

# Global Cardiovascular Risk of the HIV Positive Patients Receiving Antiretroviral Therapy in Brazzaville

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## Abstract

A cross-sectional, descriptive and analytical study was conducted from January to August 2015 at the Brazzaville Ambulatory Treatment Center and at the National Blood Transfusion Center. The objective was to contribute to improving the care of people living with HIV under antiretroviral therapy by assessing their global cardiovascular risk (CVR). The variables studied focused on the epidemiological, clinical and biological aspects. The global CVR was assessed by the Framingham and WHO/ISH scores. There were 135 HIV-positive subjects, including 64 treated patients and 71 untreated HIV+ subjects. The subjects were divided into 83 men (61.5%) and 52 women (38.5%), with an average age of  $42.6 \pm 2.9$  old years. The subjects were single people (62.2%), of a secondary educational level (63.7%), and civil servants (32.6%). The main risk factors found were dyslipidaemia (60%), obesity (36%), smoking (12.6%), hypertension (5.9%), diabetes (0.7%). The metabolic syndrome was found in seven cases (11.3%). The global CVR according to the score of Framingham, initially moderated at 17.2%, and mean at 1.5% within treated patients, was mean at 9.4% and high at 1.6% of the subjects respectively at the sixth month of treatment ( $p < 0.03$ ). For the score of the WHO/ISH, the risk was high at 2% and very high at 3% within treated patients initially. This risk was increased to 3.1% for the high and very high risk respectively at sixth month of treatment ( $p < 0.04$ ). In Congo, the HIV population involves a high global CVR under antiretroviral therapy. Preventive actions are highly recommended.

## Keywords

HIV Infection, Antiretroviral Therapy, Metabolic Disorders, Global

## 1. Introduction

HIV/AIDS is a major public health problem in sub-Saharan Africa, where live nearly 70% of people living with HIV (PLHIV), equals about 25.8 million people, among them 41% are on antiretroviral therapy [1] [2] [3]. In Congo, the prevalence of HIV infection is 3.2% among people aged 15 - 49 years [4] [5]. According to WHO/UNAIDS data, published in 2014, the Republic of Congo counted 81,000 PLHIV, and free antiretroviral therapy have been effective since 2000 [1]. Since the beginning of highly effective antiretroviral therapy (HAART) in 1996, HIV infection is considered as a chronic disease [6]. Indeed, HIV patients under antiretroviral treatment found their life expectancy increased, with a reduction of nearly 48% in HIV deaths [6]. Thus, there is currently a transition from cardiovascular complications related to immunosuppression (myocarditis, pericarditis) to complications related to antiretroviral-induced metabolic disorders [6]. Cardiovascular complications currently represent the third leading cause of death, and the fourth leading cause of hospitalization in HIV patients behind infectious, oncologic and hepatic complications [7]. To prevent these complications, assessing cardiovascular risk (CVR) in HIV patients becomes crucial. This preliminary study is aiming to identify the main cardiovascular risk factors of HIV patients, and to evaluate their global CVR before and during ART.

## 2. Patients and Methods

It was a longitudinal cohort study, analytical and comparative data collection. It took place from January 2<sup>nd</sup> to August 30<sup>th</sup> 2015 (eight months) at the Ambulatory Treatment Center (ATC) of Brazzaville, and at the National Blood Transfusion Center (NBTC). The study included HIV+ patients, followed by ATC, eligible or not for antiretroviral treatment, and volunteers (blood donors) from the NBTC. Patients were put on treatment according to the CD4 level, which has the threshold set at  $<500/\text{mm}^3$  according to the National Program of Fight against the AIDS, in addition to the associated comorbidities and the noncompliance to the antiretroviral treatment; the viral load was not available.

A total of 199 subjects were included by simple random pulling, divided into three groups:

- Group A: witnesses, volunteer blood donors (n = 64);
- Group B: untreated HIV+ subjects (n = 71);
- Group C: HIV+ subjects on ART (n = 64).

The evaluation of the patients was done at the first month of inclusion (Mo) and the sixth month of follow-up (M6). The evaluation covered several data, collected through a form filled out by the investigator, including:

- anamnestic data: age, sex, marital status, educational level, common cardi-

ovascular risk factors (hypertension, smoking, diabetes, dyslipidaemia, overweight/obesity);

- clinical data: blood pressure, abdominal circumference (male < 94 cm, female < 80 cm), the body mass index by the ratio of weight on the square of the waist ( $N < 25 \text{ kg/m}^2$ );
- biological data: blood sugar, lipid profile (total cholesterol, HDL and LDC cholesterol, triglycerides).

