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Influence of Antiretroviral Therapy on the Metabolic Profile of People Living with HIV Followed at University Hospital, Cotonou, Benin

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Abstract

Introduction: Since the advent of antiretroviral therapy, the vital prognosis of people living with HIV (PLWHA) has improved significantly. However, the risk of metabolic complications is high, thus making the bed of cardiovascular disease. Our objective was to compare the prevalence of metabolic abnormalities among PLWHA receiving ARVs to that observed in those who are not treated. Methods: We conducted a cross-sectional study (January to April 2010) at the PLWHA ambulatory care center of national university hospital (CNHU-Hubert K. Maga) in Cotonou, Bénin. We recruited 420 PLWHA (210 treated for at least 6 months and 210 untreated). We determined the prevalence of metabolic syndrome (MS) defined by the criteria of NCEP-ATP III, and the prevalence of abnormal glucose and lipid, and lipodystrophy. Association between metabolic syndrome and ARVs used was analyzed by binomial regression. Confidence intervals were calculated at 95% and 5% alpha level. Results: The prevalence of MS was 16% (18% of patients treated vs. 13% of non-treated, p = 0.18). That of hyperglycemia was 18% (30% of patients treated vs. 6% of untreated; p < 0.001) and of diabetes 7% (12% of patients treated vs 2% of untreated; p < 0.0001).

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The total cholesterol prevalence was 29% (44% of treated vs 13% of untreated; p <0.02). That of lipodystrophy in 210 patients was 29% (lipoatrophy16%, lipohypertrophy 8%, mixed form 6%). Factors associated with metabolic syndrome were age, hypertension, diabetes (personal or family), BMI, exposure to stavudine (OR = 1.59 [1.02 to 2.47], p = 0.04) and indinavir booted with ritonavir (OR = 2.23 [1.11 to 4 46], p = 0.02). Conclusion: The metabolic abnormalities are more common in PLWHA treated with ARVs. Preventing these anomalies should be made to the initiation of antiretroviral therapy and during the therapeutic monitoring.

Keywords

Metabolic Syndrome, Diabetes, Dyslipidemia, Antiretroviral Therapy, HIV Infection

1. Introduction

Since the advent of antiretroviral therapy (ART), the vital prognosis of people living with HIV (PLWHA) have improved significantly. However, the risk of metabolic complications including metabolic syndrome is high [1]. These complications make the bed of cardiovascular disease in PLWHA regardless of the virus's own complications [2]. The incidence of cardiovascular disease will be explosive in PLWHA treated with ART. The study "Data collection on adverse events of anti-HIV Drugs (DAD)" provides, for example, a 26% increase in the incidence of myocardial infarction per year during the first 4 to 6 years of exposure to ARVs [3]. In addition, cardiovascular diseases are cited in France since 2000 as the third leading cause of death among PLWHA treated with ART and who have immuno-virologic success [4]. In one of our previous studies [5], metabolic syndrome according to definition of the IDF (International Diabetes Federation) appeared in 13% of patients after a median of 15 months of antiretroviral therapy. Diabetes (8%) and hypercholesterolemia (35%) were also observed. We had worked on a small sample of 88 patients treated. To appreciate the real impact of antiretroviral therapy on metabolic syndrome we choose to compare PLWHA treated by ARVs to those who are untreated. Our goals were to:

1) Determine the prevalence of metabolic syndrome and other metabolic abnormalities in PLWHA treated by ART and in those who are untreated.

2) Identify factors associated to metabolic syndrome in these patients.

2. Patients and Methods

2.1. Type of Study

The work was performed at the PLWHA ambulatory care center (CTA) of national university hospital (CNHU-Hubert K. Maga) in Cotonou, Bénin. This is a cross-sectional study, descriptive and analytical, conducted from January to April 2010 within the CTA active cohorte.

2.2. Study Population

***Sampling*:** The study involved two groups of patients living with HIV: those treated with ART and those who had just been admitted to the center or that were followed but had not yet started treatment. The sample size was determined by comparison of two proportions formula and was 356 subjects. For convenience, we had successively recruited during consultations 420 patients: 210 treated with ART and 210 untreated.

Inclusion criteria: Selected patients should be 18 years or older, be regularly followed in the center; have given their informed consent to participate in the study. Those treated should have started ART for at least 6 months. Patients with a Karnofsky index <70% or suffering from any ailment requiring hospitalization and pregnant women were not included.

