Progetto ArchiPrevaleat. Ecografia color-Doppler dei vasi epi-aortici in HIV.
ArchiPrevaleat Project. Color-Doppler ultrasonography of the epi-aortic vessels in HIV.

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Riassunto

Obiettivo di questo studio era la valutazione della prevalenza di ispessimento dell'intima-media (>1.00-1.20 mm) e di placche (>1.20 mm), in una coorte di persone che vivono con HIV, e i fattori di rischio per queste condizioni.
Il Progetto è iniziato nel 2019 e coinvolge otto centri italiani. Le misurazioni della carotide erano eseguite da un medico appositamente preparato, che valutava i seguenti parametri: spessore medio-intimale delle carotidi comuni e interne, sia a sinistra che a destra. Sono state raccolte informazioni sui fattori di rischio per le malattie cardiovascolari, la conta dei CD4+, i lipidi serici, la glicemia, e l'indica di massa corporea (BMI). L'associazione tra risultati patologici e potenziali fattori di rischio è stata valutata utilizzando la regressione logistica, con gli odds ratio (OR) e gli intervalli di confidenza al 95% (95% CI).
Tra 1147 pazienti valutati, con età media di 50 anni, 347 (30.2%) avevano risultati patologici (15.8% placche e 14.5% IMT). Oltre ai fattori di rischio soliti, come età avanzata, sesso maschile, sovrappeso e dislipidemia, una conta dei CD4+ nadir < 200 celle/mm3 era associata con una prevalenza maggiore di placche (OR aggiustato 1.79, 95% CI 1.23-2.61). L'uso di INSTI era suggerito come associato con risultati patologici.
Questi dati mostrano che la percentuale complessiva di lesioni della carotide è ancora elevata. L'ecografia color-Doppler potrebbe ricoprire un ruolo chiave nell'indentificare e quantificare le lesioni aterosclerotiche nelle persone che vivono con HIV, anche a uno stadio molto precoce, e dovrebbe venire inclusa nell'algoritmo di gestione delle comorbidità in questi pazienti.

Abstract

Objective of this study was to evaluate the prevalence of carotid intima-media thickness >1.00-1.20 mm and plaques in a cohort of persons living with HIV and risk factors for these conditions.
This project was initiated in 2019 and involves eight Italian Centers. Carotid measurements were performed by a trained physician, who evaluated the following parameters: intima-media thickness of both the right and left common and internal carotids. Information was collected on risk factors for cardiovascular disease, CD4+ cell counts, serum lipids, glycaemia, and body mass index (BMI). The associations between pathological findings and potential risk factors were evaluated by logistic regression, with odds ratios (OR) and 95% confidence intervals (95% CI).
Among 1147 evaluated patients, aged 50 years on average, 347 (30.2%) had pathological findings (15.8% plaques and 14.5% IMT). Besides usual risk factors, such as older age, male sex, overweight and dyslipidemia, CD4+ cell nadir <200 cells/mL was associated with higher prevalence of plaques (adjusted OR 1.79, 95% CI 1.23-2.61). INSTI use was suggested as associated with pathological findings.
Our data show that the overall percentage of carotid impairments is still high. Color-Doppler ultrasonography could play a pivotal role in identifying and quantifying atherosclerotic lesions among persons living with HIV, even at a very premature stage, and should be included in the algorithms of comorbidity management of these patients.

Introduction

The natural history of HIV infection was deeply impacted by the introduction of effective antiretroviral (ARV) regimens, that led to a dramatic decrease in its mortality rate and a considerable increase in the life expectancy of Persons Living with HIV (PLWH). However, a higher risk of developing several co-morbidities, such as cardiovascular disease (CVD), id still present in these patients (1, 2). A well-validated research tool, widely used in clinical practice (3), is the measurement of the carotid intima-media thickness (IMT) with color-Doppler ultrasonography. Besides IMT, this technique allows the measurement of arterial diameter, presence of plaques, blood flow and velocity.

It is a non-invasive, sensitive, and highly reproducible technique aimed at identifying and quantifying atherosclerotic lesions, even at a very premature stage, besides assessing vascular anatomy and function.

