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Biological and clinical abnormalities leading to cardiovascular disease during antiretroviral treatment in a university hospital in Abidjan

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ABSTRACT

Antiretroviral drugs are involved in the occurrence of adverse effects. In Côte d'Ivoire, HIV1 treatment protocols are non-nucleoside reverse transcriptase inhibitors based. No study has been undertaken in the country about cardiovascular risk. Thus, the objective of our study was to assess the prevalence of biological abnormalities and clinical markers of cardiovascular risk during antiretroviral therapy. We conducted a prospective cross-sectional study with 238 patients who were on antiretroviral treatment including non-nucleoside reverse transcriptase inhibitors for at least 6 months in the Pneumophysiology department of the university hospital of Cocody (Abidjan). Metabolic syndrome was determined according to NCEP-ATP III criteria. Biological parameters investigated were: triglyceride, HDL cholesterol and LDL, glucose and clinical parameters: blood pressure and waist circumference. Eleven patients (4.62%) have a metabolic syndrome, 17.6% had hypertriglyceridemia. An increase in LDL cholesterol and lower HDL-cholesterol were found in both cases in 13.9% of patients and an atherogenic index greater than 4.5 in 5% of patients. Hyperglycemia occurred during antiretroviral therapy in 28% of the study population. Patients who developed hypertension and increased waist circumference during antiretroviral therapy were 9.75% and 15.5% respectively. Our results testify to the potential existence of a cardiovascular risk during the non-nucleoside inhibitor used.

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INTRODUCTION

Antiretroviral (ARV) drugs in the treatment of HIV infection have dramatically changed the natural history of the disease; significantly reducing the morbidity and mortality rate of this disease. Despite proven efficacy of the combination therapy, these molecules are involved in the occurrence of

adverse effects that could have a biological and / or clinical effect (Awah and Agugasi 2011; Chow et al., 2003; DAD 2003; Jeroen et al., 2012; Muhammad et al., 2013, Roula et al., 2000), and occur immediately after initiation of treatment, or months or years of ARV treatment. These side effects constituting components of the metabolic

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syndrome can lead to over a long period complications of cardiovascular disease, the leading causes of death worldwide (Currier 2002). These metabolic complications constitute metabolic syndrome (MS), including abnormal fat distribution, hypertension, dyslipidemia (hypertriglyceridemia, low HDL-cholesterol) and insulin resistance. An increase of approximately 26% of the risk of myocardial infarction has been reported in patients on highly active antiretroviral therapy (HAART) (Jeroen et al., 2012).

In Côte d'Ivoire, HIV1 first line treatment protocols are protocols including first line two nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitor. These protocols have changed the prognosis with improved life expectancy of patients infected with HIV. However, few studies describe the biological and clinical abnormalities prelude to cardiovascular complication during antiretroviral therapy. So, in order to detect cardiovascular risk involving ARVs, we conducted a clinical study to assess the prevalence of biological abnormalities and clinical markers of cardiovascular risk during antiretroviral therapy. Specifically, our purpose was to determine the prevalence of metabolic syndrome and the frequency of its determinants on the one hand and find a correlation between determinants of metabolic syndrome and antiretroviral therapy on the other hand.

MATERIALS AND METHODS

This is a prospective cross-sectional study based on a single assessment conducted during patient routine follow up visit. It took place in the care center for HIV patients of the University Teaching Hospital of Cocody. This study is authorized by the scientific medical direction of the University Teaching Hospital of Cocody.

The study began in February and ended in July 2012. The inclusion concerned:

HIV1 + patients under HAART for at least 6 months aged 15 years and above; patients regularly monitored with a favorable result and agreed to join the study.

Were excluded in our study HIV patients in second-line treatment (receiving PI), HIV + patients with recent infections, patients on anti-lipid treatment, steroids or hormone therapy, patients with kidney failure or liver cytolysis, patients with comorbidity (hypertension, obesity, diabetes).

