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Characteristics and Associations of Renal Dysfunction at Presentation in Haart-Naïve HIV-Infected Subjects in Port Harcourt, Nigeria

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ABSTRACT
Renal impairment is a major concern for HIV-infected individuals. It affects the way of life of the patients and could lead to a poor prognosis during the course of treatment. A retrospective study of 375 newly-diagnosed HAART naïve HIV-infected individuals from April 2014 to April 2015 was carried out. Information collected from the patients' hospital folders include: Data and reports of biochemical and hematological investigations. Estimated glomerular filtration rate was calculated using the MDRD equation. Patients were grouped according to the WHO clinical stage of HIV disease and the KDIGO CKD stages. The Kruksall-Wallis's and Dunn's posts test was used to compare the difference between the PCV and CD4 cell counts of the different groups. Chi-square analysis of the proportions of subjects according to WHO clinical stage of HIV disease at presentation and CKD Stages was also performed. Renal failure (eGFR< 60mL/min) was highly prevalent (13.7%) in the study subjects with a high proportion (90.1%, n=46/51) observed in individuals at Stage 3 and Stage 4 of HIV-disease. A decline in the average packed cell volume (PCV) from CKD stage 1 through 5 and HIV clinical stages1 to 4 was observed, however it was not significant ($p < 0.05$). Hyperfiltration was observed in 2.9% (11/375) of the study subjects, with a majority (81.8%, 9/11) at HIV clinical stages 3 and 4. The study showed that renal dysfunction is prevalent in HAART naïve HIV-infected individuals at initial diagnosis. Individuals with a CD4 cell count <300cells/mm^3 are at a higher risk for renal dysfunction. Thorough evaluation and identification of at risk individuals is imperative.
Key words: *Renal Dysfunction, HIV, CKD, CD4, PCV*

INTRODUCTION

HIV infection is a complex hypercatabolic disease, often associated with comorbidities. The earliest reports of kidney disease in HIV infection were published in the 1980s; retrospectively, these subsequently became recognized as HIV-

associated nephropathy, HIVAN [1]. The clinical features of HIVAN were distinctive, with heavy proteinuria and rapid progression to end-stage kidney disease [2, 3].

HIVAN in the pre-HAART era was so frequent/prevalent, especially among Black subjects, it overshadowed all other types of HIV-associated chronic kidney disease, that it almost became synonymous with it [1]. Following the advent and widespread administration of HAART in the mid-1990s, however, the prevalence and spectrum of kidney disease began to change [1, 4].

By the turn of the millennium, the clinical course of kidney disease in HIV infection was reportedly more indolent, the risk of developing end-stage disease had reduced by about 40% to 60%, 1-year survival rate on dialysis therapy had improved from about 25% to 75%, and kidney transplantation had become a viable option [1, 5]. Despite these changes, risk factors for kidney disease among HIV-infected persons have remained prevalent, and kidney disease has persisted as an important cause of ill-health and death even among those on HAART [2].

Hence, as persons infected with HIV live longer while receiving HAART, kidney disease has emerged as a significant cause of morbidity and mortality. Kidney disease should be diagnosed in its earliest stages through thorough screening and evaluation of suspected subjects at the earliest contact with the healthcare system following diagnosis of HIV infection. This is necessary as strategies for early detection and intervention of kidney disease potentially hold promise for profound improvements in clinical outcomes, including meaningful reductions in morbidity and mortality.

METHODOLOGY

Study population

A retrospective study of 375 newly-diagnosed HIV-infected adults at the University of Port Harcourt Teaching Hospital, Port Harcourt from April 2014 to June 2015 was carried out. All 375 newly-diagnosed HIV-infected subjects subsequently commenced anti-retroviral treatment at the hospital. Ethical approval was obtained from the Ethic Board of the Hospital.

Data Collection

Information collected from the patients' hospital folders included demographic data and reports of biochemical and hematological investigations. The subjects were separated into different groups of clinical stages of HIV disease as described by WHO (6). Estimated glomerular filtration rate was calculated using the MDRD equation as described by Cooper et al (7). The subjects were grouped according to the CKD staging according to the KDIGO guidelines [8].

