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Prevalence of Chronic Kidney Disease and Associated Factors among HIV Patients in the Era of HAART in Ivory Coast: A Cross Sectional, Analytical Study

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Abstract

Background: Chronic kidney disease (CKD) may be common among HIV patients living in sub-saharan Africa due to the confluence of CKD risk factors and genetic predisposition. Preventive strategy through early detection and treatment has been advocated for CKD in Africa where majority of patients present late and cannot afford the cost of renal replacement therapy which is not widely available. The purpose of this study was to identify the prevalence and factors associated with CKD among HIV infected adults receiving HAART in a teaching hospital in Ivory Coast. Methods: This is a cross-sectional study of HIV patients on Highly Active Anti Retroviral Therapy followed at the HIV clinic of the medical out-patient department of the University teaching hospital of Bouaké from January to December 2021. CKD was defined as a serum creatinine-based estimated glomerular filtration rate ≤ 60 ml/min/1.73 m^2. The collected data was analyzed by using Epi Info 2002 software. Results: Four hundred and two HIV-infected adults 18 years and over were recruited during the study period. We noticed 123 (30.6%) males. The mean age was 40 years. CKD was observed in 42 (10.44) patients infected-HIV. Eighty eight point three percent of patients had CD4 more than 500 cells. Low eGFR correlated with age more than 60 years old, worker in public sector, unemployed, no formal education and HIV type 2. Conclusion: Our study identified a prevalence of CKD of 10.44% by CKD EPI equations among HIV patients on HAART that attended the teaching hospital of Bouaké in Ivory Coast. Early screening and follow up of renal functions is important to minimize the risk of developing end stage kidney disease.

Keywords

HIV, CKD, Prevalence, Africa

1. Introduction

The introduction of highly active antiretroviral therapy (HAART) has reduced mortality and the overall prognosis for Human Immunodeficiency virus (HIV)-infected patients shifted from years to decade [1]. Prolonged use of antiretroviral therapy and the consequent increased of longevity of HIV patients had led to emergence of non-AIDS-related outcomes, including cardiovascular disease, malignancies, bone and renal disease. Now, increasing attention is directed towards prevention and treatment of co morbidities and the side effects of antiretroviral therapy. Kidney disease in patients with HIV, considered as one of the most common complication, is caused by different pathophysiological mechanism and has as an aggravating factor: the inflammatory processes resulting from HIV infection and the cumulative exposure of potentially nephrotoxic antiretrovirals [2]. HIV infection is a well-established risk factor for Chronic Kidney Disease (CKD) and end stage renal disease (ESRD) also renal diseases increase the risk of progression to AIDS and deaths as well as the risks of side effects of antiretroviral with proteases inhibitors [3].

The prevalence of CKD associated with HIV varies geographically, by population, due to genetic heterogeneity, to the initiation of the ART and to the different definition methods for CKD in each region, varying between 2% and 38% [4]. On a worldwide scale, the prevalence of chronic kidney disease (CKD) among people living with HIV (PLHIV) is estimated at 6.4%. This prevalence varies across regions, with 7.9% in Africa, 7.1% in North America, 5.7% in Asia and 3.7% in Europe [4]. In the African continent, West Africa has highest rate with a prevalence of 14.6% and Southern Africa is the least affected with a prevalence of 3.2% [4]. Given the high burden of HIV in Africa, HIV afflicts kidney, majority of patients present late and cannot afford the cost of renal replacement therapy which is not widely available, there is a need for identification of early modifiable risk markers of CKD and an investigation of kidney function to promote the identification of new therapeutic targets and the formulation of effective treatment and prevention strategy. The aim of our study was to assess the prevalence of CKD and to determine factors associated with CKD in a west Afica country among HIV-infected patients on HAART.

2. Methods

This is a cross-sectional study carried out at the Day Care Unit (DCU) of the teaching hospital of Bouaké over one year (January to December 2021). Bouaké is located in central part of the country, about 300 km far away from Abidjan, the economic capital of Côte d'Ivoire. With a population of approximately 1.5

million persons, it is the second most populous city of the country. The DCU is part of the Infectious Disease Department and specializes in the care of Person Living with HIV (PLHIV). This HIV clinic is the first one of the thirteen specialized care services for PLHIV in the city.

