

Prevalence of Chronic Kidney Failure and Associated Factors in Patients Treated by Antiretroviral in the National Teaching Hospital of Cotonou

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Abstract

Objectives: To determine the frequency of the chronic kidney failure (CKF) in people living with HIV (PLHIV) on antiretroviral treatment (ART) and to identify associated factors.

Methods: This cross-sectional, descriptive and analytical study, conducted in the Outpatient Centre of PLHIV in the National Teaching Hospital of Cotonou from April to July of 2013. Were included, PLHIV aged over 16 years, taking ART for at least three months and having in their file, creatinine at ART initiation. Creatinine was performed at inclusion in the study. Proteinuria was sought on the strip. Chronic kidney failure was defined as creatinine clearance calculated according to Cockcroft-Gault less than 60mL/min for at least 3 months. Factors associated were searched by logistic regression univariate and multivariate analysis. Confidence intervals were calculated at 95% and alpha level was 5%.

Results: A total of 480 patients participated in the study (73.3% women; mean age 41.4 ± 9.16 years, in school: 64.6%). The prevalence of chronic kidney failure was 18.7%. The main factors associated in univariate analysis were age ($p < 0.001$), BMI ($p < 0.001$), educational level ($p = 0.03$), the exposure time to ART ($p < 0.001$) and the loss of kidney function at the initiation of ART ($p < 0.001$); in multivariate analysis: age ($p < 0.001$), sex ($p < 0.001$), the body mass index ($p < 0.001$), the loss of kidney function at ART initiation ($p = 0.034$) and didanosine ($p = 0.007$).

Discussion and conclusion: The prevalence of chronic kidney failure in patients receiving ART is high. The creatinine serum in biological monitoring in the ART or better to determine the glomerular filtration rate among PLHIV at least every six (6) months remains a necessity.

Keywords: Antiretroviral treatment; Benin; Chronic kidney failure; Clearance of creatinine; HIV; Logistic regression; Prevalence

Introduction

HIV infection is globally a public health issue. According to estimates, in 2012, 35.3 million people were living with HIV worldwide, including 25 million in sub-Saharan Africa. An overall increase is recorded compared to previous years due to the increase in the number of people on antiretroviral therapy [1].

HIV spares no organ: the digestive tract, brain, lungs, and kidneys. HIV infection is the third leading cause of kidney failure among Blacks American from 20 to 64 years [2]. In the United States, in 2007, the annual incidence of chronic kidney disease in the population infected with HIV was estimated at 9.7/100 patient-years; six times higher than that observed in the non-infected with HIV population [3].

In France, the prevalence of kidney failure in a cohort study of 7378 patients with HIV was 4.7% [4].

In Africa, on the contrary, this prevalence is four times higher than in developed countries [3]. Particular genetic susceptibility to the development of HIV-Associated with Nephropathy (HIVAN) is now clearly established in the Black race [3]. The HIVAN is the leading cause of kidney failure in African HIV [2]. Benin is a country in West Africa which has 9.983 884 million inhabitants according to the results of the last census in 2013 [5]. The prevalence of HIV infection in 2013 in the general population was estimated at 1.1% [6]. It is a low-prevalence country. According to national standards and procedures for the management of HIV infection in Benin, the detection of kidney disease in people with HIV is necessary at the initiation of antiretroviral treatment followed by regular biannual control [7]. This directive is not always respected for various reasons, as is probably the case in many developing countries, especially in Africa. This study aims to determine the frequency of chronic kidney failure in people with HIV on Anti-

retroviral Treatment (ART) and to identify associated factors.

Framework and Study Methods

This is a cross-sectional, descriptive and analytical study which is conducted from 24 April to 5 July 2013 in the national teaching Hospital "Hubert Maga Koutoukou" (CNHU-HKM) of Cotonou specifically in the Ambulatory Treatment Centre (ATC) of HIV bearers.

Were included patients aged over 16 years treated with antiretroviral for at least three months received in consultation during the study period and having in their record serum creatinine at initiation of treatment antiretroviral. Pregnant women, postpartum women (less than three months) and patients who refused to participate to the study were excluded. So we included only prevalent patients who came for control during the period of study which is 3 months. All patients were receiving antiretroviral therapy for several months or several years. Each enrolled patient received a clinical examination, research proteinuria by dipstick and serum creatinine dosage. The data at initiation of antiretroviral therapy such as WHO stage, CD4 count and creatinine serum, as well as molecules of antiretroviral treatment used were recorded from medical records.