Data Analysis

The median and interquartile range of CD4 counts and PCV were calculated and compared with the Kruksall-Wallis test between the groups and the Dunn's posts test was used to compare the difference between two groups. The chi-square test was used to compare the proportions of subjects according to WHO clinical stage of HIV disease at presentation and CKD Stages. All statistical analysis was carried out using the Graphpad prism software; tests were considered significant at p-value of < 0.05.

RESULTS

Median age of subjects was 35 (IQR, 29.5 – 42) years. There were 259 (69.1%) female and 116 (30.9%) male subjects. Amongst the subjects, 180 (48.1%) were married, 102 (27.2%) were single, 20 (5.3%) were widowed, 11 (2.9%) were divorced and 6 (1.6%) were separated 56 (14.9%) did not disclose their marital status. According to the WHO clinical staging of HIV disease, 54.9% (206/375) of the patients were in Stage 4 of disease presentation. There were 30.9% (116/375) in Stage 3 of HIV disease, 8.5% (32/375) were in stage 2, while 5.6% (21/375) were in Stage 1 of HIV disease (Table 1).

Table 1: Demographic Characteristics of Patients

Variable	Description	Frequency (%)
Age (median, IQR)		35 (29.5 – 42)
Sex	Male	116 (30.9%)
	Female	259 (69.1%)
Marital Status	Single	102 (27.2%)
	Married	180 (48.1%)
	Divorced	11 (2.9%)
	Separated	6 (1.6%)
	Widowed	20 (5.3%)
	Undisclosed	56 (14.9%)
WHO Clinical Stage	Stage 1	21 (5.6%)
	Stage 2	32 (8.5%)
	Stage 3	116 (30.9%)
	Stage 4	206 (54.9 %)

IQR: Interquartile range

Table 2 shows the median CD4 cell counts and Packed Cell Volume (PCV, %) of the subjects according to their clinical stages of HIV disease. Median CD4 cell count of 632 (563 – 728) and PCV of 36.0 (34.0 – 39.5) were observed in subjects at Stage 1 of HIV disease. Subjects at Stage 2 had a median CD4 cell count of 364 (213 – 422) and PCV of 33.9 (31.0 – 37.1). The median CD4 cell count and PCV of individuals at Stage 3 of HIV disease were 271 (219 – 308) and 32.8 (30.1 – 36.5) respectively, while subjects at Stage 4 of HIV disease had a median CD4 cell count and PCV of 99 (48 – 148) and 32.0 (28.4 – 36.0), respectively. There was a significant difference ($p < 0.05$) between the median CD4 count of subjects in the different clinical stages of HIV disease, while the difference between the median PCV of subjects at the different clinical stages of disease presentation was not significant ($p > 0.05$).

Table 2: Average CD4 and Packed cell volume (PCV) of patients according to WHO clinical stages of Disease Presentation

WHO Clinical Stage	CD4 (Median, IQR)	PCV % (Median, IQR)
Stage 1	632 (563 – 728)[a]	36.0 (34.0 – 39.5)[b]
Stage 2	364 (213 – 422) [a]	33.9 (31.0 – 37.1) [b]
Stage 3	271 (219 – 308) [a]	32.8 (30.1 – 36.5) [b]
Stage 4	99 (48 – 148) [a]	32.0 (28.4 – 36.0)[b]

[a]Difference is statistically significant ($p < 0.05$)
[b]Difference is not statistically significant ($p > 0.05$).
IQR: Interquartile range PCV: Packed Cell Volume

