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URINE MARKERS OF KIDNEY DISORDERS AND THEIR RISK ASSOCIATIONS IN HIV-INFECTED PATIENTS ATTENDING NYANZA PROVINCIAL GENERAL HOSPITAL IN KISUMU, WESTERN KENYA
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W. O. OPIYO, A. G. M. NG'WENA and A. V. O. OFULLA

ABSTRACT

***Objective*: To identify abnormal levels of urine metabolites and cells that serve as markers of existing kidney disorders in ambulatory HIV-infected patients.**
***Design*: A cross sectional study.**
***Setting*: Nyanza Provincial General Hospital's patient support centre.**
Subjects: A total of 593 HIV infected patients were studied.
***Intervention*: Dipstick urinalysis test was used to screen mid stream urine to detect constituents with altered levels.**
***Results*: Out of the 593 participants, the urine of 214 (36.1%) had abnormally altered levels of urine constituents, with more females afflicted than males [41.5% vs. 27.8%; OR 1.84 (1.28-2.63), χ^2= 11.08, p=0.0009]. Urobilinogen was the most common urine metabolite while ketones were least commonly present. More participants had altered levels of leucocytes than erythrocytes in urine. Patients with pyuria were three times more likely to have elevated erythrocytes in their urine as well (χ^2= 34.37, p<0.0001). Similarly, the risk of having proteinuria was three times higher in patients with pyuria (p<0.0003, Fisher's test). Patients with erythrocytes in urine also had a threefold likelihood of having proteinuria (P<0.0003, Fisher's test). Fewer ARV users had abnormal urine markers [15.7% vs 24.3% OR 0.62 (0.41-0.94), χ^2= 5.2, p<0.05].**
***Conclusion*: Metabolites and cellular markers of kidney disorders were prevalent in the urine of HIV patients especially females and those with pronounced immune depletion (CD4 counts equal to or below 500). ARVs use was associated with reduced manifestation of these markers.**

INTRODUCTION

Kidney complications are fast surpassing opportunistic infections as causes of morbidity and mortality in HIV patients in the post highly active anti-retroviral (HAART) drugs era (1). However, the prevalence of kidney disorders among HIV patients has been difficult to estimate due to the diverse spectrum of renal disorders encountered in this population and lack of standardised recognition and appropriate reporting mechanism (2). Gerntholtz and colleagues (3) in a South African study reported that 27% of the renal biopsies showed HIV associated kidney disease.

Kidney damage can be induced by diseases intrinsic or extrinsic to the kidneys. Damaged kidneys cannot regulate appropriately the amounts of electrolytes, metabolites and cells excreted through it. Subsequently, the levels of these constituents in urine are gradually altered. In HIV patients, kidney disease has been attributed to direct infection and indirect damage of kidney cells by the virus and to toxic damage induced by anti-retroviral drugs (ARVs) (4). Szczech *et al* (5) reported that the HIV virus induces histological damage to the kidney glomeruli, tubules and interstitium. Generally, damage to the kidney parenchyma can lead to excessive excretion of metabolites, electrolytes and cellular elements in urine (6). The metabolites, electrolytes or cellular elements present in abnormal levels in urine are therefore at times typical of the particular underlying damage to the kidney (7). Haematuria accompanied

by persistent proteinuria iscommon manifestation of underlying glomerulardisease (8), while leukocyturia is commonly indicative of urinary tract infection (9). Various tests can assess the presence of these constituents in urine including the dipstick urinalysis test which was employed in the current study (10). The most common HIV related kidney disease is HIV associated nephropathy (HIVAN). Studies in USA and Europe have demonstrated that HIVAN has a higher prevalence among patients of African descent (11). An estimated 85-97% of HIVAN patients are black African or Afro- Caribbean (12). The risk factors for HIV associated kidney disease have therefore been suggested to be more in the black race and lower CD4 lymphocyte cells count (5). It is unknown why patients of black African descent predominantly suffer HIV induced pathology. In the USA therefore, it has been recommended that all patients with newly diagnosed HIV infection should be screened for the presence of chronic kidney disease (4).

