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Chronic Venous Insufficiency in Human Immunodeficiency Virus-Positive Patients Undergoing Highly Active Antiretroviral Therapy

Authors: Marcelo Burihan Calil, MD[1], Andre Fonseca Duarte, MD[2], Catherine Puliti Hermida Reigada, MD[3], Adnan Neser, MD[1], Felipe Nasser, MD[1], Jose Carlos Ingrund, MD[1], Viviane de Almeida Jabur, MD[4], Patrícia Carla Piragibe Ramos Burihan, MD4, Gilberto Mitsuo Ukita, PhD[2]

Adress:[1] Santa Marcelina Hospital, [2] University of São Paulo, [3] University of Campinas, [4] University of Santo Amaro

E-mail: mcburihan@osite.com.br *corresponding author

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Abstract

Introduction: The acquired immunodeficiency syndrome (AIDS) is a chronic and progressive disease with an important worldwide epidemiological impact. Likewise, chronic venous insufficiency (CVI) also represents an extremely relevant pathology. There are no studies correlating both of them. Aim: Characterize human immunodeficiency virus (HIV) positive patients undergoing highly active antiretroviral therapy (HAART) as to the presence of varicose veins and CVI of the lower limbs. Method: A descriptive transversal study. 106 HIV positive patients were evaluated. The majority of the patients were assisted in an infectious disease clinic. The non-parametric test of association qui-square (X2) was used. Results:The time of HIV infection was significant associated with the symptom cramps (P = 0.049). The time of HAART showed a significant association in relation to tingling sensation (P= 0.048). Regarding the time of use of zidovudine, a significant association was observed with tingling sensation (P< 0.01) and edema (P= 0.017). A significant association with referred edema (P= 0.016) was also shown. There was also a significant increase in the prevalence of burning sensation after 3 years of lamivudine (P= 0.028). There was a significant association between the use of efavirenz and fatigue in the lower limbs and a significant increase in tingling (P= 0.03). Conclusion: This is the first study investigating the presence of CVI of the lower limbs in HIV infected patients undergoing HAART. Further studies must be encouraged in order to elucidate the real role of the HIV infection and HAART on the worsening of CVI in this group.

Key words: venous insufficiency; varicose veins; antiretroviral; HIV

Introduction

The acquired immunodeficiency syndrome (AIDS) is a chronic and progressive disease with an important worldwide epidemiological impact. Likewise, chronic venous insufficiency (CVI) also represents an extremely relevant pathology. However, there are no studies correlating both of them.

CVI is defined as an abnormality of the function of the venous system caused by a valvular incompetence or changes of the venous wall. It might be related or not to an obstruction of the venous flow, which can lead to varicose veins1,2,3.

In 1998, Carr described a redistribution of body fat and metabolic abnormalities in AIDS patients undergoing highly active antiretroviral therapy (HAART) called liposdistrophy4,5. Some studies have shown risk factors related to the development of this syndrome, such as: age, white gender, AIDS severity by CD4 cells and viral charge and the use and duration of HAART6.

After clinical observation that HIV positive patients undergoing HAART developed varicose veins in

the lower limbs, a hypothesis has been raised if there are any selected role of HAART in the dilatation of the venous wall with consequent progression and the worsening of CVI.

Objective

Characterize human immunodeficiency virus (HIV) positive patients undergoing HAART as to the presence of varicose veins and CVI of the lower limbs.

Method

A descriptive transversal study without any conflicts of interest. After signing the free informed term of consent during the period from February to December 2006, 106 HIV positive patients were evaluated by one vascular surgeon according to the approved protocol by the Research Ethics Committee of the Municipal Secretary of Health in the city of São Paulo (Brazil). This study corresponds to the first phase of a prospective study. These patients were assisted at the Specialized Assistance Service (SAE) STD/AIDS Cidade Dutra, at the specialty ambulatory José Bonifácio IV and at the Vascular Surgery Ambulatory of Santa Marcelina Hospital. All of them are located in the São Paulo city. The vast majority of the patients (91/106) were assisted in the SAE STD/AIDS which is an infectious disease ambulatory.

The inclusion criterion was HIV patients undergoing HAART. Those who have never initiated HAART, whose data was incomplete, who have denied participating on this study, who had previous surgical intervention in the lower limbs, who had personal antecedent of neoplasias, thrombosis and post-thrombotic syndrome and patients under 18 years old or above 70 years old were excluded. After applying those criteria, 6 patients were excluded, characterizing a sample of 100 patients.

The following criteria were investigated: age, body mass index (BMI), physical activity, personal antecedents such as arterial hypertension, diabetes mellitus, smoking status and alcohol intake, personal and family antecedent of varicose veins and deep vein thrombosis, number of pregnancies, practice of physical exercise and use of venotonics and elastic compression stockings.

