Original Article

The Prevalence of Kidney Dysfunction and Associated Risk Factors among ART-Naïve HIV-1 infected Adults at the University Teaching Hospital in Lusaka, Zambia

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ABSTRACT

Background: Chronic HIV infection is associated with renal complications including renal dysfunction. Risk factors found in literature for kidney disease in the HIV population include hypertension, Diabetes mellitus, cardiovascular disease, low CD4 count, high viral load, hepatitis C virus co-infection, hypoalbuminemia, a family history of CKD, black race, and nephrotoxic drugs. The 2016 Zambian Consolidated guidelines for the prevention and treatment of HIV recommends use of a kidney disease screening algorithm to guide choice of a cART regimen in the absence of serum creatinine.

Despite using the Kidney disease screening algorithm, the risk factors listed in this algorithm have not been validated in our HIV-infected population. Therefore, this study aimed to determine the prevalence of renal dysfunction and validate the risk factors listed in the kidney disease screening algorithm in the ART naïve HIV-infected adults.

General objective: To determine the prevalence of renal dysfunction and associated risk factors in ART naïve HIV infected adults at the University Teaching Hospital, Lusaka.

Methods: This was a cross sectional analytical study with 360 participantsenrolled. A structured questionnaire was used to collect data. Blood and urine samples were collected for creatinine, CD4 count, HIV-1 viral load, serum albumin, hepatitis B surface antigen, Hepatitis C antibody, Random blood sugar, and urinalysis.Data was entered onto a Microsoft office excel spread sheet, and analyzed using STATA version 13.We investigated the association between the dependent variable and each independent variable.

Results: The prevalence of renal dysfunction was 24.76%. The overall mean age for the sample population was 36.62 years comprising more females (54.63%) than males. Hypertension OR=2.63, (95% CI 1.11, 6.12) was the only factor found to be predictive of renal dysfunction.

Conclusion: We recommend routine screening for hypertension in HIV cART naïve individuals and those found to be hypertensive should be further investigated for renal dysfunction prior to initiation of cART.

1.0 INTRODUCTION

The burden of the HIV epidemic varies considerably among countries and regions, with Sub-Saharan Africa being the most severely affected region globally. The region has nearly 1 in every 20 adults living with HIV and accounts for nearly 71% of the people living with HIV worldwide.[1]

Chronic HIV infection is associated with numerous renal complications. The prevalence of renal dysfunction among HIV infected individuals varies

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from six to 48.5% in different population.[2] Mulenga et al. found that the prevalence of renal dysfunction was 33.5% among HIV-infected adults initiating first line cART in Lusaka Urban District Clinics Out Patient Departments in 2008.[3] In 2010, an In-patient study by Banda et al. at the University Teaching Hospital in Lusaka, Zambia, showed 42% and 27% renal dysfunction among the HIV-infected and HIV-uninfected adult patients respectively.[4]

Renal dysfunction in HIV can be attributed to HIV-related and non-HIV-related factors.[5] The etiology of renal disease in HIV-infected patients isvast.[5] Naicker et al. in a review article found that black race, CD4 count < 200 cells/mm^3, HIV RNA levels > 4,000 copies/ml, family history of kidney disease, presence of diabetes mellitus, hypertension and hepatitis C co-infection were associated with a high risk of developing chronic kidney disease in HIV-infected individuals.[2] The Veterans' study evaluated 22,156 HIV-infected veterans without pre-existing End Stage Renal Disease (ESRD) between 1996 and 2004 and found 366 incident cases of ESRD. Factors associated independently with ESRD risk were Hypertension, Diabetes Mellitus, Cardiovascular disease, CD4 lymphocyte count <200 cells/mm^3, HIV viral load ⩾ 30,000 copies/mL, Hepatitis C virus co-infection, and Hypoalbuminemia <3.5mg/dL.[6]

Hypertension and Diabetes mellitus are the most common causes of CKD worldwide both in the general population and in HIV infected individuals.[8] Robert N Peck et al. in Tanzania found that HIV-infected adults on ART >2 years had two-fold greater odds of hypertension than HIV-negative controls.[9] HIV-infected adults with hypertension were rarely aware of their diagnosis but often had evidence of kidney disease.[9]

