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Chronic Kidney Disease among Ghanaian HIV Individuals on HAART in the Ho Municipality: A Single-Center Descriptive Cross-Sectional Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SYL, WKBAO, JOY, GKN, LEK, MTA and FAU conceptualised and designed the study. Authors STQ, FA, EYB, TN, PSKN and RA recruited study participants and generated the data. Authors JOY and EYB performed the statistical analysis. Authors SYL, WKBAO, JOY, GKN, LEK, MTA and FAU wrote the first draft of the manuscript. Authors SYL, WKBAO, JOY, GKN, LEK, MTA, FAU, STQ, FA, EYB, TN, PSKN and RA reviewed the manuscript for intellectual content and each author approved the final manuscript.

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ABSTRACT

Background: Chronic kidney disease (CKD) remains one of the complications of HIV infection among individuals on antiretroviral medication. This study aimed to determine the prevalence of CKD among Ghanaians with HIV on antiretroviral medications at the Ho Municipal Hospital.

Materials and Methods: This is a hospital-based cross-sectional study involving 170 previously diagnosed HIV-infected patients on HAART treatment at the ART Clinic of the Ho Municipal Hospital. The participants aged between 24 and 78 years were conveniently and purposively recruited into the study from February to May 2017. Using patients' folders, data on patients' age, gender, type of medication(s) and duration on HAART medication were obtained. Patients' blood samples were obtained for the estimation of CD4 count and serum creatinine concentration. Estimated Glomerular Filtration Rate (eGFR) was calculated based on serum creatinine levels using the four-Variable Modification of Diet in Renal Disease (4v-MDRD) and the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equations.

Results: The prevalence of CKD was estimated at 17.06% and 18.82% based on the 4v-MDRD and the CKD-EPI equations respectively. Females recorded a higher prevalence (20.00% and 22.14%) compared to their male counterparts (3.33% and 3.33%) using the 4v-MDRD and the CKD-EPI equations respectively. Low immunological recovery (CD4 cell count <500 cell/mm^3) and longer duration on HAART (7-9 years) accounted for higher CKD prevalence.

Conclusion: In these patients receiving HAART treatment at the Ho Municipal Hospital, a high burden of CKD was observed among the female group. HAART regimen containing concurrent Nevirapine and Tenofovir had the highest CKD among the participants.

Keywords: Chronic kidney disease; estimated glomerular filtration rate; HAART toxicity; human immunodeficiency virus; nevirapine.

1. INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) has changed the characteristic history of HIV-infection profoundly and transformed the disease into a chronic condition since its introduction decades ago [1]. The advent of HAART has been linked to a significant reduction in morbidity and mortality from HIV/AIDS [2]. The therapeutic target is to suppress viral load and facilitate the resuscitation of the immune system as well as protect the individual from the development of AIDS and death [3]. However, comorbid conditions have been associated with HAART-treated patients, often frustrating the clinical management of these immune compromised individuals [4]. Renal disease, for instance, is progressively prevalent in individuals with HIV and it is a major cause of death in this population [5]. Renal damage due to antiretroviral drug toxicity could bring about a variety of toxic drug effects which may manifest as acute renal failure, tubular necrosis, kidney stones, or chronic renal disease [4]. Hence, renal dysfunction may be a typical finding in patients infected with HIV, and requires increased surveillance and adjustment of dosages of HIV medications [6]. Despite its clinical importance among HIV individuals on antiretroviral therapy, very few studies have been conducted to ascertain the burden of renal toxicity in the Ghanaian HIV population. The prevalence of CKD among Ghanaians with HIV infection who were under management with various combination-based anti-retroviral therapies with individual drug components including Tenofovir, Efavirenz, Nevirapine, Stavudine, Lamivudine and Zidovudine is reported to range from 3.7% in the Ashanti Region to 12.6% in the Upper-East Region respectively [2,4,7]. However, there is very little information in the literature about the burden of CKD among HIV registrants attending antiretroviral therapy (ART) clinics in the Volta Region of Ghana. To fill this knowledge gap, the present study sought to determine the prevalence of Chronic Kidney Disease among HIV cohorts at the Ho Municipal Hospital in Ghana. Knowledge on the renal capacity status of such people could enhance management approaches and guide future prescribing practice [4,8].