The study population consisted of all individuals in the HIV registry who met the following 5 inclusions criterias: [1] of both genders, [2] over 18 years of age, [3] receiving HAART more than one year, [4] having medical records and more than one creatinine test result done in 2021 and [5] giving the written informed consent. Individuals with risk factors for chronic kidney disease such diabetes mellitus, hypertension, pre-existing renal failure, sickle cell disease, exposure to nephrotoxic agents such as traditional therapy or non-steroidal anti-inflammatory drugs; those diagnosed with acute or chronic kidney disease prior to the diagnosis of HIV positive; being on hemodialysis before starting ART, and having abandoned the use of anti-retroviral therapy were excluded from the study.

The data related to socio-demographic (age, gender, marital status, employment status, educational status and economic status), HIV infection parameters (type of HIV, recorded morbidities, CD4 lymphocyte count, clinical stage of HIV-infection, antiretroviral medications), clinical (weight, body mass index, blood pressure) and laboratory (serum creatinine, hemoglobin level) variables found in the medical records of patients were collected by the researcher using an instrument built for this study and submitted to face validation and content examination by three specialized professionals (one infectologists and two nephrologists). The data collection instrument, the free and Informed Consent Form, and the validation instrument of the collection instrument were filled by researcher for each participant. The researchers evaluated the instrument in terms of acceptance of the questioning, easy understanding, relevance of the items, clarity in the wording, presence of ambiguities, and were able to make suggestions for changes. After the analysis of the judges and necessary adjustments, a pilot study was carried out with 15 records of PLHIV in this DCU.

For assessment of kidney function, ten milliliters of venous blood was then obtained for serum creatinine at least 3 months after the first creatinine test done in 2021. Serum creatinine was estimated using the kinetic enzymatic method and estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula [5]. CD4+ T cell count was measured.

The diagnosis of CKD was documented if the patient had two consecutive determinations, measured with a 3-month interval or more, of an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 using the CKD-EPI formula that includes gender, ethnicity, age and creatinine values. The stage of CKD was determined by the eGFR rate (G1 stage: eGFR > 90 mL/min/1.73 m^2; G2 stage: eGFR 60 - 89 mL/min/1.73 m^2; G3 stage: eGFR 30 - 59 mL/min/1.73 m^2; G4 stage: eGFR 15 - 29 mL/min/1.73 m^2; G5 stage: eGFR < 15 mL/min/1.73 m^2) according to the diagnostic and classification criteria for CKD of the Kidney Disease Improving Global Outcomes (KDIGO) foundation [5]. Staging of HIV

infection was done according to clinical categories (category A: asymptomatic infection, acute infection, persistent generalized lymphadenopathy; category B: symptomatic infection, not A or C; category C: defining conditions of AIDS) and immunological categories (category 1: lymphocyte count > 500 cells/μL; category 2: lymphocyte count of 200 - 499 cells/μL; category 3: lymphocyte count < 200 cells /μL) of the revised classification system of HIV infection of the Centers for Disease Control [6].

Data were coded, cleaned, entered into excel spreadsheet and analyzed using Epi info 2002. Continuous variables were expressed as mean. Categorical variables were expressed as proportions and compared with the chi-square or Fischer exact test as appropriate. All statistical tests were two sided, and $p < 0.05$ was considered to be statistically significant. Data were compared between patients with and without CKD.

Ethical approval was obtained from the Teaching Hospital of Bouake Ethical review board. All participants provided signed informed consent written in French and explained in their preferred languages. The information obtained from the patient will remain confidential indefinitely.

3. Results

From a total of 510 HIV patients, 402 had quality data to assess the renal function at baseline and accepted to participate to the study.

The analysis of the demographic data found reveals the following results regarding age, sex, educational and marital status of the HIV patients (**Table 1**). One hundred twenty three (30.6%) and two hundred seventy nine (69.4%) patients were males and females respectively. The mean age was 48.1 years-old. Among the participants, 21 (5.2%) were less than 30 years. The majority (64.6%) was between 40 and 60 years-old. Those of 60 years-old and above were 53 (13.4%). Regarding marital status of the participants, 219 (64.9%) of them were single while thirty six were married, 36 (9%) were divorced and 61 (15.2%) widowed/widower. Concerning the educational background of the patients, 155 (38.5%) attended non formal education (illiterate), 124 (30.8%) attended primary education. Eighty eight (21.9%) of HIV patients attended secondary education and 35 (8.7%) attended College or University education level. When comparing the demographic characteristics between CKD patients and non-CKD patients, we noticed that statistically significant difference was observed for age over 60 years-old, being illiterate and unployement status.

