Received: 26 July 2022 | Accepted: 14 November 2022

DOI: 10.1111/hiv.13448

ORIGINAL ARTICLE

Subclinical atherosclerosis as detected by carotid ultrasound and associations with cardiac and HIV-specific risk factors; the Archi-Prevaleat project

Paolo Maggi[1] | **Elena Delfina Ricci**[2] | **Camilla Muccini**[3] | **Laura Galli**[3] | **Benedetto Maurizio Celesia**[4] | **Sergio Ferrara**[5] | **Yara Salameh**[6] | **Rosa Basile**[7] | **Giovanni Di Filippo**[8] | **Francesco Taccari**[9] | **Alessandra Tartaglia**[10] | **Antonella Castagna**[3]

[1]Università della Campania Luigi Vanvitelli, Naples, Italy

[2]Fondazione ASIA Onlus, Milan, Italy

[3]Università Vita e Salute San Raffaele, Milan, Italy

[4]Azienda Ospedaliera ARNAS Garibaldi, Catania, Italy

[5]Università degli Studi, Foggia, Italy

[6]University Balamand, Koura, Lebanon

[7]Grande Ospedale Metropolitano, Reggio Calabria, Italy

[8]Università degli Studi Federico II, Naples, Italy

[9]Università Cattolica del Sacro Cuore-Campus, Rome, Italy

[10]Azienda Ospedaliera Foggia-Italy, Foggia, Italy

Correspondence
Paolo Maggi, AORN S. Anna e S. Sebastiano, via F. Palasciano, 1 81100 Caserta, Italy.
Email: paolo.maggi@unicampania.it

Abstract

Objectives: To evaluate the prevalence of carotid intima-media thickness (IMT) and plaques in a cohort of people living with HIV (PLWH), the role of cardiovascular risk factors, the impact of the antiretroviral regimens and the difference between naïve and experienced patients in the onset of carotid lesions.

Methods: This project was initiated in 2019 and involves eight Italian centres. Carotid changes were detected using a power colour-Doppler ultrasonography with 7.5 MHz probes. The following parameters were evaluated: IMT of both the right and left common and internal carotids, data regarding risk factors for cardiovascular disease, HIV viral load, CD4 cell counts, serum lipids, glycaemia and body mass index. The associations between pathological findings and potential risk factors were evaluated by logistical regression, with odds ratios (ORs) and 95% confidence intervals (95% CI)s.

Results: Among 1147 evaluated PLWH, with a mean age of 52 years, 347 (30.2%) had pathological findings (15.8% plaques and 14.5% IMT). Besides the usual risk factors, such as older age, male sex and dyslipidaemia, CD4 cell nadir < 200 cells/mL (adjusted OR = 1.51, 95% CI: 1.14–1.99) and current use of raltegravir (adjusted OR = 1.54, 95% CI: 1.01–2.36) were associated with higher prevalence of pathological findings.

Conclusions: Our data show that the current overall percentage of carotid impairments remains high. Colour-Doppler ultrasonography could play a pivotal role in identifying and quantifying atherosclerotic lesions among PLWH, even at a very premature stage, and should be included in the algorithms of comorbidity management of these patients.

KEYWORDS

cardiovascular risk, carotid vessels, HIV, intima-media thickness, plaques

The Archi-Prevaleat project is a national cohort of colour-Doppler ultrasonography of the epi-aortic vessels in patients living with HIV.

INTRODUCTION

The introduction of effective antiretroviral (ARV) regimens had a deep impact on the natural history of HIV infection, leading to a dramatic decrease in its mortality rate and a considerable increase in the life expectancy of people living with HIV (PLWH). Nevertheless, these patients still appear to be at higher risk of developing several comorbidities, such as cardiovascular disease (CVD) [1, 2]. Measurement of the carotid intima-media thickness (IMT) and detection of plaques with colour-Doppler ultrasonography is a non-invasive, sensitive and highly reproducible technique aimed not only at assessing vascular anatomy and function, but also at identifying and quantifying atherosclerotic lesions, even at a very premature stage. It is a well-validated research tool and is widely used in clinical practise [3]. This technique allows the measurement of a variety of parameters, including the IMT, arterial diameter, presence of plaques, and blood flow and velocity.

PREVALEAT (PREmature VAscular LEsions and Antiretroviral Therapy) is an ongoing multicentre, longitudinal cohort involving several Italian centres that began in 1998, aimed at evaluating the cardiovascular (CV) risk in PLWH using colour-Doppler ultrasonography. The cohort has resulted in several studies being done in this field over the years, [4–7]. Considering that the use of this technique is, at present, widely diffused among the Italian HIV outpatient facilities, we generated a national cohort of colour-Doppler ultrasonography (Archi-Prevaleat) to better evaluate the presence of subclinical vascular damage, the characteristics of vascular lesions and their correlation with CV risk factors and ARV therapies in PLWH, based on a large amount of data.