The 2014 Zambia Consolidated HIV treatment guidelines for HIV infected adolescents and adults utilizes a kidney disease screening algorithm to screen for risk factors for renal dysfunction in individuals initiating first line cART.[7] These include hypertension, hypotension, black race, Diabetes mellitus, Body Mass Index (BMI) <18.5kg/m^2, persistent hematuria, persistent proteinuria, chronic diarrhea, chronic NSAID use and acutely ill patients or recent hospitalization.[7]The recommended first line cART regimen has a backbone of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs), and a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). The preferred first line cART is a composition of Tenofovir Disoproxil Fumarate (TDF) and Lamivudine (3TC) as NRTIs and Efavirenz (EFV) as an NNRTI. TDF is contraindicated in the presence of moderate to severe renal dysfunction (eGFR< 50mls/min/1.73m^2) and Abacavir (ABC),an alternative NRTI is recommended.[7]

The Kidney disease screening algorithm is meant to aid in the choice of initiating cART with either TDF or ABC-based regimens in the absence of serum creatinine. Presence of any of the risk factors listed in the algorithm in a patient is a contraindication to initiation of a TDF-based regimen without serum creatinine or estimated glomerular filtration rate.[7]

Despite using the Kidney disease screening algorithm, the risk factors listed in this algorithm have not been validated in our HIV-infected population. Therefore, this study aimed to determine the prevalence of renal dysfunction and validate the risk factors listed in the kidney disease screening algorithm in the ART naïve HIV-infected adults.

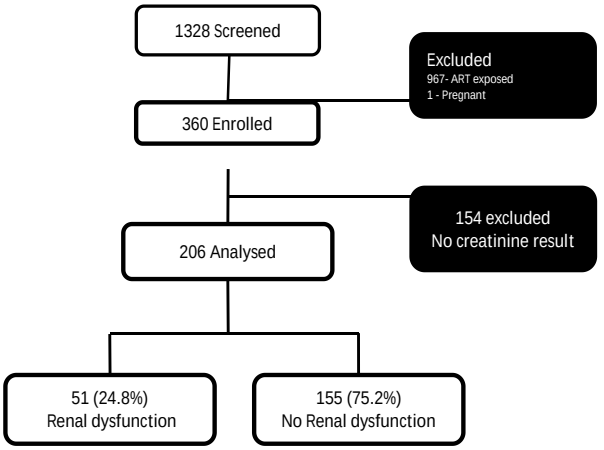
2.0 METHODS

This was a cross sectional analytical study conducted at the University Teaching Hospital in Lusaka, Zambia. We enrolled 360 ART naïve HIV-1 infected individuals aged16years between 30th November 2015 and 30th April, 2016 who presented to UTH out-patient and in-patients points of care including the Adult Infectious Disease Center (AIDC), the Adult Medical Emergency Unit (AMEU), and the all medical wards. Participants were enrolled if they were HIV infected with/without renal dysfunction.

We used published clinical guidelines from the National Kidney Foundation's Kidney Disease

Outcome Quality Initiative (K/DOQI) to categorize renal insufficiency[10] using the Cockcroft Gault formula and eGFR90 ml/min/1.73m^2 was considered normal. Renal dysfunction was further divided into; mild renal dysfunction (60-89mls/min/1.73m^2), moderate renal dysfunction (15-29mls/min/1.73m^2), and severe renal dysfunction (eGFR<15mls/min/1.73m^2).

Figure 1: Study Algorithm



Peripheral venous blood samples were collected for full blood count, creatinine, CD4 T- cell count, Viral Load, Hepatitis C antibody, Hepatitis B Surface Antigen, serum albumin, Rapid Plasma Reagin (RPR). Blood was tested for anti-HIV antibodies using two sequential rapid tests; Alere Determine™ and Unigold™. Serum Creatinines were processed using the Beck Man Coulter AU480™ with Beck Man Coulter AU480 reagents™. CD4 T-cell counts were performed using flow cytometry using a Becton Dickinson Facs Count machine with BD Facs Count Reagent™. Hematology panel was processed with Sysmex 2000 and micros-60 machines.