The history of HIV and clinical data has been shown in **Table 2**. Patients were infected by HIV 1 in 380 (85.8%) cases, HIV 2 in 19 (12.9%) cases and HIV Dual in 3 (1.4%). Most (78.9%) HIV-infected patients had been diagnosed for 5 years and above. The HIV patients reported an episode of Herpes zoster virus infection in 116 (28.9%) and tuberculosis in 34 (8.4%). Sixty four (15.9%) patients were clinical stage A; 264 (65.7%) stage B and seventy four (18.4%) stage C. Blood pressure measured was high in 82 (20.4%) cases and normal in 320 (79.6%). Obesity (BMI > 30 kg/m^2) was seen in 54 (13.4%) patients of the study

Table 1. Demographics characteristics by CKD status (n = 402).

Variables	CKD (n = 42)	No CKD (n = 360)	p value	Overall
Gender				
Males	31% (13)	30.6% (110)		30.6% (123)
Females	69% (29)	69.4% (250)	0.9579	69.4% (279)
Age (years)				
Less than 20	0% (0)	0.8% (3)	0.5526	0.7% (3)
[20 - 30]	0% (0)	5% (18)	0.1382	4.5% (18)
[30 - 40]	9.5% (4)	17.5% (63)	0.1893	16.7% (67)
[40 - 50]	21.4% (9)	35.8% (129)	0.0628	34.3% (138)
[50 - 60]	35.7% (15)	29.7% (107)	0.4241	30.3% (122)
60 and over	33.3% (14)	11.1% (40)	**0.0001**	13.4% (53)
Marital status				
Single	69% (29)	72.8% (262)	0.3547	72.4% (291)
Married	4.8% (2)	9,4% (34)	0.3145	9% (36)
Divorced	2.4% (1)	3.6% (13)	0.6807	3.5% (14)
Widower	23.8% (10)	14.2% (51)	0.0993	15.2% (61)
Employment status				
Private sector	69% (29)	64.4% (232)	0.5541	64.9 % (261)
Retired	7.1% (32)	4.2% (15)	0.3775	4.5% (18)
Public sector	0% (0)	18.3% (66)	**0.0024**	16.4% (66)
unemployed	23.8% (10)	13.1 % (47)	**0.0078**	14.1 %(57)
Educational status				
Illiterate	50% (41)	37.2% (132)	**0.0001**	38.5 % (155)
Primary school	26.2% (11)	31.4% (113)	0.49	30.8% (124)
Secondary school	21.4% (9)	21.9% (79)	0.94	21.9% (88)
University level	2.4% (1)	9.4% (34)	0.13	8.7% (35)
Economic status				
Low	2.4% (1)	7.5% (27)	0.22	7% (28)
Middle	97.6% (41)	89.7% (323)	0.098	90.5% (364)
High	0% (0)	2.8% (10)	0.27	2.5% (10)

Table 2. Relationship between HIV history, clinical parameters by CKD status (n = 402).

Variable	CKD (n = 42)	No CKD (n = 360)	p value	Overall
Type of HIV				
HIV-1	88.1% (37)	95.3% (343)	0.0528	85.8% (380)
Dual HIV	0% (0)	0.8% (3)	0.5526	12.9% (19)
HIV- 2	11.9% (5)	3.9% (14)	**0.0205**	1.4% (3)

Continued

Duration of the infection				
Less than 2 years	0% (0)	0.7% (3)	1	0.7 (3)
2 - 5 years	12.2% (5)	21.3% (77)	0.1599	20.4% (82)
More than 5 years	87.8% (37)	78% (280)	0.1353	78.9% (317)
Opportunist infections				
Herpes Zoster virus infection	19% (8)	30% (108)	0.1382	28.9% (116)
Toxoplasmosis	2.4% (1)	1.4% (5)	0.6158	1.5% (6)
CMV infection	2.4% (1)	0.3% (1)	0.0668	0.5% (2)
Candidiasis	4.8% (2)	3.3% (12)	0.6327	3.5% (14)
Pneumonia	0% (0)	0.6% (2)	0.6282	0.5% (2)
Herpes virus infection	0% (0)	2.8% (10)	0.274	2.5% (10)
Tuberculosis	7.1% (3)	8.6% (31)	0.7462	8.4% (34)
CDC Stage				
Category A	11.9% (5)	16.4% (59)	0.4523	15.9% (64)
Category B	64.3% (27)	65.8% (237)	0.8416	65.7% (264)
Category C	23.8% (10)	17.8% (64)	0.3398	18.4% (74)
Body mass index				
Underweight	19% (8)	21.9% (79)	0.6662	21.6% (87)
Normal	73.8% (31)	55.3% (199)	**0.0216**	57.2% (230)
Overweight	2.4% (1)	8.3% (30)	0.1712	7.7% (31)
Obesity	4.8% (2)	14.4% (52)	0.0816	13.4% (54)
High blood pressure				
Yes	19% (8)	20.6% (74)	0.8185	20.4% (82)
No	81% (34)	79.4% (286)		79.6% (320)