Median estimated glomerular filtration rate (eGFR) of subjects according to CKD stages are as follows: 106ml/min (Stage 1), 77ml/min (Stage 2), 55ml/min (Stage 3a), 39.4ml/min (Stage 3b), 22.7ml/min (Stage 4), 7.2ml/min (Stage 5), while subjects with Hyperfiltration had a median eGFR of 159ml/min. Median PCV in subjects at CKD Stage 1 and Stage 3a were 30.0% respectively, those in Stage 2 had a median PCV of 31.0%. A median PCV of 30.6% was observed in subjects at CKD Stage 3b, subjects at CKD Stage 4 had a median PCV of 31.2%, with a median PCV of 32.0% observed in subjects at CKD stage 5, while median PCV in subjects with Hyperfiltration was 30.1%. Median CD4 cell counts observed include: 175 cells (Stage 1), 183

cells (Stage 2), 134 cells (Stage 3a), 104 cells (Stage 3b), 54 cells (Stage 4), 160 cells (Stage 5), while a median CD4 cell count of 210 was observed in subjects with Hyperfiltration (Table 3).

Table 3. Average eGFR, PCV and CD4 Cell counts according to CKD stages.

CKD Stage	eGFR (ml/min)	PCV (%)	CD4 (cells/µL)
Hyperfiltration	159.0	30.1	210
Stage 1	106.0	30.0	175
Stage 2	77.0	31.0	183
Stage 3a	55.6	30.0	134
Stage 3b	39.4	30.6	104
Stage 4	22.7	31.2	54
Stage 5	7.2	32.0	160

eGFR: estimated glomerular filtration rate
PCV: Packed Cell Volume

Table 4 shows the frequency of the individuals in the different Chronic Kidney Disease (CKD) stages according to the WHO clinical stages of disease presentation. Of the individuals in Stage 1 of clinical disease presentation, 9 (42.9%) were in CKD Stage 1, 6 (28.6%) were in Stage 2, 4 (19.0%) were in Stage 3a, and 2 (9.5%) had Hyperfiltration. None of the individuals in Stage 1 of disease presentation were in CKD Stages 3b, 4 and 5. Fourteen (43.8%) of the individuals at WHO Stage 2 of clinical disease presentation were at CKD Stage 1, 17 (53.1%) were at Stage 2, only 1 (3.1%) was at Stage 3a, while none of them were at CKD Stages 3b, 4, 5 and Hyperfiltration. CKD distribution of individuals at WHO Stage 3 of disease presentation was: Stage 1 (n = 48, 41.4%), Stage 2 (n = 52, 44.8%), Stage 3a (n = 6, 5.2%), Stage 3b (n = 2, 1.7%), Stage 5 (n = 3, 2.6%), while 5 (4.3%) of the subjects had Hyperfiltration and none was in CKD Stage 4. The CKD distribution of subjects in Clinical Stage 4 of disease presentation include: Stage 1 (n = 153, 40.8%), Stage 2 (n = 160, 427%), Stage 3a (n = 28, 7.5%), Stage 3b (n=13, 3.5%), Stage 4 (n = 4, 1.1%), Stage 5 (n = 6, 1.6%) and 11 (2.9%) had Hyperfiltration.

Table 4. Frequency of Stages of Renal Dysfunction according to WHO Clinical stages of Disease Presentation

CKD Stages	**eGFR range**	**HIV Clinical Stage, n (%)**				**Total**	χ^2
		Stage 1	**Stage 2**	**Stage 3**	**Stage 4**		
Hyperfiltration	> 150	2 (9.5)	0 (0.0)	5 (4.3)	4 (1.9)	11 (2.9)	5.4885 [b]
Stage 1	90+	9 (42.9)	14 (43.8)	48 (41.4)	82 (39.8)	153 (40.8)	0.1494 [b]
Stage 2	60-89	6 (28.6)	17 (53.1)	52 (44.8)	85 (41.3)	160 (42.7)	2.0203 [b]
Stage 3a	45 – 59	4 (19.0)	1 (3.1)	6 (5.2)	17 (8.3)	28 (7.5)	5.5680 [b]
Stage 3b	30 – 44	0 (0.0)	0 (0.0)	2 (1.7)	11 (5.3)	13 (3.5)	4.9383 [b]
Stage 4	15 – 29	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.9)	4 (1.1)	3.2815 [b]
Stage 5	< 15	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.5)	6 (1.6)	1.5797 [b]
Total		21 (100)	32 (100)	116 (100)	206 (100)	375(100)	