Our study included 238 HIV + patients on HAART. During the usual scheduled visit, according national recommendations, the patients fasting blood sample were collected. Venous blood taken at the elbow was collected in EDTA tube and two dry tubes, one of which was used in our study.

Then, the patients were taken to a room where a series of questions were asked in order to fill the survey form. The survey form included patient identification, socio-demographic parameters, the initial clinical and biological assessment, the current clinical and laboratory assessment, blood pressure was measured after 5 minutes, the weight was measured on a mechanical balance, abdominal obesity was assessed by measuring waist circumference (abnormal value: greater than or equal to 102 cm for men and 88 cm for women), the body mass index (BMI) was calculated using the following formula: $\text{weight (kg)} / \text{height (m)}^2$ (values: BMI < 18.5: Insufficient weight, BMI between 18.5 and 24.9: Normal; BMI between 25 and 29.9: Overweight; BMI between 30 and 34.9: Obesity)

The biological analyses of samples were performed at the Laboratory of Biochemistry of the University Teaching Hospital of Cocody. Fasting Venous blood was collected (10-12 hours). These samples were collected on the one hand in dry tubes (without anticoagulant) and on the other hand in gray tubes with anticoagulants (sodium fluoride). Serum was aliquoted after centrifugation (3000 rpm / 3 min).

Carbohydrate and lipid profile (glucose, total cholesterol, HDL-cholesterol, triglyceride), were determined on the serum by routine enzymatic colorimetric method according to Trinder on analyzer controller HITACHI 902. The LDL-cholesterol was calculated by Friedwald formula: $LDL-C = Total\ cholesterol - (Triglycerides / 5 + HDL-cholesterol)$.

Statistical analysis

The statistical analysis of the data was realized by means of the software SPSS 17.0. The averages are compared with Anova and the qualitative variables (in %) are compared with the test of Khi square; with $p < 0.05$.

RESULTS

The average age of the population studied is 42.78 years \pm 10.438 years with a minimum age of 16 years and a maximum age of 74 years. The age group 26 to 55 years represents 84.90% of the population studied (Figure 1). The sex ratio is 0.47 with a female predominance (68%).

The most prescribed protocols are AZT / 3TC / EFV and AZT / 3TC / NVP with the respective proportions of 59.24% and 24.78% (Table 1).

The duration of the treatment is of 6 months at least and of 134 months at most with an average of 55.21 ± 30.693 months.

In our results, it appears that 11 patients or about 4.62% of the study population have a MS according to NCEP-ATP III criteria with at least three after ARV treatment with NNRTIs at least 6 months. Table 2 reported frequency of metabolic syndrome parameters. About lipids abnormalities, 17.6% of patients had hypertriglyceridemia. An increase in LDL cholesterol and lower HDL-cholesterol were found in both cases with 13.9% of the study population and an atherogenic index greater than 4.5 in 5% of patients' population. Hyperglycemia occurred during antiretroviral therapy in 56 patients that is 23.5% of the study population. Clinically, the percentage of patients who developed blood pressure up to 130/85 mm Hg and increased waist circumference during antiretroviral therapy was 13.9% and 15.5% respectively. No significant differences in these abnormalities were found between Nevirapine based protocol and Efavirenz-based protocol ($p > 0.05$) (Table 3).

Table 1: Antiretroviral treatment protocols in the study population.

Protocols	Number	Proportion %
AZT/3TC/EFV	141	59.25
AZT/3TC/NVP	59	24.79
TDF/FTC/EFV	15	6.30
D4T/3TC/EFV	9	3.78
TDF/3TC/EFV	8	3.36
D4T/3TC/NVP	4	1.68
AZT/3TC/ABC	1	0.42
TDF/FTC/NVP	1	0.42
<i>Total</i>	238	100

ABC = Abacavir ; FTC = Emtricitabine ; AZT = Zidovudine ; NVP = Nevirapine ;
D4T = Stavudine ; TDF = Tenofovir ; EFV = Efavirenz; 3TC = Lamivudine.