population, and overweight (BMI 25.0 - 29.9 kg/m^2) in 31 (7.7%). Comparing the groups, the type of HIV, they were more CKD in the genotype HIV 2. No statistically significant difference was found for the remaining variables shown in Table 2.

The prevalence of CKD (G3 stage, G4 stage and G5 stage) in our HIV-infected population was 10.4% (n = 42) according eGFR criterion (eGFR < 60 mL/min). Overall 88.3% had CD4 counts above 500 cells/mm3. Up to 15% had moderate anemia hemoglobin level below 10 g/dl (Table 3). There was no significant association between CD4 counts, hemoglobin level between the group of patients with CKD and those without CKD.

The three most-prescribed treatment regimens for first line of treatment (93.5%) were tenofovir (TDF) + lamivudine (3TC) + efavirenz (EFV) (72.9%), or stavudine (d4T) + 3TC + EFV (10.4%) or zidovudine (AZT) + lamivudine (3TC)

Table 3. Laboratory characteristics of HIV patients (n = 402).

Biological Parameters	Number	Percentage
eGFR		
G1 stage	252	62.6
G2 stage	108	26.8
G3 stage	37	9.2
G4 stage	3	0.7
G5 Stage	2	0.5
Hemoglobin level		
7 - 10 g/dl	62	15.4
10 - 12 g/dl	180	44.8
More than 12 g/dl	160	39.8
CD4 counts		
Less than 350	12	3.0
350 - 500	35	8.7
More than 500	355	88.3

+ efavirenz (EFV) or nevirapine (NVP) (10.2%). The second line ARTs (6.2%) were based on Integrase Inhibitors (INsTI), Abacavir (ABC)/Lamivudine (3TC)/ Dolutegravir (DTG) or TDF/FTC/Elvitegravir/Cobicistat (EVG/COBI). Their mean time on antiretroviral therapy was over 5 years (Table 4). There was no significant association between the treatment used, duration of treatment and the occurrence of CKD.

4. Discussion

Infection with HIV is epidemic in Sub-Saharan Africa and is a well-established risk factor for kidney disease. CKD is currently one of the most important causes of morbidity and mortality among so called non-AIDS diseases in HIV-infected patients, ranking the fourth after malignancies, cardiovascular diseases, and liver diseases, according to some authors [7]. Guidelines recommend screening for CKD in HIV-infected patients before initiation of ARV treatment and during the follow-up. In Ivory Coast, as in most countries in SSA, despite the recommendations, screening the kidney disease is not routinely performed. A wide variation in the prevalence of CKD is found in different locations, which is justified by the heterogeneous population, regional, cultural, structures of access to health services and differences in diagnostic criteria. Based on the first systematic review that provided prevalence estimates for CKD in PLHIV in various regions of the World Health Organization, using the CKD-EPI equation, a prevalence of 4.8% was identified, with the highest prevalence found in Africa and the lowest in Europe [4].

Among the 402 HIV patients analyzed in our study, we found that the prevalence of CKD was 10.4%. Age ≥ 60 years old, illiterate patient, unemployed

Table 4. Comparison of therapeutics data between patients with and without CKD.

Parameters	CKD (n = 42)	CKD (n = 360)	p value	Overall
Use of Cotrimoxazole				
Yes	42.9% (18)	39.4% (142)	0.669	39.8% (160)
No	57.1% (24)	60.6% (218)		60.2% (200)
Antiretroviral therapy				
First line	97.6% (41)	93.1% (335)	0.2552	93.5% (376)
Second line	2.4% (1)	6.9% (25)		6.5% (26)
Duration of the treatment				
Less than 2 years	0% (0)	1.3% (5)	1	1.2% (5)
2 to 5 years	16.3% (7)	26.7% (96)	0.1419	25.6% (103)
Over 5 years	83.7% (35)	72% (259)	0.1019	73.2% (294)