Symptoms related to the venous disease of the lower limbs such as leg heaviness, fatigue in the legs, burning and tingling sensation, cramps, sensation of swelling and pain were questioned apart from asking whether there was any worsening of them after the beginning of HAART. All the antiretrovirals used since the beginning of HAART, time of use of each antiretroviral, total time of HAART, time of HIV infection, CD4+ cell count and viral charge at the moment of evaluation were obtained.

During the physical examination, the patients were weighed and measured by the same professional to calculate the BMI for further grouping in the categories according to the World Health Organization (WHO)7: underweight (BMI<18.5 kg/m2), normal range (BMI between 18.5 and 24.99 kg/m2), pre-obese (BMI between 25 and 29.99 kg/m2) and obese (BMI>30 kg/m2).

Firstly, the physical examination was conducted with the patient in the orthostatic position to evaluate the inspection of the lower limbs. Then, the palpation and percussion of the small (SSV) and great (GSV) saphenous veins from theirs origins to theirs junctions besides the palpation of SSV in the popliteal fossa was performed. The circumferences of the lower limbs (ankles, legs and thighs) were obtained with the patient in dorsal decubit and then the dosalis pedis, posterior tibial, popliteal and femoral pulses were palpated. The presence or not of telangiectasias, reticular veins, dilatation of tributary veins, small and great saphenous vein insufficiency, dermatitis ocre, eczema, edema and venous ulcer was evaluated. As a result of physical examination, the patients were classified regarding the clinical category of CEAP8, adopting the presence of varicose veins when clinical CEAP was equal or higher than 2.

Asymptomatic patients were informed about the venous disease and they were advised on prophylactic measures, such as loss of weight and practice of physical exercises. Patients with CVI were advised in the first consultation to the need of elastic or inelastic compression, drug treatment, and bandage combined with clinical measures in cases of venous ulcer.

Firstly, patients were stratified according to the average time of use of HAART. Secondly, if there was a statistic significant result, they were rearranged in the time interval of use of HAART every two years. This had the proposal of obtaining higher precision of determination in which interval of time it would observe the occurrence of signals and symptoms of the venous disease.

The non-parametric test of association qui-square (X2) was used to evaluating whether there was a correlation between the variables analyzed, adopting P<.05 as a statistic significant result. Values of P between 0.05 and 0.1 were considered marginally significant.

Results

The average age of the patients was 40.69 years, ranging from 21 to 64 years, 51% of which were male. Regarding personal antecedents, 50% were smokers or had been smokers, 15% had systemic arterial hypertension and 5% had diabetes mellitus. As for the BMI, 52.1% were at normal range, 33.3% were pre-obese, 14.6% were obese and none of them were underweight. The average time of the HIV infection was 6 years, having 17% of the patients being infected less than 2 years, 20% between 2 and 4 years, 15% between 4 and 6 years, 16% between 6 and 8 years, 9% between 8 and 10 years and 23% over 10 years. When CD4+ cell count was analyzed, 15% had less than 200/mm^3, 26% between 200 and 349/mm^3, 23% between 350 and 500/mm^3 and 36% were higher than 500/mm^3. The viral charge was undetectable, that is to say below 400 copies/ml, in 70% of the patients, below 10.000 copies/ml in 8%, between 10.000 and 20.000 copies/ml in 5% and over 20.000 copies/ml in 17%.

The most frequent antiretrovirals used were lamivudine (3TC) in 91% of the patients, zidovudine (AZT) in 89%, efavirenz (EFV) in 61%. With lower frequency, stavudine (d4T) in 24%, didanosine (ddI) in 24%, atazanavir (ATV) in 24%, nevirapine (NVP) in 20%, lopinavir/ritonavir (LPV/r) in 18%, indinavire (IDV) in 13%, nelfinavir (NFV) in 12%, saquinavir (SQV) in 6%, abacavir (ABC) in 4%, tenofovir (TDF) in 4% and zalcitabine (DDC) in 2% were also used.

The average time of HAART was 3 years and 6 months where 33% were undergoing HAART for less than 2 years, 25% between 2 and 4 years, 17% between 4 and 6 years and 25% over 6 years.

The worsening of CVI after initiating HAART was referred in 38% of the patients. The most frequently referred symptom related to venous disease was fatigue in the lower limbs in 47% of the cases, followed by characteristic venous pain in 43%, leg heaviness in 39%, burning sensation in 39%, referred edema in 39%, tingling sensation in 36% and cramps in 36%, all of them in the lower limbs.

As a result of physical examination, it was observed 67.6% of GSV insufficiency (33% bilaterally), 25.4% of SSV insufficiency (10.3% bilaterally), 39% of telangiectasias, independently of the presence of varicose veins, 9.2% of dermatitis ocre, 1% of healed venous ulcer and 1% of open venous ulcer.

Considering the clinical category of CEAP classification[8], 4% were at C0 (no evidence of venous disease), 11% at c1 (telangiectasis and reticular veins), 59% at c2 (only varicose veins), 14% at c3 (edema and varicose veins), 10% at c4 (hyperpigmentation, eczema, lipodermatosclerosis, atrophie blanche and varicose veins), 1% at c5 (healed venous ulcer) and 1% at c6 (open venous ulcer). Therefore, the prevalence of varicose veins was 85%.