In Africa, despite having a higher population of HIV infected people at over 25 million, adequate information is not available concerning HIV associated renal diseases (13). It has therefore not been established whether the prevalence of HIVAN among indigenous black African patients mirrors that of HIV-1 infected black patients in the United States. Wools-Kaloustian *et al* (14) found that the prevalence of renal dysfunction ranged between 1-15% in a cross sectional study of 373 HIV patients in western Kenya. Han *et al* (15) evaluated 615 HIV patients in South Africa and reported that 6% had overt proteinuria while 36% showed micro albuminuria. A cross sectional survey of HAART naïve Ugandans by Olson *et al* (16) revealed that 21% had dipstick proteinuria. In a study of a cohort of HAART naïve Rwandan women, it was established that the prevalence of proteinuria was 13% (17).

Despite the fact that HIV related nephropathies rapidly progresses to end stage renal disease (ESRD) and death, kidney disease has not received as much attention as the opportunistic infections and malignancies that contribute to AIDS (18). Even though it has been observed that highly active anti-retroviral therapy has heralded improved survival, kidney, liver and cardiac diseases have become increasingly important sources of mortality and morbidity in patients with HIV (2). Vigilant attention to the kidneys and renal function is therefore necessary for optimal care of HIV patients (19). Assessment of kidney function and recognition of acute or chronic kidney disease is also essential for appropriate dose modification in HIV-infected patients exposed to complex medication regimens in the HAART era. As such, attention needs to be focused on early detection, prevention and control of kidney diseases in this group.

Cho *et al* (20) recommended routine urinalysis in HIV patients and especially for patients receiving potentially nephrotoxic drugs or exhibiting signs of kidney disease such as oedema and hypertension. They noted that urinalysis is an excellent screening test for providing clues concerning the three cardinal manifestations of kidney disease namely haematuria, proteinuria and pyuria. This study was therefore designed to investigate the frequency of presentation of markers of kidney dysfunction in urine in HIV patients attending the patient support centre in Nyanza Provincial General Hospital in Kisumu, Kenya.

MATERIALS AND METHODS

This study was carried out at the Nyanza provincial hospital's patient support center in Kisumu municipalityof Kisumu county, western Kenya. The most prevalent diseases in Kisumu county are malaria, anemia and HIV/AIDS; HIV prevalence is about 14.9% and is the highest in the country (21). This was a cross sectional and the participants enrolled were above 18 years, HIV-infected, able and willing to provide consent. Ethical review and approval was done by the provincial hospital's research committee.

Five hundred and ninety three participants were enrolled in the study out of the nine hundred and fifty (950) clients from beginning of September to the end of October 2009. After administering the requisite information in the consent forms and routine medical history and examination, volunteers were requested to donate five mls of midstream urine for screening.

The urine samples were tested immediately using urinalysis strips to assess the presence of abnormally raised concentrations of electrolyte, metabolites and cellular entities of interest. The strips were dipped in the urine briefly and withdrawn. The observed colour changes in the segments of the strips were compared to a colour chart to obtain results, which were entered in a proforma designed specifically for the study. The urinalysis strips used were Uriscan 10 SGL strips (Diagnostics, Korea) for assessing the presence of eight parameters associated with kidney disorders. These parameters included proteins, white blood cells (leukocytes), glucose, bilirubin, urobilinogen, nitrites, red blood cells (erythrocytes), and ketones. The dip stick screen is a qualitative and semi-quantitave assessment tool which by use of graded colour charts, detects the variations of concentrations of specified urine constituents. Information concerning the HIV profile of the patients such as CD4 cell levels and ARVs used as well as demographic data were abstracted from the most recent reports contained in the patient's hospital records.

The study did not assess the magnitude of reduction of kidney functional efficiency and the actual underlying kidney pathology. It did not quantify the actual levels of individual markers present in the urine samples, and function specific tests such as 24 hour glomerular filtration rate and creatinine clearance were not done.

Data were entered in Microsoft Excel spreadsheet (Microsoft Corporation) and analysed using SPSS (Version 10.0) and R computer programmes for basic descriptive and inferential statistics. The dependent variables included the eight parameters; proteins, leucocytes, glucose, nitrites, urobilinogen, bilirubin, erythrocytes, and ketones. To analyse these parameters, age, gender, ARV use, and CD4 cell count served as the independent variables. To determine the relationship between the dependent and independent variables, a Chi-square test or a Fisher's exact test was used with $p<0.05$ considered statistically significant.

RESULTS

Table 1 shows the characteristics of the study population. Out of the 593 participants, 366 (61.7%) were females while 227 (38.3%) were males. The mean age of the participants was 37.7 years with 50% falling between 31 and 44 years. The majority of participants (69.1%) had CD4 cell count equal to or below 500 cells per microliter and their mean CD4 count was 412.7 cells per microliter of blood. A large majority of the patients (80.4%) screened were undergoing anti-retroviral treatment.