2.3. Variables Studied

***Demographic variables, anthropometric and lifestyles*:** The age, gender, tobacco and alcohol consumption were recorded by a questionnaire and patient's clinical file. Height was measured with a wall-mounted microtoise to

the nearest 0.5 cm. Weight was measured with a weighing scale in adults marque "SECA". Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). The BMI was classified in accordance with the WHO classification. Waist circumference was measured midway between the inferior angle of the ribs and the suprailiac crest with a measuring tape to the nearest 1 cm.

***Clinical, biological and therapeutic variables*:** Personal and family history of hypertension and diabetes were searched by questionnaire. The type of HIV, WHO clinical stage, CD4 count and, ART regimen and duration were obtained by patient's clinical records. We measured Blood pressure with a mercury sphygmomanometer mark "VAQUEZ", in the sitting position on the upper arm after-15-min rest period. A venous sample was performed in patients at baseline, before breakfast, to dose fasting glucose, triglycerides, total cholesterol, LDL cholesterol and HDL cholesterol. These samples were aliquoted and then stored in the laboratory of CTA. Laboratory tests were carried out by the enzymatic method end point in the hospital laboratory biochemistry after subjects recruitment phase. The dependent variable was the presence of metabolic syndrome. It was determined in the 2 groups.

***Operational definitions*:** Smoking was retained if the subject claims to have an estimated smoking at least 10 pack-years and alcoholism if the daily consumption of alcoholic beverage is more than one liter in women and one and a half liters in humans. Metabolic abnormalities have been determined as follows:

- Metabolic syndrome was defined according to the criteria of NCEP-ATP III (National Cholesterol Education Program-Adult Treatment Panel III), namely, the existence of at least 3 of 5 following criteria: waist circumference > 102 cm in women and > 88 cm for men; systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 85 mmHg; a triglyceride fasting > 150 mg/dL; a cholesterol HDL < 40 mg/dL in men and <50 mg/dL in women and fasting glucose greater than or equal to 110 mg/dL [6].
- Glycemic abnormalities: Hyperglycemia if fasting glucose is ≥110 mg/dL and diabetes if the fasting glucose is ≥126 mg/dL.
- Dyslipidemia: Total Hypercholesterolemia (values ≥ 200 mg/dL), LDL Hypercholesterolemia (≥130 mg/dL), HDL hypocholesterolemia (<35 mg/dL in men and <45 mg/dL in women), hypertriglyceridemia (≥200 mg/dL).
- The lipodystrophy was defined by the presence of at least one characteristic sign reported by the patient and confirmed by the doctor or objectified by the doctor and approved by the patient. Lipoatrophy were distinguished (thinned skin atrophy of the face, protrusion of the muscles and/or veins, flattening of the buttocks), lipohypertrophy (abdominal hypertrophy, breast, buffalo hump) or a mixed form.

2.4. Statistics

Computer tools Epi Data and SAS version 9.2 (SAS Institute, Cary, North Carolina, USA) were used for codification, data entry and statistical analysis. Quantitative variables were described by calculating their mean and standard deviation. Their comparisons were made by Student's test. By cons for qualitative variables, we determined the prevalence. The Khi2 or fischer tests were used for their comparisons. The binomial regression univariate and multivariate analysis was used to identify factors significantly associated with the metabolic syndrome. Tests were performed with a 5% significance level and a 95% confidence interval.

2.5. Ethical Considerations

Participation in the study was voluntary with informed consent. Data collection sheets and blood samples were identified by an anonymous number. The lipid blood test is not part of routine examinations free and was paid by the research team. Patients in whom metabolic anomalies were observed receive a treatment or adequately monitored.

3. Results

3.1. General Characteristics of the Study Population

The 420 enrolled patients included 68% women: 74% in the group of subjects treated versus 61% in those untreated (p = 0.005). Their average age was 39 ± 10 years (extremes: 19 and 81 years). Patients treated were older than untreated: average age 41 ± equal 10 years versus 36 ± 10 years (p = 0.001). The majority of the subjects treated has been received for the first time in the center at clinical stage 3 or 4 WHO: 65% versus 35% (p =

0.001) with a CD4 count ≤ 200 cells/mm^3: 81% versus 16%. The history and other clinical characteristics were comparable in both groups (**Table 1**). In treated patients (n = 210), the duration of treatment was greater than 48 months in 52% of cases between 24 and 48 months in 25% of cases and less than 24 months in 23% of cases. ART was a triple therapy consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent which is a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor. The most commonly used NRTI combination are stavudine + lamivudine (63%) and zidovudine + lamivudine (21%). NNRTIs were used by 86% of patients and protease inhibitors by 14% of patients.

