



ORIGINAL ARTICLE

Effect of Antiretrovirals on Renal Function of HIV/AIDS Patients at Two Hospitals in Yaounde, Cameroon

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Abstract

Background: Antiretroviral therapies (ART) have been reported to have renal toxicity. However, there is a lack of data on the toxicity of ART in sub-Saharan countries, especially in Cameroon. More studies on their contribution to renal dysfunction in natives from this region are required.

Methods: HIV/AIDS patients undergoing eleven different first-line ART at two hospitals in Yaoundé, Cameroon, were selected in this study. Retrospective and prospective data of serum urea and creatinine were collected, and the estimated Glomerular Filtration Rate (eGFR) was calculated. Wilcoxon signed-rank test, paired t-test and chi-square test were used for statistical analysis. The level of significance was set at $p < 0.05$.

Results: Out of 187 participants, there were 134 women (71.66%). The age ranged from 24 to 77 years, with a mean age of 42.47 ± 10.68 . The mean serum urea level increased after ART initiation for D4T40 + 3TC + NVP ($p = 0.011$) and TNF + 3TC + EFV + INH ($p = 0.03$) regimen in women and for TNF + 3TC + EFV + CTM ($p = 0.03$) in men. It decreased for D4T40 + 3TC + NVP ($p = 0.03$) in men. The mean serum creatinine increased for women following regimen AZT + TNF + NVP ($p = 0.022$) and D4T40 + 3TC + NVP ($p = 0.028$), and for men on AZT + TNF + NVP ($p = 0.03$). There was rather a decrease in blood creatinine for women on AZT + 3TC + NVP regimen ($p = 0.0032$). Mean eGFR decreased for patients on AZT + TNF + NVP ($p = 0.015$), D4T40 + 3TC + NVP ($p = 0.016$) and TNF + 3TC + EFV + INH ($p = 0.03$) regimen. The eGFR dropped below the threshold of $60 \text{ ml/min/1.73 m}^2$, for 5/12 patients on D4T40 + 3TC + NVP, 2/6 patients on TNF + 3TC + EFV + INH, 1/4 patients on TNF + 3TC, 6/74 patients on TNF + 3TC + EFV and 1/28 patients

on TNF + 3TC + EFV + CTM regimen. However, a significant increase of the eGFR has been observed for treatments with AZT + 3TC + NVP ($p = 0.0001$), 3TC + TNF + EMB ($p = 0.032$) and D4T30 + 3TC + EFV ($p = 0.032$) regimen.

Conclusion: Antiviral therapy with stavudine 40 mg (D4T40) or tenofovir-based regimen could lead to renal toxicity. However, the results show that D4T30 + 3TC + EFV, 3TC + TNF + EMB or AZT + 3TC + NVP combinations would be rather protective for renal function, and should be recommended.

Keywords

HIV/AIDS, Antiretroviral therapy, Renal toxicity

Abbreviations

3TC: Lamivudine; ABC: Abacavir; ART: Antiretroviral Therapy; AZT: Zidovudine; CTM: Cotrimoxazole; D4T30: Stavudine 30 mg; D4T40: Stavudine 40 mg; EFV: Efavirenz; eGFR: Estimated Glomerular Filtration Rate; EMB: Emtricitabine; HAART: Highly Active Antiretroviral Therapy; INH: Isoniazid; NVP: Nevirapine; TNF: Tenofovir

Introduction

HIV/AIDS is one of the leading causes of death in the world. According to an UNAIDS report [1], in 2019, 38 million people were living with HIV/AIDS and 1.7 million people were newly infected. HIV/AIDS causes a decrease in immune defenses leading to immunosuppression, making the patient vulnerable to complications including organ damage and/or metabolic disorder [2]. Thus, 32.7 million people have died from AIDS-related

illnesses since the start of the epidemic. However, since the advent of triple antiretroviral therapy in 1996, mortality due to this infection has decreased by more than 75% [1]. The use of antiretrovirals (ARV) has therefore become widespread throughout the world, so that 25.4 million people were accessing antiretroviral therapy in 2019 [1].