Variables studied were:

- socio-demographic parameters: age, sex, educational level, marital status;
- cardiovascular risk factors, as well as the existence of a metabolic syndrome, defined according to the criteria of the International Diabetes Federation [8];
- the WHO clinical stage of HIV/AIDS infection;
- the antiretroviral protocol used;
- Global cardiovascular risk.

For the antiretroviral protocol, two regimens were used:

- Scheme 1: Tenofovir + Emtricitabine + Efavirenz or Nevirapine;
- Scheme 2: Zidovudine + Lamivudine + Efavirenz or Nevirapine.

The alternative to these two regimens was Abacavir + Didanosine + Efavirenz and Duovir + LP/r.

For the calculation of global cardiovascular risk, we used two models: the Framingham model [9] and the WHO model [10], considering certain clinical and biological parameters, including age, sex, smoking, systolic blood pressure, diabetes mellitus, total cholesterol, and LDL-c for the first model. Thus, different levels of risk were defined according to each of the models. Thus, according to Framingham, the risk was low if <5%, moderate between 5% - 10%, average between 10% - 20%, high between 20% - 40%, and very high if >40%. For WHO, the risk was low if <10%, average between 10% - 20%, high between 20% - 30%, and very high if >30%.

The data, were expressed as proportions, means or variances, were analysed with Epi-info 3.5.1 and Stata 12 software. For comparisons, we used the Khi-2 or Fisher test for qualitative variables and the ANOVA test for quantitative variables. The threshold of significance was set at  $p < 0.05$ .

### 3. Results

The 135 HIV+ patients were divided into 83 men (62.5%) and 52 women (37.5%), with an average age of  $42.6 \pm 2.9$  years (range: 30 to 65 years). Patients were predominantly single (62.2%), with secondary education level in 86 (63.7%), and at clinical stage 3 of the WHO classification in 76 (56.3%). The main characteristics of the HIV+ population are presented in **Table 1**.

The regimen 1 combining (tenofovir + emtricitabine + efavirenz or nevirapine) was used in 44 (68.8%), 2 (zidovudine + lamivudine + efavirenz or nevirapine) in 18 (28.1%), and alternative protocol in two cases (3.1%). In these protocols, Efavirenz was used in 45 cases (70.4%) and nevirapine in 19 cases (29.6%).

**Table 1.** Main characteristics of HIV+ patients.

	<b>N = 135</b>
<i>Men, n (%)</i>	83 (61.5)
<i>Mean age (years)</i>	42.6 ± 2.9
<i>Educational level, n (%)</i>	
- none	4 (3.0)
- primary	8 (6.0)
- secondary	86 (63.7)
- superior	37 (27.3)
<i>Marital status, n (%)</i>	
- single people	84 (62.2)
- married	34 (25.2)
- divorced	9 (6.7)
- widower	8 (5.9)
<i>Socio-professional category, n (%)</i>	
- civil servant	44 (32.6%)
- trading	28 (20.7)
- without profession	25 (18.5)
<i>AIDS clinical stage, n (%)</i>	
- WHO clinical stage 3	76 (56.3%)
- WHO clinical stage 4	13 (10.0)
<i>Cardiovascular risk factors, n (%)</i>	
- tobacco use	17 (12.6)
- arterial hypertension	8 (6.0)
- diabetes	1 (0.7)

WHO: world health organisation; AIDS: acquired immunodeficiency syndrome.