Tables 1 to 8 show all prevalences obtained by the associations between the studied variables and the time of HIV infection, and the time of use of HAART and each ARV individually.

Table I. Presence of variable in the lower limbs in patients with less or higher than 6 years of HIV infection.

	Time of HIV infection		
Presence of variable	**< 6 years (n=52) No. (%)**	**≥ 6 years (n=48) No. (%)**	**P value**
Fatigue	23 (44.23)	24 (50)	.564
Heaviness	20 (38.46)	19 (39.58)	.909
Burning sensation	19 (36.54)	20 (41.67)	.599
Tingling sensation	18 (34.62)	18 (37.50)	.764
Cramps	14 (26.92)	22 (45.83)	.049
Swelling sensation	17 (32.69)	22 (45.83)	.178
Pain	22 (42.31)	21 (43.75)	.884
Dermatitis ocre	6 (11.54)	3 (6.25)	.356
Eczema	2 (3.85)	2 (4.17)	.935
Edema	10 (19.23)	9 (18.75)	.951
Varicose veins	42 (80.77)	43 (89.58)	.217

HIV, human immunodeficiency virus; No., number of patients.

Table II. Presence of variable in the lower limbs every 2 years of HAART.

	Time of use of HAART				
Presence of variable	**< 2 years (n=33) No. (%)**	**2 - 4 years (n=25) No. (%)**	**4 - 6 years (n=17) No. (%)**	**≥ 6 years (n=25) No. (%)**	**P value**
Fatigue	14(42.42)	12(48)	11(64.71)	10(40)	.404
Heaviness	13(39.39)	7(28)	10(58.82)	9(36)	.243
Burning sensation	11(33.33)	7(28)	9(52.94)	12(48)	.266
Tingling sensation	11(33.33)	6(24)	11(64.71)	8(32)	.048
Swelling sensation	12(36.36)	6(24)	7(41.28)	14(56)	.137
Pain	15(45.45)	9(36)	9(52.94)	10(40)	.715
Dermatitis ocre	6(18.18)	1(4)	2(11.76)	0(0)	.790
Eczema	2(6.06)	2(8)	0(0)	0(0)	.368
Edema	8(24.24)	4(16)	5(29.41)	2 (8)	.273
Varicose veins	28(84.85)	21(84)	15(88.24)	21(84)	.981

Table IV. Presence of variable in the lower limbs every 2 years of AZT use.

Presence of variable	Time of use of AZT: < 2 years (n=35) No. (%)	2 - 4 years (n=21) No. (%)	4 - 6 years (n=18) No. (%)	≥ 6 years (n=15) No. (%)	P value
Fatigue	13 (37.14)	10 (47.62)	12 (66.67)	7 (46.67)	.244
Heaviness	10 (28.57)	7 (33.33)	11 (61.11)	5 (33.33)	.124
Burning sensation	10 (28.57)	7 (33.33)	10 (55.56)	8 (53.33)	.155
Tingling sensation	10 (28.57)	7 (33.33)	13 (72.22)	3 (20)	.005
Swelling sensation	10 (28.57)	6 (28.57)	9 (50)	10 (66.67)	.040
Pain	12 (34.29)	7 (33.33)	11 (61.11)	8 (53.33)	.175
Dermatitis ocre	4 (11.43)	1 (4.76)	2 (11.11)	0 (0)	.487
Eczema	2 (5.71)	2 (9.52)	0 (0)	0 (0)	.405
Edema	6 (17.14)	2 (9.52)	7 (38.89	0 (0)	.017
Varicose veins	28 (80)	17(80.95)	17 (94.44)	12 (80)	.559

AZT, zidovudine; No., number of patients.

HAART, highly active antiretroviral therapy; No., number of patients.

Table III. Presence of variable in the lower limbs in patients with less or higher than 3 years of AZT use.

Presence of variable	Time of use of AZT: < 3 years (n=52) No. (%)	≥ 3 years (n=37) No. (%)	P value
Fatigue	22 (42.31)	20 (54.05)	.273
Heaviness	16 (30.77)	17 (45.95)	.144
Burning sensation	16 (30.77)	19 (51.35)	.050
Tingling sensation	15 (28.85)	18 (48.65)	.056
Swelling sensation	15 (28.85)	20 (54.05)	.016
Pain	19 (36.54)	19 (51.35)	.163
Dermatitis ocre	5 (9.62)	2 (5.41)	.467
Eczema	4 (7.69)	0 (0)	.084
Edema	8 (15.38)	7 (18.92)	.660
Varicose veins	42 (80.77)	32 (86.49)	.477

AZT, zidovudine; No., number of patients.

Table V. Presence of variable in the lower limbs with or without 3TC use.

