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High Prevalence of Subclinical Atherosclerosis in Low-Cardiovascular-Risk HIV Patients on HAART

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Abstract

Background: Lipid abnormalities and insulin resistance induced by protease inhibitor-based HAART could increase the risk of premature atherosclerosis.
Whether the treatment alone directly contributes to accelerating atherosclerosis has not been studied in depth.
This study aimed to ascertain the relationship between subclinical atherosclerosis and HAART.
Methods: We enrolled in a cross-sectional study 132 HIV-infected patients, 64 of whom were at low cardiovascular risk, 34 at moderate risk, and 34 at high risk. Subjects with known cardiovascular diseases or diabetes mellitus were excluded.
High-resolution B-mode ultrasound imaging was used to examine femoral and carotid arteries; subclinical atherosclerosis was defined when plaques were observed in one or more sites.
Cardiovascular risk was assessed by the Framingham risk score-sex, age, total cholesterol, HDL cholesterol, systolic blood pressure, and smoking-and was categorized as: A: low risk (< 5%), B: moderate risk (5 to 10%), and C high risk (> 10%) of 10-year risk of coronary events.
Univariate and multivariate logistic regression analyses were performed, with the
presence of subclinical atherosclerosis being the depend variable.
Results: Baseline characteristics of the 132 enrolled patients were: mean age (SD) 43.1 years (10); 78% male; 50.8% current smokers; mean years (SD) of HIV infection 8.1 (4.8); mean years of antiretroviral therapy (SD) 7.7 (3.1).
As for therapy, 39 were naive, 44 were currently on PI-based treatment, and 49 were currently on NRTI-based treatment.
The prevalence of subclinical atherosclerosis in relation to the Framingham risk score group was: group A 34.4%, group B 70.6%, and group C 94.1% (p: 0.0001); in relation to therapy: naives 23.1%, PI-based 75%; and NNRTI-based 73.5%.
Prevalence in the group with low cardiovascular risk: naives 4 (12.5%); PI-based 11 (68.8%); and NNRTI-based 7 (43.8%) (p = 0.0001).
In multivariate analysis, independent variables associated with subclinical atherosclerosis (HR: 95% CI) were Framingham risk score group B (3.2, 1.2 to 8.4), Framingham risk score group C (16.9, 3.5 to 80.6); PI-based therapy (5.1, 1.7 to 15.2); NRTI-based therapy (4.4, 1.5 to 12.9).
In low cardiovascular risk group, only age (per 10 years: 3.4, 1.2 to 9.6) and PI-based therapy (10, 2.1 to 47.7) were independent predictors of subclinical atherosclerosis.
Conclusions: When adjusted for known cardiovascular risk factors, HAART, mainly PI-based, should be considered an independent and strong predictor of subclinical atherosclerosis.

Background

Combination antiretroviral therapy (CART) has dramatically reduced the morbidity and mortality in HIV-infected patients. However, the potential for maintaining these patients on treatment for decades may be limited by a variety of adverse effects observed in patients on CART, including dyslipidemia, fat redistribution, insulin resistance and premature atherosclerosis, particularly when therapy contains protease inhibitors. The absolute cardiovascular risk in any individual is determined by a complex interplay of several risk factors, which include older age, positive family history, smoking, hypertension, elevated blood lipids, diabetes and other determinants. Proatherogenic metabolic abnormalities induced by CART and chronic inflammation associated with HIV infection can certainly increase the cardiovascular risk in HIV patients. Whether the treatment alone directly contributes to accelerated atherosclerosis, however, has not been scrutinized vigorously.
In order to assess the relationship between CART and atherosclerosis we have evaluated the presence of subclinical atherosclerosis in HIV infected patients according to the estimated cardiovascular risk.

Methods

One hundred and thirty-two HIV-infected patients, 64 with very low cardiovascular risk (CVR), 34 with low CVR and 34 with moderate-high CVR were enrolled in a cross-sectional study.
Subjects with known cardiovascular diseases or diabetes mellitus were excluded.
High-resolution B-mode ultrasound imaging was used to examine femoral and carotid arteries; using a Sequoia 512 system (Acuson, Pris, France). When a plaque was identified at a predefined point, the IMT was determined in adjacent segments. To descriptive purpose three different criteria for the presence of subclinical atherosclerosis was used: a) IMT higher than 0.8 mm, the presence of a plaque, or both in either carotid or femoral territories, b) the presence of a plaque only in the carotid artery, and C) the presence of plaque in either carotid or femoral territories. The latter definition of subclinical atherosclerosis was used for all statistical analysis.
Cardiovascular risk (CVR) was assessed by the Framingham Risk Score (FRS), which considers sex, age, total cholesterol, HDL cholesterol, systolic blood pressure and smoking, and was categorized as: A: very low risk < 5%, B: low risk 5-9%, and C: moderate-high risk 10 or higher % of 10-year risk of coronary events.
Univariate and multivariate logistic regression analyses were performed, with the presence of subclinical atherosclerosis being the depend variable.

