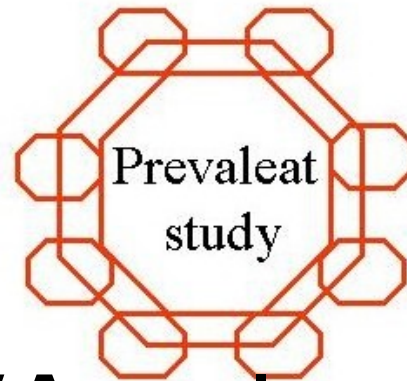


N-25



Corresponding author:

**Paolo Maggi :**

Inst. Infectious Disease

Policlinico- P. G. Cesare, 11, 70124 Bari, Italy

p\_maggi@yahoo.com

# **PREmature VAScular LESions and Antiretroviral Therapy**

**A color-doppler ultra-**

**sonographic comparative study**

**between patients treated with**

**PI-including regimens vs NNRTI-**

**including regimens**

***University of Bari,***

**Institute of infectious diseases: Maggi P., Epifani G ,  
Favia A, Ladisa N**

**Chair of vascular surgery: Lillo A, Perilli F, Regina G,  
*Cotugno hospital Naples***

**III division of infectious diseases: Gargiulo M, Chirianni A  
Cardiology service: Ferraro S.**

***University of Pavia,***

**Institute of Infectious Diseases: Maserati R, Ravasi G.  
Institute of Internal Medicine: Martignoni A.**

***General hospital Foggia,***

**Division of Infectious diseases: Grisorio B, Ferrara S.  
Division of general surgery: Pellegrino C.**

**Italy**

# Abstract

**Background:** HIV-positive patients seem to have an increased risk of cardiovascular diseases, although the role of treatment with PI remains a controversial issue.

In the present study we have compared PI-treated patients (group A) with PI-naïve patients treated with a regimen including NNRTI (group B) and with patients treated with two NRTI or naïve to antiretroviral therapy (group C)

**Methods:** Group A included 105 patients, group B 120, group C 68. All treated patients had treatment for at least 12 months and were evaluated for familial history of cardiovascular disease, sedentary life, cigarette smoking, alcohol abuse, active drug addiction and values for fasting glycemia, cholesterolemia and triglyceridemia. Intima characteristics, pulsation and resistance indexes, minimal, peak and mean speed were evaluated using an AU5 ESAOTE color power doppler. Atherosclerotic plaques were described.

**Results:** In group I 55 patients (52.4%) demonstrated acquired lesions of the vascular wall including 25 patients with intima media thickness (IMT), 24 with IMT plus atheromatous plaques and six with plaques. In group II 19 (15.2%) showed lesions, 10 of whom demonstrated IMT, three plaques and six IMT plus plaques. Of the 63 patients in group III, lesions were observed in nine (14.3%) including three patients with IMT, four with IMT plus plaques and two with plaques. The logistic regression model evidenced that the risk of vascular lesions is significantly correlated with type of therapy (Wald  $\chi^2=44.24$   $p<0.0001$ ), age (Wald  $\chi^2=14.78$   $p=0.0001$ ), cigarette smoking (Wald  $\chi^2=4.99$   $p=0.025$ ) and CD4+ cell count (Wald  $\chi^2=6.88$   $p=0.032$ ), whereas the risk of lesions is significantly higher for patients with a CD4 cell count  $<200 \times 10^6/l$  or between 200 and  $500 \times 10^6/l$  compared to those with a CD4 cell count  $>500 \times 10^6/l$ . The Mantel-Haenszel test confirmed a strong relationship between vascular damage and use of PI during every stage of the disease ( $\chi^2=33.89$   $p=0.0002$ ). Evaluating the interaction between the single risk factors and the presence of vascular damage, the only significant factor was the PI-based therapy ( $\chi^2=46.65$   $p=0.0001$ ) When considering the presence of atheromatic plaques as a dependent variable in the logistic regression model, the predictive risk factors were, once again, the PI-based therapy and age.

**Conclusions:** These data in our ongoing study show an higher prevalence of acquired carotid lesions in patients treated with PI-based regimens, when compared with patients treated with NNRTI-including regimens.

# Objective

Several reports have indicated that HIV-positive patients seem to have an increased risk of cardiovascular diseases although the role of treatment with PI remains a controversial issue. In the present study, to obtain a more specific correlation between antiretroviral therapy and lesions of the carotid vessels, we compared PI-treated pts (group I) with PI-naive pts treated with a NNRTI-including regimen (group II) and pts treated with 2 NRTIs or naive to antiretroviral therapy (group III). All pts were evaluated with color doppler ultrasonography, a safe and sensitive technique capable of detecting initial lesions of the vascular wall.