Pin prick was used to test for random blood sugar using a portable point of care glucometer.

About 5 mls of urine was collected in sterile urine containers for an on the spot urine analysis of Protein and Hematuria.

The respondents Blood Pressure were measured in the sitting position using a sphygmanometer while Weight and Height were measured with a weighing scale and astadiometer scale in the upright position respectively.

Data was analyzed using Stata version 13. Descriptive statistics were used to show the baseline characteristics. We used a chi-square test and/or fishers exact where necessary to determine the association between the dependent and independent variables. In the bivariate logistic regression, a P-value of 0.2 was used to determine possible predictors or factors associated with kidney dysfunction in ART naïve HIV infected individuals. Multivariate logistic regression was used to determine predictors of kidney dysfunction with P-Value set at 0.05.

***Ethical considerations**:* The study was approved by the Ethics Committee of ERES Converge approval number **2015-Feb-010**. Written informed consent was obtained from all study participants.

3.0 RESULTS

From 30th November 2015 to 30th April, 2016, 360 treatment naive participants were enrolled into the study. Baseline serum creatinine was documented in 206 (57.2%)of these individuals as shown in figure 1. 154 (42.8%) participants did not have a creatinine result recorded and were thus excluded from the analysis. Of those analyzed, 51(24.8%) had kidney dysfunction and 22 (43%) of these had moderate to severe renal dysfunction (Table 1). The mean age of all participants was 36.6 years with more female respondents (54.6%) than males. The mean age of the respondents with renal dysfunction was 37.7years (SD=10.9) while those with normal kidney function was 35.9years (SD=11.41). The overall proportions of individuals with Diabetes and hypertension were two (1%) and 31 (15.5%) respectively. These baseline characteristics are illustrated in table 1.

Table 1: Baseline characteristics

Characteristic	No Kidney Disease **n (%)** 155 (75.2)	Kidney Disease **n (%)** 51 (24.8)	*P* Value
Mean Age (SD)	37.7(10.9)	35.9(11.41)	0.413
Gender			0.309
Male	73 (47.4)	20 (39.2)	
Female	81 (52.6)	31 (60.8)	
Hypertension			0.018**
No	132 (88.0)	37 (74.0)	
Yes	18 (12.0)	13 (26.0)	
Body Mass Index (BMI)			0.124*
Under weight	32 (23.4)	9 (19.2)	
Normal weight	79 (57.7)	22 (46.8)	
Over weight	20 (14.6)	10 (21.3)	
Obese	6 (4.4)	6 (12.8)	
Proteinuria			0.167*
<2+	128 (83.7)	47 (92.2)	
>2+	25 (16.3)	4 (7.8)	
Hematuria			0.710
<2+	146 (95.4)	47 (94.0)	
≥2+	7 (4.6)	3 (6.0)	
CD4 Count			0.749
< 200 cells/?L	35 (38.0)	14 (41.2)	
≥ 200 cells/?L	57 (62.0)	20 (58.8)	
Viral Load			0.538
< 30,000 copies/?L	86 (76.8)	31 (81.6)	
≥ 30,000 copies/?L	26 (23.2)	7 (18.4)	
Hypoalbuminemia (g/L)			0.310
<35	38 (45.8)	9 (60.0)	
>35	45 (54.2)	6 (40.0)	
Syphilis			0.118*
Negative	47 (78.3)	17 (94.4)	
Positive	13 (21.7)	1 (5.6)	
Diarrhea > 1 Month			0.117*
No	27 (17.5)	4 (8.0)	
Yes	127 (82.5)	46 (92.0)	
Current Diarrhea			0.048**
No	18 (12.1)	1 (2.1)	
Yes	131 (87.9)	46 (97.9)	
Diabetes			0.406
No	154 (99.4)	50 (98.0)	
Yes	1 (0.6)	1 (2.0)	
Hepatitis B			0.061*
No	64 (85.3)	26 (100.0)	
Yes	11 (14.7)	0 (00.0)	
Herbal Medication			0.366
No	86 (57.3)	25 (50.0)	
Yes	64 (42.7)	25 (50.0)	
NSAID Use			0.642
No	12 (7.7)	5 (9.8)	
Yes	143 (92.3)	46 (90.2)	
Renal dysfunction Severity			<0.001
Severe	0 (0.00)	4 (7.84)	
Moderate	0 (0.00)	18 (35.29)	
Mild	(0.00)	29 (56.86)	
Normal	155 (100)	0 (0.00)	