Considering that this technique is currently common in the Italian HIV outpatient facilities, we generated a national cohort of color-Doppler ultrasonography (Archi-Prevaleat) to better evaluate the characteristics of vascular lesions in PLWH, based on a large amount of data. Archi-Prevaleat represent the continuation of PREVALEAT (PREmature VAscular LEsions and Antiretroviral Therapy), an ongoing multicenter, longitudinal cohort involving several Italian centers since 1998, aimed at evaluating the cardiovascular (CV) risk in PLWH by means of color-Doppler ultrasonography (4). Over time, this project generated results on the association between lesions of the carotid vessels and type of ART and immune reconstitution (5-7).

The aim of the present study is to evaluate the prevalence of carotid IMT and plaques, separately, and the role of CV risk factors in this population. We included classic CV risk factors as well as those related to HIV infection: immunological variables and antiretroviral regimens.

Methods

This project started in 2019 and involves, currently, eight Italian Infectious Diseases Centers in which the ultrasonographic examination is performed by specifically trained physicians. During a Continuing Medical Education training program organized by the coordinating Center (Università della Campania, Luigi Vanvitelli), they were specifically trained on the technique. Moreover, during annual follow up meetings comparison and standardization of the technique were performed, using images and filmed reports.

The data were collected at the first exam and at all the subsequent follow up examinations. IMT of both the right and left common and internal carotids were recorded: ultrasonography of the epi-aortic vessels was performed using a power color-Doppler instrument with 7.5 MHz probes. The characteristics of the intima, the pulsation index, the resistance index, the minimal speed, the peak speed, and the mean speed were evaluated. A minimum of three measurements was requested: on the common carotid artery, 1 cm before the carotid bifurcation and at the carotid bifurcation, and on the internal carotid, 1 cm after the carotid bifurcation and 2 cm after the carotid bifurcation.

An IMT >1.0 mm was considered pathological. A carotid was classified as affected by plaques if a localized thickening >1.2 mm was present and did not uniformly involve the whole left or right common carotid bifurcation with or without flow disturbance (8, 9). All relevant images were recorded and archived.

Data regarding risk factors for CVD (family history, smoking, active drug addiction, alcohol consumption) were collected at baseline, and re-evaluated every 12 months if susceptible of modification. Similarly, HIV viral load, CD4+ cell counts, serum total cholesterol, low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), glycaemia, triglycerides, and body mass index (BMI) were recorded at annual controls.

Written informed consent was obtained from each patient and data were anonymously collected. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the coordinating center Ethics Committee on research on humans.

The cohort data were recorded on an online platform *(http://www.archiprevaleat.com/)*.

Statistical methods

Categorical and ordinal variables were described as frequency (%) and were compared between groups using the heterogeneity χ^2 test (or the Mantel-Hanszel χ^2 test as appropriate). Numerical variables were described as mean, and standard deviation (SD) if normally distributed, or median,

Table 1. Main characteristics of 1147 HIV-positive patients included in the baseline analysis, according to the presence of plaques.