# Patients and Methods

Group I included 105 pts, group II 125 and group III 63. All treated pts had treatment for at least 12 months and were evaluated for familial history of cardiovascular disease, sedentary life, cigarette smoking, alcohol abuse, active drug addiction and values for glycemia, cholesterolemia and triglyceridemia. Intima characteristics, pulsation and resistance indexes, and speed were evaluated using an AU 5 esaote color power doppler. An intima media thickness (IMT) of  $>1$  mm was considered to be pathological. Atherosclerotic plaques were described. Ultrasonography was performed by physician specifically trained with a 10-year experience in this technique and at least 1000 documented epi-aortic examinations.

# Patients

## Epidemiological characteristics - 1

	PI	NNRTI	2 NRTI/Naive	P-value
♣Sex				
male	85 <b>80.9 %</b>	94 <b>75.2 %</b>	46 <b>73.0 %</b>	ns
♣Risk factors				
IVDA	48 <b>45.7 %</b>	48 <b>38.4 %</b>	29 <b>46.0 %</b>	ns
♣Age (Wilcoxon test)				
median	38	38	35	<b>0.003</b>
(range)	(26-50)	(23-57)	(25-52)	
♣Time from diagnosis of HIV infection (yr)				
median	8	6	6	ns
(range)	(1-17)	(1-18)	(0-16)	
Median treatment period (mos)	<b>26</b>	24	23/--	ns

# Patients

## Epidemiological characteristics - 2

	PI		NNRTI		2 NRTI/Naive		P-value
<b>◆ CD4+ (cell/<math>\mu</math>L)</b>							<b>0.09</b>
<200	17	<b>16.2 %</b>	14	<b>11.2 %</b>	16	<b>25.4 %</b>	
200-500	49	<b>46.6 %</b>	66	<b>52.8 %</b>	32	<b>50.8 %</b>	
>500	39	<b>37.1 %</b>	45	<b>36.0 %</b>	15	<b>23.8 %</b>	
<b>◆ VL (copies/ml)</b>							<b>&lt;0.0001</b>
neg	56	<b>53.3 %</b>	74	<b>59.2 %</b>	6	<b>9.5 %</b>	
80-30000	33	<b>31.4 %</b>	49	<b>39.2 %</b>	24	<b>38.1 %</b>	
30000-100000	7	<b>6.7 %</b>	2	<b>1.6 %</b>	14	<b>22.2 %</b>	
>100000	9	<b>8.6%</b>	0		19	<b>30.2 %</b>	
<b>◆ Stage of disease</b>							<b>0.0002</b>
A	51	<b>48.6 %</b>	88	<b>70.4 %</b>	47	<b>74.6 %</b>	
B	14	<b>13.3 %</b>	7	<b>5.6 %</b>	5	<b>7.9 %</b>	
C	40	<b>38.0 %</b>	30	<b>24.0 %</b>	11	<b>17.5 %</b>	

# Results /1

## Independent risk factors for CVD

	IP		NNRTI		2 NRTI/Naive		P-value
Familial history of CVD	41	<b>39.0 %</b>	66	<b>52.8 %</b>	36	<b>57.1 %</b>	<b>0.04</b>
Cigarette smoking	71	<b>67.6 %</b>	87	<b>69.6 %</b>	48	<b>76.2 %</b>	ns
Alcohol abuse	11	<b>10.4 %</b>	11	<b>8.8 %</b>	7	<b>11.1 %</b>	ns
Sedentary life	78	<b>74.2 %</b>	89	<b>71.2 %</b>	47	<b>74.6 %</b>	ns
Active drug addiction	2	<b>1.9 %</b>	6	<b>4.8 %</b>	0		ns
Hypertriglyceridemia	46	<b>43.8 %</b>	35	<b>28.0 %</b>	10	<b>15.9 %</b>	<b>0.0005</b>
<i>median (mg/dl)</i>	<i>300</i>		<i>293</i>		<i>265</i>		
Hypercholesterolemia	36	<b>34.2 %</b>	58	<b>46.4 %</b>	10	<b>15.9 %</b>	<b>0.0002</b>
<i>median (mg/dl)</i>	<i>241</i>		<i>222</i>		<i>229</i>		
Hyperglycemia	11	<b>10.5 %</b>	12	<b>9.6 %</b>	5	<b>7.9 %</b>	ns
<i>median (mg/dl)</i>	<i>122</i>		<i>139</i>		<i>118</i>		