Results

- Table 1 shows the charactheristics of the 132 HIV-infected patients, according to Framingham Risk Score.
- Table 2 shows te prevalence of subclinical atherosclerois using different definitions related to the FRS.
- Table 3 shows the univariate and multivariate logistic regression analysis of factors related to subclinical atherosclerosis in all included patients
- Table 4 shows the univariate and multivariate logistic regression analysis of factors related to subclinical atherosclerosis in patients with CHD 10-year risk of < 5 %.

Table 1. Characteristics of the 132 HIV-infected patients, according to Framingham Risk Score.

Characteristics	FRS A < 5 % CHD risk N: 64	FRS B 5-10% CHD risk N: 34	FRS C > 10% CHD risk N:34	P
Age (years, mean ± SD)	38.3 (8.5)	44.2 (6.2)	51.2 (10.5)	0.0001
Gender Male (%)	43 (67.2)	28 (82.4)	32 (94.1)	0.004
Family history of premature CHD (%)	10 (15.6)	5 (14.7)	2 (5.9)	0.3
Body mass index (Kg/m2, mean ± SD)	23.4 (3.3)	23.3 (3)	24.9 (3.9)	0.04 *
Current smokers (%)	21 (32.8)	22 (64.7)	24 (70.6)	0.0001
SBP (mm Hg, mean ± SD)	113.7 (10)	118.2 (12.8)	128.9 (21.2)	0.05
Total cholesterol (mg/dl, mean ± SD)	196.2 (53.9)	229.5 (38.3)	247.4 (53.9)	0.003
HDL cholesterol (mg/dl, mean ± SD)	43.2 (13.5)	43.2 (13)	38 (9.4)	0.07 *
Intravenous drug users (%)	4 (6.3)	12 (35.3)	7 (20.6)	0.002
Known time of HIV infection (years, IQR)	5.6 (2.2-10.6)	9.9 (5.5-14.4)	9.4 (6.8-12.8)	0.002
CD4 nadir cell count [x 106 cells/L (IQR)]	336(184-493)	230 (59-383)	149 (36-244)	0.02
CD4 cell count [x 106 cells/L (IQR)]	574(401-785)	576(475-787)	463(335-913)	0.46
Viral load < 500 copies/ml (%)	34 (53.1)	23 (67.6)	28 (82.4)	0.01
HIV disease category C (%)	10 (15.6)	12 (35.3)	10 (29.4)	0.07
Median time antiretroviral therapy (years, IQR)	0 (0-6.6)	6.2 (2.3-10.1)	8.1 (5,5-9.4)	0.004
Antiretroviral therapy exposure				
Naive (%)	32 (50)	6 (17.6)	1 (2.9)	0.0001
Current NNRTI (%)	16 (25)	16 (47.1)	17 (50)	
Past or Current NNRTI (%)	5 (7.8)	4 (11.8)	5 (14.7)	
Current PI (%)	16 (25)	12 (35.3)	16 (47.1)	
Past or current PI (%)	27 (42.2)	24 (70.6)	28 (82.4)	
Lipodystrophy				
No fat redistribution (%)	49 (76.6)	18 (52.9)	14 (41.2)	0.04
Lipoatrophy (%)	6 (9.4)	6 (17.6)	7 (20.6)	
Lipohypertrophy (%)	1 (1.6)	1 (2.9)	2 (5.9)	
Mixed lipodystrophy (%)	8 (12.5)	9 (26.5)	11 (32.4)	

CHD, coronary heart disease; IQR, interquartile range; HDL, high density lipoproteins.
SBP: Systole blood pressure
*Differences between group A and C.

Table 2. Subclinical atherosclerosis in relation to Framihgan Risk Score.