Paradoxically, the use of certain antiretroviral treatments that are particularly effective against HIV/AIDS has been accompanied by toxic side effects on vital organs such as the pancreas, kidneys, liver, giving the emergence of morphological changes in patients treated with these drugs. Peculiarly, because the kidneys plays a major role in the metabolism and excretion of most drugs including ARVs, they are routinely exposed to high concentrations of these drugs, their metabolites, or both [3], which can damage them. In the proximal tubule, there is a high rate of blood flow and consequently a high level of toxins to be processed, so this portion of the nephron is at particular risk of developing damage due to drug toxicity [4]. Thus, HIV treatment by ARVs may increase the risk of kidney damage due to drug-drug interaction or the nephrotoxicity of the drugs themselves [5-11]. A kidney transplant is not an easy option since it is very expensive. Although the option of hemodialysis is still possible, it is also time consuming and expensive. It is therefore necessary to carry out comparative studies of the effects of the different drug combinations, in order to identify those with undesirable side effects, and to make dose adjustments.

However, the pharmacogenetic research has uncovered significant differences between racial and ethnic groups in the metabolism, clinical effectiveness, and side effect profiles of many clinically important drugs. These differences must be taken into account in the design of therapeutic substitution and step-care protocols [12,13]. Sixty-nine percent (more than 2/3) of the total HIV-positive people are in sub-Saharan Africa [1]. In Cameroon, a sub-Saharan country with an exclusively black population, 23,000 new HIV infected cases were diagnosed in 2018 and 540,000 people were living with HIV. The prevalence of HIV amongst the population age 15 to 49 years in Cameroon in 2018 was estimated to be 3.6%. Furthermore, 52% of people living with HIV in the country were on ARV treatment the same year [14]. In Cameroon, ARVs nephrotoxicity has been very poorly studied [15-18]. But based on research done elsewhere in the world, stavudine has been progressively eliminated from ART protocols of patient follow up in Cameroon, due to possible side-effects [19,20], and replaced by the tenofovir disoproxil fumarate (TDF). TDF is a reverse transcriptase nucleotide inhibitor used in first and second line of ART. The efficiency and tolerability of TDF has been evaluated by some studies worldwide [8,10,21,22]. This drug is known for its possible side-effects such as renal dysfunctions (tubulopathies, nephro-

toxicity, acute or chronic kidney impairment). Assessing renal toxicity due to TDF or other ARV will allow better monitoring of patients on these molecules in Cameroon. Studies in this direction could help to determine the least toxic combinations applicable to Cameroonians or even African populations in general, and would undoubtedly be a scientific contribution that could interest global researches.

For the evaluation of potential renal toxicity, the monitoring of serum creatinine and serum urea has been introduced among the fundamental biological exams during HIV patient follow up. Renal impairment is often classified based on the GFR determined by the creatinine clearance method. Accordingly, there are normal values (≥ 90 ml/min/1.73 m²), mild (60-89 ml/min/1.73 m²), moderate (30-59 ml/min/1.73 m²), severe (15-29 ml/min/1.73 m²) and renal failure (< 15 ml/min/1.73 m²) [23]. Renal dysfunction was defined as Crcl < 60 ml/min/1.73 m².

The aim of the present study is to evaluate, by measuring the serum urea and creatinine concentrations, and by the estimation of the glomerular filtration rate, the impact of 11 combinations of first-line ART on renal function of HIV/AIDS patients followed in Cameroon.

Material and Methods

Type and study location

A study was conducted between 2017 and 2020, with retrospective and prospective data collection in a two-phase design. In the first phase, the patients' medical records were reviewed. A second phase was conducted prospectively, during a study period of one month: May-June 2017 at the Accredited Treatment Center (ATC) of AIDS of Essos Hospital; July-August 2020 at the ATC of the Jamot Hospital. Both hospitals are state-owned hospitals located in Yaoundé, the capital of Cameroon, in the Centre Region; The Centre Region was ranked third (5.8%) over 10 in the CAMPHIA 2017 HIV prevalence ranking in Cameroon [24]. In Yaoundé, this prevalence was evaluated to 4.4%.

Inclusion and non-inclusion criteria

Our study included adults (aged over 21) living with HIV on first-line antiretroviral therapy followed up since at least 2 years in the two participating centers, who voluntarily accepted to take part in this study and signed the written consent form. However, were excluded from this study: Alcoholic patients, pregnant women, patients with a blood pressure $> 140/90$ mmHg, diabetic patients, patients with nephropathy due to other than HIV/AIDS and/or its treatment, patients undergoing other treatment that may cause kidney failure and patients who had history of kidney transplant or dialysis.

Data collection

The study participants comprised of a subset of

187 well-documented HIV positive patients who were on ART for at least 2 years and registered for primary care at the Essos Hospital center or the Jamot Hospital. A standard questionnaire was used to capture the following informations: Demographic characteristics, ART regimen, duration on ART, renal function results at the time ART was started, and concomitant use of other potentially nephrotoxic agents.