# Results /2

## Comparison of ultrasonographic findings

	PI	NNRTI	2NRTI/Naive
◆ Acquired lesions	55 (52.4 %)	19 (15.2 %)	9 (14.3 %)
<i>IMT</i>	25	10	3
IMT+ <i>plaques</i>	24	6	4
<i>plaques</i>	6	3	2
<i>Total plaques</i>	30 (28.5 %)	9 (7.2%)	6 (9.5%)
◆ Normal findings	50 (47.6%)	106 (84.8 %)	54 (85.7 %)
◆ Median IMT value (mm)			
◆ right carotids	1.2 (1.01-2.47)	1.31 (1.01-2.33)	1.24 (1.02-1.4)
◆ left carotids	1.3 (1.01-3.0)	1.36 (1.01-2.08)	1.4 (1.1-3.5)
◆ Percentage of stenosis			
◆ right carotids	42.9% (15-54)	35% (25-66)	30% (20-40)
◆ left carotids	41.9% (15-70)	38% (25-52)	46.7 (one patient)

# Results /3

## Comparison of ultrasonographic findings

	PI	NNRTI	2NRTI/Naive
	<b>105</b>	<b>125</b>	<b>63</b>
◆ <b>Congenital lesions</b>	<b>5 (4.7 %)</b>	<b>7 (5.6 %)</b>	<b>3 (4.7 %)</b>
Kinking in pts without AL	1	6	2
Kinking in pts with IMT	2	1	--
Kinking in pts with IMT+PL	1	--	--
Coiling (in pt without AL)	1	--	1

# Statistical analysis (*logistic regression model*)

Effect	Df <sup>1</sup>	Wald- $\chi^2$	p	Odds Ratio		95% CI
Age	1	14.78	0.0001	for 1 y increase	1.09*	1.04-1.15
CD4+	2	6.88	0.032	<200 vs >500	1.39 ns	0.55-3.51
				200-500 vs >500	2.45**	1.23-4.89
				<200 vs 200-500	0.57 ns	0.24-1.32
Smoke	1	4.99	0.025	smokers vs non smokers	2.22*	1.1-4.47
Therapy	2	44.24	<0.0001	Group I vs III	6.77**	2.88-15.8
				Group I vs II	8.71**	4.35-17.4
				Group II vs III	0.78 ns	0.31-1.95

## Legend:

Df<sup>1</sup> = Degree of freedom \* = p<0.05 \*\* = p<0.01

Probability of developing vascular lesions =  $\exp(-6.29 + 0.09 \text{ age} + 0.33 \text{ CD4} < 200 + 0.9 \text{ CD4 } 200-500 + 0.80 \text{ smoke} + 1.91 \text{ PI} - 0.25 \text{ NNRTI})$ .

(CD4, smoke, PI and NNRTI are dummy variables =1 if condition is present, =0 if absent)

Hosmer and Lemeshow goodness of fit  $\chi^2 = 5.02$  p=0.75

# Results

In group I 55 patients (52.4%) demonstrated acquired lesions of the vascular wall including 25 patients with intima media thickness (IMT), 24 with IMT plus atheromatous plaques and six with plaques. In group II 19 (15.2%) showed lesions, 10 of whom demonstrated IMT, three plaques and six IMT plus plaques. Of the 63 patients in group III, lesions were observed in nine (14.3%) including three patients with IMT, four with IMT plus plaques and two with plaques.

The logistic regression model evidenced that the risk of vascular lesions is significantly correlated with type of therapy (Wald  $\chi^2=44.24$   $p<0.0001$ ), age (Wald  $\chi^2=14.78$   $p=0.0001$ ), cigarette smoking (Wald  $\chi^2=4.99$   $p=0.025$ ) and CD4+ cell count (Wald  $\chi^2=6.88$   $p=0.032$ ).

The risk of lesions is significantly higher for patients with a CD4 cell count  $<200 \times 10^6/l$  or between 200 and  $500 \times 10^6/l$  compared to those with a CD4 cell count  $>500 \times 10^6/l$ .

The Mantel-Haenszel test confirmed a strong relationship between vascular damage and use of PI during every stage of the disease ( $\chi^2=33.89$   $p=0.0002$ ). Evaluating the interaction between the single risk factors and the presence of vascular damage, the only significant factor was the PI-based therapy ( $\chi^2=46.65$   $p=0.0001$ ). When considering the presence of atheromatic plaques as a dependent variable in the logistic regression model, the predictive risk factors were, once again, the PI-based therapy and age.

# Conclusions

These data in our ongoing study confirm that the risk of premature damage to the carotid wall in HIV-1 infected patients, although complicated by factors such as cigarette smoking and age, is strongly related to PI-based regimens. No statistical difference resulted when patients treated with NNRTI-based regimens were compared with naïve patients or those treated with two NRTI.

In addition, the overwhelming difference between the percentage of lesions among healthy individuals\* and HIV-1 positive patients, confirms that the infection *per se* exerts a role in the risk of vascular damage

\*104 HIV-negative pts: lesions in 6.7% (from Maggi et al. AIDS 2000; 14:123-128).