Scientific Research Publishing

Open Journal of Nephrology, 2019, 9, 55-64
http://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Risk Factors of Renal Failure in HIV Patients at Initiation of ARV Treatment: Retrospective Study of 3118 Patients Followed in Infectious Diseases Department at Lomé University Hospital

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How to cite this paper: Amekoudi, E.Y.M., Sabi, K.A., Dolaama, B., Tona, K.G., Noto-Kadou-Kaza, B., Kola, E. and Saka, B. (2019) Risk Factors of Renal Failure in HIV Patients at Initiation of ARV Treatment: Retrospective Study of 3118 Patients Followed in Infectious Diseases Department at Lomé University Hospital. *Open Journal of Nephrology*, **9**, 55-64.
https://doi.org/10.4236/ojneph.2019.93007

Received: April 27, 2019
Accepted: July 5, 2019
Published: July 8, 2019

Abstract

HIV infection is a major cause of chronic kidney disease, associated with high morbidity and mortality in sub-Saharan Africa. The objective of this study is to assess the prevalence and risk factors of renal disease at initiation of antiretroviral therapy. This was a descriptive and analytical retrospective study carried out in the infectious and tropical diseases department at Sylvanus Olympio University Hospital. The data have been extracted from the ESOPE software. Kidney disease was defined by a GFR, estimated by MDRD (Modification of Diet in Renal Disease) formula, less than 60 ml/min/1.73 m^2. Risk factors associated with kidney disease were assessed using univariate and multivariate analysis. There were 3118 HIV-infected patients included in our study. The median estimated filtration rate was 94.7 ml/min/1.73 m^2: 2.9% had an eGFR < 15 ml/min/1.73 m^2. 1303 had kidney disease (41.8%). Most patients (30.8%) were in the WHO clinical stage 1. The median CD4 count was 165/µL [IQR = 72 - 274/µL]; the median hemoglobin level was 10.4 g/dL [IQR = 8.8 - 11.9 g/dL]; all patients had thrombocytopenia less than 100.000/mm^3; 8.5% had leukocytosis greater than 10.000/mm^3. Most of patients had HIV1. In the multivariate analysis, age greater than 40 years ($p < 0.0001$), and female gender and hyperleukocytosis greater than 10,000/mm^3 were significantly associated with renal disease. The prevention of kidney disease must go through the identification of its risk factors in the target populations.

Keywords

HIV, Chronic Kidney Disease, Epidemiology, Togo

1. Introduction

Renal affection due to HIV has been described for the first time by Rao *et al.* in 1984 in patients with nephrotic proteinuria progressing rapidly to chronic end-stage renal failure [1]. A few years later, HIV-associated nephropathy (HIVAN) has been described as a clinicopathological entity. Since then, several attacks have been described, with all the structures potentially affected during HIV infection [2].

In sub-Saharan Africa, several studies have been carried out, each using different criteria for diagnosing renal failure: it has been noted therefore the prevalence of kidney disease of 6% in South Africa [3], 25% in Kenya [4] and 42% in Congo [5]. Although Togo initiated its first national multisectoral strategy against HIV/AIDS and Sexually Transmitted Infections (STIs) in 2002, like most countries in sub-Saharan Africa, very few studies have been conducted and have been made concerning kidney damage during HIV infection [6]. Faced with this statistical void, and the constant and galloping progression of kidney disease in this population, the organization of a riposte is necessary. It therefore seemed necessary to describe the risk factors associated with renal disease before initiation of highly active antiretroviral therapy (HAART) in PLWHA (person living with HIV/AIDS).

2. Methodology

2.1. Framework and Duration of Study

Our study was conducted in the Department of Infectious and Tropical Diseases at Sylvanus Olympio University Hospital Center (CHU-SO) in Lomé, which is the reference hospital of Togo. This was a retrospective descriptive and analytical study of the cases of PLWHA seen at initiation of antiretroviral therapy (ART).