Laboratory procedures

Urea and creatinine assay kits, as well as sampling and analysis equipment, were mainly provided by the hospital centers, other materials having been purchased from Yaoundé specialized stores. Blood samples were collected on dry tubes using needles adapted for the vacutainer system. In order to obtain the serum, the samples were centrifuged at 3000 to 4000 rpm for 5 minutes after coagulation. The serum collected was immediately used for the determination of biochemical markers of renal damage, namely serum urea and creatinine, in a Biochrom Libra S12 spectrophotometer. Urea was analyzed using the kinetic method [25]. For serum creatinine, the Jaffe kinetic method was used [25]. Since serum creatinine alone does not provide sufficient information on renal function, because of the physiological differences of patients related to age, sex or race, the estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation, which considers all those factors [26-28]:

$GFR \text{ in mL/min/1.73 m}^2 = 175 \times \text{Serum Cr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if patient is black)} \times 0.742 \text{ (if female)}$.

Statistical analysis

Data were entered into Microsoft excel 2016, and then analysed with the XLSTAT 2020.4 software. The evolution of the quantitative parameters before and after ART initiation was analysed by the Wilcoxon signed-rank test or by the paired t-test when applicable. Categorical data were compared using chi-square test. A P -value < 0.05 was considered statistically significant.

Ethical consideration

Data were collected after administrative authorizations were obtained from the Essos Hospital Center and the Jamot Hospital. Ethical clearance was obtained from the Centre Regional Ethics Committee for Human Health Research. This project was carried out with informed consent without financial contribution from patients in strict respect of medical confidentiality. Patients were free to accept our study or not after understanding its scope and scientific interest. Each file has been identified by an anonymous number.

Results

Demographic characteristics and regimen

Our sample consisted of 187 patients, grouped according to the medications received. A majority of the participants on ART were on tenofovir (TNF) and lamivudine (3TC)-based regimen (Figure 1).

Among the 187 participants, there were 134 women (71.66%) and 53 men (28.34%), therefore a female predominance. The participants had ages ranging from 24 to 77 years, with a mean age of 42.47 ± 10.68 . Women's mean age was 42.3 ± 11.0 years while men had a mean