Presence of variable	Use of 3TC: Without use (n=9) No. (%)	With use (n=91) No. (%)	P value
Fatigue	4 (44.44)	43 (47.25)	.872
Heaviness	5 (5.56)	34 (37.36)	.286
Burning sensation	4 (44.44)	35 (38.46)	.726
Tingling sensation	5 (55,56)	31 (34,07)	.200
Swelling sensation	4 (44.44)	35 (38.46)	.726
Pain	6 (66.67)	37 (40.66)	.133
Dermatitis ocre	2 (22.22)	7 (7.69)	.146
Eczema	0 (0)	4 (4.4)	.521
Edema	4 (44.44)	15 (16.48)	.041
Varicose veins	9 (100)	76 (83.52)	.186

3TC, lamivudine; No., number of patients.

Table VI. Presence of variable in the lower limbs in patients with less or higher than 3 years of 3TC use.

Presence of variable	Time of use of 3TC: < 3 years (n=57) No. (%)	≥ 3 years (n=34) No. (%)	P value
Fatigue	25 (43.86)	18 (52.94)	.648
Heaviness	20 (35.09)	14 (41.18)	.561
Burning sensation	17 (29.82)	18 (52.94)	.028
Tingling sensation	16 (28.07)	15 (44.12)	.118
Swelling sensation	19 (33.33)	16 (47.06	.192
Pain	22 (38.60)	15 (44.12)	.604
Dermatitis ocre	5 (8.77)	2 (5.88)	.616
Eczema	4 (7.02)	0 (0)	.114
Edema	11 (19.30)	4 (11.76)	.348
Varicose veins	46 (80.70)	30 (88.24)	.348

3TC, lamivudine; No., number of patients.

Varicose veins	41 (83.67)	12 (100)	.133

EFV, efavirenz; No., number of patients.

The time of HIV infection has shown a significant association with cramps (figure IA) (P = .049), with an increase of its prevalence after 6 years of infection (45.83%) in relation to the group with less than 6 years (26.92 %).

In figure IB, a significant association is observed between the time of use of HAART and tingling sensation (P= .048). There was a raise in its prevalence between 4 to 6 years of use of HAART, in which 64.71% of the patients in this period had the symptom.

The time of use of AZT had a significant association with referred edema (P= .016) in figure IC. A higher prevalence of this symptom was observed after 3 years of use (54.05%) in comparison to those which used for less than 3 years (28.85%). From the same figure, a marginally significant association was observed with burning sensation (P=.05), with an increase of its prevalence from 30.77% in those with less 3 years of use of AZT to 51.35% after 3 years of use. Likewise, its association with tingling sensation was marginally significant (P< .06), with a boost of its prevalence from 28.85% to 48.65% after 3 years of use.

Table VII. Presence of variable in the lower limbs with or without EFV use.

	Use of EFV		
Presence of variable	**Without use (n=39) No. (%)**	**With use (n=61) No. (%)**	**P value**
Fatigue	13 (33.33)	34 (55.74)	.029
Heaviness	15 (38.46)	24 (39.34)	.930
Burning sensation	16 (41.03)	23 (37.70)	.740
Tingling sensation	12 (30.77)	24 (39.34)	.384
Swelling sensation	17 (43.59)	22 (36.07)	.452
Pain	17 (43.59)	26 (42.62)	.924
Dermatitis ocre	3 (7.69)	6 (9.84)	.715
Eczema	2 (5.13)	2 (3.28)	.645
Edema	6 (15.38)	13 (21.31)	.461
Varicose veins	32 (82.05)	53 (86.89)	.509

EFV, efavirenz; No., number of patients.

Table VIII. Presence of variable in the lower limbs in patients with less or higher than 3 years of EFV use.

	Time of use of EFV		
Presence of variable	**< 3 years (n=49) No. (%)**	**≥ 3 years (n=12) No. (%)**	**P value**
Fatigue	26 (53.06)	8 (66.67)	.395
Heaviness	17 (34.69)	7 (58.33)	.133
Burning sensation	16 (32.65)	7 (58.33)	.099
Tingling sensation	16 (32.65)	8 (66.67)	.030
Swelling sensation	16 (32.65)	6 (50)	.262
Pain	19 (38.78)	7 (58.33)	.219
Dermatitis ocre	5 (10.20)	1 (8.33)	.845
Eczema	2 (4.08)	0 (0)	.476
Edema	10 (20.41)	3 (25.00)	.727

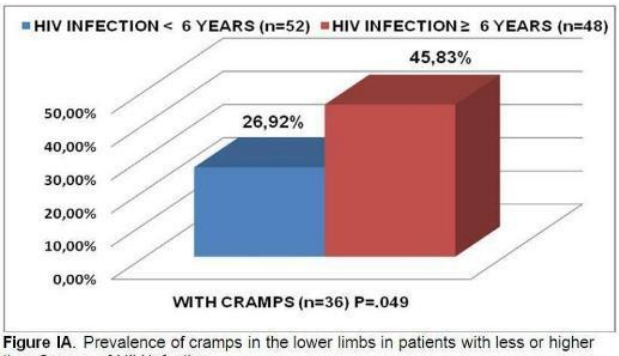

Figure IA. Prevalence of cramps in the lower limbs in patients with less or higher than 6 years of HIV infection.