Table 2: Frequency of metabolic syndrome parameters.

Parameters	Number (n =238)	Percentages (%)
Triglycerides > 1.5 g/l	42	17.6%
HDL-c < 0.4 g/l in man < 0.5 g/l in woman	33	13.9%
BP > 130/85 mmHg	33	13.9%
Glucose > 1.1 g/l	56	23.5%
Elevated waist circumference	38	16%

HDL = High density lipoprotein; Bp = Arterial blood pressure

Table 3: Biological and clinical abnormalities and antiretroviral treatment protocols.

Parameters		EFV-pro	NVP-pro	p	OR, IC95 %
AI	> 4.5	7 (5.7%)	2 (4.1%)	0.501	1.093
	< 4.5	116 (94.3%)	47 (95.9%)		
Triglycerides	> 1.5 g/l	24 (19.5%)	9 (18.4%)	0.525	1.021
	≤ 1.5 g/l	99 (80.5%)	40 (81.6%)		
HDL-c	low	17 (13.8%)	7 (14.3%)	0.555	0.989
	Normal	106 (86.2%)	42 (85.7%)		
Waist circumference	elevated	18 (14.6%)	12 (24.5%)	0.096	0.811
	Normal	105 (85.4%)	37 (75.5%)		
Fasting glucose	> 1.1 g/l	53 (43.1%)	26 (53.1%)	0.155	0.891
	≤ 1.1 g/l	70 (56.9%)	23 (46.9%)		
Bp (mmHg)	>130/85	19 (15.4%)	6 (12.2%)	0.392	1.074
	<130/85	104 (84.6%)	43 (87.8%)		

There is no significant differences in parameters between NVP-pro and NVP-pro (p>0.05). ; HDL = High density lipoprotein; NVP-pro = Nevirapine base Protocol; AI = atherosclerosis Index; EFV-pro = Efavirenz base protocol; BP = Arterial blood pressure.

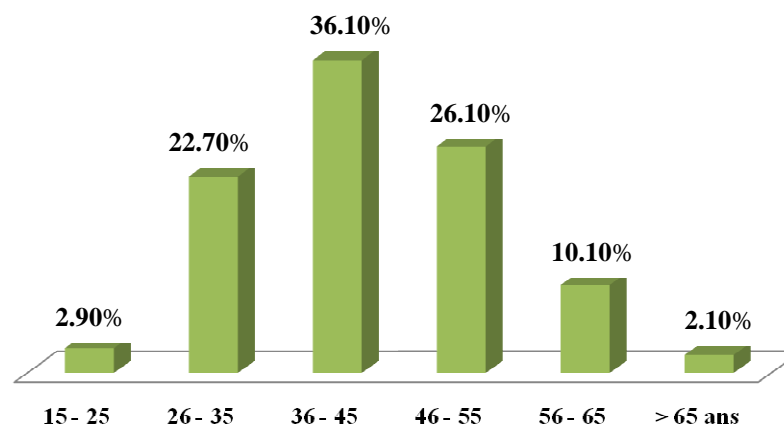


Figure1: Distribution of age in the population studied.

