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Urine Abnormalities and Chronic Kidney Disease in Highly Active Antiretroviral Therapy-naive Adults: A Cross-sectional Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors RKDE, MEG and RCB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MEG and CN managed the analyses of the study. Authors FOB and CN managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Objective: This study investigated chronic kidney disease (CKD) and urine abnormalities in highly active antiretroviral therapy naïve (HAART-naïve) human immunodeficiency virus (HIV) infected adults, presenting to two antiretroviral therapy (ART) clinics in the Volta region of Ghana.
Methods: A cross-sectional study of 100 newly diagnosed HIV/AIDS patients attending ART clinics of the St. Anthony's and Ho Municipal hospitals both in the Volta region was conducted. Vital clinical history and socio-demographic data were recorded from the folder of eligible participants. Blood and urine samples were collected for serum creatinine estimation; urinalysis was performed with dipstick and light microscopy. CKD was assessed with the Kidney Disease Improving Global Outcome (KDIGO) guidelines.

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Results: Nine percent (9%) of the participants had CKD (eGFR<60 mL/min/1.73 m²). Prevalence of CKD was higher (88.9%) in females than in males (11.1%). Median creatinine levels were significantly higher in males than in females (*P*=0.0103). Eighteen percent (18%), 13%, 11% of the participants had proteinuria, pyuria and haematuria respectively. On urine microscopy, we recorded 8% (8/100) crystalluria (7/8 -calcium oxalate and 1/8 -triple phosphate), 9% epithelial cells, 20% pus cells and 7% red blood cells among our participants. Participants with confirmed CKD had more pyuria and haematuria than those without CKD.

Conclusion: This study revealed a 9% prevalence of CKD among our participants with the condition being more common in females. Urine abnormalities like proteinuria, haematuria, pyuria and crystalluria were common in our participants. Routine urinalysis and screening for CKD in HIV/AIDS patients should be strengthened as it will help in early detection of renal abnormalities.

Keywords: Chronic kidney disease; urine abnormalities; highly active antiretroviral therapy naïve; estimated GFR; HIV/AIDS.

1. BACKGROUND

Kidney function has been implicated in human immunodeficiency virus (HIV) infection, which may further progress to acquired immune deficiency syndrome (AIDS) and subsequently death [1-3]. It may present as acute kidney injury or chronic kidney disease (CKD), with an estimated prevalence in sub-Saharan Africa ranging from 6% to 48.5% [4]. CKD is essentially compromised kidney function that persists for more than three months or more [5]; and can be caused by infections and inflammation due to HIV [2].

Renal involvement in HIV is more common in patients of African descent than those of Caucasian origin [6]; and is found in up to 30% of HIV infected persons [1,7]. Patients from sub-Saharan Africa are therefore of concern, since they accumulate risk factors for CKD both related and unrelated to HIV/AIDS [8]. Among HIV/AIDS related CKD risk factors are late HIV diagnosis, opportunistic infections, nephrotoxicity due to drugs used in HIV treatment [8], immune complex mediated glomerulonephritis, thrombotic microangiopathy, interstitial nephritis and various electrolyte disturbances [9,10]; as well as hepatitis C infection [2], ethnicity, and co-morbid diseases like hypertension and diabetes [8].

Renal impairment has shown to be an important predictor of early mortality in patients starting antiretroviral therapy in both western settings and Africa [6]. In Ghana, it has been established that renal dysfunction exists among both patients on HAART and those yet to start HAART [6]. In addition, urinary abnormalities exist in HIV-infected patients naive to highly active antiretroviral therapy, with prevalence between 30% and 44% [4]. Meanwhile, the few studies conducted in HIV/AIDS patients in Ghana by Obirikorang et al. [11] and Owiredu, et al. [7], failed to include one of either urine chemistry by dipstick or urine microscopy for crystalluria [12] and other urine abnormalities. A similar study in Tanzania also failed to include urinalysis which is a relevant proxy for the detection of renal impairment [2].

This study therefore sought to investigate urine abnormalities, CKD and identify risk factors associated with CKD in HAART naïve HIV/AIDS patients.