patients and HIV type 2 were variables that showed a statistically significant association with CKD. The prevalence found in our study was similar to that obtained by Halle and colleagues in Cameroun using the same definition and same population with a CKD prevalence of 11.6% among 709 HIV patients [8]. High prevalence were observed in Nigeria (38%) and in Tanzania (28.4%) [9] [10]. The method of evaluation of CKD prevalence is dependent on the approach used to assess GFR. The method used to determine GFR in the absence of a direct measure of GFR was the serum creatinine-based-estimated GFR. We used CKD EPI among the formulas existing. The three main equations used to estimate the kidney also yielded different results and have limitations. The Cockcroft-Gault equation adjusts for muscle mass and gender but not for tubular reabsorption of creatinine. The MDRD also using serum creaitinine, again does not account for tubular reabsorption of creatinine. The CKD-EPI (CKD Epidemiology Collaboration) also based upon serum creatinine is more accurate than the MDRD equation or the Cockcroft-Gault in the persons with the normal functions and HIV person. Cystatin C has been proposed as an alternative to creatinine as is not influenced by muscle mass and tubular secretion. Measuring GFR using inulin, iohexol or iothalamate clearance result in a more accurate understanding of the prevalence of CKD. Some authors concluded that until creatinine and cystatin C based eGFR are compared to a gold standard the best estimate of renal function in HIV infected persons remains unclear [11].

Being the age of 60 and over has been shown in our study to be a factor associated for CKD. This corroborates with other researchers who point out that, with increasing age there is a greater predisposition to lower eGFR, to greater regression of renal function and, consequently, to develop CKD [12]. The relationship between increasing age and CKD was also studied by some studies. In a multi-center cohort carried people aged between 50 and 60 years old, there was an increase from 5.2% to 7.2% while, among those over 60, there was an increase

from 18.5% to 23.2% of CKD [13]. As with any organ, the immune system shows change with aging. These changes are a progressive thymic involution, increased level of pro-inflammatory cytokines and aging of the stem cell populations [14]. Manifestations of chronic immune activation include increased T cell turnover and increased serum levels of pro-inflammatory cytokines and chemokines. Characteristic of premature aging among PLHIV causes middle-aged adults using ART to have a high inflammatory exposure and, therefore, premature onset can occur of chronic comorbidities, such as CKD [15]. Also, aging leads to a physiological decline in eGFR of about 8 ml/min/1.73 per decade after 40 years.

HIV-2 was another factor associated with CKD in our study. HIV-2 infection is characterized by lower plasma viral loads, slower CD4 count decline, longer symptomatic stage, and slower disease progression. However, the majority of HIV-2-infected persons will progress to AIDS and death if untreated because HIV-2 is intrinsically resistant to many antiretroviral agents and treatment options are limited [16]. Scarce data are available about chronic kidney disease and HIV-2.

The aetiology of CKD in PLWHIV may be related to the HIV-infection and associated viral replication itself or, more commonly, be due to manifestations of a patient's NICMs, or from side effects of ART. Antiretroviral agents can cause direct toxicity to the kidney, in particular, tubular dysfunction, interstitial nephritis and renal calculi. TDF has also been associated with CKD. The precise mechanisms of TDF-associated nephrotoxicity are complex; it is associated with acute tubular necrosis of proximal renal tubular cells and with abnormally enlarged mitochondrial within these cells. Risk factors for TDF-nephrotoxicity include increased age, lower baseline renal function and duration of exposure [17]. Unfortunately we did not find any association between antiretroviral therapy (regimen with or without TDF) and CKD.

Our study has some limitations. Assessment of proteinuria was not done and may have affected the prevalence of CKD. Proteinuria has been shown to be an important marker of CKD. The viral load was not done due to financial constraints but if could have helped to relate low eGFR to viral load.

5. Conclusion

Our study reports a CKD prevalence of 10.4 in a cohort of 402 PLVIH in Ivory Coast where 64.6% were more than 40 years of age. Age ≥ 60 years old, illiterate, unemployed and HIV type 2 were associated with CKD. There is a critical need of data that would help to further characterize the magnitude of CKD burden in HIV population. Thus, knowing the prevalence of CKD and factors associated with CKD helps in its identification and can support the clinical decision of the health professionals.

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Author's Contribution

All authors participated in the preparation of this manuscript and have read and approved the final version.

Conflicts of Interest

The authors declare no competing interests.

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