The questionnaire data was extracted from the ESOPE version 5 database. The ESOPE software is a tool developed to improve hospital and community management, to support decentralization, to monitor and evaluate programs.

At the CHU Sylvanus Olympio, the data are introduced by two Secretaries already trained, from the pre-filled care books by physicians. The data began to be introduced on 28 June 2009. It concerned all PLWHA (person living with HIV/AIDS) who consulted between August 18, 2009 and March 25, 2017. Were included all PLWHA naïve to HAART seen in consultation for initiation of antiretroviral therapy.

Before being analyzed, the data was verified and purified. All aberrant values

of creatinine (less than 3 mg/l) and hemoglobin levels (greater than 20 g/dL) have been purified.

2.2. Collection of Data

The variables studied were:

- Sociodemographic variables: frequency, age, sex, residence, profession.
- Clinical variables: blood pressure, body mass index, existence of comorbidity *i.e.* diabetes and hepatitis C infection.
- Biological variable: proteinuria, HIV type, eGFR (glomerular filtration rate calculated according to the MDRD formula), CD4 count, blood sugar, cholesterolemia, triglyceride, hemoglobin rate, leukocyte count, lymphocytes, neutrophils, platelets and transaminase levels.

2.3. Operational Definition

Renal disease was defined by an estimated Glomerular Filtration Rate (GFR) of less than 60 ml/min/1.73 m with or without urinary tract proteinuria. The estimated GFR is obtained by calculating the serum creatinine clearance according to the simplified MDRD (Modification of Diet in Renal Diseases) formula.

Simplified MDRD formula [7] [8]: Simplified version (in humans) = $186 \times (\text{creatinine (mg/dl)})^{-1154} \times \text{age}^{-0.203}$.

We did not have the urinary sediment, nor the study of proteinuria for our patients. The capital and its suburbs have been defined as urban areas. The rest of the settlements have been defined as rural areas. The blood pressure was measured in various ways either by electronic or manual tensiometer. The normal value is a blood pressure lower than 140/90mm Hg. The body mass index is calculated according to the formula (Weight/Height^2): It allows to classify in thinness for a value lower than 18 kg/m^2, normal when between 18 and 25 kg/m^2, overweight between 25 and 30 kg/m^2 and obesity if greater than 25 kg/m^2. The level of CD4 is measured by flow cytometry with thresholds of normal between 600 and 1200/mm^3. The hemoglobin rate: it is measured by automaton. Its normal value depends on age. Nevertheless, severe anemia is defined by a hemoglobin level of less than 8 g/dl. The count of leukocytes and platelets is made by automaton with smear control. The leukocyte count was divided into three (03) classes: less than 4000/mm^3 (leukopenia), 4000 to 10,000/mm^3 (normal) and greater than 10,000/mm^3 (leukocytosis). Thrombocytopenia is defined by a platelet count of less than 150,000/mm^3.

2.4. Descriptive Analysis

The statistical analysis was carried out with the software RStudio version 3.3.2. In terms of descriptive analysis, the results were expressed in terms of size and percentage for the qualitative or median and interquartile range variables for the quantitative variables.

Comparative analysis:

A comparative analysis was conducted to find a difference between the variables collected at baseline, whether there was kidney disease. The statistical tests used were the Pearson Chi-square test or Fisher's exact test for qualitative variables and the Student's test for quantitative variables. The threshold of significance was set at 0.05. Missing data were not considered in the analysis.

Logistic regression:

Univariate and multivariate logistic regression was performed to investigate associated factors. The dependent variable was the disease status coded 1 if GFR is <60 ml/min/1.73 m with or without proteinuria and 0 if not. The explanatory variables were certain sociodemographic, clinical and biological variables. Variables statistically associated with renal disease during univariate analysis with a significance level $p < 0.20$ were introduced in the initial model. The step-down procedure was used to select the final model. The multivariate analysis made it possible to estimate the Adjusted Coast Ratio (RCa) and its 95% confidence interval for each selected variable. After obtaining the final model, interactions were sought between the different variables of the final model by including interaction terms (product of the 2 variables concerned) in the model and verifying their non-significance. The adequacy of the model has been verified based on the R^2 value.