	Normal N=800, 69.8%	IMT 1.01-1.20 N=166, 14.5%	Plaques N=181, 15.8%	P
Age (years), mean ± SD	50.0 ± 9.7	55.1 ± 9.1	58.2 ± 9.1	<0.0001
Male, n (%)	632 (79.0)	146 (88.0)	163 (90.1)	<0.0001
Risk for HIV acquisition, n (%)				
IDU	103 (12.9)	23 (13.9)	27 (14.9)	
Sexual	513 (64.1)	89 (53.6)	109 (60.2)	
Other	184 (23.0)	54 (32.5)	45 (24.9)	0.64
Smoking habits, n (%)				
Never	172 (21.5)	31 (18.7)	28 (15.5)	
Current	311 (38.9)	72 (43.4)	66 (36.5)	
Former	153 (19.1)	40 (24.1)	45 (24.9)	
Unknown	164 (20.5)	23 (13.9)	42 (23.2)	0.65
BMI (kg/m2), mean ± SD	24.6 ± 3.7	24.9 ± 3.9	25.6 ± 3.9	0.006
BMI class (kg/m2), n (%)				
<18.5	22 (2.8)	2 (1.2)	4 (2.2)	
18.5-25.0	411 (51.4)	81 (48.8)	73 (40.3)	
>25.0-30.0	234 (29.2)	49 (29.5)	68 (37.6)	
>30.0	55 (6.9)	14 (8.4)	21 (11.6)	0.001
missing	78 (9.8)	20 (12.0)	15 (8.3)	
Cardiovascular diseases, n (%)				
Hypertension	237 (29.6)	70 (42.2)	96 (53.0)	<0.0001
Diabetes	60 (7.5)	15 (9.0)	35 (19.3)	<0.0001
Ictus	8 (1.0)	2 (1.2)	5 (2.8)	0.08
Angina	3 (0.4)	0	5 (2.8)	0.003
IMA	10 (1.2)	6 (3.6)	6 (3.3)	0.02
PAD	3 (0.4)	1 (0.6)	3 (1.7)	0.06
HCV coinfection, n (%)	209 (26.1)	58 (34.9)	56 (30.9)	0.06
Systolic blood pressure (mm Hg), mean ± SD	125.2 ± 15.4	126.8 ± 15.8	130.1 ± 16.3	0.0009
Diastolic blood pressure (mm Hg), mean ± SD	79.2 ± 10.3	80.6 ± 10.8	78.8 ± 11.1	0.25
Cholesterol (mg/dL), mean ± SD	190 ± 41	187 ± 39	192 ± 41	0.57
HDL-C (mg/dL), mean ± SD	50 ± 17	46 ± 13	45 ± 19	0.004
LDL-C (mg/dL), mean ± SD	119 ± 37	119 ± 34	119 ± 36	0.99
Triglycerides (mg/dL), median (IQR)	120 (86-171)	113 (86-175)	157 (100-214)	<0.0001
Blood glucose§ (mg/dL), mean ± SD	88 ± 12	89 ± 12	93 ± 17	<0.0001
AST (U/L), median (IQR)	24 (19-32)	24 (20-32)	27 (21-36)	0.02
ALT (U/L), median (IQR)	29 (22-43)	28 (22-42)	31 (23-45)	0.59
eGFR (mL/min), mean ± SD	95.9 ± 17.3	91.6 ± 17.1	91.3 ± 22.4	0.001
HIV infection duration (years),	13.9 ± 3.8	14.6 ± 2.9	14.5 ± 4.6	0.04
Nadir CD4 (cells/mL), median (IQR)	223 (127-229)	207 (100-323)	141 (90-272)	0.002
Current CD4 (cells/mL), median (IQR)	715 (522-919)	686 (486-936)	687 (498-904)	0.63
Current CD8 (cells/mL), * median (IQR)	888 (652-1190)	839 (597-1123)	895 (641-1212)	0.52
CD4/CD8 ratio, * median (IQR)	0.81 (0.54-1.16)	0.82 (0.53-1.09)	0.73 (0.46-1.15)	0.62
Naive, n (%)	17 (2.1)	0	0	0.01
NRTI, n (%)				
Current use	673 (84.1)	134 (80.7)	151 (83.4)	0.60
Past use	601 (75.1)	126 (75.9)	125 (69.1)	0.14
PI, n (%)				
Current use	378 (47.2)	80 (48.2)	91 (50.3)	0.46
Past use	377 (47.1)	83 (50.0)	94 (51.9)	0.21
NNRTI, n (%)				
Current use	263 (32.9)	57 (34.3)	48 (26.5)	0.17
Past use	243 (30.4)	55 (33.1)	40 (22.1)	0.08
InSTI, n (%)				
Current use	166 (20.8)	39 (23.5)	56 (30.9)	0.004
Past use	132 (16.5)	35 (21.1)	33 (18.2)	0.35

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; eGFR: estimated glomerular filtration; HCV: hepatitis C virus; HDL-C: high density lipoprotein cholesterol; InSTI: integrase strand transferase inhibitors; LDL-C: low density lipoprotein cholesterol IQR: interquartile range; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; SD: standards deviation
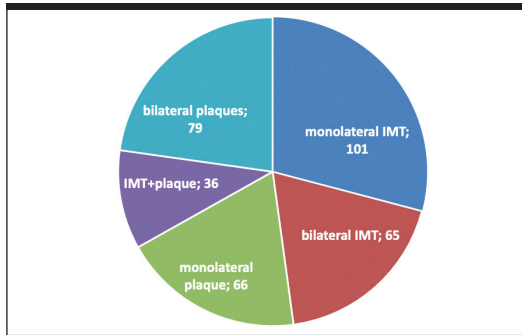**N=770*
§ nondiabetic patients

Figure 1. Pathological findings at left and right carotids

Table 2. Details of ARV treatment in 1147 HIV-positive patients included in the baseline analysis, according to the presence of plaques.