DISCUSSION

The metabolic syndrome (MS) as defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), includes at least three of the following five biological and / or clinical abnormalities following: waist circumference greater than 102 cm in men and greater than 88 cm in women; triglycerides higher than 1.5 g / l; HDL-cholesterol less than 0.4 g / L in men and less than 0.5 g / l in women; blood pressure greater than 130 / 85 mmHg; Fasting glucose greater than 1.1 g / l. The rate of MS in our study (4.62%) was similar to that found by Hauhouot *et al.* (2008) in an apparently healthy population. This rate is lower than the prevalence observed in a study in Cotonou (IMEA, 2007) establishing a diagnosis of metabolic syndrome in 13% of patients on HAART without PI for a period of 15 months of average and in a study in Kano (Nigeria) where the prevalence reach 21% (Muhammad *et al.* 2013). Elsewhere, in Western countries, the prevalence of metabolic syndrome reaching values of 17-42% is found mainly in PI-based ARV treatment (Jeroen *et al.*, 2012). In our study, the most common ARV regimens were AZT / 3TC / NVP (24.78%) and AZT / 3TC / EFV (59.24%). Among the 11 patients with metabolic syndrome majority of them about 72.73% received ARV treatment with EFV and 27.27% were on NVP based regimen. Seeking a correlation between the occurrence of metabolic syndrome and ARV regimens, it is clear that there is no significant difference between the ARV regimens in patients with and without metabolic syndrome. MS is established as an independent predictor and marker of morbidity and cardiovascular mortality (Isomaa *et al.*, 2001), 4.62% of patients in our study would be exposed to cardiovascular disease.

Although the prevalence of MS is relatively low in our study, we investigated the frequency of these determinants because they each represent a potential factor for cardiovascular disease caused by antiretroviral

therapy. The body mass index is typically used to assess cardiovascular risk. But, the simple measurement of waist circumference, easy to make, is equally relevant for predicting cardiovascular risk. Our study shows that approximatively 16% of the population has an increased waist circumference and no relationship was established with the occurrence of MS. Also, no significant relationship was found between the waist circumference and the ARV protocol. Laiz *et al.* (2011) reported a high rate (17%) of increased waist circumference in women HIV + patients.

Glucose level > 1.1 g / l observed in a large portion of our sample (23.5%) showed the presence of an insulin resistance frequently encountered in patients with HIV infection. This insulin resistance could be as a result of direct effects of antiretrovirals through their mitochondrial toxicity, also HIV infection and fat redistribution. Studies investigating cases of diabetes in patients under HAART in sub-Saharan Africa are rare. Elsewhere in the Western countries, Brown *et al.* (2005) found a value of 14%; study conducted by Hadigan *et al.* (2001) showed 35% cases of hyperglycemia in patients with ARV protocols PI, NRTIs and / or NNRTIs. Among the inhibitors of reverse transcriptase, D4T and EFV are involved in the appearance of type-2 diabetes in HIV + patients (Jeroen *et al.*, 2012). In our study, we did not find any significant relationship between ARV regimens and glycemic > 1.1 g / l. Thus NVP and EFV could be equally involved in the occurrence of diabetes under HAART.

The introduction of ARVs in HIV + patients has led to marked changes in lipid profile (Jeroen *et al.* 2012) involving an increase in triglycerides and LDL cholesterol, and decreased HDL-cholesterol (Carr, 2003; Grinspoon and Carr, 2005; Akawu *et al.*, 2013). In our study, 17.6% of patients reported presented elevated triglycerides. An increase in LDL cholesterol, and reduced HDL cholesterol were found in 13.9% both cases of the study population. Besides HIV,

ARVs have been widely associated to lipid abnormalities. In a study conducted in Burkina Faso (Sakandé et al., 2012), the authors highlight, especially in men, an increase in total cholesterol and triglycerides correlated; positively to the presence of ARV treatment with NVP over a period ranging from 1 to 5 years. An increase in triglycerides was also observed in a study conducted in Nigeria (Awah and Agughasi, 2011). In a large cross-sectional study conducted by DAD (2003), the proportion of hypercholesterolemia, hypertriglyceridemia, and low HDL-cholesterol were 10-27%, 23-40%, and 19-27%, respectively, depending on antiretroviral treatment. In our study majority of patients with dyslipidemia took EFV based ARV treatment (59.24%). When comparing ARV regimens in patients without dyslipidemia to those with dyslipidemia, no significant correlation between ARV treatment protocol and dyslipidemia was found. EFV and NVP show no significant difference in their involvement in the development of lipid abnormalities. Our results are in contrast to those of Leth et al. (2004) who, in their study, reported that the EFV is more associated to a more pronounced elevation of cholesterol and triglycerides than NVP after treatment duration of 48 weeks. This advantage of the NVP over EFV is also reported by Tashima et al. (2003) in a study in which it appears that the replacement of a PI by NVP is associated with a significant decrease in triglycerides and cholesterol, an effect rarely observed with EFV.

