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Chronic Kidney Disease (CKD) in Patients Living with HIV under Antiretroviral Treatment: Prevalence and Risk Factors

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Abstract

CKD is one of the major complications when infected by HIV. The surveillance of **CKD** indicators and control of its determinants in the HIV-infected population in our African communities is essential. This was a descriptive and analytical cross-sectional study of people living with HIV received at the Ambulatory Treatment Center (ATC) at Infectious Diseases department of Sylvanus Olympio University Hospital (CHU-SO). The study period was 6 months—from January 1, 2018 to June 30, 2018—**CKD** was defined by a clearance below 60 ml/min/1.73 m^2 for at least 3 months. A total of 117 patients were enrolled during the study period. The average age of patients for trial treatment was between 9.49 and 42.0 7 years. The duration of follow-up for antiretroviral treatment was ±3.22 to ±5.64 years. The female gender was predominant (70.09%) with a sex ratio (M/F) of 0.43. Most of people living with HIV were mostly classified at clinical stage 2 (31.03%) and 3 (31.90%) of WHO at initiation of HAART. The main CD4 rate was 223.30 ± 143.764 at initiation of HAART and 462.58 ± 202.723 at the time of the study. The majority of patients were placed in a fixed combination of Tenofovir/Lamivudine/Efavirenz in a proportion of 81.20% cases. **CKD** was found in 13 patients—that is 11.11% of patients. Univariate analysis shows that age greater than 45 years plus ($p = 0.017$) and pathological proteinuria ($p = 0.021$) were associated with **CKD**. In multivariate analysis, only ages ($p = 0.045$) and pathological proteinuria ($p = 0.035$) were significantly associated with **CKD**. The prevalence of **CKD** in HIV-infected patients is significant in Togo. The occurrence of proteinuria is linked to the delay in taking antiretroviral therapy.

Keywords

CKD, HIV, HAART, Togo

1. Introduction

The prevalence of Human Immunodeficiency Virus (HIV) infection is high in African regions, with more than 25.7 million people living with HIV [1]. In 2017, Africa alone counted 25.7 million people living with HIV (PLHIV) [1]. In Togo, in 2017 the average prevalence in the general population aged 15 to 45 decreases from 2.5% to 2.1% [2]. The survival of people living with HIV depends on several factors: early diagnosis of HIV infection, early antiretroviral therapy, therapeutic compliances, and finally diagnosis and management of complications of infections and treatment [3] [4] [5]. **CKD** is one of the major complications during HIV infection [5]. In 2004, in the United States for example, 4000 cases of end stage **CKD** were attributed to HIV [6] infection. Its prevalence is constantly increasing and can reach up to 38% of cases depending on races and countries [7] [8] [9].

Metabolic complications (diabetes, dyslipidemia), high blood pressure (hypertension), nephrotoxicity due to Antiretroviral treatment and HIV-associated with nephropathy would explain this considerable frequency of **CKD** during HIV [6] infection. A very noticeable fact is that the majority of people living with HIV in **CKD** are black. In several studies, the black race was reported as a risk factor for **CKD** [10]. These facts suggest that surveillance of **CKD** indicators and control of its determinants in the HIV-infected population in our African communities is essential. In Togo, no studies have yet been conducted to assess the extent of **CKD** in people living with HIV.

The objective of this study is therefore to assess the prevalence of **CKD** in people living with HIV in Togo and to identify any associated factors.

2. Patients and Methods

This was a descriptive and analytical cross-sectional study of people living with HIV received at the Ambulatory Treatment Center (ATC) at the Infectious Diseases department of **Sylvanus Olympio University Hospital** (CHU-SO) for their follow-up consultation. The study period was 6 months from January 1rst, 2018 to June 30th, 2018. The CHU-SO infectious and tropical diseases department is the reference service for the care of patients infected with HIV. The patients included in this study were people known living with HIV older than 15 years, who have been regularly treated at Ambulatory Treatment Center (ATC) on Antiretroviral treatment for at least 3 months. Each of these patients were infused the creatinine serum at the beginning of the treatment. Every involved patient had received a thorough physical examination, creatinine serum test, and urine test to check proteinuria (Proteinuria was said to be pathological to the

urine test strip if it was positive at a cross and more). Information at the initiation of treatment such as the World Health Organization (WHO) clinical internship, CD4 count, creatinine serum and antiretroviral therapy molecules were collected in the medical care record. Children, pregnant women, or HAART-naive patients were not included and those who did not have a minimum of basic nephrology checkup (at least one creatinine serum with three months duration, proteinuria with the urine test strip).