The aim of the present study is to evaluate the prevalence of carotid IMT and plaques in this cohort of PLWH, the role of classic CV risk factors and of the risk factors related to HIV infection, as well as the impact of the different ARV regimens, and finally, the difference between ARV-naïve and experienced people in the onset of these carotid lesions.

METHODS

This ongoing project was initiated in 2019 and currently involves eight Italian infectious disease centres in which the ultrasonographic examination is performed by competent physicians. These physicians were specifically trained in the technique during a continuing medical education training programme previously organised by the coordinating centre (Università della Campania, Luigi Vanvitelli). Comparison and standardization of the technique were performed using images and filmed reports during annual follow-up meetings. Written informed consent was obtained from each PLWH. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study protocol has previously been approved by the coordinating centre's ethics committee on research on humans. The cohort's data were registered on an online platform (http://www.archiprevaleat.com/). The data collected concern adult PLWH aged >18 years with documented HIV infection for at least 12 months, willing to provide informed consent when they presented to the examination for the first time and routinely at all the subsequent follow-up examinations. The results reported in this paper were from the first visit they underwent.

The following parameters were evaluated:

1. Intima-media thickness of both the right and left common and internal carotids: ultrasonography of the epiaortic vessels was performed using a power colour-Doppler instrument with 7.5 MHz probes. The characteristics of the intima together with the pulsation index, the resistance index, the minimal speed, the peak speed and the mean speed were evaluated. A minimum of three measurements were requested: on the common carotid artery, 1 cm before the carotid bifurcation and at the carotid bifurcation; and also on the internal carotid, 1 cm after the carotid bifurcation and 2 cm after the carotid bifurcation. The higher IMT value detected in the sections examined was taken in consideration.
   An IMT > 1.0 mm was considered pathological. Atherosclerotic plaques, if present, were described. A carotid was classified as being affected by plaques if there was a localized thickening > 1.2 mm that did not uniformly involve the whole left or right common carotid bifurcation with or without flow disturbance [8, 9]. All relevant images were photographed and properly archived.
2. Data regarding risk factors for CVD (family history, smoke, active drug addiction, alcohol consumption) were collected at baseline, and re-evaluated every 12 months. Cigarette smoking was defined according to the Progressi Aziende Sanitarie Salute in Italia (PASSI) guidelines (www.epicentro.iss.it/passi/), and alcohol abuse was defined as alcohol consumption > 12 g for females and 24 g for females according to the Italian Ministry of Health guidelines (www.crea.gov.it/). Information regarding the active drug abuse was collected during the routine visits. Blood pressure was measured when the patient was relaxed and

seated with the arm outstretched and supported. Two readings were taken; if the average was ≥ 140/90 mmHg, an additional reading was taken at the end of the consultation for confirmation. Patients were classified as having hypertension if confirmed blood pressure was ≥ 140/90 mmHg.

3. 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 every annual control.

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 and interquartile range (IQR) if not normally distributed. Comparisons were performed using ANOVA, the Mann–Whitney test (or the Kruskal–Wallis test, as appropriate).

Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were used to evaluate the association between IMT pathological findings (IMT-PF, IMT > 1.00–1.20 mm or plaques in either the right or left carotid) and patients' characteristics and clinical variables, using an unconditional logistic regression model. Two models for multivariate analyses were chosen to select for potential confounders. All variables that were significantly associated with IMT-PF at the univariate analysis were controlled in a model including sex and age. Variables still significantly associated with IMT-PF in this analysis were included in the final model. To avoid losing observations, classes were created for missing values of selected variables and included in the models to evaluate the presence of non-random bias. Finally, we performed a multinomial regression model that incorporated both outcome groups (PLWH with IMT > 1.00–1.20 mm and PLWH with plaques) in the same model.

Data analysis was conducted with SAS for Windows 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 1147 PLWH who underwent colour-Doppler ultrasonography in the participating centres (82% males, mean age 52.1 years, SD 10.0) were enrolled. The overall percentage of PLWH with IMT-PF was 30.2% ($n = 347$) while the remaining 69.8% ($n = 800$) had normal results (Table 1). Among people with IMT-PF, 15.8% ($n = 181$) had plaques, whereas 14.5% ($n = 166$) had only IMT > 1.00–1.20 mm. Demographic and metabolic data, data regarding HIV infection and cardio-cerebral-vascular comorbidities are summarized in Table 2.