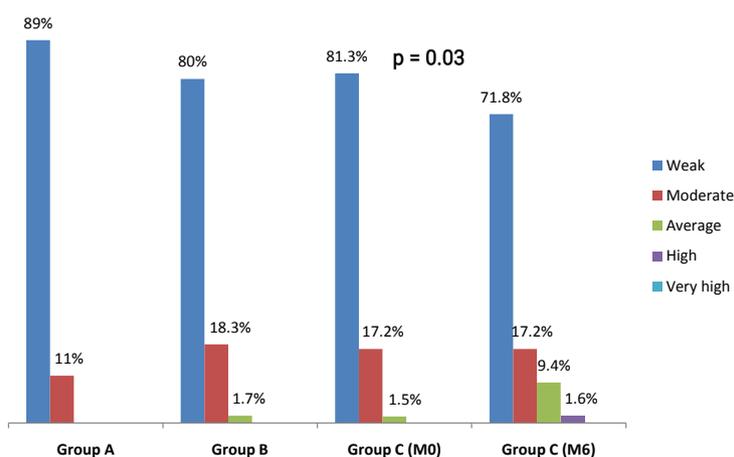
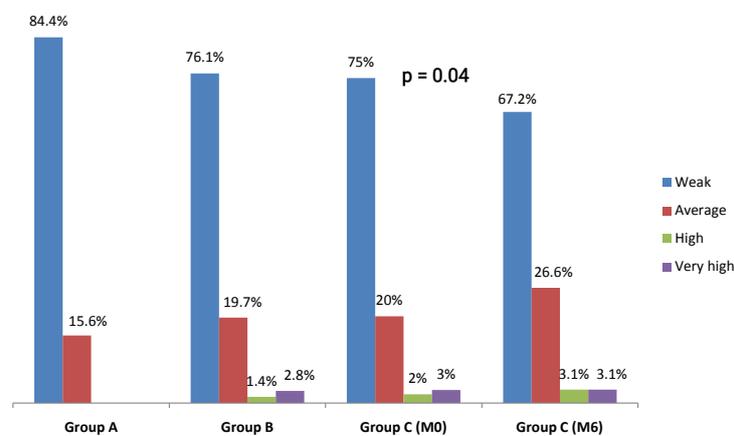
According to height and weight, there was a statistically significant difference between treated HIV+ patients and untreated patients at the sixth month on weight ( $61.8 \pm 10.6$  vs  $58.4 \pm 10.3$  kg; 0.0001), and the abdominal circumference (men:  $82.8 \pm 9$  vs  $75.5 \pm 10.8$  cm,  $p = 0.015$  and women:  $79.7 \pm 10.5$  vs  $72.1 \pm 10.3$  cm;  $p < 0.0001$ ). Metabolic abnormalities were hyperglycemia (4.7% vs 1.4%,  $p < 0.0001$ ), hypercholesterolemia (60% vs 17%,  $p < 0.0001$ ), hypertriglyceridemia (20% vs 14%, 1%,  $p = 0.031$ ), hyper-LDLemia (38% vs 8.5%,  $p < 0.0001$ ), and hypo-HDLemia (6.2% vs 49.3%,  $p < 0.0001$ ). A metabolic syndrome was noted in seven cases (11.3%) of patients on ART. The groups B and C being comparable according to the biological parameters at the inclusion, it was noted a clear increase in the different biological findings, specially the glycemia ( $0.8 \pm 0.1$  vs  $0.9 \pm 0.1$  g/l;  $p < 0.0004$ ), and the LDL-cholesterol ( $1.1 \pm 0.3$  vs  $1.3 \pm 0.4$  g/l;  $p = 0.0008$ ) in the group C at the sixth month of the treatment with a significant statistical difference. The metabolic profile of the patients is shown in **Table 2**.

The global cardiovascular risk according to the Framingham score (**Figure 1**), initially moderate at 17.2% and average at 1.5% within treated patients, was average at 9.4% and high at 1.6% at sixth month of the treatment ( $p = 0.03$ ). For the WHO/ISH score (**Figure 2**), the cardiovascular risk initially high at 2% and very high at 3% within treated patients has increased to 3.1% for both, high risk and very high risk at sixth month of the treatment ( $p = 0.04$ ).

**Table 2.** Metabolic profile of patients.

	<b>M<sub>0</sub></b>		<b>M<sub>6</sub></b>	<b>p</b>
	<b>Group A</b> (n = 64)	<b>Group B</b> (n = 71)	<b>Group C</b> (n = 64)	
<i>Glycemia (g/l)</i>				
Mean ± SD	0.9 ± 0.2	0.8 ± 0.1	0.9 ± 0.1	<0.0004
(ranges)	(0.6 - 1.3)	(0.6 - 1.4)	(0.7 - 1.4)	
<i>Triglycerides (g/l)</i>				
Mean ± SD	0.7 ± 0.4	0.9 ± 0.5	1.0 ± 0.5	0.0001
(ranges)	(0.2 - 1.9)	(0.4 - 2.4)	(0.3 - 3.0)	
<i>Total cholesterol (g/l)</i>				
Mean ± SD	1.8 ± 0.4	1.7 ± 0.4	2.1 ± 0.5	<0.0001
(ranges)	(0.9 - 2.7)	(0.9 - 2.9)	(1.1 - 3.7)	
<i>HDL cholesterol (g/l)</i>				
Mean ± SD	0.5 ± 0.2	0.4 ± 0.1	0.6 ± 0.1	<0.0001
(ranges)	(0.1 - 0.8)	(0.1 - 0.8)	(0.3 - 0.9)	
<i>LDL cholesterol (g/l)</i>				
Mean ± SD	1.1 ± 0.4	1.1 ± 0.3	1.3 ± 0.4	0.0008
(ranges)	(0.5 - 2.2)	(0.4 - 2.0)	(0.6 - 2.8)	

SD: standard deviation; M<sub>0</sub>: at inclusion; M<sub>6</sub>: at sixth month.