3.2. Prevalence of the Metabolic Syndrome and Other Metabolic Abnormalities

Of the 420 PLWHA, 66 (16%) had metabolic syndrome including 38 treated and 28 untreated subjects. The prevalence of metabolic syndrome was 18% in the group of subjects treated versus 13% in the group of untreated: OR = 1.36 [0.87 to 2.13]; p = 0.18 (**Figure 1**). The prevalence of other metabolic abnormalities as the subject is treated or untreated with antiretroviral drugs is presented in **Table 2**.

3.3. Factors Associated with Metabolic Syndrome

In univariate analysis, the clinical factors associated with metabolic syndrome were age, hypertension, diabetes (personal or family) and BMI (**Table 3**). Exposure to NNRTIs increased the risk of developing metabolic syndrome by 25% (OR = 1.25 [0.80 to 1.96]; p = 0.31). It is the same for exposure to protease inhibitors (OR = 1.26 [0.62 to 2.56]; p = 0.51). A more detailed analysis was then carried out with different antiretroviral drugs (**Table 4**). A statistically significant relationship was observed for exposure to stavudine or indinavir boosted by ritonavir which increased by 59% and 123% respectively, the risk of developing the metabolic syndrome. In multivariate analysis, hypertension ($OR_{ajusted}$ = 1.38 [1.38 to 3.54]; p = 0.0009) and exposure to stavudine ($OR_{ajusted}$ = 1.55 [1.06 to 2.27]; p = 0.02) had proved to be predictors of metabolic syndrome.

Table 1. General characteristics of the study population.

	Total enrollment n = 420	**Patients treated n = 210**	**Patients untreated n = 210**	**p value$^{\mu,\dagger}$**
Mean age ± SD (years)	39 ± 10	41 ± 10	36 ± 10	0.001
Gender n (%)				
Male	135 (32)	54 (26)	81 (39)	
Female	285 (68)	156 (74)	129 (61)	0.005
Antecedent to admission n (%)				
Alcoholism	32 (8)	11 (5)	21 (10)	0.06
Smoking	19 (5)	7 (3)	12 (6)	0.24
Hypertension	35 (8)	19 (9)	16 (8)	0.59
Diabetes	13 (3)	8 (4)	5 (2)	0.39
Family hypertension	172 (41)	78 (37)	94 (45)	0.11
Family diabetes	71 (17)	37 (18)	34 (16)	0.69
HIV-1 n (%)	418 (99)	210 (100)	208 (99)	0.5
BMI (kg/m^2) n (%)				
<25	280 (67)	143 (68)	137 (65)	
25 - 30	96 (23)	48 (23)	48 (23)	
≥30	44 (10)	19 (9)	25 (12)	0.62
WHO stage at admission (%)				
Stage 1 and 2	209 (50)	73 (35)	136 (65)	
Stage 3 and 4	211 (50)	137 (65)	74 (35)	0.001
Initial CD4 (cells/mm^3) n (%)				
≤200	203 (48)	170 (81)	33 (16)	
200 - 350	84 (20)	34 (16)	50 (24)	
≥350	133 (32)	6 (3)	127 (60)	< 0.001
Last CD4 > 200 cells/mm^3 n (%)	329 (78)	158 (75)	171 (82)	0.30

†: chi-square test for comparing proportions; μ: Student test for comparison of averages.