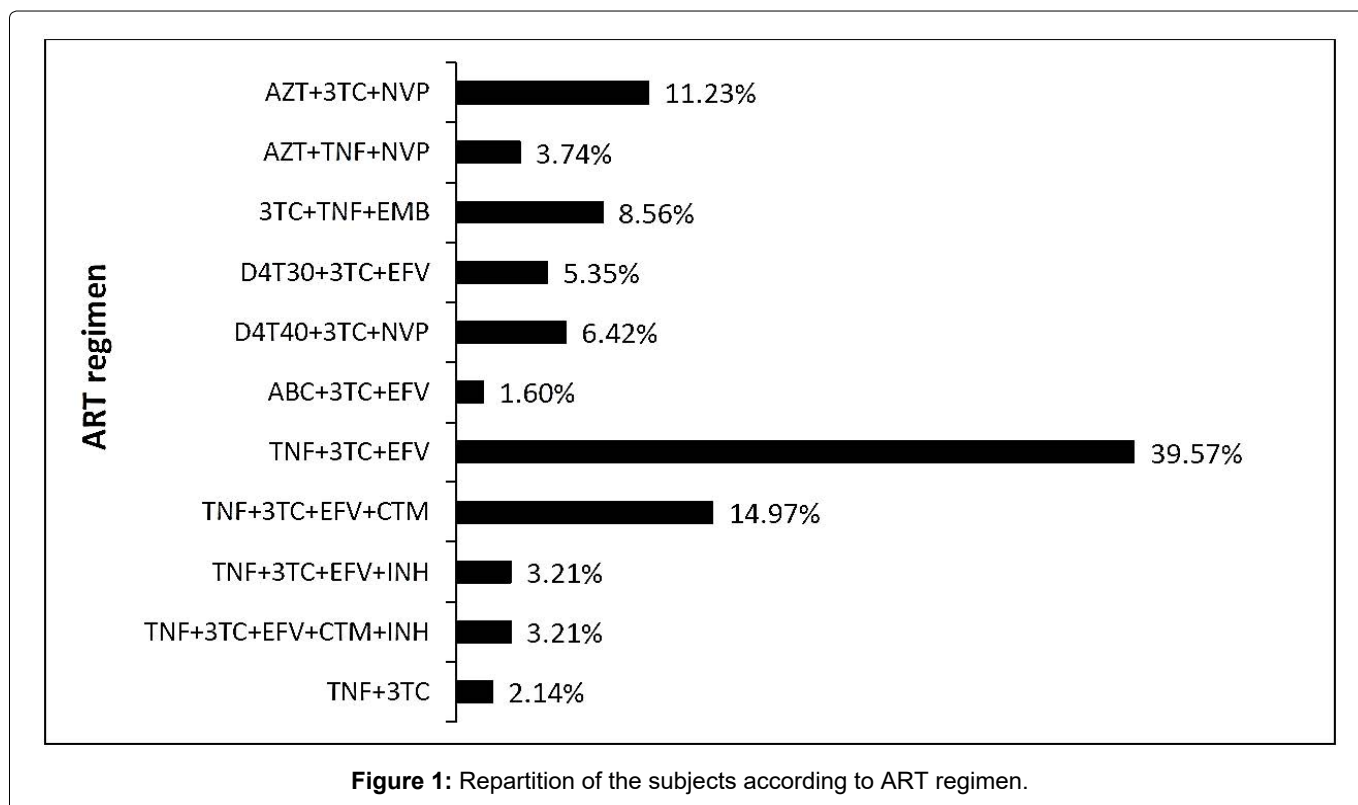


Table 1: Distribution of the study population by gender for each ART regimen.

	Women		Men		Total n (%)
	n (%)	Mean Age	n(%)	Mean Age	
AZT + 3TC + NVP	16 (76.2)	42.2 ± 12.2	5 (23.8)	39.0 ± 9.3	21 (100)
AZT + TNF + NVP	5 (71.5)	47.2 ± 10.8	2 (28.5)	35.5 ± 12.0	7 (100)
3TC + TNF + EMB	14 (87.5)	40.0 ± 9.9	2 (12.5)	49.0 ± 11.2	16 (100)
D4T30 + 3TC + EFV	8 (80)	45.0 ± 12.6	2 (20)	39.5 ± 6.3	10 (100)
D4T40 + 3TC + NVP	9 (75)	45.1 ± 12.0	3 (25)	36.6 ± 7.5	12 (100)
ABC + 3TC + EFV	2 (66.7)	41.0 ± 15.5	1 (33.3)	60.0	3 (100)
TNF + 3TC + EFV	47 (63.5)	41.4 ± 11.2	27 (36.5)	43.0 ± 10.3	74 (100)
TNF + 3TC + EFV + CTM	20 (71.4)	41.6 ± 11.8	8 (28.6)	48.0 ± 5.3	28 (100)
TNF + 3TC + EFV + INH	6 (100)	45.4 ± 8.6	0 (0.0)	NA	6 (100)
TNF + 3TC + EFV + CTM + INH	3 (50)	41.7 ± 3.1	3 (50.0)	39.3 ± 8.9	6 (100)
TNF + 3TC	4 (100)	44.0 ± 6.6	0 (0.0)	NA	4 (100)
All regimen	134 (71.66)	42.3 ± 11.0	53 (28.34)	42.9 ± 10.0	187 (100)