2. MATERIALS AND METHODS

2.1 The Study Site, Design and Population

A single-center hospital-based, descriptive cross sectional study was conducted between

February and May 2017 at the ART Clinic and the Medical Laboratory of the Ho Municipal Hospital in the Volta Region, Ghana. One hundred and seventy (170) previously diagnosed HIV-infected patients who were attending ART Clinic were conveniently and purposively recruited for this study. The study population consisted of participants who were of consent age (24 – 78 years) and were all living in the Ho Municipality. Participants included in this study were ART registrants at the clinic being managed with anti-retroviral therapy for at least one year. All participants who were HAART naive and those who had not attained at least one year of anti-retroviral treatments at the time of the study were excluded.

2.2 Sample Size Determination

Using the average monthly attendance of HIV-infected patients at the ART Clinic (55) for two previous months (December 2016 and January 2017), a total study population of 220 was generated for the four months study duration. Using the Raosoft online sample size calculator (http://www.raosoft.com/samplesize.html), the recommended minimum sample of 141 participants was calculated at 95% confidence level, 5% margin of error, and a response distribution of 50%.

2.3 Laboratory Analysis

All laboratory assays were carried out at the Ho Municipal Hospital laboratory. Venous blood samples were drawn from the antecubital vein of which three (3) milliliters was dispensed into a vacutainer® serum separator tube and one (1) milliliter was dispensed into an EDTA anticoagulant tube using the closed vacutainer system. CD4 lymphocyte count by flow cytometry was performed using 50 uL of non-haemolyzed whole blood with the BD FACSCount™ system according to the manufacturers' method (Becton Dickenson and Company, California, USA). The sample in the serum separator was centrifuged at 2500 revolutions per minute (rpm) for 5 minutes at room temperature to obtain the serum used for the assay of creatinine. Creatinine assay was carried out using predetermined methods by the reagent manufacturer (ELITech Clinical Systems, SAS, Zone Indusrrielle-61500 SEES, France) on the Random Access Fully Automated Vitalab Selectra Junior Chemistry analyzer (Vital Scientific, BV Kanaalweg 24, The Netherlands).

2.4 Glomerular Filtration Rate Estimation

Renal function among study participants were estimated using the following CKD equations:

I. Four Variable Modification of Diet in Renal Disease (4v-MDRD) a. Males $= 186 \text{ X } \text{Scr}^{-1.154} \text{ X } \text{Age}^{-0.203} \text{X}(1.210)$
b. Females
$= 186 \text{ X } \text{Scr}^{-1.154} \text{X } \text{Age}^{-0.203} \text{X}(1.210) \text{X} 0.742$
Where Scr= Serum creatinine concentration

II. Chronic Kidney Disease Epidemiology collaboration (CKD-EPI)

$$a.\ \text{Females } \left(\leq 62\boldsymbol{\mu}\frac{\mathbf{mol}}{\mathbf{L}}\right) \text{ eGFR} = 166 \text{ X } \left(\frac{\text{serum creatinine}}{0.7}\right)^{-0.329} \text{ X } (0.993)^{\text{Age}}$$

$$b.\ \text{Females } \left(> 62\boldsymbol{\mu}\frac{\mathbf{mol}}{\mathbf{L}}\right) \text{ eGFR} = 166 \text{ X } \left(\frac{\text{serum creatinine}}{0.7}\right)^{-1.209} \text{ X } (0.993)^{\text{Age}}$$

$$c.\ \text{Males } \left(\leq 80\boldsymbol{\mu}\frac{\mathbf{mol}}{\mathbf{L}}\right) \text{ eGFR} = 163 \text{ X } \left(\frac{\text{serum creatinine}}{0.9}\right)^{-0.411} \text{ X } (0.993)^{\text{Age}}$$

$$d.\ \text{Males } \left(> 80\boldsymbol{\mu}\frac{\mathbf{mol}}{\mathbf{L}}\right) \text{ eGFR} = 163 \text{ X } \left(\frac{\text{serum creatinine}}{0.9}\right)^{-1.209} \text{ X } (0.993)^{\text{Age}}$$

2.5 Chronic Kidney Disease Definition

The eGFR results from the various renal function equations were used to stratify the study population into five categories corresponding to the five stages of CKD in the K/DOQI CKD classification. Chronic Kidney Disease was classified as eGFR < 60 mL/ min/1.73 m2 (stages 3, 4 and 5; See Table 3) [9].