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The dependent variable was chronic kidney failure (CKF) defined by creatinine clearance calculated by Cockcroft and Gault less than 60mL/min for at least 3 months. The independent variables were socio-demographic characteristics (age, gender, and education level), the history, CD4 count at initiation, creatinine clearance at the initiation of ARV treatment, proteinuria by dipstick and molecules of ART. The data collection was done through a survey sheet. These were entered and saved using the EPI DATA 3.1 software. Their analysis was performed using STATA software. Factors associated with the chronic kidney failure were searched by logistic regression univariate and multivariate analysis. Confidence intervals were calculated at 95% and the significance level of 5%.

Results

In total, 480 people living with HIV which 99.4% were living with HIV-1 were included in this study.

General characteristics of the population

Socio-demographic characteristics of the population: The average age of the population was 41.42 ± 9.16 years, ranging from 18 to 73 years. Other socio-demographic characteristics were presented in Table 1.

History and clinical data: A history of hypertension was found in 12.3% of patients; 3.1% had diabetes known; and 25.2% had lost of kidney function at the initiation of antiretroviral therapy. The stage 2 of the WHO was represented with 44.8%. Other clinical data are presented in Table 2.

Therapeutics characteristics: The therapeutic regimens of first-line anti-retrovirals prescribed to patients based on two (02) nucleosides reverse transcriptase inhibitors + one (1) non-nucleoside reverse transcriptase inhibitor. Those second line comprised two (02) nucleosides reverse transcriptase inhibitors + one (1) protease inhibitor. Table 3 shows the distribution of patients according to exposure to antiretroviral drugs.

Prevalence of chronic kidney failure among people living with HIV on ART

The prevalence of chronic kidney failure in people living with HIV treated with anti-retroviral was 18.7% (Figure 1).

| | Number N=480 | Percentage |
|------------------------|--------------|------------|
| Age (year) | | |
| < 35 | 114 | 23.7 |
| [35-41] | 121 | 25.2 |
| [41-47] | 111 | 23.1 |
| ≥ 47 | 134 | 30 |
| Gender | | |
| Male | 128 | 26.7 |
| Female | 352 | 73.3 |
| Education level | | |
| Not schooled | 135 | 28.1 |
| Primary | 175 | 36.5 |
| Secondary | 146 | 30.4 |
| Higher | 24 | 5 |
| Origin | | |
| Cotonou | 248 | 51.7 |
| Other cities | 232 | 48.3 |

Table 1: Distribution of patients by socio-demographic characteristics.

| | Number N=480 | Percentage |
|--|--------------|------------|
| Hypertension | | |
| No | 421 | 87.7 |
| Yes | 59 | 12.3 |
| Diabetes | | |
| No | 465 | 96.9 |
| Yes | 15 | 3.1 |
| Loss of KF at the ART initiation | | |
| No | 359 | 74.8 |
| Yes | 121 | 25.2 |
| WHO[™] stage at the ART initiation | | |
| Stage 1 | 52 | 10.8 |
| Stage 2 | 215 | 44.8 |
| Stage 3 | 191 | 39.8 |
| Stage 4 | 22 | 4.6 |
| CD4 rate at the ART initiation | | |
| < 350 | 454 | 94.6 |
| ≥ 350 | 26 | 5.4 |
| Body Mass Index | | |
| < 18.5 | 55 | 11.5 |
| [18.5-25] | 271 | 56.4 |
| [25-30] | 106 | 22.1 |
| ≥ 30 | 48 | 10.0 |
| Proteinuria | | |
| No | 423 | 88.1 |
| Yes | 57 | 11.9 |

Table 2: Distribution of patients according to the history and clinic data. *Kidney Function; [™]World Health Organisation

Factors associated with chronic kidney failure in PLHIV on univariate analysis

Among the socio-demographic factors, only age (p<0.001) and education level (p=0.03) were associated with chronic kidney failure in PLHIV. No history was associated. The body mass index (p<0.001), the time of exposure to ART (p<0.001) and the loss of kidney function at the initiation of ART (p<0.001) were also associated (Table 4).

CD4 rate, proteinuria and no antiretroviral molecule were not associated with chronic kidney failure as shown in Table 5.