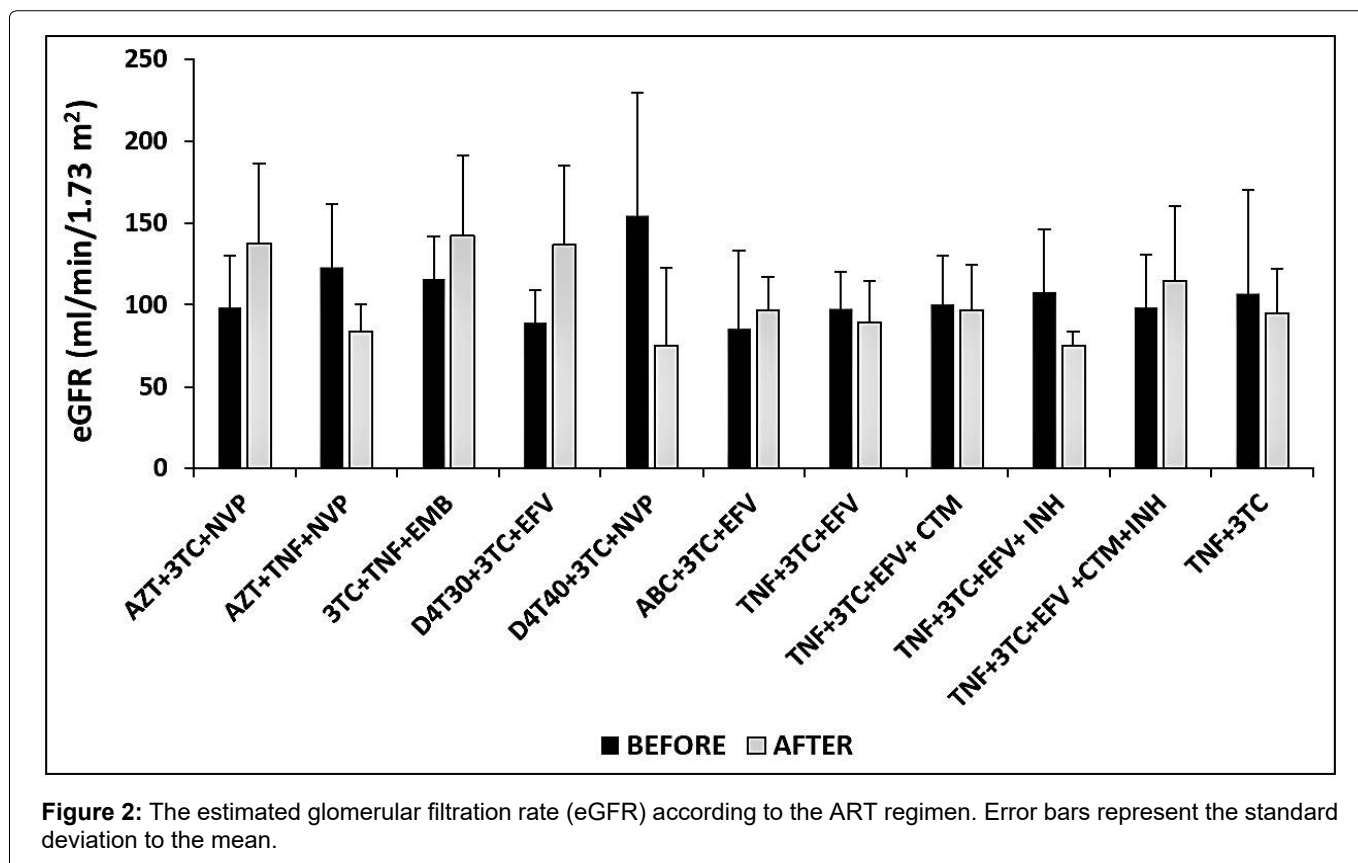
NA: Not Applicable.

Table 2: Serum urea and creatinine levels before and after initiation to treatment according to ART regimen.

	Mean Serum Urea Level (mmol/l)					
	Women Reference Values (2.5-7)			Men Reference Values (3.0-7.5)		
	Before	After	Significant p-value (< 0.05)	Before	After	Significant p-value (< 0.05)
AZT + 3TC + NVP	4.25 ± 1.25	5.23 ± 2.16		4.39 ± 1.28	5.29 ± 2.61	
AZT + TNF + NVP	4.76 ± 0.36	4.52 ± 2.0		4.49 ± 1.64	6.24 ± 2.94	
3TC + TNF + EMB	4.06 ± 1.59	4.95 ± 2.0		3.82 ± 1.64	3.91 ± 3.17	
D4T30 + 3TC + EFV	3.62 ± 1.60	4.59 ± 2.31		5.41 ± 0.58	3.99 ± 2.35	
D4T40 + 3TC + NVP	3.70 ± 2.15	6.43 ± 1.27	Yes	5.43 ± 0.41	2.77 ± 0.69	Yes
ABC + 3TC + EFV	4.32 ± 0.23	4.07 ± 0.58		3.99 ± 0.0	4.82 ± 0.0	NA
TNF + 3TC + EFV	3.94 ± 0.82	3.23 ± 0.66		3.99 ± 0.47	3.33 ± 0.47	
TNF + 3TC + EFV + CTM	4.60 ± 0.41	4.71 ± 0.91		3.99 ± 0.69	5.2 ± 0.45	Yes
TNF + 3TC + EFV + INH	3.08 ± 0.58	5.07 ± 0.35	yes	NA	NA	NA
TNF + 3TC + EFV + CTM + INH	4.16 ± 0.60	4.16 ± 0.33		4.93 ± 0.25	5.10 ± 0.53	
TNF + 3TC	0.95 ± 1.12	1.54 ± 1.79		NA	NA	NA
	Mean Serum Creatinine Level (µmol/l)					
	Women Reference Values (53-115)			Men Reference Values (88-150)		
	Before	After	Significant p-value (< 0.05)	Before	After	Significant p-value (< 0.05)
AZT + 3TC + NVP	85.1 ± 18.3	64.2 ± 11.3	Yes	91.9 ± 30.3	61.8 ± 18.7	
AZT + TNF + NVP	56.2 ± 30.8	81.3 ± 14.5	Yes	44.2 ± 25.0	83.9 ± 18.7	Yes
3TC + TNF + EMB	70.2 ± 15.9	58.7 ± 15.7		79.5 ± 25.0	66.3 ± 31.2	
D4T30 + 3TC + EFV	81.9 ± 25.8	32.0 ± 36.4		110.5 ± 18.7	75.1 ± 6.2	