2.6 Statistical Analysis

Normality of all continuous variables were tested. Continuous parametric variables were expressed as their mean ± standard deviation, continuous nonparametric variables were expressed as median (minimum and maximum), whereas categorical variables were expressed as frequency and proportion. Gender variation in the prevalence of Chronic Kidney Disease was tested by Fishers exact test. IBM Statistical

Package for the Social Sciences version 22.00 was used for data analysis (SPSS Inc, Chicago, USA; www.spss.com).

2.7 Ethical Consideration

Informed consent was obtained from all participants after the study procedure was clearly explained to them in a language they understood (either English or Ewe). Approval for the study was obtained from the Ho Municipal Hospital. Ethical Clearance for the study was granted by the Ethical Review Committee of the School of Allied Health Sciences of the University of Health and Allied Sciences, Ho (UHAS-SAHS-ERSC:019A/2017). The research was anonymous and non-linked and no patient name or identity was used during analysis of data.

3. RESULTS

Out of the 170 participants who were recruited into this study, 140(82.35%) were females and thirty 30(17.65%) were males. Among the study participants, 68(40.00%) were on TDF/3TC/EFV, the most common ART regimen, followed by TDF/3TC/NVP 46(27.06%), AZT/3TC/EFV 39(22.94%) and the least, AZT/3TC/NVP 17(10.00%). All the combination therapy administered had Lamivudine (3TC) 170(100%) as part of the regimen. Tenofovir (TDF) was found in 67.06% of the regimen, whereas Effavirenz (EFV) was found in 62.94% of the combination therapy. No significant gender difference in ART regimen selection nor the individual therapeutic agents was found (See Table 1).

The average age of the study participants was 44.42±11.60 with majority distributed within the 31 to 50 years age range 108(63.53%). Among this study population, the female patients clustered at a younger age than their male counterpart (p=0.0203). The duration on HAART ranged from a minimum of 1 year to 9 years maximum. The median CD4 count among the participants was 526.50 µ/L, ranging from a minimum of 83 µ/L to 1682 µ/L. The average creatinine concentration was 91.05±32.82 among the female patients and 94.99±20.60 among the male patients. Using the Chronic Kidney Disease Epidemiology Collaboration equation, the mean estimated glomerular filtration rate was 87.74±28.60 (mL/min/1.73 m^2) and 89.15±34.39 (mL/min/1.73 m^2) when the 4v-MDRD: Four Variable Modification of Diet in Renal Disease equation was used (See Table 2).

Using the 4v-MDRD equation in the estimation of glomerular filtration rate, 47.06% of the respondents were classified as stage 1 CKD, 35.88% were classified as stage 2 CKD and 17.06% were classified as stage 3 CKD. No patient presented with stage 4 and stage 5 CKD. The prevalence of CKD was estimated as 17.06% among the study population.

Using the CKD-EPI equation, 17.65% and 1.18% presented with stage 3 and 4 CKD respectively. The prevalence of CKD, according to the CKD-EPI was therefore 18.82% among the study population (See Table 3).

Table 1. Antiretroviral selection profile of HIV-infected patients in Ho, stratified by gender

Parameter	Total 170(100)	Female 140(82.35)	Male 30(17.65)	p value
ARV Combination Therapy				
TDF/3TC/EFV	68(40.00)	59(42.14)	9(30.00)	0.3045
TDF/3TC/NVP	46(27.06)	39(27.86)	7(23.33)	0.8211
AZT/3TC/EFV	39(22.94)	30(21.43)	9(30.00)	0.3411
AZT/3TC/NVP	17(10.00)	12(8.57)	5(16.67)	0.1868
ARV Single Component				
Lamivudine (3TC)	170(100)	140(100)	30(100)	*Nd*
Tenofovir (TDF)	114(67.06)	98(70.00)	16(53.33)	0.0894
Effavirenz (EFV)	107(62.94)	89(63.57)	18(60.00)	0.8353
Nevirapine (NVP)	63(37.06)	51(36.43)	12(40.00)	0.8353
Zidovudine (AZT)	56(32.94)	42(30.00)	14(46.67)	0.0894

Values are number of sample and corresponding percentage in parenthesis. 3TC-Lamivudine, TDF-Tenofovir, EFV- Effavirenz, NVP- Nevirapine, and AZT- Zidovudine. p is significant at 0.05. nd- not done

Table 2. Demographic and biochemical characteristics of HIV-infected patients on HAART stratified by gender