Note: Pearson's chi-square test was used to obtain p values. For frequencies less than 5, fishers exact was used.
*p<0.2, **p<0.05
Renal severity: mild (60-89mls/min/1.73m^2), moderate (15-29mls/min/1.73m^2), severe (eGFR<15mls/min/1.73m^2), normal (>90mls/min/1.73m^2)

Table 2: Baseline laboratory characteristics

Characteristic	Mean [Median]
Serum Albumin (g/L), Mean (SD)	33.8 (7.9)
Hemoglobin (g/dL), Median [IQR]	10.5 [8.5 – 12.4]
Creatinine (?mol/L), Mean (SD)	93.9 (120.1)
eGFR (Kgs/m^2), Mean(SD)	137.5 (70.4)
Random Blood Sugar (mmol/L), Mean (SD)	5.1 (1.1)
Viral Load (copies/ml), Median [IQR]	176,827 [39,059 – 581,148]
CD4 count (cells/?L), Median [IQR]	134 [79 – 270]

The univariate analysis showed that, hypertension (p-value = 0.018), BMI (p-value = 0.124), proteinuria (p-value = 0.167), syphilis (p-value = 0.118), chronic diarrhea (p-value = 0.117) and current diarrhea (p-value = 0.048) were significantly associated with increased risk of renal dysfunction. We considered these variables as a priority in the multivariate analysis. The p value for the bivariate analysis was set at 0.200.

Table 3: Univariate Logistic Regression

Characteristic	Odds Ratio (OR)	*P* Value	95% CI
Gender			
Male	Ref		
Female	1.397	0.310	0.733 – 2.663
Body Mass Index (Kg/m^2)	Ref		
Under weight	0.990	0.982	0.412 – 2.381
Normal weight	1.778	0.287	0.616 – 5.130
Over weight	3.556	0.066	0.920 – 13.74
Obese			
Proteinuria			
< 2+	Ref		
≥ 2+	0.436	0.141	0.144 – 1.318
Hypertension			
No	Ref		
Yes	2.577	0.021	1.156– 5.741
Syphilis			
No	Ref		
Yes	0.213	0.150	0.026 – 1.751
Diarrhea > 1 Month			
No	Ref		
Yes	2.445	0.112	0.811 – 7.366
Current Diarrhea			
No	Ref		
Yes	6.321	0.077	0.821 – 48.68

P<0.2 was taken as statistically significant

The multivariate analysis showed that only Hypertension OR=2.63, (95% CI 1.11 – 6.12; p=0.027) was predictive of renal dysfunction. All the factors considered from the renal disease screening algorithm were not predictive of renal dysfunction.

Table 4: Multivariate Logistic Regression

Characteristic	Odds Ratio (OR)	*P* Value	95% CI
Hypertension			
No	Ref		
Yes	2.630	0.027	1.115 – 6.199

4.0 DISCUSSION

In this study, we found a high prevalence of renal dysfunction among HIV-infected cART naïve individuals. A prevalence of 24.67% is still considered high even when it is lower than previously reported by Mulenga et al. (33.5%) and Banda et al. (42%) in 2008 and 2010 respectively.[3, 4]This prevalence is also lower than other studies outside Zambia.[12, 13] Among Nigerians, Agaba et al. and Emem et al. documented a prevalence of 51.8% and 38% respectively.[12,13]In Tanzania, Janabi et al.found the prevalence to be 28% among Tanzanians.[14]Fernando et al found a prevalence of 24%, a similar finding to ours, among HIV infected Americans.[11]it is Important to note that these studies had methodological differences with our study which may explain the differences in prevalence rates. There were differences in study designs and definitions of CKD between these studies and our study. The finding of a high proportion of renal dysfunction among cART naïve HIV-infected individuals is still worrying because renal dysfunction at all stages of disease was associated with an increased risk of early mortality when compared with HIV-infected individuals with normal kidney function in a Zambian study by Mulenga et al.[3]Even more important is the impact of severity of renal dysfunction on mortality: Moderate to severe renal dysfunction was associated with a higher mortality compared to mild renal dysfunction in the same study.[3] In our study, 43% of participants with renal dysfunction had moderate to severe renal