D4T40 + 3TC + NVP	72.3 ± 46.6	109.0 ± 70	Yes	79.5 ± 17.6	97.2 ± 15.3	
ABC + 3TC + EFV	75.5 ± 33.09	72.8 ± 11.8		174.8 ± 0.0	96.2 ± 0.0	NA
TNF + 3TC + EFV	78.9 ± 17.6	84.9 ± 21.5		93.0 ± 15.8	94.1 ± 17.9	
TNF + 3TC + EFV + CTM	80.4 ± 15.1	81.5 ± 15.3		82.2 ± 18.5	87.3 ± 17.3	
TNF + 3TC + EFV + INH	70.8 ± 18.0	91.4 ± 8.95		NA	NA	NA
TNF + 3TC + EFV + CTM + INH	85.6 ± 12.7	82.7 ± 20.2		89.5 ± 31.3	74.4 ± 27.2	
TNF + 3TC	77.9 ± 26.4	78.8 ± 24.7		NA	NA	NA

NA: Not Applicable.



age of 42.9 ± 10.0 years (Table 1).

Determination of serum urea and creatinine

By comparing the mean urea level of patients reported before ART initiation to the values obtained after ART initiation (Table 2), we found a significant increase for D4T40 + 3TC + NVP and TNF + 3TC + EFV + INH regimen in women and for TNF + 3TC + EFV + CTM in men (p-value 0.011, 0.03 and 0.03 respectively). However, we found a significant decrease for D4T40 + 3TC + NVP in men (p-value 0.03). The mean serum creatinine increased significantly for women following regimen AZT + TNF + NVP and D4T40 + 3TC + NVP (p-value 0.022 and 0.028 respectively). In men, a significant increase in serum creatinine was only observed for those on AZT + TNF + NVP (p-value 0.03). There was rather a decrease in blood creatinine for AZT + 3TC + NVP regimen in women (p-value 0.0032).

Assessment of renal function

The eGFR was calculated, for all patients, using the

MDRD method. Since this method considers gender, the calculated averages relate to patients of both sexes combined, for each group. Figure 2 shows that, on average, eGFR decreased significantly after treatment for the AZT + TNF + NVP ($p = 0.015$), D4T40 + 3TC + NVP ($p = 0.016$) and TNF + 3TC + EFV + INH ($p = 0.03$) regimen. We noted rather a significant increase for AZT + 3TC + NVP ($p = 0.0001$), 3TC + TNF + EMB ($p = 0.032$) and D4T30 + 3TC + EFV ($p = 0.032$) regimen.

Table 3 displays the prevalence of renal dysfunction within the groups. Of the total study population, 5 (3%) had eGFR < 60 ml/min/1.73 m² before ART initiation, and 15 (8%) after ART initiation. The difference in prevalence of renal dysfunction between study groups changed from no significant before ART initiation to significant after ART initiation (chi-square p-value 0.117 and 0.0002 respectively before and after ART initiation). Patients treated with D4T40 + 3TC + NVP had a higher prevalence of renal dysfunction (41.67%) after ART initiation, followed by those treated with TNF + 3TC +

Table 3: Prevalence of renal dysfunction within the groups.

	Before ART Initiation		After ART Initiation		Total
	eGFR \geq 60	eGFR < 60	eGFR \geq 60	eGFR < 60	
	n (%)	n (%)	n (%)	n (%)	
AZT/ + 3TC + NVP	20 (95.24)	1 (4.76)	21 (100)	0 (0)	21 (100)
AZT + TNF + NVP	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)
3TC + TNF + EMB	16 (100)	0 (0)	16 (100)	0 (0)	16 (100)
D4T30 + 3TC + EFV	9 (90)	1 (10)	10 (100)	0 (0)	10 (100)
D4T40 + 3TC + NVP	12 (100)	0 (0)	7 (58.33)	5 (41.67)	12 (100)
ABC + 3TC + EFV	2 (66.67)	1 (33.33)	3 (100)	0 (0)	3 (100)
TNF + 3TC + EFV	72 (97.3)	2 (2.7)	68 (91.89)	6 (8.1)	74 (100)
TNF + 3TC + EFV + CTM	28 (100)	0 (0)	27 (96.43)	1 (3.57)	28 (100)
TNF + 3TC + EFV + INH	6 (100)	0 (0)	4 (66.67)	2 (33.33)	6 (100)
TNF + 3TC + EFV + CTM + INH	6 (100)	0 (0)	6 (100)	0 (0)	6 (100)
TNF + 3TC	4 (100)	0 (0)	3 (75)	1 (25)	4 (100)
All regimen	182 (97.33)	5 (2.67)	172 (91.98)	15 (8.02)	187 (100)