	FRS A <5% CHD risk (Naives) N: 32	FRS A <5% CHD risk (CART) N:32	FRS B 5-10% CHD risk N: 34	FRS C >10% CHD risk N: 34	P
Carotid plaque (%)	1 (3.1)	14 (43.8)	11 (32.4)	23 (67.6)	0.0001
Carotid and /or femoral plaque (%)	4 (12.5)	18 (56.3)	24 (70.6)	32 (94.1)	0.0001
IMT> 0.8 and/or carotid and/or femoral plaque (%)	7 (21.9)	18 (56.3)	24 (70.6)	34 (100)	0.0001
IMT carotid, median (IQR)	0.54 (0.5-0.6)	0.55 (0.45-0.63)	0.59 (0.5-0.7)	0.65 (0.57-0.75)	0.001 *
IMT femoral, median (IQR	0.55 (0.5-0.61)	0.55 (0.45-0.61)	0.6 (0.5-0.85)	0.75 (0.62-0.94)	0.0001* 0.036**

* Significative diffeence between group FRS A naives and FRS C group
** Significative difference between group FRS A naives and FRS B group.

Table 3. Univariate and multivariate logistic regression analysis of factors associated with subclinical atherosclerosis..

	Univariate. OR (95% CI)	P	Multivariate (OR 95%CI)	P
Age per 10 years	3.8 (2.2-6.7)	0.0001	#	
Time (yearts) of known HIV infection	1.2 (1.1-1.3)	0.0001	1.07 (0.95-1.12)	0.28
Time(years) exposure to CART	1.2 (1.1-1.3)	0.0001	1.08 (0.96-1.25)	0.20
CD4 cell count nadir < 200/ml	3.3 (1.4-6.4)	0.003	1.49 (0.49-4.52)	0.48
Lipodystrophy				
No lypodistropohy	1		1	
Lipoatrophy	2.33 (0.81-6.74)	0.12	0.45 (0.1-2.07)	0.3
Lipoaccumulation or mixed	4.67 (1.74-12.55)	0.002	1.08 (0.29-4.04)	0.9
Antiretroviral theraphy				
Naives	1		1	
PI-based	10 (3.64-27.46)	0.0001	5.1 (1.7-15.2)	0.004
NNRTI-based	9.23 (3.47-24.55)	0.0001	4.4 (1.5-12.9)	0.006
FRS				
CHD 10-year risk of < 5 %	1		1	
CHD 10-year risk of 5-10 %	4.58 (1.86-11.27)	0.001	3.2 (1.2-8.4)	0.01
CHD 10-year risk of > 10 %	30.54 (6.69-139.50)	0.0001	16.9 (3.5-80.9)	0.0001

Model 1 included all cases (Not included in the model because age form part of the Framigham Risk Score.

Table 4. Univariate and multivariate logistic regression of factors associated with subclinical atherosclerosis in patients with CHD 10-year risk of < 5 %.

	Univariate OR (95% CI)	P	Multivariate Model 2 (OR 95%CI)	P
Age per 10 years	4.81 (1.72-13.48)	0.003	3.41 (1.2-9.68)	0.002
Gender (female)	4.4 (1.44-13.44)	0.009	7.82 (1.44-42.49)	0.02
Time (years) of known HIV infection	1.24 (1.09-1.42)	0.002	1.13 (0.94-1.36)	0.21
Time(years) exposure to CART	1.26 (1.1-1.44)	0.002	0.89 (0.64-1.23)	0.48
CD4 cell count nadir < 200/ml	2.5 (0.82-7.82)	0.1	2.82 (0.51-15.57)	0.23
Lipodystrophy				
No lypodistropohy	1		1	
Lipoatrophy	3.08 (0.55-17.35)	0.2	1.13 (0.1-13.43)	0.92
Lipoaccumulation or mixed	10.79 (1.97-59.13)	0.006	2.45 (0.22-26.79)	0.46
Antiretroviral theraphy				
Naives	1		1	
PI-based	15.4 (3.48-68.22)	0.0001	10.03 (2.11-47.70)	0.004
NNRTI-based	5.44 (1.29-22.98)	0.021	3.25 (0,67-15.71)	0.14
Total Cholesterol	1.02 (1-1.03)	0.009	1 (0.99-1.1)	0.66
Systolic blood pressure	1.07 (1.01-1.13	0.02	1.1 (1.01-1.19)	0.02

Conclusions

- High prevalence of subclinical atherosclerosis in patients with very low cardiovascular risk (CHD-10 year risk < 5 %) exposed to HAART (43.8% to 56.3% depending to the definition of subclinical atherosclerosis used).
- When adjusted for known cardiovascular risk factors, HAART, mainly PI-based, should be considered an independent and strong predictor of subclinical atherosclerosis.