2. MATERIALS AND METHODS

2.1 Study Design and Study Setting

This multi-center non-randomized cross-sectional study was conducted between September 2015 and April 2016 among newly diagnosed HIV/AIDS patients attending the HAART clinics of the St. Anthony's hospital, Dzodze and Ho Municipal hospital, Ho, both located in the Volta Region of Ghana. Dzodze is a small town and is the capital of Ketu North district, a district in the South-eastern corner of the Volta Region of Ghana. Ho is the capital town of Ho Municipal district, and the capital of Volta Region (one of ten regions in Ghana). It is located on coordinates: 6º36'43"N 0º28'13"E, between Mount Adaklu and Mount Galenukui (Togo Atakora Range) around the middle belt of the Volta region.

2.2 Study Participants

One hundred (100) HIV/AIDS patients enrolled in the HAART clinic of the two selected hospitals (44 from Dzodze and 56 from Ho) yet to start

antiretroviral therapy were considered eligible to participate in the study. We excluded participants with a history of the following diseases: hepatitis B, hepatitis C, hypertension, diabetes, febrile illness and renal diseases. Pregnant women and HIV/AIDS patients on HAART were also excluded.

2.3 Ethical Consideration

The study was approved by the ethics committees of the two health facilities used for the study (SAH/REQUEST/2014). The purpose of the study was explained to participants and implied consent was obtained. Informed written consent was obtained from the participants and the protocols thoroughly explained before enrollment into the study.

2.4 Data Collection

Socio-demographic data of participants, vital clinical history and body mass index (BMI) were recorded from the folder of the participants.

2.4.1 Blood specimen collection and analysis

Three (3) mls of venous blood was collected into plain vacutainer tubes, allowed to clot at room temperature then centrifuged at 2000 rpm for 5 minutes. The sera were separated into labelled plain tubes and stored at -20℃ until assayed.

2.4.2 Serum creatinine estimation and eGFR calculation

An automated chemistry analyzer (Junior Selectra, model: Junior series-SN 9-9048; Vital Scientific, Dieren-The Netherlands) was used to estimate the serum creatinine of participants. The CKD-EPI equation was used to calculate eGFR. CKD was accessed using the Kidney Disease: Improving Global Outcome (KDIGO) guidelines. The CKD-EPI equation per the National Kidney Foundation is as follows:

$$141 \times \min\left(\frac{SCr}{K}, 1\right)^{\alpha} \times \max\left(\frac{SCr}{K}, 1\right)^{-1.209} \times 0.993^{Age} [\times 1.018\ if\ female] [\times 1.159\ if\ black]$$

Where, SCr is serum creatinine (in mg/dl), k is 0.7 for females and 0.9 for males, αis 0.329 for females and 0.411 for males, min is the minimum of SCr/k or 1, and max is the maximum of SCr/k or 1 [5].

2.4.3 Urine specimen collection and analysis

With the aid of a clean screw capped container we collected 10 mls of freshly voided urine for urinalysis (biochemistry and microscopy). Urine reagent strips (URIT 10V, URIT Medical Electronic Co., Ltd. China) were used to determine the following biochemical parameters: leukocytes, urobilinogen, bilirubin, blood, nitrite, pH, specific gravity, protein, glucose and ketones. Urine specimens were centrifuged at 1500 rpm for 2 minutes, and the deposits examined microscopically (Olympus CX21FS1; Olympus Corporation, Tokyo, Japan. Made in Philippines) for pus cells, epithelial cells, red blood cells, crystals, casts and other sediments.

2.5 Statistical Analysis

Data obtained were entered in Microsoft excel and analyzed with GraphPad Prism® 6 for Windows, version 6.01 (GraphPad Software Inc.). Means, frequencies, standard deviations (SD) and percentages were estimated. Multivariate logistic regression was used to identify the determinants of urine abnormalities. A p value of ≤ 0.05 was considered statistically significant.

3. RESULTS

Table 1 shows socio-demographic characteristics and creatinine levels of study participants stratified by gender. The ages of the male and female participants were similar. Majority of the participants were married (54.0%), had completed primary education (44.0%), and worked in the informal sector (80.0%). Median creatinine levels were significantly higher among males than in female counterparts (*P*=0.010).

As shown in Fig. 1 the overall prevalence of CKD was 9.0% (5% stage 3A; 1.0% Stage 3B; 2.0% Stage 4 and 1.0% stage 5).

Table 2 shows dipstick urinalysis (biochemistry) among participants with and without CKD. Eighteen percent (18%), 15%, 15% of the participants had proteinuria, leukocyturia and haematuria respectively. Proteinuria (44.4% vs 15.4%), haematuria (22.2% vs13.3%), increased urobilinogenuria (11.1% vs 2.2%) were more common in participants with CKD than those without CKD. Urine pH and specific gravity were higher in participants with CKD. However, leukocytouria (14.3% vs 11.1%), nitrituria (3.3%

vs 0.0%) were more prevalent in participants without CKD.