dysfunction. Therefore, routine screening and monitoring with serum creatinine for all at risk patients should be adhered to.

There was a reduction in prevalence of renal dysfunction in HIV infected individuals from 33.5% (Mulenga et al) in 2008 and 42% (Banda et al) in 2010 to 24.67% in 2016.[3,4] Whereas Mulenga et al. andBanda et al. were an outpatient and inpatient studies respectively;[3, 4] our study included participants drawn from both in-patient and out-patient points of care, which may explain the lower prevalence rate in our study. The other explanation could be the change in the treatment guidelines. Banda et al and Mulenga et el studies were conducted when the CD4 thresholds for initiating cART was much lower at< 350 cells/L and 200 cells/L respectively; our study was conducted when the CD4 threshold was <500copies/l.

Several studies have shown that CD4 nadir <200 cells/L is significantly associated with renal dysfunction.[2,6,14,15,17]. However, in our study, the level of CD4 count was not associated with renal dysfunction. This confirms the findings by both Mulenga et al. and Banda et al. that low CD4 count was not associated with renal dysfunction in our settings.[3,4]

Diabetes Mellitus, a known risk factor for renal dysfunction in the general population and HIV individuals was not associated with renal dysfunction in our study.[2,6,8,17]This result is consistent with the findings by Banda et al. Other risk factors like viral Load, Hepatitis C viral infection, proteinuria and hematuria have all been associated with renal dysfunction in other studies[2,6,15,19,21]but were not associated with renal dysfunction in our study. The only reasonable explanation for the negative results for all risk factors but one could be attributed to a small simple size for our study which was underpowered for these risk factors.

The prevalence of Hepatitis C virus in Zambia is as low as 1.2% in Lusaka.[20]It is therefore not surprising that no patient had Hepatitis C virus infection in our study. Similarly, Hepatitis B virus infection was not a risk for renal dysfunction. 26 participants had co-infection with hepatitis B and none of them had renal dysfunction.

Hypertension was the only independent predictor of renal dysfunction in our study. Other studies including Banda et al. have all shown that hypertension is an important risk for renal dysfunction in HIV infected individuals and the general population.[2,6,22] Therefore, It seems reasonable to recommend that all HIV infected individuals with hypertension would require serum creatinine measurement before initiating a TDF based regimen.

Study Limitations

The study had missing data especially laboratory variables like syphilis (67%),CD4 count (39%), viral load (27%), creatinine (42.8%) and albumin (52%). The missing data impacted negatively on the power of the study making it difficult to make conclusions on the factors which were found not increase the risk of renal dysfunction. The sample size was based on the prevalence formula and underpowered for the risks listed in the renal disease screening algorithm.

Diabetes mellitus was diagnosed by patient reporting (whether they were diabetic or not) or by performing a once off random blood sugar. We did not perform Fasting Blood Sugar or HbA1c. This may have compromised the proportional of participants with Diabetes mellitus.

In this study, we could not differentiate between acute kidney injury and chronic kidney disease. This was because we had no prior or baseline assessment of renal function in the participants. We also did not perform renal ultrasound scans due to cost limitations. In addition, most participants were unaware if they previously had been diagnosed of CKD or not.

We recommend routine screening for hypertension in HIV cART naïve individuals and those found to be

hypertensive should be further investigated for renal dysfunction prior to initiation of cART. We cannot make conclusions on the other risk factors mentioned in the renal disease screening algorithm due to study limitations.