Factors associated with chronic kidney failure in PLHIV receiving antiretroviral treatment in multivariate analysis

In multivariate analysis, age (p<0.001), sex (p<0.001), the body mass index (p<0.001) and the loss of kidney function at the initiation of antiretroviral therapy (p=0.034) remained associated with chronic kidney failure in PLHIV. The didanosine (6.85 [1.59-29.43], p=0.007) was associated and patients treated with this drug had nearly seven (7) times the risk of developing chronic kidney failure than those who were not treated by this molecule as shown in Table 6.

Discussion

All patients were received and examined by the same doctor who

| | Number N=480 | Percentage |
|--|--------------|------------|
| Nucleoside Reverse Transcriptase Inhibitors | | |
| Zidovudine (AZT) | 412 | 85.8 |
| Lamivudine (3TC) | 471 | 98.1 |
| Stavudine (D4T) | 228 | 47.5 |
| Abacavir (ABC) | 16 | 3.3 |
| Didanosine (DDI) | 12 | 2.5 |
| Emtricitabine (FTC) | 3 | 0.6 |
| Nucleotide Reverse Transcriptase Inhibitor | | |
| Ténofovir (TDF) | 62 | 12.9 |
| Non Nucleoside Reverse Transcriptase Inhibitors | | |
| Efavirenz (EFV) | 286 | 59.6 |
| Névirapine (NVP) | 206 | 42.9 |
| Protease Inhibitors | | |
| Lopinavir (LPV) | 42 | 8.7 |
| Indinavir (IDV) | 18 | 3.7 |
| Nelfinavir (NFV) | 10 | 2.1 |
| Saquinavir (SQV) | 4 | 0.8 |
| Amprénavir (APV) | 2 | 0.4 |

Table 3: Distribution of patients according to exposure to antiretroviral drugs.

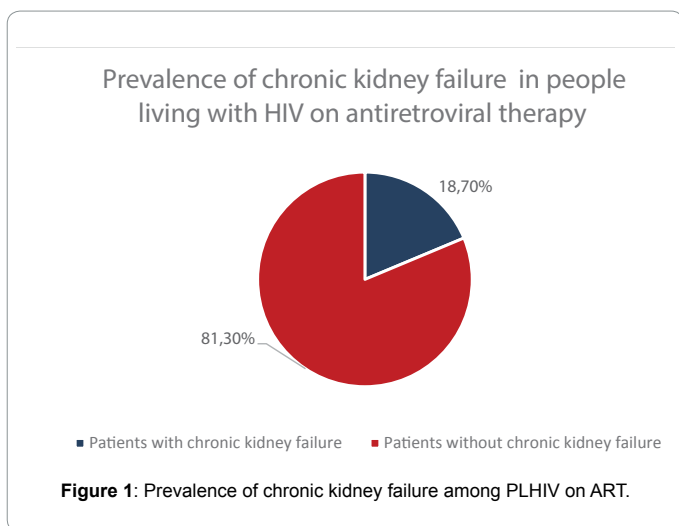


Figure 1: Prevalence of chronic kidney failure among PLHIV on ART.

carried out the data collection. The serum creatinine dosage was performed in the same laboratory. It's a single centre study though.

Prevalence of chronic kidney failure in people with HIV

There is a high variability in the prevalence of kidney failure in people with HIV. This is related to the parameters of assessment of kidney function that differ from one study to another. It can be qualitative or quantitative proteinuria associated or not with an estimate of the glomerular filtration rate. According to Naicker, the prevalence of chronic kidney disease in Sub-Saharan Africa varied between 6% and 48.5% [8]. Emem studying kidney disease defined by the presence of proteinuria positive dipstick and/or serum creatinine higher than or equal to 132 $\mu\text{mol/L}$ (15 mg/L) in seropositive-HIV patients in Nigeria had found a prevalence of 38% [9]. Similarly, in Uganda, Andia had found a prevalence of chronic kidney disease to 48.5% in Patients with HIV [10].