Table 1
Characteristics of the study population (n= 593)

Characteristic	Population percentage
Male	38.3
Females	61.7
CD4 > 500	29.7
CD4 ≤ 500	69.1
ARV users	80.4
No ARVs	19.6

Key: ARVs- Anti-retroviral drugs: CD4- CD4 lymphocytes

Table 2 shows the frequency of samples that tested positive for abnormally raised levels of individual markers of altered kidney health in the entire study population. At least one marker was detected in urine samples of 214 (36.1%) participants. The most common constituents detected were leucocytes in 17.5% (95% C.I. 14.5-20.6%) of participants, erythrocytes 15% (95% C.I. 12.1-17.9%), and urobilinogen 10.1% (95% C.I. 8-12.9%). The least common markers were ketones and glucose.

Analysis of the association of gender, CD4 lymphocyte levels and anti-retroviral drugs with presence of markers in urine revealed that only gender and antiretroviral drugs usage were significantly associated with the occurrence of abnormal markers in urine (Table 3). A higher proportion of female participants had with markers of kidney disorders in their urine samples compared to male participants [OR 1.84 (1.28-2.63), χ^2= 11.08 p=0.0009]. This disparity occurred in gender at all the levels of CD4 lymphocyte immune cells depletion. Females with CD4 count above 500 cells / μL had significantly higher markers than males with CD4 count above 500 [OR 3.80 (1.58-9.14), χ^2= 9.7, p=0.002]. Similarly at CD4 cell count equal to or below 500, females had more markers than males [OR 1.59 (1.06-2.40), χ^2= 4.99, p=0.02]. Among the male participants, those with progressive immune depletion (CD4 count below 500) were more likely to have markers of kidney disorders in their urine than those with more robust immunity (CD4 count above 500) [OR 2.6885 (1.137-6.3644), χ^2= 5.4, p=0.02]. Among female patients only, there were no significant variations in marker occurrence across immunity levels as observed in male patients.

ARV use was associated with a reduction in the prevalence of markers while non usage of ARVs was associated with increase of the markers [OR 0.62 (0.41-0.94), χ^2= 5.2, p=0.02] (Table 3). The reduction of markers associated with ARV use was more prominent in males compared to females [OR 0.55 (0.37-0.82), χ^2= 8.7, p=0.003]. This impact of medication was more pronounced at CD4 count below 500, where ARV use led to more reduction in prevalence of markers in males than in females. However at CD4 cell levels above 500, ARV use was not associated with significant difference in prevalence of markers among male and female patients. Within each gender, apart from males with CD4 cell levels below 500, ARV use was not associated with significant changes in the proportions of individuals depicting these markers. Males with CD4 count below 500 undergoing ARV treatment however had less markers than those not on ARVs [OR 0.3273 (0.14-0.765), χ^2 = 7.1, p=0.008)] with the same level of CD4 lymphocyte count (Table 3).

Table 2
Frequency of urine markers for the entire study population (n=593)

	Urine markers							
	Erythrocytes	Ketones	Glucose	Protein	Bilirubin	Urobilinogen	Leucocytes	Nitrate
Negative	504	591	589	561	579	531	489	581
Positive	89	2	4	32	14	62	104	11
Prevalence	15%	0.3%	0.7%	5.4%	2.4%	10.5%	17.5%	1.9%

Table 3
Chi-square (χ^2) analysis of the distribution of urine markers of kidney disorders among gender, ARV use and CD4 counts in the HIV population.

Patient profile	Markers present	Markers absent	χ^2	p-value
Females	151	215	11.08	0.0009
Males	63	164		
ARV yes	161	315	5.22	0.0223
ARV no	52	63		
CD4>500	58	118	0.25	
CD4≤500	154	256		
Males ARV yes	49	140	8.73	0.0031
Females ARV yes	112	175		
Males CD4>500	7	41	5.36	0.0206
Females CD4>500	50	77	9.74	0.0018
Males CD4<500	56	122		
Females CD4<500	98	134	4.99	0.0255
Males ARV yes CD4<500	42	110	7.71	0.0055
Females ARV yes CD4<500	80	110		
Males CD4<500, ARV yes	42	110	7.08	0.0078
Males CD4<500 ARV no	14	12		

Key: CD4≤500- CD4 cell count equal to or less than 500/μL: CD4>500- CD4 cell count more than 500/μL: ARV no- not on anti-retroviral drugs; ARV yes-using anti-retroviral drugs.