The variables studied were socio-demographic parameters (age, sex and level of education); anthropometric parameters (weight, height and Body Mass Index (BMI)); clinical and biological parameters (WHO clinical stage of HIV (Table 1) at initiation of HAART, CD4 count). Patients' creatinine clearance was estimated by the simplified MDRD formula [11]. **CKD** was defined by a clearance below 60 ml/min/1.73 m^2 for at least 3 months. **CKD** was classified into 5 stages according to K-DIGO [12]. Age was divided into two categories: higher or lower than 45 years old.

The age are chosen randomly.

The CD4 rate is divided into two categories: low if less than 200 cells/microliter and not low if higher than 200 cells/microliter.

Definition of operational terms:

- High Blood Pressure (HBP) was defined by a systolic blood pressure higher than 140 mm/Hg and a diastolic blood pressure as higher than 90 mm/Hg.
- Diabetes is defined by fasting glucose higher than 1.21 g/l.
- BMI is classified according to the WHO in four stages (Table 2).

WHO classification [13]:

- Inadequate weight: BMI < 18.5 (Kg/m^2)

Table 1. Distribution of HIV-infected patients according to WHO clinical stage.

Initiation stages	Effective (n)	Percentage (%)	Cumulative Percentage (%)
Stage 1	24	20.69	20.69
Stage 2	36	31.03	51.72
Stage 3	37	31.90	83.62
Stage 4	19	16.38	100.00
Total	**116**	**100.00**	

Table 2. Patient distribution according to weight class.

Interpretation of BMI	Frequency	Percentage	Cumulative Percentage
Underweight	14	11.97	11.97
Normal BMI	62	52.99	64.96
overweight	31	26.50	91.45
Moderateobesity	7	5.98	97.44
Morbidobesity	3	2.56	100.00
Total	**117**	**100.00**	

BMI: Body Mass Index.

- Normal body weight: 18.5 ≤ BMI < 24.99 (Kg/m^2)
- Overweight: BMI ≥ 25 (Kg/m^2)
- Obesity: BMI ≥ 30 (Kg/m^2)

Data collection was performed using Epidata 3.1 software; analysis by SPSS software version 13.0 and R software. Univariate and multivariate comparative analysis with logistic regression of socio-demographic, clinical and therapeutic data of **CKD** versus **non-CKD** patients was performed with statistical tests (Pearson's Chi square test and Fisher's test). One variable was considered significantly associated with **CKD** if $p < 0.05$.

3. Results

3.1. Descriptive Aspect

A total of 117 patients were enrolled during the study period following the inclusion criteria. **CKD** was found in 13 patients, which corresponds to hospital frequency of 11.11%. Only one patient was in **CKD** prior to the initiation treatment. The main age of patients at initiation of treatment was ±9.49 to ±42.07 years and the age at the time of the study was ±9.88 to ±47.68 years with an average duration of follow-up under ARV of ±3.22 to ±5.61 years. The female sex was predominant (70.09%) and a sex ratio (M/F) of 0.43 of these people living with HIV who were on HAART, 88.29% had no undergraduate certificate (Table 3). High blood pressure was found in 13.68% of enrolled patients and diabetes in 1.71% cases. The average body mass index (BMI) was 23.80 kg/m^2. Overweight and obesity were found in 26.50% and 8.54% of cases respectively (Table 2). Pathological proteinuria was present in 25.64% patients. Most people living with HIV were mostly classified at clinical stage 2 (31.03%) and 3 (31.90%) by WHO at initiation of HAART (Table 1). The main CD4 rate was ±143.764 to ±223.30 cells per cubic millimeter at initiation of HAART and ±202.723 to ±462.58 cells per cubic millimeter at the time of study.

At the therapeutic level, the majority of patients were placed in a fixed combination of Tenofovir/Lamivudine/Efavirenz in a proportion of 81.20% of cases. The remaining data on HAART is summarized in Table 4 and Table 5.

3.2. Comparative Analysis

Univariate analysis shows that age pass 45 years is associated (RR = 4.71, 95% IC

Table 3. Level of education of HIV-infected patients with CKD.

Level of education	Effective (n)	Percentage (%)	Cumulative Percentage (%)
None	31	27.93	27.93
Primary	31	27.93	55.86
Middle School	36	32.43	88.29
Secondary school	8	7.21	95.50
High	5	4.50	100.00
Total	**111**	**100.00**	

Table 4. Distribution of antiretrovirals used in patients.

Prescribed molecules	Yes	No	Total
Tenofovir (TDF)	111 (94.87)	6 (5.13)	117 (100)
Efavirenz (EFV)	98 (83.76)	19 (16.24)	117 (100)
Atazanavir (ATV)	15 (12.82)	102 (87.18)	117 (100)
Zidovudine (AZT	3 (2.56)	114 (97.44)	117 (100)
Abacavir (ABC)	3 (2.56)	114 (97.44)	117 (100)
Lopinavir (LOP)	3 (2.56)	114 (97.44)	117 (100)
Nevirapine (NEV)	1 (0.85)	116 (99.15)	117 (100)

Table 5. Distribution according to HAART therapeutic diagrams.