3. Results

In total, 5604 patients were seen in our study duration. 3118 patients (53.6%) who had serum creatinine to calculate GFR were included in the study. The incidence of renal disease at baseline was 41.8% or 1303 patients [95% CI: 40.0% - 43.5%]. The median eGFR was 94.7 ml/min/1.73 m^2: 10.4% had renal failure, *i.e.* eGFR < 60 ml/min/1.73 m^2. The median age was 40 years [IQR = 34 - 48 years] with a sex ratio of 0.50. The median BMI was 20.6 kg/m^2. Two-thirds of the patients (69.2%) were in the WHO clinical stage 2 and over. The median CD4 count was 165/µl [IQR = 72 - 274 /µl]. The median hemoglobin rate was 10.4 g/dl [IQR = 8.8 - 11.9 g/dl], all patients had thrombocytopenia less than 100,000/mm^3, and 8.5% had leukocytosis greater than 10,000/mm^3. The majority of patients (99.9%) had HIV1. Table 1 presents the socio-demographic, clinical and biological characteristics of the study population.

3.1. Univariate Analysis

Table 1 presents the result of univariate analyzes. Seven (7) variables were associated with kidney disease: sex, age, hemoglobin, WHO stage, blood sugar, leukocyte count, and neutrophils.

3.2. Multivariate Analysis

Table 2 presents the results of the final model. The final model was adjusted for sex, age and leukocyte count. Adjusted for sex, the risk of having kidney disease is significantly higher for females than males (43.1% females versus 39.2% males,

RCa = 1.55; at 95% [1.31 - 1.83] p < 0.0001). In addition, the risk of having kidney disease is significantly higher in subjects over 40 years of age (53.5% in the over 40 s versus 31.3% in the under 40 s, RCa = 2, 81, 95% CI [2.40 - 3.29] p < 0.0001). Finally, the risk of having renal disease was significantly higher in subjects with leukocytosis (RCa = 5.13, 95% CI [2.06 - 13.82] p value < 0.0001).

Table 1. Univariate analysis by logistic model of sociodemographic, clinical, and biological characteristics of renal disease cases (n = 3118).

Features	Univariate model				
	n/N	%	RR	IC at 95%	p values
Gender					0.0343**
Male	410/1047	39.2	1.00	-	
Female	893/2071	43.1	1.18	[1.01 - 1.37]	
Age (years)					0.0001**
<40	514/1643	31.3	1.00		
≥40	789/1475	53.5	2.53	[2.18 - 2.93]	
BMI (kg/m²)					0.2336
<25	113/253	42.7	0.70	[0.42 - 1.30]	
≥25	16/45	35.5	0.40	[0.18 - 1.02]	
WHO clinical stage					0.0005**
1	397/1073	37.0	1.00	-	
2	284/659	43.1	1.29	[1.05 - 1.57]	
3	265/614	43.2	1.29	[1.05 - 1.58]	
4	341/735	46.4	1.47	[1.22 - 1.78]	
CD4 count (/µl)					0.1859
0 - 200	753/1757	42.8	1.00	-	
200 - 500	462/1145	40.3	0.90	[0.78 - 1.05]	
500 et plus	64/173	37.0	0.70	[0.57 - 1.08]	
Rate of hb (g/dl)					0.0001**
<12	970/2270	42.73	0.58	[0.46 - 0.74]	
≥12	281/731	38.4	0.57	[0.44 - 0.72]	
Leukocytes (/mm³)					0.0002**
<4000	301/774	38.89	1.00		
4000 – 10,000	542/1340	40.45	1.07	[0.89 - 1.28]	
>10,000	78/135	57.78	2.15	[1.49 - 3.13]	
Platelets (/mm³)					0.0773
<50,000	631/1573	40.11	1.00		
≥50,000	50/102	49.02	1.43	[0.96 - 2.14]	

BMI: Body Mass Index, WHO: World Health Organization, RC: Rib Ratio, 95% CI: 95% Confidence Interval, **: Found Significance.