The observed prevalence in our study (18.7%) is higher than that observed in Rwanda (2.4%) [11]. In this Rwandan study led by Wyatt et al., [11] it is the equation of MDRD (Modification of Diet in Renal

| | CKF ^a n (%) | No CKF ^a n (%) | OR [IC-95%] | P |
|---|------------------------|---------------------------|-------------------|------------------|
| Age (years) | | | | |
| < 35 | 13(11.4) | 101(88.6) | 1 | <0.001 |
| [35 – 41] | 19(15.7) | 102(84.3) | 1.44[0.67 – 3.08] | |
| [41 – 47] | 14(12.6) | 97(87.4) | 1.12[0.50 – 2.50] | |
| ≥ 47 | 44(32.8) | 90(67.2) | 3.79[1.92 – 7.50] | |
| Education level | | | | |
| Not schooled | 27(20.0) | 108(80.0) | 1 | 0.03 |
| Primary | 42(24.0) | 133(76.0) | 1.26[0.73 – 2.18] | |
| Secondary | 19(13.0) | 127(87.0) | 0.59[0.31 – 1.13] | |
| Higher | 2(8.3) | 22(91.7) | 0.36[0.08 – 1.64] | |
| BMI^b | | | | |
| < 18.5 | 30(54.5) | 25(45.5) | 5.43[2.94– 10.04] | <0.001 |
| [18.5-25] | 49(18.1) | 222(81.9) | 1 | |
| [25-30] | 9(8.5) | 97(91.5) | 0.42[0.19 – 0.88] | |
| ≥ 30 | 2(4.2) | 46(95.8) | 0.19[0.04 – 0.83] | |
| Exposure time (month) | | | | |
| < 29 | 14(11.7) | 106(88.3) | 1 | <0.001 |
| [29-51] | 15(12.5) | 105(87.5) | 1.08[0.49 – 2.35] | |
| [51-97] | 26(21.7) | 94(78.3) | 2.09[1.03 – 4.24] | |
| ≥ 97 | 35(29.2) | 85(70.8) | 3.11[1.57 – 6.16] | |
| Loss of KF^c at the ARV initiation | | | | |
| No | 43(12.0) | 316(88.0) | 1 | <0,001 |
| Yes | 47(38.8) | 74(61.2) | 4.67[2.87 – 7.58] | |

Table 4: Factors associated with chronic kidney failure in PLVIH in univariate analysis.

Disease) that was used to estimate the GFR.

In Europe, Mocroft had found in a study of chronic kidney failure in patients infected with HIV a prevalence of 3.5%. In this study, chronic kidney failure was defined as a glomerular filtration rate less than or equal to 60 mL / min/1.73 m² dating back at least three months [12].

The highest prevalence's are observed in black Africa. This can be explained by the fact that in a HIV population, the black is more affected by the kidney disease than the white [8].

Factors associated with chronic kidney failure among HIV patients on antiretroviral treatment in univariate analysis

Chronic kidney failure affects all age groups in this population. We observed that age was associated with chronic kidney failure; and those over 47 years had more than 3 times the risk (OR=3.79; p<0.001) of developing chronic kidney failure. Emem had found that age was associated with chronic kidney failure (p=0.016). He noted that more patients are older; more the risk to chronic kidney failure appears [9].

We observed the level of education was associated with the occurrence of chronic kidney failure (p=0.03) and a subject of primary level and HIV carrier had a higher risk (OR [95%] = 1.26 [0.73 to 2.18])

| | CKF n (%) | No CKF n (%) | OR [IC-95%] | P |
|--|-----------|--------------|--------------------|-------------|
| Gender | | | | 0.05 |
| Male | 17(13.3) | 111(86.7) | 1 | |
| Female | 73(20.7) | 279(79.3) | 1.70[0.96 – 3.02] | |
| Hypertension | | | | 0.17 |
| No | 75(17.8) | 346(82.2) | 1 | |
| Yes | 15(25.4) | 44(74.6) | 1.57[0.83 – 2.97] | |
| Diabetes | | | | 0.17 |
| No | 89(19.1) | 376(80.9) | 1 | |
| Yes | 1(6.7) | 14(93.3) | 0.30[0.03 – 2.32] | |
| WHO[®] stage at initiation | | | | 0.23 |
| Stage 1 | 6(11.5) | 46(88.5) | 1 | |
| Stage 2 | 45(20.9) | 170(79.1) | 2.02[0.81 – 5.05] | |
| Stage 3 | 37(19.4) | 154(80.6) | 1.84[0.73 – 4.63] | |
| Stage 4 | 2(9.1) | 20(90.9) | 0.76[0.14 – 4.13] | |
| CD4 rate at initiation | | | | 0.12 |
| < 350 | 82(18.1) | 372(81.9) | 1 | |
| ≥ 350 | 8(30.8) | 18(69.2) | 2.01[0.84 – 4.79] | |
| Proteinuria | | | | 0.17 |
| No | 75(17.8) | 346(82.2) | 1 | |
| Yes | 15(25.4) | 44(74.6) | 1.57[0.83 – 2.97] | |
| Didanosine | | | | 0.06 |
| No | 85(18.2) | 383(81.8) | 1 | |
| Yes | 5(41.7) | 7(58.3) | 3.21 [0.99– 10.38] | |
| Indinavir | | | | 0.34 |
| No | 85(18.4) | 377(81.6) | 1 | |
| Yes | 5(27.8) | 13(72.2) | 1.70 [0.59 – 4.91] | |
| Lamivudine | | | | 0.29 |
| No | 3(33.3) | 6(66.7) | 1 | |
| Yes | 87(18.5) | 384(81.5) | 0.45 [0.11 – 1.84] | |