Type of triple therapy	Effective (n)	Percentage (n)
TDF/3TC/EFV	95	81.20
TDF/3TC/ATV	13	11.11
TDF/3TC/LOP	3	2.56
ABC/3TC/EFV	3	2.56
AZT/3TC/ATV	2	1.71
AZT/3TC/NEV	1	0.85
Total	**117**	**100.00**

HAART: Highly active Antireviral therapy.

= [1.09, 20.34], p = 0.017) with CKD. Sex (p = 0.339); BMI (p = 0.49), the clinical stage of HIV, the antecedent of HBP (p = 0.078) and diabetes (p= 0.21) were not associated with **CKD** (Table 6). The presence of pathological proteinuria was associated with **CKD** (RR = 3.38; 95% IC = [1.23; 9.27]) (Table 6). Regarding anti-retroviral drugs administered to patients, none was associated with the occurrence of **CKD** (Table 7).

In multivariate analysis, only age and pathological proteinuria were significantly associated with **CKD** with OR of 5.50 (p = 0.045) and OR 4.11 (p = 0.045), respectively (Table 8); however the presence of hypertension and diabetes was not associated with **CKD** (Table 8).

4. Discussion

This is the first ever study in our country of **CKD** for people living with HIV on HAART. The prevalence of **CKD** in our sample was 11.11%. This prevalence is variable according to the studies and this depends on the population studied and the estimation method of the GFR [14]. Zannou found 18.7% of Beninese population of 480 HIV-infected people using the Cockcroft and Gault formula; the middle age was ±9.16 to ±41.4 years old [15]. Elevated creatinine serum (≥15 mg/l) was used during the study in another study; it gives a prevalence of 31.1% with a main age of ±34.6 to ± 9.4 years [7]. In contrast Umeizudike [16] found

Table 6. Univariate analysis of sociodemographic and clinical data.

Characteristics	CKD+ (N = 13)		CKD− (N = 104)		OR IC95%	P
	N	(%)	n	(%)		
Sexes					1.21 [0.90; 3.60]	0.339
Male	2	15.38	33	31.73		
Female	11	84.62	71	68.27		
Age (years)					4.17 [1.09; 20.34]	0.017
≤45	2	15.38	52	50.00		
>45	11	84.62	52	50.00		
HBP					2.81 [1.98; 8.04]	0.078
Yes	4	30.77	12	11.54		
No	9	69.23	92	88.46		
Diabetes					4.79 [1.08; 21.17]	0.21
Yes	1	7.69	1	0.96		
No	12	92.31	103	99.04		
BMI (kg/m²)					0.82 [0.27; 2.51]	0.49
<25	4	30.77	37	35.58		
≥25	9	69.23	67	64.42		
WHO Clinical Stage					-	0.857
Stage 1	3	23.08	21	20.39		
Stage 2	5	38.46	31	30.10		
Stage 3	4	30.77	33	32.04		
Stage 4	1	7.69	18	17.48		
Pathological proteinuria					3.38 [1.23; 9.27]	0.021
Yes	7	53.85	23	22.12		
No	6	46.15	81	77.88		
CD4 rate					8.58 [0.31; 4.51]	0.51
<200	7	53.85	52	50		
≥200	6	46.15	52	50		

BMI: Body Mass Index; HBP: High Blood Pressure; WHO: World Health Organization.

Table 7. Univariate analysis of antiretroviral related characteristics.

Characteristics	CKD+ (N = 13)		CKD− (N = 104)		OR IC 95%	P
	N	(%)	n	(%)		
TDF					0.65 [0.1; 4.2]	0.515

Continued

Yes	12	92.31	99	95.19		
No	1	7.69	5	4.81		
EFV					0.44 [0.15; 1.27],	0.22
Yes	9	69.23	89	85.58		
No	4	30.77	15	14.42		
ATV					3.02 [1.06; 8.60].	0.063
Yes	4	30.77	11	10.58		
No	9	69.23	93	89.42%		
Treatment lines					0.35; [0.99; 1.21]	0.114
Line 1	9	69.23	90	86.54		
Line 2	4	30.77	14	13.46		

Table 8. Multivariate analysis of characteristics associated with CKD.