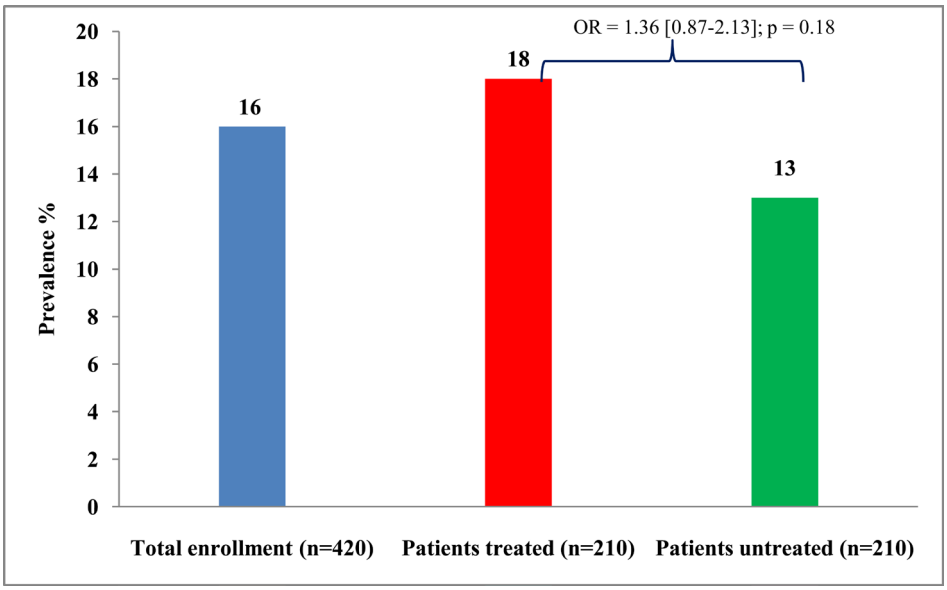

Figure 1. Prevalence of metabolic syndrome among people living with HIV treated or untreated by antiretroviral drugs.

Table 2. Other metabolic abnormalities observed in treated and untreated patients by antiretrovirals.

	Total enrollment n = 420	Patients treated n = 210	Patients untreated n = 210	value p†
Glycemic abnormalities n (%)				
Hyperglycemia	46 (11)	38 (18)	8 (4)	<0.0001
Diabetes	29 (7)	25 (12)	4 (2)	<0.0001
Dyslipidemia n(%)				
Hyper TC	121 (29)	93 (44)	28 (13)	0.02
Hyper LDL-C	156 (37)	121 (78)	35 (22)	<0.0001
Hypo HDL-C	281 (67)	121 (58)	160 (76)	0.0001
Hyper TG	8 (2)	4 (2)	4 (2)	1
Lipodystrophy n (%)	NA	62 (29)	NA	
Lipoatrophy	NA	34 (16)	NA	
Lipohypertrophy	NA	17 (8)	NA	
Mixedlipodystrophy	NA	11 (5)	NA	

†Comparison of treated versus untreated patients; TC: Total Cholesterol; LDL-C: LDL cholesterol; HDL-C: HDL cholesterol; TG: triglycerides; NA: not applicable.

Table 3. Association between metabolic syndrome and clinical factors in people living with HIV.

	Metabolic syndrome n (%)		OR [IC‡(95%)]	Value p†
	Yes	No		
Age¥ (year)	-	-	1.03 [1.01 - 1.04]	<0.0001
Gender				
Male	20 (15)	115 (85)	1	
Female	46 (16)	239 (84)	1.09 [0.67 - 0.87]	0.72
Hypertension				
No	48 (12)	337 (88)	1	
Yes	18 (51)	17 (49)	4.12 [2.72 - 6.26]	<0.001
Diabetes				
No	59 (15)	348 (85)	1	
Yes	7 (54)	6 (46)	3.71 [2.13 - 6.47]	<0.001
Family Hypertension				
No	40 (16)	208 (84)	1	
Yes	26 (15)	146 (85)	0.94 [0.59 - 1.48]	0.77

Continued

Family diabetes				
No	47 (13)	302 (87)	1	
Yes	19 (27)	302 (87)	1.98 [1.24 - 3.18]	0.004
Alcoholism				
No	57 (15)	331 (85)	1	
Yes	9 (28)	23 (72)	1.9 [1.04 - 3.50]	0.03
Smoking				
No	63 (16)	338 (84)	1	
Yes	3 (16)	16 (84)	1[0.35 - 2.91]	0.99
WHO Stage				
Stage 1 and Stage 2	29 (19)	180 (81)	1	
Stage 3 and Stage 4	37 (18)	174 (82)	1.26 [0.81 - 1.98]	0.30
BMI (kg/m^2)				
<25	24 (9)	256 (91)	1	
25-30	23 (24)	73 (76)	2.80 [1.66 - 4.71]	
≥30	19 (43)	25 (57)	5.04 [0.22 - 0.87]	<0.001
InitialCD4 (cells/mm^3)				
≤200	32 (16)	171 (84)	1	
200 - 350	9 (11)	75(89)	0.68 [0.34 - 1.36]	
≥350	25 (19)	108 (81)	1.19 [0.74 - 1.92]	0.3
Last CD4[¥] (cells/mm^3)	-	-	1 [1 - 1.03]	0.08

OR = Odds ratio; [‡]IC (95%): confidence interval = 95%; [¥]continuously variable treated; [†]p value of the Wald chi-square; BMI = body mass index.