Table 5: Factors not associated with chronic kidney failure in PLHIV treated by ART in univariate analysis.

of developing chronic kidney failure. Emem et al. did not observe any relationship between the level of education and the occurrence of kidney disease in people living with HIV ($p=0.423$) [9]. However, in recent years, socioeconomic factors are recognized as major determinants of general population health status [13]. So for Krop et al., the occurrence of chronic kidney disease seems to be correlated to education [14].

According to Emem et al. a low Body Mass Index was associated with kidney disease in HIV infected patients ($p<0.001$) [9]. Indeed, more than half of patients (59.2%) in this study were thin. We also found that BMI was associated with chronic kidney failure and lean patients had more than 5 times the risk of developing chronic kidney failure (OR [95% CI] = 5.43 [2.94 - 10.04], $p<0.001$).

The time of exposure to antiretroviral therapy was associated with the occurrence of chronic kidney failure ($p<0.001$). Our results show that the risk of developing chronic kidney failure increases with the exposure time (Table 4).

The loss of kidney function at the initiation of ART was associated with chronic kidney failure ($p=0.034$). The loss of kidney function was observed in 121 patients at the initiation of ART. It persisted in only 47 patients at the time of the study. We note that kidney function improved in 74 patients after the initiation of ART. We can explain that by many patients had acute kidney injury at the initiation of antiretroviral therapy which has evolved favorably after care. The HIVAN (HIV-Associated Nephropathy) is the first diagnosed kidney disease in people living with HIV in most studies [9,15]. These polymorphic clinical manifestations appear rare in Europe due to the early management of these patients [16]. The diagnostic confirmation of HIVAN requires achieving renal histological examination.

The sex was not associated with chronic kidney failure in our study ($P=0.05$). Emem et al. had found no link between gender and chronic kidney failure (OR = 0.062; $P = 0.80$) [9]. Cailhol et al. on the contrary had found that gender was associated with chronic kidney failure in people with HIV in Burundi, and female had a higher risk (OR=4.7; $P<0.01$) [17].

Hypertension is not associated with chronic renal failure ($P=0.17$). Hypertension is known as a “traditional risk factor” of chronic kidney failure in the general population and more with HIV patients. Indeed, Flandre and al. had found in France, in 2011, in a study of risk factors for chronic kidney disease in patients infected with HIV-1 that hypertension was associated with chronic kidney failure in these patients (OR=2.39, $p<0.01$) [4]. Krawczyk et al. had found in the United States that taking anti-hypertensive treatment is a factor associated with chronic kidney failure ($p=0.004$) [18]. It's important to note also that hypertension is one of the criteria used by the Infectious Diseases Society of America (IDSA) to describe HIV patients with a high risk of developing kidney disease [19].

Diabetes is found in only 3.1% of patients and was not significantly associated with chronic kidney failure ($p=0.17$). Diabetes is already a traditional risk factor for chronic kidney disease in the general population. Several studies had demonstrated that diabetes plays an important role in kidney disease in the HIV infected patients [3,10,20]. Krawczyk et al. in the United States ($p=0.259$) and Flandre et al. in France ($p=0.30$) did not find an association between diabetes and chronic kidney failure among HIV infected patients [4,18].

Proteinuria was not associated with chronic kidney failure in PLHIV ($P=0.17$). But early diagnosis of proteinuria is essential in HIV infected patients, because the abnormal increase in the urinary excretion of protein precede the elevation of serum creatinine and decreased glomerular filtration rate [21]. For Zaidana, urinary protein profile is a very interesting diagnostic guidance tool because it predicts the type of histological lesions [22].