The prevalence of occurrence of individual markers such as leukocytes, erythrocytes and urobilinogen significantly varied between gender and ARV use and they tended to be less in males and ARV users and higher in females and ARV non users. The proportion of females with leucocytes in urine was significantly higher than that of males [OR 3.57 (2.08-6.12), χ^2= 2.5, p<0.0001] (Table 4). Similarly, females with erythrocytes in urine were significantly more than males with erythrocytes in urine [OR 1.71 (1.04-2.81), χ^2 = 4.6, p=0.03] (Table 5). The prevalence of leucocytes among participants not using ARVs was significantly higher than those using ARVs detected with leucocytes in urine [OR 1.73 (1.05-2.82), χ2=4.8, p=0.03] (Table 4). Similarly, urobilinogen was detected more frequently in ARV users than in ARV non users [OR 0.55 (0.30-0.98), χ^2=4.1, p=0.04] (Table 6).

Table 4
Association of gender and ARV use with leucocytes in urine.

Patient	Leucocyte present	Leucocytes absent	OR	χ^2	P-value
On ARV	75	402	1.73	4.8	0.03
Not on ARV	28	87			
Males	18	209	3.57	2.5	<0.0001
Females	86	280			

Table 5
Association of gender with erythrocytes in urine

Gender	Erythrocytes present	Erythrocytes absent	Total
Males	25	202	227
Females	64	302	366
Total	89	504	593

OR 1.71, χ^2= 4.6, p=0.03

Table 6
Association of ARV use with urobilinogen in urine

ARV use	Urobilinogen present	Urobilinogen absent	Total
On ARV	44	433	477
Not on ARV	18	97	115
Total	62	530	592

OR 0.55, χ^2=4.1, p=0.04

Among routinely clinically assessed markers of kidney disorders in urine (leucocytes, glucose, erythrocytes and proteins), leucocytes tended to be more common, followed by erythrocytes, proteins and glucose in descending order. Patients presenting with leucocytes, erythrocytes or protein were also found to be more likely to have other markers of kidney disorders in their urine. Having leucocytes, predisposed one to three times the risk of having erythrocytes in urine as well, compared to patients without leucocytes in urine (RR=3.047; =34.37,p<0.0001) (Table 7). Similarly, having leucocytes elevated the risk of having protein in urine threefold compared to those deficient of leucocytes in urine (RR= 3.657; p<0.0003 by Fisher's test). The risk of having protein in urine was four times higher in patients with erythrocytes in urine than in patients without erythrocytesin urine (RR=3.874; p<0.0003 by Fisher's test) (Table 8).

Table 7
Comparison of risk of having erythrocytes and protein in urine in individuals with leucocytes and without leucocytes in urine.

Patient	Leukocytes present	Leukocytes absent	RR	χ^2	P-value
Erythrocytes present in urine	35	54	3.0475	34.37	<0.0001
Erythrocytes absent in urine	69	435			
Protein present in urine	14	18	3.6571	16.07	<0.0001
Protein absent in urine	90	471			

RR – Risk ratio

Table 8
Comparison of risk of having protein in individuals with erythrocyte in urine

Patient	Protein present	Protein absent	Total
Erythrocytes present	13	76	89
Erythrocytes absent	19	485	504
Total	32	561	593

Risk ratio=3.8746; p<0.0002

DISCUSSIONS

The results of this study have shown that markers associated with kidney disorders are not common in HIV patients in western Kenya. All the tested markers were found to be present in abnormally raised levels in the urine of some of the participants. Indicators of deranged kidney health and functions were observed in urine samples of 36.1% of the patients assessed. In Kenya, a study by Wools-Kaloustian *et al* (14)noted that the prevalence of HIV related renal impairment was 11.5%, while in Tanzania it was reported at 28%. In Zambia, the prevalence was cited as 33.5% at baseline (22). Yet in South Africa it was reported

at 6%, Nigeria at 38% and Ivory Coast at 26% (23). Choi *et al* (24) cited the prevalence of chronic kidney disease in HIV patients as ranging from 3.5 to 32.6%. As such the prevalence established from the current study falls within the range of what has been described in other studies.

