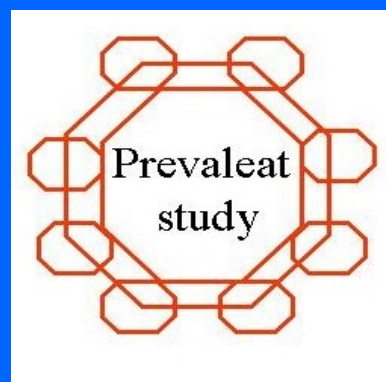


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Rapid Progression of Carotid Lesions in HAART-treated HIV-1 Patients

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Abstract

Background: In previous reports within the PREVALEAT study, a higher than expected prevalence of premature carotid lesions was observed in HIV-1-infected pts treated with PI-including regimens compared to naive or NNRTI-treated patients with color doppler ultrasonography of the epiaortic vessels. In the present study, to obtain data on the evolution of the lesions, a subgroup of these pts was followed for a period of at least two years from the start of therapy.

Methods:The PREVALEAT study evaluated a total of 293 HIV-1-positive pts at their first antiretroviral regimen. From these pts 102 subjects had been selected, 51 of whom were being treated with PI-based regimens (group A) and another 51 with NNRTI-based regimens (group B). All pts were subjected to ultrasonography of the epi-aortic vessels using a last generation power color-doppler.

Results: In group A, at baseline 29 (56.8%) were normal and 22 (43.2%) had lesions. At follow-up, among the previously normal pts, 7 (24%) developed lesions while 14 (48.2%) remained normal. The remaining 8 (27.6%) shifted to other regimens. The lesions developed were: 4 pathologic IMT, 2 plaques and 1 pathologic IMT plus plaque. Among the 22 previously pathologic pts, 11 (50%) showed worsening of the lesions, 2 (9%) were stable, and in 2 (9%) the lesions had disappeared. The remaining 7 (32%) shifted to other regimens. Among the worsened pts 6 of them had pathologic IMT, 3 had plaques and 2 pathologic IMT plus plaques. In group B, at baseline 44 (86.2%) were normal and 7 (13.8%) had lesions. At follow-up, among the previously normal pts, 6 (13.6%) developed lesions while 37 (84%) remained unaltered. 1 pt (2.4%) shifted to PI. The lesions developed were: 4 pathologic IMT, 1 plaque and pathologic IMT plus plaque. Among the 7 previously pathologic pts of the B group, 1 (14.3%) worsened with increase of IMT, the pathologic IMT reversed in 2 (28.5%), the lesions remained stable in 3 (42.8%) and 1 pt (14.3%) shifted to PI. When comparing the pts developing lesions in the 2 groups, no significant difference was found ($\chi^2 = 2.75$; $p = 0.05$), while in group A the percentage of pts who worsened was significantly higher ($\chi^2 = 5.61$; $p = 0.05$).

Conclusions: The follow up data of the present study evidence a trend towards a more rapid onset of lesions in pts treated with PI-based regimens in respect with pts treated with NNRTI (24.0% vs 13.6%) but, above all towards a more rapid and significant evolution of the previously diagnosed lesions (50.0% vs 14.3%). Moreover, the shift from PI-based regimens to NNRTI or three NRTI seems related to a lower rate of evolution. Interestingly, a disappearance of lesions was detected in both groups.

Objective

In previous reports within the PREVALEAT study (PREmature VAScular LESions and Antiretroviral Therapy), a higher than expected prevalence of premature carotid lesions was observed in HIV-1-infected patients treated with PI-including regimens compared to naive or NNRTI-treated patients with color doppler ultrasonography of the epiaortic vessels. In the present study, to obtain data on the evolution of the lesions, a subgroup of these pts was followed for a period of at least two years from the start of therapy.

PATIENTS AND METHODS-1

The patients evaluated had been enrolled in the PREVALEAT study which had selected a total of 293 HIV-1-positive patients at their first antiretroviral regimen. The group included 102 subjects, 51 of whom were being treated with PI-based regimens (group A) and another 51 with NNRTI-based regimens (group B). The patients were submitted to an initial color doppler ultrasonography after at least 12 months of therapy and to a second doppler after a further 12 months. Intima characteristics, pulsation, and resistance indexes, minimal, peak and mean speed were evaluated. Atherosclerotic plaques were described. Subjects affected by hypertension were excluded from the study.

The main patient characteristics are reported in Table 1 and 2.