Table 3 shows urine deposits among participants with or without CKD. Pyuria (15% vs 5%), RBC (15% vs 2%), triple phosphate (11.1% vs 0%) and granular casts (33.3% vs 11.0%) were more prevalent in participants with CKD than in those without CKD. However, participants without CKD had more epithelial cells (6% vs 3%), calcium oxalate (7.7% vs 0.0%), hyaline (1.1% vs 0.0%) and yeast like cells (3.3% vs 0.0%).

Table 4 shows logistic regression of socio-demographic, clinical and biochemical characteristics of study participants. None of the factors associated with CKD were significant in our population.

Table 1. Socio-demographic characteristics and creatinine levels of study participants

Variables	Total (N=100)	Male (N=15)	Females (N=85)	p-value
Age (Mean ± SD)	39.45 ± 1.07	41.87 ± 2.30	39.02 ± 1 .196	0.3472
Marital status				0.0275
Single	14(14.0)	2(13.3)	12(14.1)	
Married	54(54.0)	13(86.7)	41(48.2)	
Divorced	18(18.0)	0	18(21.2)	
Widowed	14(14.0)	0	14(16.5)	
Education				0.0608
No education	11(11.0)	0	11(12.9)	
Primary	44(44.0)	8(53.3)	36(42.4)	
JHS	36(36.0)	4(26.7)	32(37.6)	
SHS	8(8.0)	2(13.3)	6(7.1)	
Tertiary	1(1.0)	1(6.7)	0	
Occupation				0.3867
Former	13(13.0)	3(20.0)	10(11.8)	
Informal	80(80.0)	12(80.0)	68(80.0)	
Unemployed	7(7.0)	0	7(8.2)	
Cr (umol/L)	91.67 (73.3-110)	86.70 (76.10-98.24)	72.57 (60.19-84.80)	0.0103