Table 4. Association between metabolic syndrome and exposure to antiretroviral drugs in people living with HIV.

	Metabolic syndrome n (%)		OR [IC[‡](95%)]	Valeur p[†]
	Oui	Non		
Zidovudine				
No	45 (15)	260 (85)	1	
Yes	21 (18)	94 (23)	1.24 [0.77 - 1.98]	0.37
Stavudine				
No	249 (87)	38 (13)	1	
Yes	28 (21)	105 (79)	1.59 [1.02 - 2.47]	0.04
Didanosine				
No	62 (16)	336 (84)	1	
Yes	4 (18)	18 (82)	1.17 [0.47 - 2.91]	0.74
Tenofovir				
No	65 (16)	352 (84)	1	
Yes	1 (33)	2 (67)	2.14 [0.42-10.7]	0.35
Efavirenz				
No	36 (14)	228 (86)	1	
Yes	30 (19)	126 (81)	1.41 [0.91 - 2.19]	0.13
Névirapine				
No	55 (15)	302 (85)	1	
Yes	11 (17)	52 (83)	1.13 [0.63 - 2.04]	0.67
Nelfiavir				
No	62 (16)	335 (84)	1	
Yes	4 (17)	19 (83)	1.11 [0.44 - 2.79]	0.81
Indinavir + ritonavir				
No	60 (15)	342 (85)	1	
Yes	6 (33)	12 (67)	2.23 [1.11 - 4.46]	0.02
Lopinavir + ritonavir				
No	65 (16)	346 (84)	1	
Yes	1 (11)	8 (89)	0.7 [0.11 - 4.51]	0.71

OR = Odds ratio; [‡]IC (95%): confidence interval = 95%; [¥]continuously variable treated; [†]p value of the Wald chi-square for comparison of patients who have undergone at least once exposure to each molecule, versus those who have never suffered, including untreated patients.

4. Discussion

The prevalence of metabolic syndrome in our study population, according to the NCEP-ATP III was 16%: 18% in the group treated versus 13% in untreated with no significant difference. In Africa, the frequency of metabolic syndrome varies from 10% to 21% in patients receiving ART [5] [7] [8]. This frequency is strongly related to the diagnosis criteria which are those of IDF (International Diabetes Federation) or those of NCEP-ATP III. The reported studies also showed just as we observed that there is no significant difference between the treated and untreated subjects. Therefore, the authors question the real impact of ARV treatment on the onset of metabolic syndrome. Actually, the duration of exposure to ARV was highly variable in the cohort of patients studied. Nearly half of the patients had less than 48 months of exposure (between 24 and 48 months in 25% of cases and less than 24 months in 23% of cases); which could explain the difference between our two patient groups was not significant. Logically, the incidence of metabolic disorders increases with the duration of exposure to ARVs [5]. If we compared subjects treated for more than 48 months to untreated subjects, we could probably observe a significant difference. In our study, although there was no significant difference between the 2 groups, ART increased to 36% the risk of developing metabolic syndrome. On the other metabolic abnormalities, the impact of ART is significantly remarkable. Indeed, hyperglycemia was observed in 18% of patients (including 12% diabetes) versus 4% in untreated subjects (including 2% diabetes), $p < 0.0001$. Guira O. in Burkina Faso found that 29.6% of subjects had hyperglycemia [7]. Likewise the lipid profile of subjects treated is different from that of untreated: 44% had hypercholesterolemia versus 13%, $p = 0.02$. In fact, the high frequency of these anomalies is reported by several studies but in widely varying proportions [5]-[10]. Lipodystrophy was observed in nearly one patient treated for three, and more than half of the cases were the atrophic form. Others have made the same observation emphasizing the determining role of stavudine which was widely used in most national programs in developing countries [5] [7] [11]. The impact of ART on the occurrence of metabolic syndrome is due to the mechanism of action of ARVs Drugs which determine dysfunction of lipid and glucose metabolism of patients [12]-[15]. The high prevalence of metabolic syndrome in patients exposes them more to cardiovascular disease [16] [17] and diabetes [18] [19]. The risk to develop diabetes in our patients treated was 6 times that of untreated. Some studies have shown that IP was the most complained therapeutic class in the occurrence of metabolic syndrome [3] [6] [9]. In ours, we achieved the same results. Indinavir boosted with ritonavir was associated with a high risk to developed metabolic syndrome, with a measure of association of 2.23. Besides the IP, other studies have also incriminated some NRTIs, particularly the stavudine, in the occurrence of metabolic syndrome [5] [6]. This association was also documented in our cohort in which exposure to stavudine increased to 59% the risk to develop metabolic syndrome.