All patients were subjected to ultrasonography of the epi-aortic vessels using a last generation power color-doppler with 7.5 mgHz probes. Characteristics of the intima, pulsation index, resistance index, minimal speed, peak speed, and mean speed, were evaluated; An intima media thickness (IMT) of >1 mm was considered to be pathological. Atherosclerotic plaques, if present, were described. Ultrasonography was performed by physicians specifically trained on carotid vessels with a 10-year experience in the ultrasound color-doppler technique and at least 1000 documented epi-aortic examinations. Moreover, during the study, periodical meetings were held using filmed reports aimed at the comparison and standardization of the technique.

PATIENTS AND METHODS-2

Patients were submitted to the investigation in a supine position after at least 10 minutes of acclimatization in a comfortable room. Patients were informed that the investigation was non-invasive. The common, internal, and external carotid vessels were examined in the short and long axis. The percentage of stenosis was always quantified by calculating the stenosis areas in the short axis using a strong magnification.

The speed measurements were performed at an 45°-60° inclination with respect to the lumen. The morphological investigation of the plaque was performed using both ultrasonography and the ultrasound power color-doppler in order to better characterize the profile of the plaque and the IMT. Risk factors for cardiovascular diseases were evaluated, such as familial history (angina, myocardial infarction, cerebral stroke, transitory ischemic attack), sedentary life (<1 hour/week of sport activity), cigarette smoking, alcohol consumption (> 80 g/day), active drug addiction, hyperglycemia, hypercholesterolemia, hypertriglyceridemia; in addition, risk factors for HIV-1 infection including CDC stage, CD4 cell count, viral load and antiretroviral therapy were assessed.

The statistical analysis was performed using the chi-square test.

RESULTS-1

Group A (PI)

At baseline 29 (56.8%) were normal and 22 (43.2%) had lesions. At follow-up, among the previously normal patients, seven (24%) developed lesions while 14 (48.2%) remained normal. The remaining eight (27.6%) shifted to other regimens. The lesions developed were: four pathologic IMT, two plaques and one pathologic IMT plus plaque.

Among the 22 previously pathologic patients, 11 (50%) showed worsening of the lesions, two (9%) were stable, and in two (9%) the lesions had disappeared. The remaining seven (32%) shifted to other regimens. Among the worsened patients six of them had pathologic IMT, three had plaques and two pathologic IMT plus plaques.

Group B (NNRTI)

At baseline 44 (86.2%) were normal and seven (13.8%) had lesions. At follow-up, among the previously normal patients, six (13.6%) developed lesions while 37 (84%) remained unaltered. One patient (2.4%) shifted to PI. The lesions developed were: four pathologic IMT, one plaque and pathologic IMT plus plaque.

Among the seven previously pathologic patients of the B group, one (14.3%) worsened with increase of IMT, the pathologic IMT reversed in two (28.5%), the lesions remained stable in three (42.8%) and one patient (14.3%) shifted to PI.

RESULTS-2

When comparing the patients developing lesions in the 2 groups, no significant difference was found ($\chi^2 = 2.75$; $p = 0.05$), while in group A the percentage of patients who worsened was significantly higher ($\chi^2 = 5.61$; $p = 0.05$).

Considering the 15 patients of the A group who modified the therapeutic regimen, among the eight resulted normal at their first control, two were shifted to a three-NRTI-based regimen and six to an NNRTI-based regimen. At follow-up we observed that all of them were unmodified. While, among the seven patients pathologic at their first control, one withdrawn the therapy resulting worsened at follow up (plaque increased), six shifted to NNRTI-based regimens: of them two showed the reversion of the lesions (one with previous pathologic IMT and previous IMT plus plaque in the other), three resulted unaltered and one worsened (IMT unaltered but increase of the plaque).

Considering the two patients of the B group who modified the therapeutic regimen, one of them showed an increase both of the IMT and of the plaque, the other one remained normal.

CONCLUSIONS-1

Various studies have hypothesised an increased risk of cerebro- and cardiovascular diseases in HIV-positive patients submitted to PI-based therapies. Many of the studies dealing with this issue are controversial and the role of these molecules in determining vascular damage still remains uncertain.

Ultrasound color doppler is a safe, inexpensive and fast technique which allows an accurate evaluation of the vascular vessel. Using this procedure, in a recent issue (1) we have studied a sample of 293 patients, to evaluate HIV-positive patients. In that study aimed to evaluate the correlation between antiretroviral therapy and lesions of the vessel's wall we observed a significantly higher percentage (52.4%) of acquired lesions of the epiaortic vessels among patients treated with regimens including PI in respect with patients treated with NNRTI (15.2%).