eGFR is done in ml/min/1.73 m².

EFV + INH (33%). For these two groups, we previously noted a 0% prevalence of renal dysfunction before ART initiation. Furthermore, even if there were no significant decrease of mean eGFR for the group with the highest population (TNF + 3TC + EFV), the prevalence of renal dysfunction increased from 3% (2 patients) to 8% (6 patients). Data having shown that the 2 patients initially with eGFR < 60 ml/min/1.73 m² in that group had recovered an enhanced creatinine clearance after ART initiation, all the 6 patients with renal dysfunction had been in this situation only after the beginning of ART.

Discussion

After dividing the study population into 11 groups according to the ART received, we found that, the mean values of serum urea were increased after ART initiation for D4T40 + 3TC + NVP and TNF + 3TC + EFV + INH regimen in women, and for TNF + 3TC + EFV + CTM regimen in men. However, we found a significant decrease for D4T40 + 3TC + NVP in men. The increase in serum urea suggests a glomerular filtration defect or a rise in urea reabsorption, hence possibly a problem with the kidney structure, although other causes, such as dehydration, are possible. Notably, the U:C ratio (serum urea/serum creatinine) provides information on the pre-renal, post-renal or intra-renal nature of the injury, in the case of acute renal failure. However, serum urea level is highly variable, and depends on other factors such as diet and diuresis [29]. As a result, we cannot draw a conclusion based on variations of this parameter alone.

The mean serum creatinine increased significantly for women following regimen AZT + TNF + NVP and D4T40 + 3TC + NVP (45% and 51% increase respectively). In men, a significant increase in serum creatinine was only noted for those on AZT + TNF + NVP (90% increase). This increase of creatinine level was accom-

panied by a significant decrease in mean eGFR for the same regimen, as well as for TNF + 3TC + EFV + INH. In the case of AZT + TNF + NVP and TNF + 3TC + EFV + INH combinations, we believe that tenofovir (TNF) could be responsible for this renal dysfunction. Indeed, several observations of tenofovir-induced nephropathies have been published [30-32]. This nucleotide inhibitor of HIV reverse transcriptase can cause renal failure associated with tubular abnormalities that may be due to down-regulation of diverse ion transporters. This nephrotoxicity of tenofovir has been confirmed by reports of reversal of renal toxicity on tenofovir withdrawal [33-35]. In addition, we noticed in our study that, for 3 of the 5 tenofovir-based combinations for which there was no decrease in mean eGFR, the prevalence of patients with eGFR < 60 ml/min/1.73 m² after initiation of ART has nevertheless increased, as well as for the combinations for which the mean eGFR decreased. Some studies carried out in Cameroon have also revealed renal toxicity of tenofovir-based combinations [16,18]. By contrast, another research conducted in Cameroon revealed the lack of nephrotoxicity of various antiretroviral treatments [17]. But, regarding this other study, the nature of the ART combinations had not been specified.

The possibility of nephrotoxic interaction between isoniazid (an anti-tuberculosis drug) and other drugs also exists [36,37]. Chia-Hao, et al. [38] also reported a 7.1% prevalence of acute kidney injury in patients on anti-tuberculosis treatment. The decrease in mean eGFR observed in patients on TNF + 3TC + EFV + INH could therefore be partly due to the effect of isoniazid (INH). This supposedly harmful effect of INH could be rectified by the concomitant use of another antibiotic drug, cotrimoxazole, according to the results of the present study.