	Normal	IMT 1.01-1.20	Plaques	P
	N=800, 69.8%	N=166, 14.5%	N=181, 15.8%	
Current NRTI, n (%)				
Tenofovir	380 (47.5)	79 (47.6)	80 (44.2)	0.47
Abacavir	198 (24.7)	34 (20.5)	48 (26.5)	0.92
Lamivudine	294 (36.8)	55 (33.1)	71 (39.2)	0.76
Current PI, n (%)				
Atazanavir	175 (21.9)	35 (21.1)	42 (23.2)	0.78
Darunavir	169 (21.1)	41 (24.7)	38 (21.0)	0.79
Current NNRTI, n (%)				
Efavirenz	103 (12.9)	20 (12.0)	21 (11.6)	0.61
Current InSTI, n (%)				
Raltegravir	65 (8.1)	24 (14.5)	30 (16.6)	0.0002
Dolutegravir	72 (9.0)	11 (6.6)	19 (10.5)	0.78
Elvitegravir	29 (3.6)	4 (2.4)	7 (3.9)	0.92

and interquartile range (IQR) if not normally distributed. Comparisons were performed using the analysis of variance, the Mann-Whitney test (or the Kruskal-Wallis test as appropriate), respectively.

Odds ratios (ORs) and the corresponding 95% confidence intervals (CI) were used to evaluate the association between pathological IMT and plaques, and patients' characteristics and clinical variables. All variables that were significantly associated with pathological results at the univariate analysis were controlled in a model including sex and age. Variables still significantly associated with pathological IMT and plaques in this analysis were included in the final model. To avoid losing observations, classes were created for missing values of selected variables.

All analyses were conducted with SAS for Windows 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In 8 participating centers, we enrolled 1147 patients who underwent color-Doppler ultrasonography (82% males, mean age 52.1, SD 10.0 years). Prevalence of pathological IMT and plaques at the left carotid were 12.1% (n=139) and 12.5% (n=143) respectively, and at the right carotid 11.2% (n=129) and 10.1% (n=116) respectively. Overall, 14.5% (n=166) had only pathological IMT (right, left or both), and 15.8% (n=181) of patients had plaques (right, left or both) (**Figure 1**). The overall percentage of patients with carotid impairments (pathological IMT or plaques either in the right or left carotid) was 30.2% (n=347) while the remaining 69.8% (n=800) were normal.

Demographic and metabolic data, data regarding HIV infection and cardio-cerebral-vascular comorbidities according to pathological findings are summarized in **Table 1**.

We observed that, regarding demographics, carotid impairments were significantly related to age (p<0.0001), male sex (p<0.0001), and BMI (p=0.006 as a continuous variable and 0.04 in ca-

tegories). Regarding comorbidities, individuals with pathological findings had more frequently hypertension (p<0.0001) and diabetes (p<0.0001), angina (p=0.003) and previous myocardial infarction (p=0.02). Systolic blood pressure was also significantly different among groups (p=0.0009), as well as HDL-C (p=0.0004), triglycerides (p<0.0001), blood glucose (p<0.0001), and eGFR (p=0.001). Hepatitis C virus (HCV) coinfection showed a borderline association (p=0.06).

Considering variables related to HIV infection, there was a significant relationship between the presence of IMT or plaques and HIV infection duration (p=0.04), CD4+ cell nadir (p=0.002) and current use of integrase inhibitors (p=0.004). Exploring details of current antiretroviral treatments, we found that the current use of raltegravir is significantly associated with pathological findings (p=0.0002, **Table 2**). On the contrary, all naïve patients had normal findings (p=0.01), although the sample had a very small size (17 patients).

Table 3 reported the sex- and age-adjusted ORs (aOR), with corresponding 95% CI).