χ^2 = Chi-square statistics
[b]Difference between the groups are not statistically significant.
eGFR: estimated glomerular filtration rate

DISCUSSION

This study showed a greater proportion (30.9 + 54.9 = 85.8%) of the HAART- naïve HIV patients had an average CD4 cell count below 300 cells/mm^3. This is in agreement with similar studies in Nigeria which reported a relatively high proportion (50 – 85%) of individuals at WHO clinical Stage 3 and Stage 4 at initial presentation [9, 10]. This high proportion of relatively low CD4 counts of the individuals at diagnosis may be attributed to the poor health seeking habits experienced especially in developing countries such as Nigeria [11, 12].

Overall, difference in average packed cell volume (PCV) observed through CKD 1 to 5 was not significant ($p > 0.05$). However, this decline in PCV as the clinical stages of the HIV infection progressed, corresponded with declining renal function (< 60mL/min). This is in agreement with Choi et al. [13], which reported corresponding decrease in average PCV as CD4 cell counts decline in a group of HIV infected patients. Anemia has been previously reported to be prevalent among HIV-infected individuals, while the severity of anemia tends to increase as the HIV infection progresses [2, 14].

It was observed that 13.7% of the HIV infected individuals exhibited low renal function (< 60mL/min). This is relatively higher than the 3.5% - 9.7% proportion of individuals with diminished renal function as reported in Asian and European HIV-infected populations [2, 15, 16]. However, this finding was consistent with the findings of Lucas et al., which reported a 6-fold GFR decrease in HIV- infected blacks, compared to HIV-infected whites [17]. It has also been previously reported, that about 91% of HIV-infected persons receiving dialysis in the United States were blacks [1,15]. Individuals of African descent have been considered to have a higher risk of HIV-associated nephropathy due to their peculiar predilection to podocyte proliferation and tubular dilatation with atrophy and flattening of the tubular cells [15-17]. In the pre-HAART era, HIVAN with its dramatic clinical features, was so frequent that it became almost synonymous with HIV-associated chronic kidney disease especially in black person between 20 – 64 years of age [2,18].

In this study, 90.2% (46/51) of the individuals with renal dysfunction (eGFR< 60 mL/min) was found in HIV clinical stages 3 and 4. Ando and Yanagisawa, have stated that low CD4 cell count was a risk factor for associated chronic kidney disease [3]. This could also be attributed to the accelerated aging due to persistent viral replication and chronic systemic inflammation in HIV-infected individuals [19]. Commonly-abused, readily-available antipyretic and analgesics agents such as NSAIDS, could lead to nephrotoxicity causing renal failure.

Hyperfiltration (eGFR ≥ 150mL/min) was observed in 2.9% (11/375) of the study subjects, with 81.8% (9/11) of the subjects in HIV clinical stages 3 and 4. This is consistent with the report of Ng et al., which showed that HIV infection is associated with higher odds of hyperfiltration [20]. Hyperfiltration is an important marker for future renal dysfunction and end-stage kidney disease [2, 20]. This phenomenon may also be due to direct viral injury to the kidney, accelerated organ aging or individual dietary habits [19]. Direct viral infection of renal epithelial cells disturbs podocyte structure and function with subsequent up-regulation of renin-angiotensin system which is held to central to the pathophysiology of hyperfiltration [20-22].

CONCLUSION

The study showed that renal dysfunction was prevalent in HIV-infected persons at first presentation and diagnosis. Majority of these subjects were at HIV clinical stages 3 and 4. Anemia was mild across all stages of HIV-disease and CKD stage. Thorough clinical examination and evaluation for CKD should be conducted, especially at the earliest contact with health care system. Early detection of chronic kidney disease (CKD) is imperative to identify those most at risk of further deterioration of renal function, and

institution of optimal care. A multi-center study of this phenomenon is recommended.

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