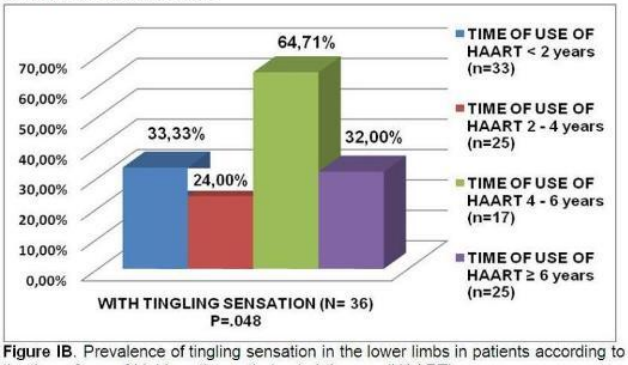

Figure IB. Prevalence of tingling sensation in the lower limbs in patients according to the time of use of highly active antiretroviral therapy (HAART).

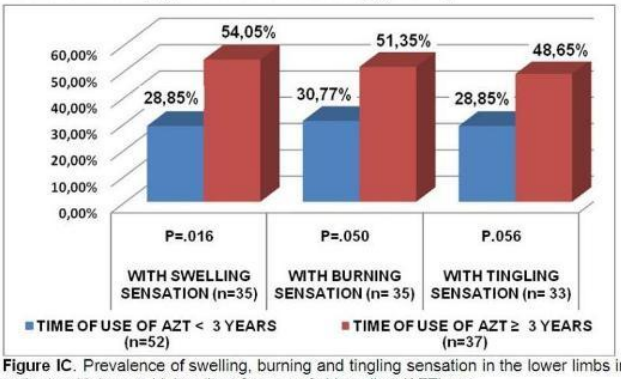

Figure IC. Prevalence of swelling, burning and tingling sensation in the lower limbs in patients with less or higher than 3 years of zidovudine (AZT) use.

Figure IIA represents the stratification of time of use of AZT each 2 years in relation to the same variables.

A significant association with tingling sensation (P< .01) is observed with a raise of its prevalence in 4 to 6 years of use (72.22%).

In figure IIA, it can also be observed a significant association with edema at physical examination (P= .017) with a raise of its prevalence between 4 to 6 years of use (38.83%) in comparison to the prevalence between 2 to 4 years (9.52%) and less than 2 years of AZT use (17.14%).

Finally, in figure IIA it is also shown a significant association with referred edema (P= .04). There is no difference in its prevalence until 4 years of use (28.57%), although after that there is a gradual increase of its prevalence each 2 years (50% from 4 to 6 years and 66.67% after 6 years of use of AZT).

In figure IIB, the use or not of lamivudine 3TC had a significant association with edema at physical examination (P=.041) with a decrease of its prevalence in the group who has used this drug (16.48%) in relation to the ones who have not used it (44.44%).

There is in figure IIC a significant association between the use of 3TC with burning sensation (P= .028), with a higher prevalence of this symptom after 3 years of use (52.94%) in comparison to those which used for less than 3 years (29.82%).

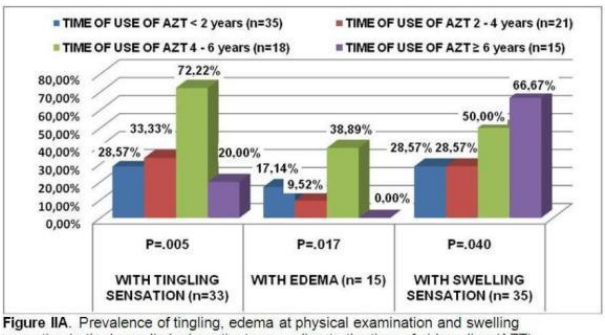

Figure IIA. Prevalence of tingling, edema at physical examination and swelling sensation in the lower limbs in patients according to the time of zidovudine (AZT) use.

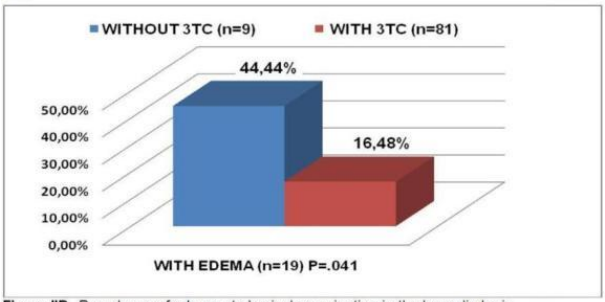

Figure IIB. Prevalence of edema at physical examination in the lower limbs in patients with or without lamivudine (3TC) use.