As regards IMT, it was associated with age, adjusted for sex (OR by 1 year 1.06, 95% CI 1.04-1.07) and sex, adjusted for age (OR for female 0.58, 95% CI 0.35-0.96). HCV coinfection (OR 1.56, 95% CI 1.08-2.26) and current raltegravir use (OR 1.70, 95% CI 1.01-2.84) were significantly associated with increased risk of IMT between >1.00 and 1.20 mm.

As regards plaques, mutually adjusted ORs were significant for age (1.09, 95% CI 1.07-1.11) and sex (0.48, 95% CI 0.28-0.82). Higher BMI was asso-

Table 3. Age- and sex-adjusted odds ratios (OR) and 95% confidence interval (95% CI).

	IMT 1.01-1.20 n=166			Plaques N=181		
	OR	95% CI		OR	95% CI	
Age (by 1 year)	**1.06**	**1.04**	**1.07**	**1.09**	**1.07**	**1.11**
Female (ref. Male)	**0.58**	**0.35**	**0.96**	**0.48**	**0.28**	**0.82**
Smoking habits (ref. Never)						
Current	1.23	0.72	2.09	1.57	0.94	2.62
Former	1.31	0.82	2.10	1.57	0.90	2.74
BMI (by 1 kg/m²)	1.02	0.97	1.07	**1.07**	**1.02**	**1.12**
BMI class (ref. 18.6-25.0 kg/m²)						
<18.5	0.46	0.10	2.04	0.94	0.29	3.07
>25.0-30.0	1.02	0.68	1.52	**1.63**	**1.10**	**2.41**
>30.0	1.28	0.69	2.47	**2.08**	**1.14**	**3.82**
Hypertension	1.28	0.89	1.84	**1.61**	**1.12**	**2.31**
Diabetes	0.85	0.46	1.56	**1.70**	**1.04**	**2.77**
Angina	n.d.			3.50	0.73	16.54
IMA	2.16	0.75	6.18	1.74	0.50	5.09
HCV coinfection (ref. N)	**1.56**	**1.08**	**2.26**	1.32	0.91	1.93
HDL-C (ref. ≥40 (M) ≥50 (F) mg/dL)	1.27	0.86	1.88	**2.11**	**1.44**	**3.10**
Triglycerides (ref. <150 mg/dL)	0.98	0.68	1.42	**2.17**	**1.51**	**3.19**
Blood glucose (ref. <100 mg/dL)	0.69	0.40	1.18	0.83	0.49	1.41
Systolic blood pressure (by 5 mm Hg)	0.99	0.94	1.05	1.03	0.98	1.09
AST (by 2 U/L)	0.99	0.98	1.01	1.00	0.99	1.02
eGFR	0.99	0.94	1.06	1.05	1.00	1.11
HIV infection (by 5 years)	1.08	0.82	1.44	0.96	0.75	1.24
Nadir CD4 (ref. ≥ 200 cells/mm³)	1.23	0.87	1.74	**1.99**	**1.40**	**2.84**
Past NNRTI (ref. N)	1.05	0.73	1.51	**0.59**	**0.40**	**0.89**
Current INSTI use (ref. N)	1.16	0.77	1.74	**1.68**	**1.15**	**2.47**
Current raltegravir use (ref. N)	**1.70**	**1.01**	**2.84**	**1.83**	**1.11**	**3.02**
Bold: p<0.05						

Table 4. Adjusted odds ratios (OR) and 95% confidence interval (95% CI)

	IMT 1.01-1.20 n=166			Plaques N=181		
	OR	95% CI		OR	95% CI	
Age (by year)	**1.06**	**1.03**	**1.08**	**1.09**	**1.07**	**1.11**
Female (ref. Male)	**0.55**	**0.32**	**0.93**	**0.55**	**0.31**	**0.97**
BMI (ref. 18.6-25.0 kg/m2)						
≤18.5	0.47	0.10	2.14	1.13	0.34	3.74
>25.0-30.0	1.01	0.67	1.52	**1.60**	**1.06**	**2.44**
>30.0	1.31	0.67	2.57	1.84	0.98	3.47
Hypertension	1.23	0.84	1.81	1.32	0.89	1.94
Diabetes	0.72	0.38	1.37	1.26	0.73	2.17
HCV coinfection (ref. N)	1.42	0.97	2.07	1.26	0.84	1.89
HDL-C (ref. ≥40 (M) ≥50 (F) mg/dL)	1.19	0.79	1.80	**1.76**	**1.16**	**2.67**
Triglycerides (ref. <150 mg/dL)	0.92	0.62	1.36	**1.65**	**1.11**	**2.45**
Nadir CD4 (ref. ≥ 200 cells/mm3)	1.20	0.84	1.70	**1.79**	**1.23**	**2.61**
Past NNRTI (ref. N)	1.10	0.76	1.60	0.67	0.44	1.04
Current INSTI use	1.15	0.75	1.75	1.49	0.99	2.25
Current raltegravir use (ref. N)	1.62	0.96	2.76	1.56	0.90	2.69
All variables significantly associated with pathological IMT or Plaques at the age- and sex-adjusted analysis were included in the model. **Bold:** p<0.05						