Cr = Creatinine

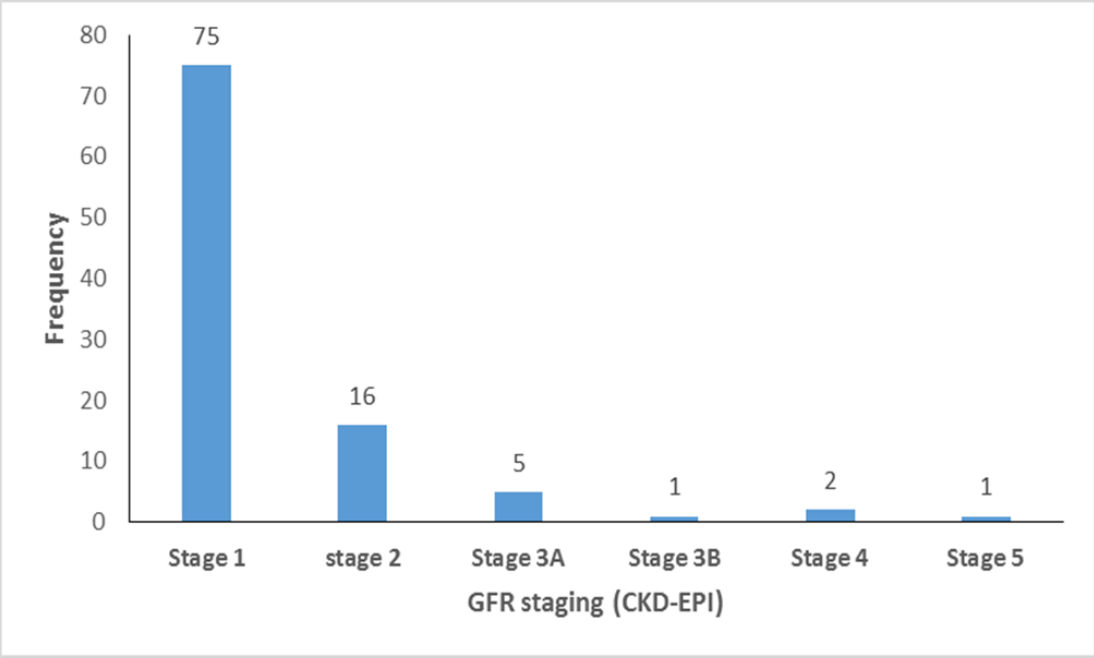

Fig. 1. GFR staging and prevalence of CKD among participants

Table 2. Dipstick urinalysis among participants with and without CKD

Variables	Total (N=100)	CKD (n=9)	No CKD (N=91)
Protein			
Neg	74 (74.0)	4(44.4)	70(76.9)
Trace	8(8.0)	1(11.1)	7(7.7)
1+	15(15.0)	4(44.4)	11(12.1)
2+	2(2.0)	0	2(2.2)
3+	1(1.0)	0	1(1.1)
Leucocyte			
Neg	86(86.0)	8(88.9)	78(85.7)
Trace	1(1.0)	0	1(1.1)
1+	7(7.0)	0	7(7.7)
2+	5(5.0)	0	5(5.5)
3+	1(1.0)	1(11.1)	0
Blood			
Neg	85(85.0)	7(77.8)	78(85.7)
Trace	4(4.0)	0	4(4.4)
1+	3(3.0)	1(11.1)	2(2.2)
2+	3(3.0)	0	3(3.3)
3+	2(2.0)	0	2(2.2)
4+	3(3.0)	1(11.1)	2(2.2)
Glucose			
Neg	100(100.0)	9(100.0)	91(100.0)
Nitrite			
Present	3(3.0)	0	3(3.3)
Absent	97(97.0)	9(100.0)	88(96.7)
Bilirubin			
Neg	100(100.0)	9(100.0)	91(100.0)
Urobilinogen			
Increase	3(3.0)	1(11.1)	2(2.2)
Normal	97(97.0)	8(88.9)	89(97.8)
Ketones			
Neg	99(99.0)	9(100.0)	90(98.9)
Trace	0	0	0
1+	1(1.0)	0	1(1.1)
PH	6.11 ± 0.20	6.00 ± 0.32	6.21 ± 0.08
Specific gravity	1.018 ± 0.00	1.019 ± 0.00	1.017 ± 0.00

Table 3. Urine microscopy among participants with and without CKD

Variables	Total (N=100)	CKD (n=9)	No CKD (N=91)
Epithelial cells	6	3	6
Pus cells	6	15	5
RBCs	2	5	2
Crystal			
Calcium oxalate	7 (7.0)	0 (0.0)	7 (7.7))
Triple phosphate	1 (1.0)	1 (11.1)	0 (0.0)
Cast			
Granular	13 (13.0)	3 (33.3)	10 (11.0)
Hyaline	1 (1.0)	0 (0.0)	1 (1.1)
Others			
Yeast-like cells	3 (3.0)	0 (0.0)	3 (3.3)

Table 4. Logistic regression of factors associated with CKD among HAART naïve patients

Variable	OR (95% CI)	P-value
Age (Mean ± SD)	1.04 (0.98-1.11)	0.192
Gender		
Male*	1	
Female	1.46 (0.17-12.56)	0.733
Marital status		
Single	1.00 (0.06-17.75)	1
Married	1.04 (0.11-10.11)	0.973
Divorced	2.60 (0.24-28.15)	0.432
Widowed*	1	
Education		
No education*	1	
Primary	1.58 (0.17-14.66)	0.688
JHS	0.29 (0.02-4.99)	0.391
SHS	1.43 (0.08-26.90)	0.812
Tertiary	-	-
Occupation		
Formal	0.12 (0.01-0.98)	0.862
Informal	0.56 (0.04-3.41)	0.453
Unemployed*	1	
BMI, Kg/m2	0.82 (0.66-1.00)	0.052
Blood pressure		
Normal*	1	
Hypertensive	1.50 (0.16-13.77)	0.720

4. DISCUSSION

This multi-center non-randomized cross-sectional study sought to determine the prevalence of CKD and to identify urine abnormalities in HAART-naive HIV/AIDS patients. Our findings showed a 9% prevalence of CKD among the participants with proteinuria, haematuria, pyuria and crystalluria being the most significant urine abnormalities present. The reported prevalence of CKD in this study is in consonance with the 7.1% reported in Nigeria by Adedeji et al. [13] and the 9.9% recorded in a study in the Eastern region of Ghana by Obirikorang et al. [11]. Adedeji et al. and Obirikorang et al. however used the 4v MDRD equation in contrast to the CKD-EPI equation employed in this study. Our findings are higher than observations made in studies conducted in Cameroon and Kumasi, Ghana which reported 3.0% and 3.7% prevalence respectively when the CKD-EPI equation was used [4,11]. However, our finding is comparatively lower than studies by Wools-Kaloustian et al. [14] in Western Kenyaand Struik et al. [6] in Malawi, where prevalences of 11.5% and 18.8% were reported. Both studies used the Cockroft Gault equation in estimating GFR hence the observed prevalence. In a recent study in Northern Uganda, a prevalence of 14.4% was recorded using the same definition for CKD, and the CKD-EPI equation [10]; this was however comparatively higher than that obtained in this study. Furthuremore, a much higher percentage (24.5%) was recorded in a study conducted by Msango et al. [2] (Tanzania) where both Cockroft Gault and 4v-MDRD equations were used. In general, this current report agrees with an estimated prevalence of 6% to 48.5% in Sub-Saharan Africa as stated by FolefackKaze et al. [4].