We observed that, regarding demographics, IMT-PFs were significantly related to age ($p < 0.0001$), male sex ($p < 0.0001$) and BMI ($p = 0.005$). Regarding comorbidities, PLWH with IMT-PF had: (i) more frequent prevalence of hypertension ($p < 0.0001$), diabetes ($p = 0.0003$), previous myocardial infarction ($p = 0.01$) and hepatitis C virus (HCV) coinfection ($p = 0.02$); (ii) higher values of systolic blood pressure ($p = 0.001$), triglycerides ($p < 0.0001$) and blood glucose regardless of a diagnosis of diabetes ($p = 0.0003$); (iii) lower values of HDL-c ($p = 0.001$) and estimated glomerular filtration rate ($p < 0.0001$) than people without IMT-PF. Considering variables related to HIV infection, there was a significant relationship between the IMT-PFs and longer HIV infection duration ($p = 0.01$), lower CD4 cell nadir ($p = 0.003$) and current use of integrase inhibitors ($p = 0.003$). Exploring details of current ARV treatments, we found that the current use of raltegravir was significantly associated with IMT-PF ($p = 0.0001$), as shown in Table 3. By contrast, naïve condition was related to normal findings ($p = 0.01$), although this result emerged from a limited sample of 17 PLWH.

The crude ORs, sex- and age-adjusted ORs (aOR) and the complete model aOR (with corresponding 95% CI) are reported in Table 4. The associations were shown to be statistically significant for age (by 1 year, OR = 1.08 and aOR = 1.08), female sex (OR = 0.46, aOR = 0.52),

TABLE 1 Echocolor Doppler findings in 1147 people living with HIV

Intima-media thickness (IMT)	Left	Right	Overall
IMT ≤ 1.00 mm	865 (75.4%)	902 (78.6%)	800 (69.8%)
IMT > 1.00 mm, no plaque	139 (12.1%)	129 (11.2%)	166 (14.5%)
Plaques	143 (12.5%)	116 (10.1%)	181 (15.8%)
Pathological findings (IMT > 1.00 mm, and/or plaque)	282 (24.6%)	245 (21.4%)	347 (30.2%)

TABLE 2 Main characteristics of 1147 people living with HIV, according to the presence of pathological findings [IMT-PF; intima-media thickness (IMT) > 1.00–1.20 mm and/or plaque]

Parameter	Total ($N = 1147$)	Normal IMT ($N = 800$, 69.8%)	IMT-PF ($N = 347$, 30.2%)	p
Age (years) (mean ± SD)	52.1 ± 10.0	50.0 ± 9.7	56.7 ± 9.2	< 0.0001
Male [n (%)]	941 (82.0)	632 (79.0)	309 (89.0)	< 0.0001
Risk for HIV acquisition [n (%)]				0.07
IDU	153 (13.3)	103 (12.9)	50 (14.4)	
Sexual	711 (62.0)	513 (64.1)	198 (57.1)	
Other	283 (24.7)	184 (23.0)	99 (28.5)	
Smoking habits [n (%)]				0.10
Never	231 (20.1)	172 (21.5)	59 (17.0)	
Current	449 (39.2)	311 (38.9)	138 (39.8)	
Former	238 (20.8)	153 (19.1)	85 (24.5)	
Unknown	229 (20.0)	164 (20.5)	65 (18.7)	
BMI (kg/m^2) (mean ± SD)	24.8 ± 3.8	24.6 ± 3.7	25.3 ± 3.9	0.005
BMI class (kg/m^2) [n (%)]				0.004[a]
< 18.5	28 (2.4)	22 (2.8)	6 (1.7)	
18.5–25.0	565 (49.3)	411 (51.4)	154(44.4)	
25.0–30.0	351 (30.6)	234 (29.2)	117 (33.7)	
> 30.0	90 (7.8)	55 (6.9)	35 (10.1)	
Missing	113 (9.8)	78 (9.8)	35 (10.1)	
Cardiovascular diseases [n (%)]				
Hypertension	403 (35.1)	237 (29.6)	166 (47.8)	<0.0001
Diabetes	110 (9.6)	60 (7.5)	50 (14.4)	0.0003
Ictus	15 (1.3)	8 (1.0)	7 (2.0)	0.16
Angina	8 (0.7)	3 (0.4)	5 (1.4)	0.06
AMI	22 (1.9)	10 (1.2)	12 (3.5)	0.01
PAD	7 (0.6)	3 (0.4)	4 (1.2)	0.21
HCV coinfection [n (%)]	323 (28.2)	209 (26.1)	114 (32.8)	0.02
Systolic blood pressure (mmHg) (mean ± SD)	126.2 ± 15.7	125.2 ± 15.4	128.5 ± 16.1	0.001
Diastolic blood pressure (mmHg) (mean ± SD)	79.3 ± 10.5	79.2 ± 10.3	79.7 ± 11.0	0.46
Cholesterol (mg/dL) (mean ± SD)	190 ± 40	190 ± 41	190 ± 40	0.89
HDL-c (mg/dL) (mean ± SD)	48 ± 17	50 ± 17	46 ± 16	0.001
LDL-c (mg/dL) (mean ± SD)	119 ± 36	119 ± 37	119 ± 35	0.89
Triglycerides (mg/dL) [median (IQR)]	124 (88–181)	120 (86–171)	138 (90–200)	0.004
Blood glucose[b] (mg/dL) (mean ± SD)	89 ± 13	88 ± 12	91 ± 14	0.0003
AST (U/L) [median (IQR)]	25 (19–33)	24 (19–32)	26 (20–34)	0.05
ALT (U/L) [median (IQR)]	29 (22–43)	29 (22–43)	29 (22–44)	0.73
eGFR (mL/min) (mean ± SD)	94.6 ± 18.2	95.9 ± 17.3	91.4 ± 20.0	0.0002
HIV infection duration (years) (mean ± SD)	14.1 ± 3.8	13.9 ± 3.8	14.5 ± 3.9	0.01
Nadir CD4 count (cells/μL) [median (IQR)]	210 (120–323)	223 (127–229)	185 (93–297)	0.003
Current CD4 count (cells/μL) [median (IQR)]	700 (515–921)	715 (522–919)	681 (486–922)	0.36
Current CD8 count (cells/μL)[c] [median (IQR)]	888 (644–1186)	888 (652–1190)	888 (622–1168)	0.79
CD4/CD8 ratio[c] [median (IQR)]	0.80 (0.52–1.13)	0.81 (0.54–1.16)	0.79 (0.48–1.13)	0.48
Naïve [n (%)]	17 (1.5)	17 (2.1)	0	0.003