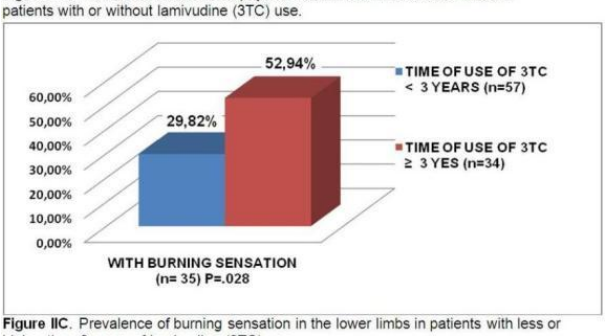

Figure IIC. Prevalence of burning sensation in the lower limbs in patients with less or higher than 3 years of lamivudine (3TC) use.

A significant association between the use or not of EFV and fatigue in the lower limbs (P< .03) is illustrated in figure IIIA, in which there is a raise of its prevalence in

the group who has used this drug (55.74%) in comparison to those who has not used it (33.33%).

In figure IIIB was observed a significant association between tingling sensation and the time of use of EFV (P= .03) with an increase of its prevalence after 3 years of use (66.67%) in comparison to those who used EFV for less than 3 years (32.65%).

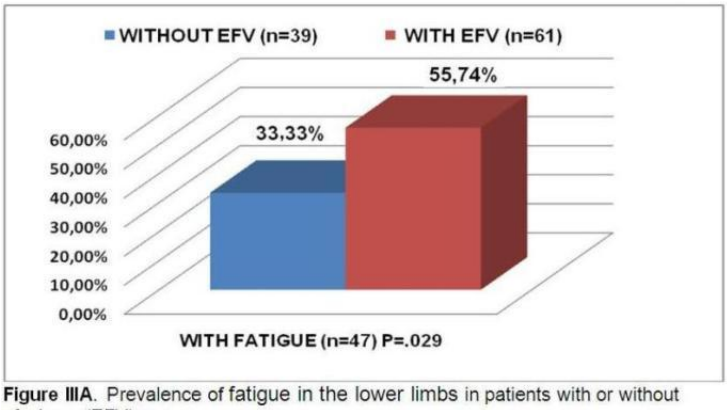

Figure IIIA. Prevalence of fatigue in the lower limbs in patients with or without efavirenz (EFV) use.

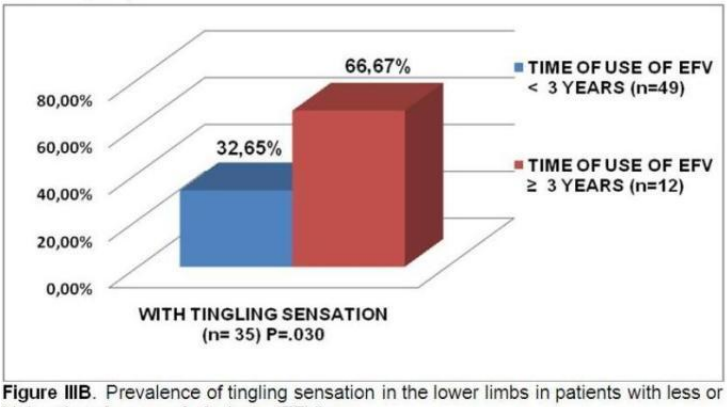

Figure IIIB. Prevalence of tingling sensation in the lower limbs in patients with less or higher than 3 years of efavirenz (EFV) use.

Discussion

Callam observed that half of the general population has minor stigmata of CVI, being it between 50-55% in women and between 40-45% in men. Less than 25% of the population has visible varicose veins, being 20-25% in women and 10-15% in men9. The Edinburgh Vein Study has shown a prevalence of varicose veins of 40% in men and 32% in women10. In the general Brazilian population, Maffei observed a prevalence of varicose veins of 47.6%, excluding clinical category 1 of CEAP11,12. The high prevalence found in our study of 85%, also excluding CEAP c1, maybe does not accurately illustrate yet the reality of this group, but surely draws attention to a possible fostering of the physiopathological evolution of CVI.

The clinical category of CEAP classification was used, not only because is it globally widespread, but also easily reproducible8,13. Andrade has shown correlation between the presence of superficial venous reflux in duplex scan and the severity of the clinical picture in patients with varicose veins of lower limbs, despite the difficulty of setting standards primarily by polymorphism of CVI14.

Stuart has observed that severity of the disease was related to the number of incompetent perforating per limb. He has also demonstrated that patients with telangiectasias had 5% of incompetent perforating, while those with active or healed ulcer had 77% of incompetent perforating of the sample15.

Our patients present a profile that deserves to be considered. They had an optimal therapeutic control in relation to AIDS, in which 70% had undetectable viral charge and 59% had CD4+ cell count over 350/mm3.
Besides, they showed constitutional and morphological characteristics higher than expected for this population. Results showed an expressive percentage of patients in the normal range (52.1%), pre-obese (33.3%) and obesity (14.6%), according to the BMI classification7. None of the patients were classified as underweight. The profile of our group was different from the literature that describes the constitutional HIV syndrome characterized by severe malnutrition and cachexia16.