Characteristics	Adjusted OR	IC95% adjusted	P
Age	5.50	[1.16; 26.03]	0.045
HBP	2.36	[0.51; 10.82]	0.266
Diabetes	3.87	[0.20; 73.76]	0.368
Proteinuria	4.11	[1.26; 13.43]	0.035
HAART	-	-	0.999
HAART Line	-	-	0.999

HBP: High Blood Pressure; HAART: Highly active Antireviral therapy.

23.5% with the main age of ±8.3 to ±35 years. It was generally accepted in sub-Saharan Africa that the prevalence of **CKD** ranged from 6% to 48.5% in HIV-infected patients [17]. Contrary to this observation, studies in Europe for white race subjects showed a prevalence around 4%; in France for example, it was only 4.7% of the population of 7378 patients using the MDRD [18] formula. The analysis of Hsieh MH [19] in Taiwan after finding a prevalence of 7.9% in its population unlike other Asian countries (15.4% in Japan and 16.8% in Hong Kong), showed that age affected the prevalence of **CKD** in the HIV-infected population. It should be noted that the prevalence of **CKD** increased after the age of 40 [17]. Consistent with this observation, the average age of ±9.49 to ±42.07 years in our study, would partly explain the superiority of our prevalence to other studies such as Umeizudike *et al.* [16]. In addition, the genetic susceptibility of the black subject to develop CKD must be added [20]. Nevertheless, our prevalence may be considered underestimated because of the small size of our sample.

In our study we reported that greater than 45 years with OR of 5.5 (p = 0.017)

was associated with the occurrence of **CKD**. Zannou *et al.* [15] in Cotonou found that age ≥ 47 years with OR = 3.79 and IC [1.92 - 7.50] ($p < 0.001$) was associated with **CKD**; in New York Wyatt and al [6] had found a slightly older age of 50 ($p < 0.0001$). The age of occurrence of **CKD** in HIV-infected patients is early in the majority of studies involving black subjects [7] [20] [21]. This precocity could be explained on the one hand by the genetic predisposition of black subjects to **CKD** characterized by histology by HIVAN (HIV Associated Nephropathy). On the other hand, the late diagnosis of the disease in our circles, most often at the stage of complication, may be a factor in favor. In addition, the low level of CD4 is a risk factor for **CKD** for infected patients in some studies [7] [18]. Flandre *et al.* [18] found that having a TCD4 ≥ 200 cells/microliter with RR of 0.63 (0.48 to 0.81) and $p = 0.03$ was associated with the occurrence of **CKD**. This correlation was not found in our study and in others [15] [22]. HBP, diabetes and dyslipidemia are traditional risk factors for **CKD** in the general population and in HIV-infected patients. In our study 13.36% of patients are hypertensive. There was no correlation found between hypertension and **CKD** in our study. In Cotonou, Zannou [15] found 12.3% of cases of hypertension and 3.1% of diabetes with OR of 1.57 [0.83 - 2.97] ($p = 0.17$) and 0.30 IC [0.03 - 2.32] ($p = 0.17$) respectively. In contrast, in France, Frantre *et al.* [18] found that 48% of patients with HIV were hypertensive and 9.8% were diabetic. They also observed that HBP was statically related to the occurrence of **CKD** with OR = 2.39 and $p < 0.0001$. Min-Han Hsieh al [19] found a risk of developing C in HIV-infected patients with hypertension (OR = 23.06, IC 4.67 - 113.87 and $p < 0.001$) and diabetes (OR 9.822 IC 1.862 - 51.08 $p = 0.007$) and hypercholesterolemia (OR = 5.52 and IC 1.23 - 4.68, $p = 0.025$). In the USA, Shwartz *et al.* [7] had shown that the presence of hypertension is a high-risk marker for developing CKD [19]. This observed difference can be explained by the size of the samples of different studies. Indeed, studies that found hypertension and diabetes as risk factor had fairly enough sample size. Moreover, the fact that the presence of hypertension and diabetes in HIV patients on treatment is not statically related to the occurrence of **CKD** in our study can be explained by the fact that hypertension and diabetes when even though are traditional risk factors for **CKD**, were not the leading causes of kidney disease in Black HIV-infected patients.

In our study, pathological proteinuria was a risk factor for **CKD**. Zannou *et al.* [15] did not reach the same conclusion in their study in Benin. Nevertheless, the association of proteinuria with **CKD** in HIV-infected patients is an indicator of the importance of the care for these patients. Because in the absence of treatment its progresses on average in two years in **CKD** and it is responsible for 50% of cases of ESRD (End-Stage Renal Disease) [23].

5. Conclusion

The prevalence of **CKD** in HIV-infected patients is significant, especially in the black population. In Togo it was 11.11%. Risk factors are numerous, but mainly

for Togolese population age and proteinuria are the most found. The occurrence of proteinuria is linked to the delay in taking antiretroviral therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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