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REFERENCES

1. Global Health Observatory Data. October, 2015. HIV/AIDS [Repository Data] Retrieved from http://www.who.int/gho/hiv/en/.
2. NaickerS, Fabian J. ClinNephrol. Risk factors for the development of chronic kidney disease in HIV/AIDS. 2010: 74 Suppl 1:S51-6. Review.
3. Mulenga LB, LakhiS, Zulu I,et al, Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia, *AIDS*. 2008; 22: 1821–1827. doi:10.1097/QAD.0b013e328307a051.
4. Banda J, Mweemba A, Lakhi Set al, Prevalence and Factors associated with Renal Dysfunction in HIV Positive and Negative Adults at the University Teaching Hospital, in Lusaka. Med J Zambia;2010:4-6.
5. Kalyesubula R, Perazella MA, Nephrotoxicity of HAART. AIDS Res Treat. 2011;562790. DOI: 10.1155/2011/562790. Epub 2011; 2.
6. Jotwani V, Yongmei L, Michael GS et al, Risk Factors for ESRD in HIV-Infected Individuals: Traditional and HIV-Related Factors. American Journal of Kidney Diseases 59, 628–635, May 2012.
7. Zambian Ministry of Health, Zambia 2013 Consolidated Guidelines for Treatment and Prevention of HIV infection, 2014; 67.
8. Moosa M R, Walt I, Naicker S, et al, Important causes of chronic kidney disease in South Africa, SAMJ, April 2015, Vol. 105, No. 4.
9. Peck RN, Shedafa R, Suthanthiran M, et al, Hypertension, kidney disease, HIV and antiretroviral therapy among Tanzanian adults: a cross-sectional study, BMC Medicine201412:125 DOI: 10.1186/s12916-014-0125-2
10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron.
11. Fernando SK, Finkelstein FO, Weissman S et al, Prevalence of chronic kidney disease in an urban HIV infected population. Am J Med Sci 2008;335:89-94. DOI:http://dx.doi.org/10.1097/MAJ.0b013e31812e6b34.
12. Agaba EI, Agaba PA, Idoko JA et al, Renal disease in the acquired immunodeficiency syndrome in north central Nigeria. Niger J Med 2003;12:120-5.
13. Emem CP, Arogundade F,Akinsola A et al, Renal disease in HIV-seropositive patients in Nigeria: an assessment of prevalence, clinical features and risk factors, Nephrol Dial Transplant 2008: 741–746 DOI: 10.1093/ndt/gfm836.
14. Janabi MY, Chale S, Magao P, Renal abnormalities associated with human immunodeficiency virus infection among police officers in Dar-es-Salaam, Tanzania. XIV International AIDS Conference; 2002, 7-12.
15. Wyatt CM, Winston JA, MalvestuttoCD et al, Chronic kidney disease in HIV infection: an urban epidemic, AIDS 2007:2101–2110.
16. Reid A, Stohr W, Kambugu, Aet al, Severe Renal Dysfunction and Risk Factors Associated with Renal Impairment in HIV-Infected Adults in Africa Initiating Antiretroviral Therapy, HIV/AIDS CID 2008:1271.
17. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J Clin Invest 1950;29:496–507.
18. Barkris GL et al, overview of diabetic nephropathy, uptodate, 2012.
19. Crum-Cianflone N, GanesanA,Barahona I, et al, Prevalence and Factors Associated with Renal

Dysfunction Among HIV-Infected Patients, AIDS PATIENT CARE and STDs, 2010, 24, DOI: 10.1089/apc.2009.0326

20. Kapembwa KC, Goldman JS,Vermund SH et al, HIV, Hepatitis B and Hepatitis C in Zambia, J Glob Infect Dis. 2011 Jul-Sep; 3(3): 269–274. DOI: 10.4103/0974-777X.83534.
21. Ayokunle DS,Olusegun OT,Olaitan RM et al,Prevalence of Chronic Kidney Disease in newly diagnosed patients with Human immunodeficiency virus in Ilorin, Nigeria, DOI: 10.5935/0101-2800.20150029.
22. Whaley-Connell AT, Sowers JR, Stevens LA, CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 2008; 51:S13.