Furthermore, the decrease in eGFR observed in pa-

tients treated with D4T40 + 3TC + NVP (stavudine 40 mg, lamivudine and nevirapine) is not a surprise, as some studies show nephrotoxicity of these three drugs. Stavudine and lamivudine have previously been associated with tubular dysfunction [39,40]. Both of these molecules, like tenofovir, are nucleoside reverse transcriptase inhibitors. It is recognized, according to some reports, that nephrotoxicity of these antiviral analogue nucleotides is explained by cellular accumulation through the entry of the organic anion transporters and decreased efflux into tubular lumen. Note also that two drug combinations for which a decrease in eGFR has been observed in the present study include nevirapine. Although this non-nucleoside reverse transcriptase inhibitor has not been implicated in nephropathies, further studies need to be conducted to determine whether its association with other molecules could exacerbate nephrotoxicity.

In our study, there was a decrease in blood creatinine for AZT + 3TC + NVP regimen in women. This decrease in creatinine concentration was accompanied by a significant increase in mean eGFR for the same regimen, as well as for 3TC + TNF + EMB and D4T30 + 3TC + EFV regimen. This improvement in eGFR could be due to reduction of HIV development by these drug combinations. Some renal complications often observed in patients may indeed be related to the virus itself, according to studies carried out in Cameroon and elsewhere in the world [41-43]. It has been reported that control of viral replication by ART has a considerable improvement in renal function in patients initially having a drop in glomerular filtration rate ($< 89 \text{ ml/min/1.73 m}^2$) and a low level of CD4 ($< 200/\text{mm}^3$) [44]. The renal damage related to HIV itself and not to its treatment could therefore be more common than we think, and controlling virus activity with ART may therefore result in improved kidney function. Moreover, it may be that combination of tenofovir with lamivudine and emtricitabine (3TC + TNF + EMB) reverses its nephrotoxicity. Indeed, the side effects of a drug are sometimes lifted by the activity of other drugs taken in combination, as has already been demonstrated for the case of taking tenofovir concomitantly with rosiglitazone. Rosiglitazone is a drug widely used to treat patients with type 2 diabetes mellitus. It induces the expression of many of the same transporters that tenofovir down-regulates, thus reversing tenofovir-induced tubular nephrotoxicity and thereby improving glomerular filtration rate [45]. As regards D4T30 (stavudine 30 mg), it could be that stavudine, at a reduced dose in this case, unlike D4T40 (stavudine 40 mg), is less toxic, as some other studies have shown [46,47].

The present study has some limitations. Firstly, the relatively small sample size meant that for some patient groups there were less than 10 participants, or even less than 5. It is thus possible that the absence of significance in some differences observed was just a reflection of the limited statistical power. However, the study

was conducted in two distinct centres, which shares the typical characteristics of many hospitals in Cameroon. This dispersion of study centers can act in favor of the representativeness of the sample. The second limitation of this study is that patients on treatment for HIV had been on treatment for different lengths of time, thus, this study minimizes the effect of the duration of treatment. However, as already mentioned, all patients had been on the same ART regimen for at least 2 years, which is a long enough time for the biochemical signs of chronic kidney disease to be considered. Moreover, Achu, et al. [17] demonstrated in another study carried out in Cameroon the lack of association between decreased renal function to duration on HAART regimen. Another limit of this study is that, retrospective data of renal function biomarkers were sufficient to obtain the eGFR at several time intervals only for 6 of the ART regimen, so the data presented here just correspond to 2 measurements, in order to harmonize the conclusions specific to the various regimen. Finally, data on other biochemical parameters such as albuminuria and hematuria were incomplete and could not be presented here. However, it is accepted that an eGFR $< 60 \text{ ml/min/1.73 m}^2$ is sufficient to diagnose renal dysfunction, and it is this limit that we set to determine the proportions of patients with renal insufficiency [48].

Conclusion

The study we conducted is a continuation of the work done by many researchers on the evaluation of ARVs renal toxicity. We have not only acquired specific information for the different drug combinations above mentioned, but have broadened the scope of the few studies already done in Cameroon. Further studies must be carried out in order to confirm or even better understand the cellular and molecular aspects of the interactions of stavudine 40 or tenofovir-based combinations. This can help establish effective preventive and therapeutic pharmacological interventions. It is imperative in that not only the mean eGFR of patients on some of those ART regimens significantly decreased during treatment, but also a considerable percentage of these patients had their eGFR decline below the threshold of $60 \text{ ml/min/1.73 m}^2$. Waiting for other studies involving a larger sample of patients recruited from a large number of health centers, treatment with AZT + 3TC + NVP, 3TC + TNF + EMB or D4T30 + 3TC + EFV regimen may be recommended in Cameroon, since no confirmed renal toxicity has been observed in this study in patients on these regimen. These combinations would be rather protective for renal function. This recommendation must at least be taken into account for the case of black patients, while waiting for our observations to be verified also for other races.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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