ciated with plaques both as a continuous variable (aOR 1.07 by 1 unit, 95% CI 1.02-1.12) and in categories (aOR 1.63, 95% CI 1.10-2.41 for BMI 25-30 and aOR 2.08, 95% CI 1.14-3.82 for BMI >30). Hypertension (aOR 1.61, 95% CI 1.12-2.31), diabetes (aOR 1.70, 95% CI 1.04-2.77), low HDL-C (aOR 2.11, 95% CI 1.44-3.10) and TGL>150 mg/dL (aOR 2.17, 95% CI 1.51-3.19) were also significantly associated with plaques.

Considering HIV infection related variables, having a nadir CD4 <200 cells/mm3 was associated with higher risk of plaques (aOR 1.99, 95% CI 1.40-2.84), past use of NNRTIs (aOR 0.59, 95% CI 0.40-0.89) and current use of raltegravir (aOR 1.83, 95% CI 1.11-3.02).

Thus, the final model included age, sex, BMI, hypertension, diabetes, HCV coinfection, HDL-C, triglycerides, nadir CD4, past NNRTI and, in turn, current INSTI and raltegravir use. In this model, age, sex, HDL-C, TGL and nadir CD4 maintained their association with a pathological IMT (**Table 4**). Current INSTI use was still indicating an increased risk but lost statistical significance.

Discussion

Previous studies showed that HIV-infected individuals are at higher risk of CVD than the general population (1-2). In HIV patients, since chronic inflammatory processes are activated, and atherosclerosis accelerates (7, 10, 11), cardiovascular disease is one of the most common non-AIDS events, with overall increased morbidity and mortality. Although the mechanisms involved remain elusive, proinflammatory cytokines (7), pro-angiogenic hematopoietic and endothelial progenitor cells (10), circulating CD40 ligand, and Dickkopf-1 (11) could be involved, suggesting that endothelial activation due to the chronic inflammation might be the keystone of this phenomenon.

Carotid IMT and presence of plaque have been shown to predict cardiovascular events in large studies (12, 13). In the clinical practice, evaluation of the carotid artery by ultrasonography is a very useful, simple, and safe method to indirectly detect and prevent CVD. In asymptomatic patients, carotid IMT and plaque assessment were more likely to revise Framingham Risk Score (FRS) than Coronary Artery Calcium score (14), with implications for CVD screening in patients with low FRS (<10%). Common carotid blood flow (CBF) velocity was also

independently predictive of CVD, using color duplex ultrasound and Doppler spectral analysis (15). In preventive medicine, IMT measurement is especially important for subjects with an intermediate CV risk, i.e., for subjects with a 10-year risk of CV disease between 6% and 20%. (16).

Our data shows that the overall percentage of PLWH with carotid impairments, either IMT (14.5%) or plaques (15.8%), was still high. In fact, despite newer antiretroviral therapies have a lower impact on metabolism, leads to a better quality of life among PLWH, and increase their life expectancy, the proportion of subjects with carotid impairment did not show substantial decrease in the last decades, as compared with previous observations. We observed that 35.2% of patients had carotid lesions in 2000 (4) and 31.7% in 2004 (5). In 2017, in a prospective study on advanced naïve subjects, carotid lesions were observed in 38.7% of the patients, after one year of antiretroviral therapy (7). In all these studies, patients treated with some protease inhibitors showed a significantly higher percentage of lesions, consistent with data deriving from D: A: D cohort (17).