Table 2. Multivariate analysis by logistic model of sociodemographic, clinical and biological characteristics of renal disease cases (n = 3118).

	Initial model			Final model		
	RR	IC at 95%	p values	ARR	IC at 95%	p
Gender			0.0024			0.0053
Male	1.00			1.00		
Female	2.43	[1.38 - 4.38]		1.97	[1.23 - 3.19]	
Age (years)			0.0002			0.0001
4 - 40	1.00			1.00		
40 - 84	2.65	[1.58 - 4.50]		3.10	[2.01 - 4.82]	
WHO clinical stage			0.9565			
1	1.00					
2	0.94	[0.50 - 1.77]				
3	1.00	[0.46 - 2.20]				
4	0.78	[0.31 - 1.92]				
CD4 count (/µl)			0.2013			
0 - 200	1.00					
200 - 500	0.88	[0.49 - 1.55]				
500 et plus	0.45	[0.18 - 1.08]				
Rate of hb (g/dl)			0.3380			
<12	0.58	[0.46 - 0.74]		1.00		
≥12	0.57	[0.44 - 0.72]				
Leukocytes (/mm³)			0.0177			0.0016
<4000	1.00			1.00		
4000 - 10,000	2.41	[1.17 - 5.13]		1.50	[0.94 - 2.40]	
>10,000	5.33	[1.36 - 21.97]		5.13	[2.06 - 13.82]	
Platelets (/mm³)						
<50,000	1.00		0.8943			
≥50,000	0.64	[0.20 - 1.84]				

RR: Rib Report, ARR: Adjusted Rib Ratio, WHO: World Health Organization

4. Discussion

This study showed that hospital frequency of renal disease in ART-naive patients was 41.8%. Apart from Msango's work in Tanzania, which had a prevalence of 63.7% [9] higher than ours, all similar work in Africa had found prevalence equal to or lowers than our result. Ekat in Brazzaville [5], Anyabolu in Nigeria [10] found a prevalence of 42% and 22.5% respectively. The difference in methodology is the main explanation for this great variability of prevalence in these different works. Indeed, Msango in Tanzania used the Cockroft and Gault equation, which is known to underestimate eGFR in patients with low muscle mass.

In Anyabolustudies, kidney disease were defined from renal failure values as in our case, *i.e.* 60 ml/min/1.73 m^2, thus neglecting the existence of proteinuria. Ekat in Brazzaville [5] defined kidney disease as proteinuria with or without renal failure. Mouhari in his work on the biological profile of patients at the initiation of ARV treatment in 2011, performed in the same department had found a prevalence of 33.2% [11], significantly lower than our result given the methodological threshold based on serum creatinine values. Despite this wide variability, the general aspect is that the prevalence of kidney disease innaive PLWHA (person living with HIV/AIDS) is important. Indeed, in several nephrology works in Black Africa, HIV is quoted as the third leading cause of chronic kidney disease behind high blood pressure and diabetes [12].

The risk factor of kidney disease among PLWHA was the female gender with a risk of 1.97 times, the age over 40 years with a risk of 3.1 times and, hyperleukocytosis with a risk of 5 times (**Table 2**).