CONCLUSIONS-2

The follow up data of the present study evidence a trend (not statistically significant) towards a more rapid onset of lesions in patients treated with PI-based regimens in respect with patients treated with NNRTI (24.0% vs 13.6%) but, above all towards a more rapid and significant evolution of the previously diagnosed lesions (50.0% vs 14.3%). Moreover, the shift from PI-based regimens to NNRTI or three NRTI seems related to a lower rate of evolution. Interestingly, a disappearance of lesions was detected in both groups; this phenomenon, warranting further investigation, could be interpreted as a tendency to damage regression almost in the premature phase, or to a different structure of the arterial lesions in these patients in respect with the classical atheromasic plaque, as suggested by a very recent study (2) and opens new perspectives to the prevention of the damage of the vessel's wall in HIV-1 infected patients.

1) Maggi P, Lillo A, Perilli F, Maserati R, Chirianni A on behalf of the PREVALEAT group. Colour-doppler ultrasonography of carotid vessels in patients treated with antiretroviral therapy: a comparative study. *AIDS* 2004; 18:1023-1028.

2) Regina G, Impedovo G, Angiletta D, Martiradonna F, Lillo A, Perilli F, Marotta V, Marzullo A, Epifani G, Fiore JR and Maggi P. Surgical experience with carotid stenosis in young HIV-1 positive patients under antiretroviral therapy: an emergine problem? *Eur J Vasc Endovasc Surg.* 2005 ; 29 :167-170.

EPIDEMIOLOGICAL CHARACTERISTICS-Tab.1

Stage of disease	Group A		Group B	
	n.	%	n.	%
A	28	54.9	44	86.3
B	4	7.8	2	3.9
C	19	37.3	5	9.8
Familiar history of CVD	15	29.4	27	52.9
Alcohol abuse	4	7.8	16	31.4
Sedentary life	39	76.5	40	78.4
Active drug addiction	1	2.0	0	0
Hypertriglyceridemia	20	39.2	11	21.6
Hypercholesterolemia	20	39.2	17	33.3
Hyperglycemia	8	15.6	9	17.6
Age	<i>median</i>	<i>range</i>	<i>media</i>	<i>nrange</i>
	42	30-57	40	12-54
Time from diagnosis of HIV infection (years)	7-25	1-16	9	3-19

EPIDEMIOLOGICAL CHARACTERISTICS-Tab.2

	Group A		Group B	
	n.	%	n.	%
Sex				
Male	40	78.4	33	64.7
Female	11	21.6	18	35.3
Risk factors				
IVDA	24	47.0	19	37.2
Homosexual	11	21.6	6	11.7
Heterosexual	10	19.6	21	41.1
Unknown	6	11.8	5	10.0
CD4 count (cell./mm3)				
<200	26	50.9	21	41.2
200-500	19	37.3	25	49.0
>500	6	11.8	5	9.8
Viral load (copies/ mm3)				
<80	32	62.8	29	56.8
80-30000	12	23.5	20	39.2
30000-100000	2	3.9	1	2.0
>100000	5	9.8	1	2.0

PI-based regimens:

51 pts

Enrollment

normal:
29
(56.8%)

pathologic:
22
(43.2%)

2
Reversed
(9%)

Follow up

new lesions:
7
(24%)

normal:
14
(48.2%)

shift:
8
(27.6%)
2: 3NRTI
6: NNRTI

worsened:
11
(50%)

stable:
2
(9%)

6 shift
to NNRTI and 1
withdrawn
(32%)

8 normal

1 withdrawn
(worsened)

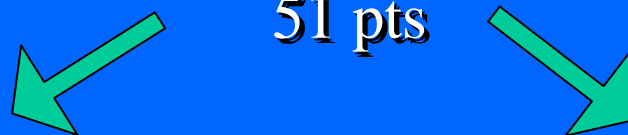
1 worsened

2 reversed

3 stable

NNRTI-based regimens:

51 pts



normal:
44
(86,2%)

Enrollment

pathologic:
7
(13.8%)

reversed
2
(28.5%)



Follow up

new lesions:
6
(13.6%)

normal:
37
(84%)

Shift to PI: 1
(2.4%)

worsened:
1
(14.3%)

stable:
3
(42,8%)

Shift to PI:1
(14.3%)



normal



worsened