On the contrary, the present study suggests that carotid impairment was only related to current use of raltegravir. By analyzing separately IMT and plaques, the role of the current use of raltegravir emerged for both, although not significantly in the final model. This is consistent with recent evidence showing that integrase inhibitors can determine weight gain in PLWH (18, 19). Moreover, another study (20) described increase in waist circumference in patients on raltegravir, and a correlation between short-term weight gain and subsequent risk of cardiovascular disease has been evidenced in the D: A: D: cohort (21). It is possible that we only observed this correlation for raltegravir because the sample size of patients on elvitegravir or dolutegravir in our cohort is smaller, and dolutegravir approval is more recent than raltegravir. However, no suggestion of a correlation emerged from our analysis for INSTI other than raltegravir.

On our subjects, past use of NNRTI seemed associated with a lower risk of plaques. This finding was consistent with a body of evidence confirming the CV safety of this class of antiretrovirals (22-24).

It can be hypothesized that in PLWH the increased CV risk was due to the HIV-related inflammation, whereas the vascular damage is currently sustained

by the increase of the average age, and by the higher incidence of age-related comorbidities, despite the advent of new antiretrovirals, more effective in controlling the infection and the consequent inflammation, and with a lower metabolic impact. In the present study, traditional risk factors, such as older age, male sex, overweight, hypertension, high systolic blood pressure, high blood glucose, diabetes, previous myocardial infarction, low HDL-cholesterol, and high triglycerides, played a central role in carotid impairments. Variables related to HIV infection, such as HIV infection duration and CD4+ cell nadir, still exerted a role. On the contrary, we did not observe any role of CDC classification and CD4+ cell count, that were significantly related to epi-aortic impairments in previous studies (4,5). In the present study, no naïve patient had pathological measurements, although the number of such patients was very low.

By analyzing separately IMT and plaques, we found that both were significantly related to male sex and age, while HCV infection was associated only with IMT. BMI, hypertension, diabetes, HDL-c, triglycerides, CD4+ cell nadir were only related to plaques. As expected, plaques provided us more information regarding the determinants of vascular damage, with respect to IMT that remains, nonetheless, a sensitive marker of an initial endothelial injury.

The main strengths of the present study are the large number of patients involved, and the fact that the cohort involves centers from all the national territory. The major limitation is that it is a cross-sectional analysis of baseline data, so we can observe association but not infer any causality.

In conclusion, in our experience, among PLWH, color-Doppler ultrasonography could play a pivotal role in identifying and quantifying atherosclerotic lesions, even at a very premature stage, and should be included in the algorithms of comorbidity management of these patients. A registry of echoic images from all the national territory represents an important source of data, allowing us to track the CV risk of PLWH, to evaluate if the role of risk factors, both traditional and related to HIV infection, modifies over time, to assess the impact of different antiretroviral regimens on CV risk. ■

BIBLIOGRAFIA

1. Maggi P, Di Biagio A, Rusconi S, Cicalini S, D'Abbraccio M, d'Ettorre G, et al. *Cardiovascular risk and dyslipidemia among persons living with HIV: a review. BMC Infect Dis. 2017; 17: 551.*

2. Rao SG, Galaviz KI, Gay HC, Wei J, Armstrong WS, del Rio C, et al. Factors Associated with Excess Myocardial Infarction Risk in HIV-infected Adults: a Systematic Review and Meta-Analysis. J Acquir Immune Defic Syndr. 2019; 81: 224-230.

3. Schmidt-Trucksäss A, Grathwohl D, Schmid A, Boragk R, Upmeier C, Keul J, et al. Structural, functional, and hemodynamic changes of the common carotid artery with age in male subjects. Arterioscler Thromb Vasc Biol. 1999; 19: 1091–1097.

4. Maggi P, Serio G, Epifani G, Fiorentino G, Saracino A, Fico C et al. Premature lesions of the carotid vessels in HIV-1-infected patients treated with protease inhibitors. AIDS 2000; 14: 123-128.

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

6. Maggi P, Volpe A, Bellacosa C, Pastore G, Perilli F, Lillo A et al. The role of immune reconstitution in the onset of subclinical atheromasic lesions. J Acquir Immune Defic Syndr. 2009 1; 52: 524-5.