TABLE 2 (Continued)

Parameter	Total ($N = 1147$)	Normal IMT ($N = 800$, 69.8%)	IMT-PF ($N = 347$, 30.2%)	*p*
NRTIs [*n* (%)]				
Current use	958 (83.5)	673 (84.1)	285 (82.1)	0.40
Past use	852 (74.3)	601 (75.1)	251 (72.3)	0.32
PIs [*n* (%)]				
Current use	549 (47.9)	378 (47.2)	171 (49.3)	0.53
Past use	554 (48.3)	377 (47.1)	177 (51.0)	0.23
NNRTIs [*n* (%)]				
Current use	368 (32.1)	263 (32.9)	105 (30.3)	0.38
Past use	338 (29.5)	243 (30.4)	95 (27.4)	0.31
INSTIs [*n* (%)]				
Current use	261 (22.8)	166 (20.8)	95 (27.4)	0.01
Past use	200 (17.4)	132 (16.5)	68 (19.6)	0.20

Abbreviations: ALT, alanine aminotransferase; AMI, acute myocardial infarction; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration; HCV, hepatitis C virus; HDL-c, high density lipoprotein cholesterol; IDU, injecting drug use; INSTIs, integrase strand transferase inhibitors; LDL-c, low density lipoprotein cholesterol; IQR, interquartile range; NNRTIs, nonnucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; SD, standard deviation.

[a]χ^2 for trend in subjects with known BMI ($N = 1034$).

[b]Non-diabetic subjects, $n = 994$.

[c]$N = 770$.

TABLE 3 Details of most frequently used antiretroviral treatment in 1147 people living with HIV, according to the presence of pathological findings [IMT-PF; intima-media thickness (IMT) > 1.00–1.20 mm and/or plaque]

Parameter	Total ($N = 1147$)	Normal IMT ($N = 800$, 69.8%)	IMT-PF ($N = 347$, 30.2%)	*p*
Current NRTI [*n* (%)]				
Tenofovir	539 (47.0)	380 (47.5)	159 (45.8)	0.60
Abacavir	280 (24.4)	198 (24.7)	82 (23.6)	0.68
Lamivudine	420 (36.6)	294 (36.8)	126 (36.3)	0.89
Emtricitabine	526 (45.9)	375 (46.9)	151 (43.5)	0.29
Current PI [*n* (%)]				
Atazanavir	252 (22.0)	175 (21.9)	77 (22.2)	0.91
Darunavir	248 (21.6)	169 (21.1)	79 (22.8)	0.54
Current NNRTI [*n* (%)]				
Efavirenz	144 (12.6)	103 (12.9)	41 (11.8)	0.62
Current INSTI [*n* (%)]				
Raltegravir	119 (10.4)	65 (8.1)	54 (15.6)	0.0001
Dolutegravir	102 (8.9)	72 (9.0)	30 (8.6)	0.85
Elvitegravir	40 (3.5)	29 (3.6)	11 (3.2)	0.70