Parameter	Total 170	Female 140	Male 30
Age	44.42±11.603	43.42±11.76	49.07±9.72
Age Range			
24-30	15(8.82)	14(10.00)	1(3.33)
31-40	56(32.94)	52(37.14)	4(13.33)
41-50	52(30.59)	40(28.57)	12(40.00)
51-60	30(17.65)	20(14.29)	10(33.33)
>60	17(10.00)	14(10.00)	3(10.00)
Duration	2.00(1-9)	2.00(1-8)	3.00(1-9)
CD4	526.50(83-1682)	535.50(112-1682)	458.50(83-1128)
Creatinine	91.74±31.00	91.05±32.82	94.99±20.60
CKD-EPI	87.74±28.60	85.94±29.41	96.15±23.06
4V-MDRD	89.15±34.39	86.67±34.93	100.68±29.64

Data is presented as mean ± standard deviation or median with minimum and maximum or number of sample with corresponding percentage in parenthesis. CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, 4v-MDRD: Four Variable Modification of Diet in Renal Disease

Table 3. Chronic kidney diseases among patients on HAART in the Ho municipality staged with 4V-MDRD and CKD-EPI equations

Parameter	4v-MDRD	CKD-EPI
Stage 1 (≥90 mL/min/1.73 m^2)	80(47.06)	86(50.59)
Stage 2 (60 To 89 mL/min/1.73 m^2)	61(35.88)	52(30.59)
Stage 3 (30 To 59 mL/min/1.73 m^2)	29(17.06)	30(17.65)
Stage 4 (15 To 29 mL/min/1.73 m^2)	0.0(0.00)	2(1.18)
Stage 5 (<15 mL/min/1.73 m^2)	0(0.00)	0.0(0.00)
CKD(Stage 3+4+5)	29(17.06)	32(18.82)

Values are number of sample and corresponding percentage in parenthesis: CKD: Chronic Kidney Disease, CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, 4v-MDRD: Four Variable Modification of Diet in Renal Disease

Using the 4v-MDRD equation, the prevalence of CKD was higher among the female participants 28(20.00%), compared to their male counterparts 1(3.33%) p=0.0305. When CKD was staged using CKD-EPI equation, 20.71% and 1.43% of the female participants presented with stage 3 and stage 4 CKD respectively. Among the male population, 3.33% presented with stage 3 CKD. The prevalence of CKD was higher among the females 22.14%, than the males 3.33% (p=0.0183) (See Table 4).

Irrespective of the predictive equation used, CKD was found to be higher among patients with CD4 count of 200 to 499 (cell/mm^{-3}). Among the HAART combination therapy, patients on TDF/3TC/NVP regimen presented with the highest prevalence of CKD, followed by those on TDF/3TC/EFV regimen. The only male participant who had CKD was on TDF/3TC/NVP regimen, presented with a CD4 count of 247 cell/mm^{-3} and was 50 years old. As seen in Table 5, NVP was the drug with the highest CKD occurrence, followed by TDF.

Using the 4v-MDRD criterion, patients within the 51 to 60 age group presented with the highest percentage CKD 7(23.33%), followed by those in the 31 to 40 age group 11(19.64%). When the CKD-EPI equation was used, those above 60 years presented with the highest percentage CKD 6(35.29%), followed by those within the age of 51 to 60 years group.

In general, percentage CKD was observed to increase with increasing duration on HAART. Using the CKD-EPI equation, 17.12%, 19.23% and 42.86% of the CKD cases were observed for patients who had been on HAART for the periods 1-3 years, 4-6 years and 7-9 years respectively. Staging CKD by the 4v-MDRD equation, 15.32%, 19.23% and 28.57% of the CKD cases were recorded among patients who have been on HAART for the periods 1-3 years, 4-6 year and 7-9 years respectively (See Fig. 1.).

Table 4. Chronic kidney diseases staged with 4V-MDRD and CKD-EPI equations stratified by gender

Parameter	4V-MDRD		CKD-EPI	
	Female 140	Male 30	Female 140	Male 30
Stage 1(≥90)	61(43.57)	19(63.33)	67(47.86)	19(63.33)
Stage 2(60 To 89)	51(36.43)	10(33.33)	42(30.00)	10(33.33)
Stage 3 (30 To 59)	28(20.00)	1(3.33)	29(20.71)	1(3.33)
Stage 4(15 To 29)	0(0.00)	0(0.00)	2(1.43)	0(0.00)
Stage 5(<15)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
CKD (Stage 3+4+5)	**28(20.00)**	**1(3.33)**	**31(22.14)**	**1(3.33)**