**Figure 1.** Stratification of global cardiovascular risk according to the Framingham model.**Figure 2.** Stratification of global cardiovascular risk according to the WHO/ISH model.

## 4. Discussion

Since the beginning of highly effective antiretroviral therapy (HAART) in 1996, HIV/AIDS has become a chronic disease characterized by a clear reduction in morbi-mortality and an increase in cardiometabolic complications, as a result of accelerated atherosclerosis, thereby increasing the risk of acute events such as myocardial infarction, ischemic stroke, and peripheral arterial occlusive disease [7] [8] [9] [10] [11]. Cardiovascular diseases have become the third leading cause of death and the fourth reason for hospitalization among HIV+ patients treated in developed countries [11]. Several factors, including antiretroviral therapy (ARV), HIV itself, and common risk factors (aging of the HIV-infected population, smoking, dyslipidemia, diabetes, arterial hypertension) contribute to the acceleration of the atherosclerosis leading to these cardiovascular complications [12] [13] [14]. Indeed, classic vascular risk factors are frequently found in the HIV-infected population, in varying proportions according to the studies [15]-[20].

In our series, classic risk factors identified in HIV+ patients were dyslipidemia, abdominal obesity, smoking, hypertension, diabetes mellitus, and metabolic syndrome. Several African authors have found the same risk factors in varying proportions in HIV+ patients [21] [22] [23] [24] [25]. In our series, the metabolic abnormalities noted were hypercholesterolemia, hyper-LDLemia, hypo-HDLemia, and hyperglycemia. Lipid abnormalities are often the consequence of treatments with protease inhibitors (PIs) [26] [27] [28], but also by non-nucleoside reverse transcriptase inhibitors (NNRTIs). Indeed, the preponderance of lipid abnormalities in our series, due to the use of PIs was rare, and very common during the use of NNRTIs, including efavirenz, a molecule widely used in our patients in nearly 2/3 cases, explains the role non-negligible NNRTIs in the occurrence of dyslipidemia in treated HIV+ patients. The impact of using NNRTIs on the global CVR is unclear. However, this drug class is a provider of dyslipidemias, including total hypercholesterolemia and hypertriglyceridemia [29]. Indeed, HIV infection leads to a decrease in HDL-cholesterol levels during its progression to AIDS, because of the predominant weight loss on lean mass. Also, this deleterious effect is counterbalanced by nevirapine which leads to an increase of HDL-c, a beneficial effect slightly raised in our series because of the under-use of this molecule. Hyperglycemia is primarily influenced by the role of nucleoside reverse transcriptase inhibitors (NRTIs). Its relatively low prevalence in our study can be explained, on the one hand, by the short duration of exposure to ARVs (6 months) in the patients included, and on the other hand, by the low use of NRTIs (zidovudine and lamivudine) in our series.

Evaluation of the global cardiovascular risk of HIV+ patients is now a necessity, occurring in all patients before the initiation and during the antiretroviral therapy [30]. In the United States [16] [31], the global Framingham-assessed CVR was higher among people living with HIV (PLHIV) compared to non-HIV-infected subjects (17% vs. 11%). This finding was also noted in France [32]. In our study,

the prevalence of high global CVR, although low compared to western series, attests to its increase over time in HIV+ patients on antiretroviral therapy. Similar proportions have been reported in some African series, notably in Benin [23] and Burkina Faso [21]. Overall, according to the literature data, the global CVR of PLHIV, particularly those treated with ARVs, appears to be higher than the one of HIV-positive patients without ARVs, and higher than the one of the general population [7]. The combination of classic cardiovascular risk factors commonly found in HIV-positive patients with the deleterious effects of ARVs, including induced metabolic disturbances in this vulnerable population, increases the risk of cardiovascular events occurrence. Thus, the metabolic complications and their corollary, the excessive risk of cardiovascular events, in particular coronary events, require from the health care professional having in common the management of these patients, in order to vulgarize the preventive measures.

### Limitation of the Study

The small size of the sample due to the lack of funding, the short period of the study, and the lack of viral load dosage prevent us to generalize the findings of this study.

### 5. Conclusion

This preliminary study shows that in Congo, HIV infection affects a relatively young population. This vulnerable population has a high global cardiovascular risk with antiretroviral therapy. Preventive measures are needed to better manage these patients, based on a multidisciplinary collaboration involving cardiologists, infectiologists, and biologists.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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