7. Maggi P, Bellacosa C, Leone A, Volpe A, Ricci ED, Ladisa N, et al. Cardiovascular risk in advanced naïve HIV-infected patients starting antiretroviral therapy: Comparison of three different regimens- PREVALEAT II cohort. Atherosclerosis. 2017; 263: 398-404.

8. Nicolaides AN, Shifrin EG, Bradbury A, Dhanjil S, Griffin M, Belcaro G et al. Angiographic and duplex grading of internal carotid stenosis: can we overcome the confusion? J Endovasc Surg 1996; 3: 158-165.

9. Belcaro G, Nicolaides AN, Laurora G, Cesarone MR, De Sanctis M, Incandela L et al. Ultrasound morphology classification of the arterial wall and cardiovascular events in a

6-year follow up study. Arterioscler Thromb Vasc Biol 1996; 16: 851-856.

10. Vecchiet J, Iachininoto MG, Capodimonti S, Nuzzolo ER, Falasca K, Martini M, et al. Effect of antiviral therapy on pro-angiogenic hematopoietic and endothelial progenitor cells in HIV-infected people. Thromb Res. 2013; 131: 238-43.

11. Falasca K, Reale M, Di Nicola M, Ucciferri C, Zecca IA, Santilli F, et al. Circulating CD40 ligand, Dickkopf-1 and P-selectin in HIV-infected patients. HIV Med. 2019; 20: 681-690.

12. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. Circulation. 2004; 109: 1089–1094.

13. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med. 2011; 365: 213–221.

14. Naqvi TZ, Mendoza F, Rafii F, Gransar H, Guerra M, Lepor N, et al. *High prevalence of ultrasound detected carotid atherosclerosis in subjects with low Framingham risk score: potential implications for screening for subclinical atherosclerosis. J Am Soc Echocardiogr. 2010; 23: 809–815.*

15. Chuang SY, Bai CH, Cheng HM, et al. Chen JR, Yeh WT, Hsu PF, et al. *Common carotid artery end-diastolic velocity is independently associated with future cardiovascular events. Eur J Prev Cardiol. 2016; 23: 116–124.*

16. Smith Jr. SC, Amsterdam E, Balady GJ, Bonow RO, Fletcher GF, Froelicher V, et al. *Prevention conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: tests for silent and inducible ischemia: writing group II, Circulation 2000; 101: E12-16.*

17. Ryom L, Lundgren JD, El-Sadr W, Reiss P, Kirk O, Law M, et al. *Cardiovascular disease and use of contemporary protease inhibitors: the D: A: D international prospective multicohort study. Lancet HIV. 2018; 5: e291-e300.*

18. Bourgi K, Jenkins CA, Rebeiro PF, Palella F, Moore RD, Altoff KN, et al. *Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc. 2020; 23: e25484.*

19. Erlandson KM, Carter CC, Melbourne K, Brown TT, Cohen C, Das M, et al. *Weight Change Following Antiretroviral Therapy Switch in People with Viral Suppression: Pooled Data from Randomized Clinical Trials. Clin Infect Dis. 2021; 14: ciab444.*

20. Bhagwat P, Ofotokun I, McComsey GA, Brown TT, Moser C, Sugar CA, et al. *Changes in Waist Circumference in HIV-Infected Individuals Initiating a Raltegravir or Protease Inhibitor Regimen: Effects of Sex and Race. Open Forum Infect Dis. 2018; 5: ofy201.*

21. Achhra AC, Mocroft A, Reiss P, Sabin C, Ryom L, de Wit S. et al. *Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D: A: D study. HIV Med. 2016; 17: 255-68.*

22. Friis-Møller N, Weber R, Reiss P, Thiébaut R, Kirk O, d'Arminio Monforte A, et al; DAD study group. *Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. AIDS. 2003; 17: 1179-93.*

23. Maggi P, Bellacosa C, Carito V, Perilli F, Lillo A, Volpe A, et al. *Cardiovascular risk factors in patients on long-term treatment with nevirapine- or efavirenz-based regimens. J Antimicrob Chemother. 2011; 66: 896-900.*

24. Lu WL, Lee YT, Sheu GT. *Metabolic Syndrome Prevalence and Cardiovascular Risk Assessment in HIV-Positive Men with and without Antiretroviral Therapy. Medicina (Kaunas). 2021; 57: 578.*