Values are number of sample and corresponding percentage in parenthesis: CKD: Chronic Kidney Disease, CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, 4v-MDRD: Four Variable Modification of Diet in Renal Disease

Table 5. Chronic kidney disease stratified by CD4 status, regimen type, component drug and age among HIV-infected patients

Parameter	4v-MDRD	CKD-EPI	Rank
CD4			
200-499	15(23.81)	17(26.98)	1st
<200	13(13.98)	14(15.05)	2nd
≥500	1(7.14)	1(7.14)	3rd
ARV combination			
TDF/3TC/NVP	12(26.09)	13(28.26)	1st
TDF/3TC/EFV	10(14.71)	12(17.65)	2nd
AZT/3TC/EFV	5(12.82)	5(12.82)	3rd
AZT/3TC/NVP	2(11.76)	2(11.76)	4th
Drugs			
Nevirapine (NVP)	14(22.22)	15(23.81)	1st
Tenofovir (TDF)	22(19.30)	25(21.93)	2nd
Lamivudine (3TC)	29(17.06)	32(18.82)	3rd
Effavirenz (EFV)	15(14.02)	17(15.89)	4th
Zidovudine (AZT)	7(12.50)	7(12.50)	5th
Age range			
>60	3(17.65)	6(35.29)	3rd / 1st*
51-60	7(23.33)	7(23.33)	1st / 2nd*
31-40	11(19.64)	11(19.64)	2nd / 3rd*
41-50	7(13.46)	7(13.46)	4th
24-30	1(6.67)	1(6.67)	5th

*Values are number of sample and corresponding percentage in parenthesis and rank. CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, 4v-MDRD: Four Variable Modification of Diet in Renal Disease. * Rank is based on 4v-MDRD and CKD-EPI respectively*

4. DISCUSSION

Chronic Kidney Disease (CKD) poses great danger to patients on HAART which could lead to a loss of optimum kidney function, kidney failure, and the development of cardiovascular disease [10]. This hospital-based descriptive study sought to determine the prevalence of CKD among HIV registrants on HAART at the ART Clinic of the Ho Municipal Hospital. The prevalence of CKD among the study population was estimated at 17.06% and 18.82% using the 4v-MDRD and CKD-EPI definitive criteria respectively (Table 3). Nephrotoxicity associated with HAART treatment remains prevalent among Ghanaian HIV population, and this has been documented in recent studies. Obirikorang and colleagues reported a prevalence of 9.9% and 3.7% using the 4v-MDRD and CKD-EPI equations respectively in a study conducted at a Sexually Transmitted Infections (STI) Clinic in Kumasi [4]. In Bolgatanga, Owiredu et al. [2] recorded a prevalence of 12.6% using both the 4v-MDRD and CKD-EPI equations in a study

undertaken at the ART Clinic of the Regional Hospital. In other jurisdictions, higher CKD burdens have been recorded in Nigeria and Burundi with estimated prevalence of 47.6% and 45.7% among HIV patients respectively [11,12]. Among factors postulated to contribute to the discordant findings in the burden of CKD in HIV populations across various geographical boundaries include differences in population characteristics including demographic profiles of participants and analytical methods, study design, severity of the disease, type of criteria used for the definition of CKD as well as access to medical care [7,13].

It had been postulated that the female gender confers protection against renal nephropathy due to enhanced cellular repair and the modulating effects of the renin-angiotensin system by oestrogen [14]. In the current study, however, the prevalence of CKD was significantly higher among women than men irrespective of the CKD equation used (Table 4). This observation is not an isolated case. Ambetsa et al. [14], Crum-Cianflone et al. [15], and Owiredu et al. [2] had earlier reported that feminity accounted for higher CKD in their studies. In a review of nephrotoxicity due to HAART therapy in HIV infected individuals, Kalyesubula and Perazella [16] found that, the female gender is associated with renal impairment among other risk variables.