The lipodystrophy syndrome is subdivided into: lipoatrophy, lipohypertrophy and mixed form4,5. Aiming at the non-interference in the ultimate interpretation of the findings, there was a concern about the characterization of the presence or absence of lipoatrophy in the studied patients.
There is still no objective measuring instrument to characterize lipoatrophy. Some articles studied the use of CT scans and bone densitometry as diagnostic tools for lipodystrophy; however, none of these methods have been standardized or accepted6,17,18.

Lichtenstein adopted in his study of 546 patients the clinical evaluation as a criterion to characterize lipoatrophy. Evaluated in three regions, the superficial fat loss (limbs, hip and malar) then patient and doctor attributed a score to each region. Agreement was observed in most cases6.

He also reports that 61.7% (337) of patients did not have lipoatrophy and pointed out that BMI <24 kg/m2 (P <.022) and low CD4 cell count less than 100/mm3 (P <.001) shows a significant correlation with presence of lipoatrophy. It must be considered that CD4 cell count also evaluates the severity of AIDS6. In none of the patients in our study the presence of lipoatrophy was marked.

By analyzing CD4 cell count, 15% of patients had cell count below 200/mm3 and only 0.03% of them had cell count below 100/mm3 at the time of the evaluation.

The main theories of the etiology of primary varicose veins of the lower limbs are related to changes in the venous wall, changes in the collagen structure and/or elastin, increased presence of elastic material with the thickening of the vase, local or segmental valvular incompetence and the arteriovenous fistulas in the microcirculation19.

Travers showed no difference in levels of collagen and elastin in varicose veins, but detected increased muscular density, with increased smooth muscle, attributing this as a factor responsible for the dilatation20.

Some studies have indicated that the reduced antiperoxidant activity21, the increased circulating levels of norepinephrine22, the infiltration by mast cells23, and the oxygen free radicals24 may be important factors for the development of varicose veins.

In a recent review, Wang studied the mechanisms of endothelial dysfunction induced by protease inhibitors. Although most of the endothelial changes are related to the arteries, leading to increased cardiovascular risk, the author also describes in vitro studies in which the exposure of smooth muscle cells to protease inhibitors, such as nelfinavir and saquinavir, led to production of oxygen-free radicals25.

The only study that relates somehow CVI and the presence of HIV infection makes it through the history of injecting drug use. Piper investigated 73 patients, 27 of which had no history of injecting drugs and 46 who had positive history. From this group, only 5 patients have used the drugs in the upper limbs. The injecting drugs used were heroin, cocaine, amphetamines, methadone and other opioids. In this study, the results related to the use of ARV therapy were not mentioned.

The mean length of HIV infection was 9.6 years and the CD4 cell count and viral load was an average of 371.3 cells/mm3 and 1500 copies / ml, respectively.

Clinical examination of lower limbs was based on clinical CEAP category. The result was obtained was 61% (28⁄46) of advanced chronic venous insufficiency (classified as CEAP 4-6) among patients that used injecting drugs, in contrast to 11% in the control group (P<.01)26.

Despite being the only one that is close to our study, the article described above does not present methodological characteristics that enabled comparisons.

In physical examination, 67.6% of GSV insufficiency (33% bilaterally) and 25.4% SSV insufficiency (10.3% bilaterally) by the Schwartz maneuver was found. This fact demonstrates that the occurrence of CVI in HIV positive patients cannot be underestimated, especially considering that in our study they did not have lipoatrophy, had a favorable metabolic profile and had just 5% of diabetics.

The time of HIV infection was significant associated with the symptom cramps.

The time of HAART showed a significant association only in relation to tingling sensation, with higher prevalence in the range of use between 4 and 6 years.

Only the associations generated by zidovudine (AZT), lamivudine (3TC) and efavirenz (EFV) were selected due to the fact that these drugs were the most prevalent in our study. The associations of the other drugs were excluded as they did not provide homogeneous statistical groups and were not open to interpretation.

Regarding the time of use of zidovudine, a significant association was observed with tingling sensation and edema at physical examination, both after 4 to 6 years of use. A significant association with referred edema and a marginally significant association with burning sensation after 3 years of use was also shown.

When lamivudine was used, there was a lower percentage of edema at physical examination in comparison to those who did not use it. There was also a statistically significant increase in the prevalence of burning sensation after 3 years of 3TC.

There was a significant association between the use of efavirenz and fatigue in the lower limbs and a statistically significant increase in tingling after three years of use of EFV.

None of the associations surveyed between the presence of varicose veins related to the use and/or duration of use of ART and each ARV individually was statistically significant.