Data from the current study has shown that female HIV patients and patients not on anti-retroviral drugs were identified with more markers of kidney dysfunction. Franey *et al* (25) found on the other hand that more male HIV patients had impaired kidney function. This difference could be attributed to investigative methodology employed or to prevailing health conditions that have skewed impact on gender health in the study setting. The current study observed that the prevalence of kidney disorders in males rises with progression of the disease especially in the absence of anti-retroviral treatment. However, it was also noted that males similarly showed more marked improvement of kidney health when put on anti-retroviral treatment. Winston and Klotman (26) reported that treatment with anti-retroviral drugs reduced the risk of kidney disease in HIV patients by 40 to 60%.

In this study, leukocytes, microscopic haematuria (erythrocytes), urobilinogen and proteins were the most common of the routinely screened constituents detected in the survey. Few studies have investigated risk factors associated with leukocyturia, haematuria and proteinuria among HIV patients. Proteinuria and haematuria indicate existence of structural damage of the kidney, while leukocyturia primarily indicate presence of active infection. Winston *et al* (27) identified uro-genital infection as a risk factor of acute kidney failure in HIV patients. In this study, leukocyturia was found in 17.5% of the population. However, patients not on anti-retroviral treatment had a higher prevalence of leukocyturia than those undergoing ARV treatment. Females had a higher prevalence of leukocyturia than males. This contrast between genders can be attributed to cyclic reproductive changes in female patients as much as to factors predisposing to ease of uro-genital infection in females. Fabian *et al* (23) reported 30% leukocyturia in routine urinary screening of patients attending anti-retroviral clinics in South Africa. The finding of the this correlates only to leukocyturia levels reported in certain patient categories in previous studies. This further highlights the importance of patients' characteristics and study methodology in determining the outcome of kidney complications in HIV patients.

This study observed microscopic haematuria in 15% of the population investigated and significant prevalence differences were only noted between the genders. Females had higher haematuria than males. This could be attributed to pathological as well as physiological events within the female population. In males, CD4 lymphocyte levels and ARV use were associated with fluctuations in the numbers detected with haematuria while in females these factors were not associated with such changes. Having CD4 count above 500 cells / μL and using ARVs led to reduction generally in levels of microscopic hematuria in males. This was exemplified by males with CD4 count above 500 and using ARVs who had only 2.8% afflicted with microscopic haematuria. On the contrary, males with CD4 count equal or below 500 and not using ARVs had 30.8% with haematuria. The reasons for these findings need to be established in future studies. Fabian and Neicker (23) reported that 33% of HIV infected outpatients in anti-retroviral clinics in South Africa had microscopic haematuria. This agrees with the prevalence reported in some of the categories from the current study. Patients with microscopic haematuria were more likely to be detected with leukocytes and proteins as well.

Proteinuria is the most common manifestation of kidney damage and persistent proteinuria is the main marker for glomerular disease (28). Despite the high prevalence of kidney markers reported in this study, proteinuria was identified in only 5.4% of the participants. This level of proteinuria prevalence remained almost constant in all categories of patients regardless of differences in gender, CD4 levels and ARV use. These findings correspond with those of Han *et al* (15) and Wools-Kaloustian *et al* (14) who observed proteinuria in 6.2 and 6%, respectively, in separate studies. Cavalcante *et al* (28) similarly reported persistent proteinuria in 5.4% of their study population. They also noted that a low CD4 lymphocyte count (<200 cells per mm^3) was significantly associated with proteinuria. However, the finding that proteinuria was detected in almost all categories of patients albeit in low prevalence, serve as a strong indication that a proportion of these patients experienced active kidney disorders. As such, further studies to investigate the utility of screening HIV patients for proteinuria as a cheap non-invasive means for assessing kidney health in our limited resource health settings may necessary.

The finding in this study that markers associated with kidney disorders are prevalent in HIV patients in western region of Kenya calls for routine assessment of kidney complications in our health settings in order to mitigate early their negative impacts on the functions of this vital organ. Future studies need to focus on the risk factors associated with kidney complications in local HIV infected populations with special attention to gender variations.More studies are needed to design a standardised and appropriate methodology of investigating the multiple kidney disorders related to HIV infection. Histopathological studies would also greatly improve the understanding of pathogenesis of HIV related kidney disorders and their pathophysiology. This would help establish

features pathognomonic of kidney disorders and set a basis for defining a common investigative criterion for diagnosing and or monitoring kidney disorders in HIV patients.

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