Classically, age is quoted in the general population, as a cardiovascular risk factor. It is the same in PLWHA. Indeed, PLWHA, aged over 50, have a history of the disease and treatment history longer than the younger subjects and thus would develop more of metabolic abnormalities. Various studies confirm these facts [5]-[8] [20]. In our study, a difference of one year of age significantly increased by 0.3% the risk to develop metabolic syndrome.

BMI was statistically associated with the occurrence of the metabolic syndrome in our study population. Patients overweight and obese had respectively 3 and 5 times the risk of those with a weight below normal. Patients who are overweight are more wear priori to present abdominal obesity and dyslipidemia than others. However, abdominal obesity and dyslipidemia are key parameters for the diagnosis of metabolic syndrome. The relationship between BMI and the metabolic syndrome can explain this fact. It was also observed in most of the previous studies. In France, the SHIVA cohort [21] in 2008, the average BMI of patients with metabolic syndrome was 26 ± 3.3 ($p = 0.002$) and in the SYMET cohort (metabolic syndrome) [10], after a four years of ART, patients with an increase in BMI during follow-up, quadrupled their risk of developing metabolic syndrome ($p = 0.002$). It is the same in a Spanish cohort in 2003, with an average BMI of 25.8 ± 3.7 (OR = 1.27, $p = 0.0001$) [6]. Immune restoration allows, in subjects with HIV infection, weight gain need to be monitored to prevent or detect early consequent metabolic abnormalities, as has been shown in the study by DUBE and al [22] in naive patients, with a correlation between weight gain in the first six months after initiation of therapy and visceral perished fat content measured by DEXA scan.

Patients who consume alcohol increase 90% their risk of developing metabolic syndrome. The metabolic syndrome is associated with an inflammation of the adipose tissue with macrophage infiltration in the original hyperproduction of pro-inflammatory cytokines, an increase in the free fatty acid stream and a decrease of adiponectin, resulting hepatic lipotoxicity, or steatohepatitis [23]. However, it has been shown greater severity of

liver damage in alcoholic patients, regardless of any other abuse of the liver, such viral hepatitis C [24]. Alcohol consumption among PLWHA could therefore accelerate by its liver toxicity, metabolic dysfunction, thereby increasing the risk of developing metabolic syndrome. High blood pressure, diabetes and a family history of diabetes, increased risk of developing metabolic syndrome in patients treated. The association between metabolic syndrome and these diseases (hypertension and diabetes) could result from the fact that they are already included risk factors in the diagnostic criteria of metabolic syndrome. In most studies, patient histories were not documented. Some studies even take as exclusion criteria, the fact of presenting one or the other of these antecedents. In the SHIVA study (Study of HIV and Atherosclerosis) on a cohort of HIV treatment in France [21], patients with a known history of hypertension, diabetes and family history of cardiovascular disease, were excluded from the sample. By integrating subjects with a family history of cardiovascular disease, the prevalence of metabolic syndrome increased from 7.1% to 10.3%. It would be interesting to conduct longitudinal studies to document the installation of the metabolic syndrome in PLWHA including patients treated with ARVs who are hypertensive or diabetic. After multivariate analysis, factors associated with statistics significantly to the occurrence of the metabolic syndrome were hypertension and exposure to stavudine. These variables collectively increased from 38% to 55% the risk to develop metabolic syndrome. So, with these variables, we can predict for the individual risk of developing metabolic syndrome.

5. Conclusion

The impact of antiretroviral therapy on the metabolic profile of PLWHA is real. Classical cardiovascular risk factors (including age, overweight, hypertension, and diabetes) and the use of certain ARVs drugs as indinavir boosted by ritonavir and stavudine predispose to the occurrence of the metabolic syndrome in these types of patients. In developing countries, in support of national programs for PLWHA the use of ARVs at high risk of metabolic disorders must definitively be ended. They also must imperatively implement prevention strategies and management of metabolic abnormalities in treated PLWHA. In doing so, we can expect long-term minimizing the risk of cardiovascular events in PLWHA.

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