting the kidney was compared for any variation between HIV patients on ARVs, those off ARVs and the HIV negative individuals using chi-square tests (Table 5).

Table 5: Prevalence of Abnormal Renal Analytes Based on HIV Statusand Treatment status

Key analytes and their upper normal limit		% HIV+ on ARVs	% HIV+ not on ARVs	%HIV-	Sig*
Renal abnormality	Creatinine>127 µmol/L	0%	2%	0%	0.434
	Urea >5.9 mmol/L	0%	8%	0%	0.781
	Protein in urine (+)	14%	28%	14%	0.06

Chi-square tests were conducted to establish the association of renal function of the participants based on HIV status, ARVs treatment status and duration of ARVs treatment, age and sex.

There was a significant relationship between HIV status and sodium levels (P=0.023). However, no significant relationship with the other five renal function tests analytes. There is therefore not enough evidence to conclude that there is a relationship between HIV status and renal function (Table 6).

Table 6: Association of HIV Status and Renal Function

Sodium	0.023**
Potassium	0.604
Chloride	0.356
Creatinine	0.434
Urea	0.781
Urine protein	0.060

**Significant at 95% CI

There was a significant relationship between ARVs treatment and sodium levels (P=0.006). However, no significant relationship with the other five renal function tests analytes (Table 7). There is therefore not enough evidence to conclude that there is a relationship between ARVs treatment and renal function.

Table 7: Association of ARV Treatment and Renal Function

Sodium	0.006**
Potassium	0.876
Chloride	0.331
Creatinine	0.177
Urea	0.870
Urine protein	0.125

**Significant at 95% CI

There was a significant relationship between the duration of ARVs treatment and potassium levels (P=0.005). However, no significant relationship statistically between duration of treatment and the other 5 analytes (Table 8). There is therefore not enough evidence to conclude that there is a relationship between duration of ARVs treatment and renal function of HIV patients on ARVs, those off ARVs and HIV negative individuals.

Table 8: Association of Duration of ARVs Treatment and Renal Function

Sodium	0.776
Potassium	0.005**
Chloride	0.911
Creatinine	0.752
Urea	0.099
Urine protein	0.247

**Significant at 95% CI

Discussion

The purpose of the study was to establish how renal profile of HIV patients on and not on Antiretroviral compares with HIV negative patients at Nyeri Provincial General Hospital. Specifically, the research aimed to establish the renal profile for HIV positive patients on ARVs and those not on ARVs at Comprehensive Care Centre (CCC), to establish the renal profile for HIV negative patients at Out Patient Department (OPD) and to determine how HIV status, ARVs status and ARVs treatment duration affect renal function tests parameters.

The study was carried out at the Nyeri Provincial General Hospital (NPGH) in the Comprehensive Care Centre (CCC) and Out Patient Department (OPD) specifically Provider Initiated Testing and Counselling services (PITC) in conjunction with the hospital Clinical Laboratory Department. A comparative cross sectional study design was adopted where ARVs treated patients attending (CCC), newly diagnosed HIV cases not on ARVs and HIV negative individuals attending (PITC) respectively were recruited for the study for the comparison of the Renal Function Tests (RETs) parameters. The study population consisted of all patients 15 years and above attending CCC and OPD departments regardless of their gender. A systematic sampling procedure was adopted in selecting the study respondents. A sample size of 153 respondents was used. Data was collected using questionnaires for demographic data and data collection sheet for laboratory analysis. Data was analysed using descriptive statistics. Chi-square tests were applied to test the level of significance between variables.

The findings showed that the mean age of the study participants was 40 years and there was no significance difference between the three study groups. The sex distribution of the HIV treated patients, those not on ARVs and the HIV negative participants did not differ significantly. However, the number of females recruited in this study where higher than that of males representing 75% of all the participants.

The first objective was to establish the renal profile for HIV patients on ARVs and those not on ARVs at Comprehensive Care Centre (CCC) Nyeri Provincial General Hospital. Presence of protein 1+ and above in urine dipstick and elevated levels of serum urea and creatinine above the upper reference limit were taken to indicate renal insufficiency. The prevalence of proteinuria was higher among HIV positive patients not on ARV treatment at 28% compared to 14% in HIV patients on ARVs treatment and HIV negative individuals. The current study found a prevalence of 8% and 2% renal insufficiency in HIV positive patients not on ARVs as compared to 0% in HIV positive on ARVs and HIV negative individuals based on urea and creatinine analysis respectively.

This study also sought to determine how HIV status affect renal function tests parameters. There was a significant relationship between HIV status and sodium levels (P=0.023). However, there was no statistically significant relationship between HIV status and the other five analytes of potassium (P=0.604), chloride (P= 0.356), creatinine (P=0.434), urea (P=0.781), urine protein (P= 0.060). There is therefore not enough evidence to conclude that there is a relationship between HIV status and renal function.

This study also sought to determine how ARVs treatment duration affect renal function tests parameters. A significant relationship between duration of ARVs treatment and potassium levels was noted (P=0.005). However no significant association statistically between duration of ARVs treatment and the other five analytes of sodium (P=0.776), chloride (P= 0.911), creatinine (P=0.752), urea (P=0.099) and urine protein (P=0.247) was noted. There is therefore not enough evidence to conclude that there is a relationship between duration of ARV treatment and renal function.

In conclusion, in the current study the prevalence of proteinuria, serum urea and creatinine were higher in HIV- infected group not on ARVs compared to HIV-infected group already on ARVs and the HIV negative individuals. There was no statistically significant relationship between duration of ARVs treatment and renal function, and no significant association of renal function with age and gender. The findings of the current study support that there is substantial improvement in renal function after initiation of ARVs therapy.

Renal insufficiency is prevalent in HIV infected persons, but changes that occur in renal function over the course of ARVs treatment are not significant. Thus suggesting the role of HIV infection, ARVs and other traditional risk factors, but not only ARVs in renal insufficiency. We recommend early initiation of ARVs on HIV- infected patients and close monitoring of renal function during the course of ARVs treatment. This will prevent kidney damage due to viral replication and aid in evaluating drug toxicity and implement dose modification when necessary. Further studies investigating earlier markers of kidney damage monitoring specific classes of antiretroviral drugs over a period of time to evaluate their renal toxicity in this population are warranted.

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