Furthermore, randomized studies conducted by Negredo et al. (2002) and Fisac et al. (2005) compared NVP and EFV and confirm the superiority of NVP over EFV in the control of lipid abnormalities due to treatment with a PI. Knowing that the effect of dyslipidemia on the increase in cardiovascular disease, particularly coronary heart is well established (Rossi et al., 2009), these lipid abnormalities manifested in our study regardless of the ARV treatment protocols

used, would demonstrate the potential existence of a cardiovascular risk.

The atherogenic index (AI) is determined by the total Cholesterol / HDL ratio greater than 4.5, our study highlights an index above normal values in 5% of patients. There is therefore a potential atherogenic risk in our study population. In patients with MS, 16.7% had a high AI against 4% in patients without MS. Thus the risk of cardiovascular disease was significantly higher in patients with MS. Hadigan et al. (2001) in the United States reported the presence of an atherogenic risk during HIV infection. In his study, 100% of patients presented a high AI. This high rate is due to fat redistribution and insulin resistance that HIV patients with lipodystrophy have. Hence, lipid abnormalities associated with MS contribute to increase in the atherogenic risk in these patients on ARV dominated by NNRTI-based regimens.

Before the advent of HAART, hypertension was often reported in patients infected with HIV (Iwuala, 2008). Recent studies highlight hypertension increasingly observed in patients infected with HIV on antiretroviral therapy (Gazzaruso et al., 2003; Jung et al., 2004). Blood pressure up than 130/85 mmHg was found in 13.9% of our study population receiving ARV treatment. Iwuala et al. (2008) in Nigeria reported a value of 51.2% of hypertension cases in HIV+ patients mainly on NNRTI-based HAART. Muhammad et al. (2013) reported a prevalence of 17% of hypertension cases in HIV patients mainly on NNRTI-based HAART during 6-84 months. In Western countries, many studies showed hypertension proportion among HIV patients on HAART ranging from 13% to 34% (Gazzaruso et al., 2003; Jung et al., 2004; Bergersen et al., 2003; Medina-Torne et al., 2012; Savès et al., 2003).

ARV protocols found in hypertensive patients (BP>130/85 mmHg) in our study were 12.2% for NVP based and 15.4% on EFV based. When comparing in our study the ARV regimens in hypertensive patients and

those in non-hypertensive patients, it was clear that there was no significant link between High Blood Pressure and ARV treatment protocol. Cohort studies seeking a correlation between HAART and hypertension produce divergent results. A large cross-sectional study showed a moderate rise in blood pressure associated with NNRTI based ARV treatment (Chow et al., 2003). Several studies have found no effect of HAART on blood pressure, while some studies reported concerning PI, either a decrease (Thiebaut et al., 2005), or an increase (Cattelan et al., 2001; Crane et al., 2006) of the incidence of hypertension. These differences may be partly explained due to weight gain after antiretroviral therapy (Crane et al., 2006) but also by the duration of ARV treatment since Seaberg et al. (2005) showed that ARV treatment for a period of 20 years is associated to an increase in blood pressure while at the end of 5 years of ARV treatment, there is no significant increase in the blood pressure. Although the correlation of ARV and hypertension is not established in our study, the presence of hypertension is an indication of cardiovascular risk in HIV + patients under HAART.

Conclusion

Knowing that these biological and clinical abnormalities are highly involved in the occurrence of cardiovascular diseases, particularly coronary, our results testify to the potential existence of a cardiovascular risk during non-nucleoside inhibitor used.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

The study was conducted by GKS and KH from data collection, exploitation of results and preparation of manuscript. LK also realized data collection. EK read and approved the final manuscript. HDK and EA-D provided their expertise.

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