In line with the findings of Struik et al. [6] in Malawi, we recorded dipstick proteinuria of 18% as the leading urine abnormality among the participants. However, dipstick proteinuria of 36% was recorded in similar studies by both FolefackKaze et al. [4] and Msango et al. [2]. On the contrary, Wools-Kaloustian et al. [14] in a study in Western Kenya, recorded proteinuria of 6.2% which is lower than that reported by most previous studies in Africa. Furthermore, the present study recorded 13% and 11% pyuria and haematuria respectively similar to the13% and 12% reported in Cameroon [4].

Urine microscopy further supported the renal insufficiency reported in our participants. The finding of epithelial cells was not significant in CKD participants as compared to those without CKD. CKD presents with significant epithelial

cells mostly of the tubular epithelial origin on urine microscopy. However, the study did not look at the types of epithelial cells. The epithelial cells detected in our participants on microscopy may be associated with HIV-associated nephropathy (HIVAN) but the low cases may be correlated with the viral load. More so, the epithelial cells that were recorded in the HAART naïve participants without CKD may be because of the yeast-like cells detected on microscopy. Similarly, the pus cells observed in participants with CKD may be linked with the HIVAN or some pathogenic bacterial infection which could not be detected with urine microscopy. However, the cases in the HAART-naïve participants without CKD can be linked in part with the yeast-like cells which elicits immune response, thus the pus cells seen on microscopy. Our observation of RBC in the urine of participants is in line with the work of Chen et al. [15] who intimated that microscopic RBC may be present in the urine of HIV/AIDS patients. However, microscopic RBC in HAART-naïve participants without CKD could be attributed to vascular injury due to yeast invasion of tissues and subsequent entry of blood circulation. Furthermore, the red blood cells present on microscopy may also be due to physiological stress on the glomerulus [16]. The findings of the urine epithelial, pus and red blood cell microscopy and urine protein is in consonance with the presence of urinary casts; most especially the granular cells, and this correlates with the cells identified on microscopy. Few hyaline casts seen on microscopy are associated with physiological stress, however significant levels detected depicts renal associated pathologies.

The presence of calcium oxalate in freshly voided urine is a useful predictor of renal calculi. Participants without CKD recorded more calcium oxalate crystals than those with CKD. Thus, this finding may have accounted for the number of red blood cells cases that were found notwithstanding the possible physiological and biological cause of haematuria. Also, the presence of calcium oxalate crystals could have been influenced by oxalate-rich diets. However, triple phosphate is a normal crystal found in alkaline urine, hence its presence and moreover the number of cases recorded. Nonetheless, if a relatively higher number of cases were recorded they would not have been of any clinical significance. The presence of the yeast-like cells depicts genitourinary infection. Severe yeast infections present with hyphal cells; hence the yeast-like cells portray a less severe infection. Contrary to the findings of Obirikorang et al. [11] we identified no significant determinants of CKD among our participants. This we can attribute to the small sample size and the multicenter nature of our study.

Our study however come with a few limitations. First, this study used a cross-sectional design with a single measurement of serum creatinine. Second, urine chemistry parameters were measured with dipstick. Third, though the study identified significant abnormalities on dipstick, there was no follow-up bacteriological testing. Fourth, the absence of $CD4^+$ count meant we were unable to correlate renal function with HIV viral burden.

5. CONCLUSION

This study revealed a high prevalence of renal insufficiency (CKD) and urine abnormalities like proteinuria, haematuria, pyuria and crystalluria. These derangements could have resulted into reduced eGFR in participants with HIV infection naive to antiretroviral therapies. Routine urinalysis and screening for CKD in HIV/AIDS patients should be strengthened as it will help in early detection of renal abnormalities.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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