In the general population, it is known that renal disease is rather associated with the male sex, due to the preponderance of cardiovascular pathologies and the increased exposure to various environmental risk factors [13] [14]. In our series, however, the female sex appears as a major risk factor for kidney disease unlike the general population. This result is like Msango's result in Tanzania and contrary to Cao in China [15] which has regained a male predominance as in the United States [15]. This difference is explained by the fact that in Africa in general and in Togo in particular, the female population appears to be more affected by HIV; The PNLS in Togo estimated that the sex ratio of HIV was 0.54 in 2014 [16]. In Burundi, a study conducted by Johan Cailhol on kidney damage during HIV infection noted a proportion of 70.3% of women [17]. Age was statistically associated with the presence of kidney disease in our work with an increased risk of 3.1 from 40 years old. Cao *et al.* also found in China this statistical link. Similar work in Africa has not found this association but it could be explained by the fact that there is a physiological decrease of 0.5 to 1 ml/min of GFR from 40 years. This would be a factor that, combined with external aggression and immunosuppression, will precipitate the evolution to a kidney disease.

Several population studies have shown that the prevalence of moderate to severe kidney disease increases with age. In the general western population, the different series have shown that one of the main determinants of kidney disease is age. Nevertheless, this age is high (around 75 years in the largest French and American series). Age is considered as a non-modifiable risk factor for disease and kidney disease [18] [19] [20]. Cao in his study found in addition to age as a risk factor for kidney disease, high blood pressure, co-infection with the hepatitis C virus and viral load greater than 100,000 copies/ml. Our work being retrospective suffers from lack of data. Arterial pressures were poorly collected, viral load was not achieved and the search for hepatitis C was non-existent in our database. In our work, outside of age and sex, leukocytosis was associated with kidney disease. Msango in 2011 in Tanzania translated this relationship between kidney disease and the severity of HIV disease by the clinical stage and especially the

BMI below 18.5 kg/m^2 which was statistically significant in her work. Although it can occur at all stages of HIV disease, the typical attack of HIV-related chronic nephropathy, known as HIVAN, is usually a complication of advanced stages [21]. The virus causes many inflammatory phenomena, infestation of podocytes and atherosclerotic lesions. Individuals of African descent are predisposed to HIVAN. Genetic variants of recent African origin might account for this susceptibility and were mapped by admixture linkage dysequilibrium (MALD) (1). The Infectious and Tropical Diseases department is not the only site for the care of PLWHA in Togo. It brings together all cases of HIV Sylvanus Olympio CHU and surrounding neighborhoods, and cases of relatively serious patients with many comorbidities. This may overestimate kidney disease cases in our sample. Our results are therefore not transferable to the general population. In addition, there were several missing data with several badly filled or unfilled notebooks. For example, serum creatinine was not always reported in mg/L, the reference unit of the Hospital and Service Software, resulting in outliers of creatinine without any use; 46.4% of the population was not included in our study. Indeed, some information sought was not found: blood pressure, viral load, weight, height. Although biochemical examinations were routinely done at the initiation of treatment, some data was not reported. Based on the estimation of glomerular filtration rate, we calculated the creatinine clearance by the simplified MDRD formula. Much better than the Cockcroft and Gault equation because it is indexed to the body surface and not to muscle mass, this MDRD equation is well known for its inaccuracy in the extreme values of eGFR, or in severe alterations of renal function [7]. The latest consensus of KDIGO recommended the use of the CKD-EPI equation which in our context remains illusory due to the lack of international indexing of creatinine. Indeed the traced creatinine or IDMS is essential to the calculation of the clearance by CKD EPI. Despite this, the MDRD equation holds its place because it has been validated in several reference works.

5. Conclusion

Kidney disease in people living with HIV is a scourge. This work shows that 41.8% of people living with HIV have kidney disease even before initiation of antiretroviral therapy. The post-HIV era, if it could exist, will give way to a bigger catastrophe, that of kidney disease, in which the costs of care are enormous. It is now necessary to work in the prevention by associating all the medical fields to the care of infectiology. A multicentric work in prospective is needed to make the clarification.

Conflicts of Interest

The authors do not declare any conflict of interest.

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