The greatest difficulty was the lack of studies relating both pathologies, precluding comparisons with the results. We also understand that only after making a drawing of a prospective cohort study, which corresponds to the next phases of our work, shall we more properly establish or rule out possible associations.

Conclusion

This is the first study investigating the presence of CVI of the lower limbs in HIV infected patients undergoing HAART. Further studies must be encouraged in order to elucidate the real role of the HIV infection and HAART on the emergence or worsening of CVI in this group. However, the high prevalence of varicose veins in this group of patients demands that during their

management, we should be familiarized with both support and prophylactic measures of CVI in the lower limbs.

References

1. Porter JM, Moneta LG. Reporting standards in venous disease: an update. J Vasc Surg 1995;21(4):635-45.

2. França LHG, Tavares V. Insuficiência venosa crônica. Uma atualização. J Vasc Br 2003;2(4):318-28.

3. Ferreira CS, Sales EA, Garrido MBM. Patologia e diagnóstico das varizes dos membros inferiores. In: Maffei FHA, Lastória S, Yoshida WB, Rollo HA, editores. Doenças vasculares periféricas. Rio de Janeiro: Medsi; 1995. p. 951-974.

4. Carr A, Samaras K, Chisholm DJ, Cooper DA. Abnormal fat distribution and use of protease inhibitors. Lancet 1998; 351:1736.

5. Carr A, Samaras K,Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998;12(Suppl):F51-8.

6. Lichtenstein KA, et al. Incidence of and risk factors for lipoatrophy (Abnormal fat loss) in ambulatory HIV-1 infected patients. JAIDS 2003;32:48-56.

7. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. The Lancet, 2004; 157-163.

8. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. J Vasc Surg. 1995;21:635-45.

9. Callam MJ. Epidemiology of varicose veins. Br J Surg. 1994 Feb;81(2):167-73.

10. Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health. 1999;53;149-53.

11. Maffei FH, Magaldi C, Pinho SZ, et al. Varicose veins and chronic venous insufficiency in Brazil: prevalence among 1755 inhabitants of a country town. Int J Epidemiol. 1986 Jun;15(2):210-7.

12. Maffei FHA. Varizes dos membros inferiores: epidemiologia, etiopatogenia e fisiopatologia. In: Maffei FHA, Lastória S, YoshidaWB, Rollo HA, editores. Doenças vasculares periféricas. Rio de Janeiro: Medsi; 1995. p. 939-949.

13. Eklof B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg. 2004;40:1248-52.

14. Andrade AR, et al. Refluxo venoso superficial em portadores de varizes primárias. J Vasc Bras. 2009;8(1):14-20.

15. Stuart WP, Adam DJ, Allan PL, Ruckley CV, Bradbury AW. The relationship between the number, competence, and diameter of medial calf perforating veins and the clinical status in healthy subjects and patients with lower-limb venous disease. J Vas Surg. 2000;32:138-43.

16. Luis DA. de, Bachiller P., Izaola O., Eiros Bouza J. M., Aller R. Estado nutricional de pacientes infectados por el virus de la inmunodeficiencia humana (VIH). An. Med. Interna. 2001;18(12): 619-623.

17. Saint-Marc T, Partisani M, Poizot-Martin I, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. AIDS 2000; 14:37-49.

18. Kotler DP, Rosenbaum K, Wang J, et al. Studies of body composition and fat distribution in HIV-infected and control subjects. J Acquir Immune Defic Syndr 1999; 20:228-37.

19. Oliveira RR; et al. Alternative therapy for microvarices and telangiectasias with use of needle. J. Vasc. Bras. 2007, vol.6, n.1, pp. 17-24.

20. Travers JP, Dalton C, Baker D, Makin G Biochemical and histological analysis of collagen and elastin content and smooth muscle density in normal and varicose veins Phlebology 1992; 7:97-100

21. Deby C, Hariton C, Pincemail J, Coget J. Decreased tocopherol concentration of varicose veins is associated with a decrease in antilipoperoxidant activity without similar changes in plasma. Phlebology, 1989; 4: 113-21.

22. CROTTY TP. The role of radial reflux in the genesis of varicose veins. Med Hypotheses. 1996 Dec ;47 (6):449-54.

23. Yamada T, Tomita S, Mori M, Sasatomi E, Suenagra E, Itoh T: Increased mast cell infiltration in the varicose veins of the lower limbs: a possible role in the development of varices. Surgery 1996; 119: 494–497.

24. Farbiszewski R. Oxygen-Derived Free Radicals as Mediators of Varicose Vein Wall Damage. Vascular and Endovascular Surgery, Vol. 30, No. 1, 47-52, 1996.

25. WANG X, et. al. Molecular mechanisms of HIV protease inhibitor–induced endothelial dysfunction. J Acquir Immune Defic Syndr, v. 44, p. 493–499, 2007.

26. PIEPER B, et al. Chronic venous insufficiency in HIV-positive persons with and without a history of injection drug use. Advances in skin and wound care, v. 19 (1), p. 37-42 2006.