Though the management of HIV infected persons with antiretroviral medications has led to some tremendous improvement in their well-being, the treatment regimen have been associated with organ toxicities, including those affecting the kidney [17]. Nevirapine had been reported to have a protective effect in patients on Tenofovir based formulations [18]. Contrary to that assertion however, our results showed that patients on Nevirapine and Tenofovir combined regimen (TDF/3TC/NVP) presented with the highest prevalence of CKD irrespective of the equation used (Table 5). This observation gives a probable indication of Nevirapine role in the pathogenesis of CKD among this HIV cohort. Nevirapine and Tenofovir drugs are primarily sequestered from circulation and excreted in the renal tubules into urine by means of a Multidrug Resistance Protein (MRP) in the proximal cells of

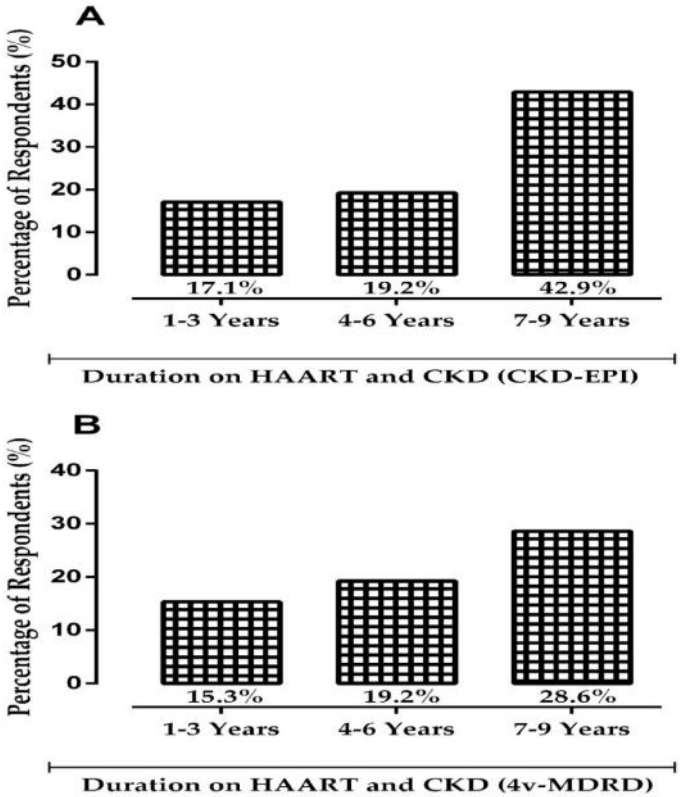

Fig. 1. Duration on HAART and chronic kidney disease according to CKD-EPI and 4V-MDRD

the renal tubule [6,19]. It is possible that a drug-drug interaction exists, with Nevirapine acting as an adjuvant for other antiretroviral drugs including Tenofovir as these agents are actively excreted together in the renal tubules and could prove lethal to the kidney due to intracellular drug concentration [6,14].

The early onset of HIV in women than men in Sub-Saharan Africa had been attributed to early sexual debut and often large age disparity in relationship which tilts towards older men [20-22]. The female patients in the present study clustered at a younger age than their male counterpart (p=0.0203) (Table 2). Age is reported to be a strong risk determinant for CKD [23,24]. Chronic Kidney Disease is said to affect typically young adults aged between 20 and 50 years in Sub-Saharan Africa [25], but the rate can be higher in the elderly [24,26]. In the present study, the modal prevalence of CKD was among the 31 to 60 year group or those above 60 years, depending on the equation used in estimating glomerular filtration rate (Table 5). The age range associated with CKD in this study is similar to that reported by Hsieh et al. [27].

Immune suppression reflecting low CD4 count and antiretroviral treatment duration have been shown to be independent risk factors for CKD in studies undertaken previously in various HIV populations [10,15,28,29]. In the current study, irrespective of the CKD equations used, the proportion of participants with CKD was found to be higher among participants with CD4 count less than 500 cells/mm^3 (37.79% and 42.03%) compared to those with higher immune recovery (CD4 count more than 500 cells/mm^3) (7.14% and 7.14%) (Table 5). In a lowered immune environment, HIV could cause direct injury to the kidneys manifesting as HIV Associated Nephropathy (HIVAN) in affected patients [30].

Chronic Kidney Disease prevalence among participants was observed to increase with increasing duration on HAART irrespective of the CKD equations used (Fig. 1). The proposed mechanism of the long-term toxicity of antiretroviral usage particularly Tenofovir induced nephrotoxicity, may be due to increased drug accumulation within the proximal renal tubules, leading to mitochondrial injury and depletion [31].

5. CONCLUSION

In these patients receiving HAART treatment at the Ho Municipal Hospital, a high burden of CKD was observed among the female group. HAART combination-based medications involving Nevirapine and Tenofovir recorded the highest prevalence of CKD among the participants. Type of HAART medication and longer duration on HAART as well as low immune recovery could be associated with increased renal toxicity.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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