CD4 count at initiation of antiretroviral therapy was not associated with chronic kidney failure ($P=0.12$). Several authors showed a significant relationship between CD4 count at initiation of ARV treatment and the occurrence of chronic kidney failure [3,9,20,23]. The severe immunosuppression generally favors the occurrence of opportunistic events (infectious, diarrhea, tuberculosis) that can be a source of renal impairment.

| | CKF ^a n (%) | No CKF ^a n (%) | OR gross [IC-95%] | OR adjusted [IC-95%] | P |
|---|------------------------|---------------------------|-------------------|----------------------|------------------|
| Age (years) | | | | | <0.001 |
| < 35 | 13(11.4) | 101(88.6) | 1 | 1 | |
| [35 – 41] | 19(15.7) | 102(84.3) | 1.44 [0.67–3.08] | 2.01 [0.87–4.66] | |
| [41 – 47] | 14(12.6) | 97(87.4) | 1.12 [0.50–2.50] | 1.11 [0.45–2.73] | |
| ≥ 47 | 44(32.8) | 90(67.2) | 3.79 [1.92–7.50] | 4.84 [2.13-11.00] | |
| Gender | | | | | <0.001 |
| Male | 17(13.3) | 111(86.7) | 1 | 1 | |
| Female | 73(20.7) | 279(79.3) | 1.70 [0.96–3.02] | 3.82 [1.85–7.89] | |
| BMI^b | | | | | <0.001 |
| < 18.5 | 30(54.5) | 25(45.5) | 5.43 [2.94–10.04] | 5.95 [2.94-12.04] | |
| [18.5-25[| 49(18.1) | 222(81.9) | 1 | 1 | |
| [25-30[| 9(8.5) | 97(91.5) | 0.42 [0.19–0.88] | 0.36 [0.16–0.82] | |
| ≥ 30 | 2(4.2) | 46(95.8) | 0.19 [0.04–0.83] | 0.11 [0.02 – 0.54] | |
| Loss of KF^c at the ARV initiation | | | | | 0.034 |
| No | 43(12.0) | 316(88.8) | 1 | 1 | |
| Yes | 47(38.8) | 74(61.2) | 4.67 [2.87–7.58] | 1.89 [1.05-3.42] | |
| Didanosine | | | | | 0.007 |
| No | 85(18.2) | 383(81.8) | 1 | 1 | |
| Yes | 5(41.7) | 7(58.3) | 3.21 [0.99-10.38] | 6.85 [1.59-29.43] | |

Table 6: Multivariate analysis of factors associated with chronic kidney failure in patients receiving ARV treatment. ^aChronic Kidney Failure; ^bBody Mass Index; ^cKidney Function

Factors associated with chronic kidney failure in people living with HIV on antiretroviral treatment in multivariate analysis

In multivariate analysis, age, sex, body mass index, didanosine and the loss of kidney function at the initiation of antiretroviral therapy were significantly associated with the occurrence of chronic kidney failure. Didanosine is a nucleoside reverse transcriptase inhibitor. It has rarely been implicated in the occurrence of kidney disease in people living with HIV. It generally results in these patients a proximal tubular dysfunction [24]. Gupta was found that of 164 cases of Fanconi syndrome, 83% were on tenofovir, 74% in ritonavir and 43% in didanosine [24]. We can also mention that the intensity of digestive disorders arising from the use of didanosine limit adequate hydration of patients which could lead to chronic kidney failure. In most studies, the molecules ARV most often associated with chronic kidney disease are tenofovir, indinavir, ritonavir and abacavir [7,25].

In our study, tenofovir was used by 12.9% of our patients and was not associated with the occurrence of chronic kidney failure. Indeed tenofovir molecule is controversial in numbers of studies. Someone had found that the use of long-term tenofovir resulted in a net decrease of glomerular flow filtration [26,27]; by against other showed a good renal safety of tenofovir [28-30]. Overall, it seems that tenofovir is not nephrotoxic in the long term at least when it is prescribed in patients without renal impairment [31].

Conclusion

The prevalence of chronic kidney failure is relatively high (18.7%) in our study. Factors associated with chronic kidney failure in univariate analysis were: age, body mass index, education level, exposure time to antiretroviral treatment and the loss of kidney function at the initiation of antiretroviral treatment. In multivariate analysis: age, sex, body mass index, the loss of kidney function at initiation of ART and didanosine

were associated.

It is important to ensure systematic monitoring of serum creatinine or better to determine glomerular filtration rate among PLHIV at least every six (6) months.

Declaration of conflict of interest

None

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