Abbreviations: INSTI, integrase strand transferase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

BMI (by 1 kg/m^2, OR = 1.05, aOR = 1.05) and > 30.0 (OR = 1.70, aOR = 1.60), hypertension (OR = 2.18, aOR = 1.45), HCV coinfection (OR = 1.38, aOR = 1.44), elevated triglycerides (OR = 1.64, aOR = 1.45), low HDL-c (OR = 1.46, aOR = 1.64), integrase strand transferase inhibitor (INSTI) use (OR = 1.44, aOR = 1.38) and raltegravir use (OR = 2.08, aOR = 1.74), in the crude and sex- and age-adjusted analyses, respectively.

TABLE 4 Odds ratio (OR), adjusted OR (aOR) and 95% confidence interval (95% CI) for pathological findings [IMT-PF; intima-media thickness (IMT) > 1.00–1.20 mm and/or plaque], crude and sex- and age-adjusted

	Crude			Age- and sex-adjusted			Complete model**		
Parameter	**OR**	**95% CI**		**aOR**	**95% CI**		**aOR**	**95% CI**	
Age (by 1 year)	1.08	1.06	1.09	1.08	1.06	1.09	1.07	1.06	1.09
Female (ref. male)	0.46	0.32	0.68	0.52	0.35	0.77	0.54	0.36	0.81
Smoking habits (ref. never)									
Current	1.29	0.90	1.85	1.35	0.92	1.97			
Former	1.62	1.09	2.41	1.31	0.86	2.06			
Unknown	1.16	0.76	1.74	1.41	0.91	2.20			
BMI (by 1 kg/m^2)	1.05	1.01	1.09	1.05	1.01	1.09			
BMI class (ref. 18.6–25.0 kg/m^2)									
< 18.5	0.73	0.29	1.83	0.71	0.26	1.89	0.77	0.29	2.07
> 25.0–30.00	1.33	1.00	1.78	1.32	0.97	1.80	1.28	0.93	1.75
> 30.00	1.70	1.07	1.70	1.60	1.04	2.67	1.50	0.90	2.49
Hypertension (ref. N)	2.18	1.68	2.82	1.45	1.09	1.92	1.28	0.95	1.72
Diabetes (ref. N)	2.08	1.39	3.09	1.29	0.84	1.97			
Angina (ref. N)	3.88	0.92	16.34	1.91	0.79	4.60			
AMI (ref. N)	2.83	1.21	6.61	1.30	0.54	3.16			
HCV coinfection (ref. N)	1.38	1.05	1.82	1.44	1.08	1.93	1.34	0.99	1.82
Low HDL-c (ref. ≥ 40 (M) ≥ 50 (F) mg/dL)	1.46	1.10	1.93	1.64	1.22	2.22	1.45	1.06	2.00
Triglycerides ≥ 150 mg/dL (ref. < 150 mg/dL)	1.64	1.26	2.14	1.45	1.10	1.92	1.21	0.90	1.64
Blood glucose ≥ 100 mg/dL (ref. < 100 mg/dL)	1.62	1.21	2.18	0.95	0.69	1.32			
Systolic blood pressure (by 5 mmHg)	1.07	1.02	1.11	1.01	0.97	1.03			
eGFR (by 5 mL/min)	0.94	0.90	0.97	1.03	0.98	1.07			
HIV infection duration (by 5 years)	1.26	1.06	1.50	1.01	0.82	1.23			
Nadir CD4 < 200 cells/μL (ref. ≥ 200 cells/μL)	1.48	1.14	1.90	1.58	1.21	2.07	1.51	1.14	1.99
Current INSTI use (ref. N)	1.44	1.08	1.93	1.38	1.02	1.89	1.28	0.93	1.77
Current raltegravir use (ref. N)	2.08	1.42	3.06	1.74	1.16	2.61	1.54	1.01	2.36

Note: PLWH with normal IMT represented the control group. **aOR: included all variables with $p < 0.05$ in the age- and sex-adjusted analyses. Estimates for raltegravir and INSTI use were derived from separate models.

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; HCV, hepatitis C virus; HDL-c, high density lipoprotein cholesterol; INSTI, integrase strand transferase inhibitor; ref. N, reference no.

Whilst some of these factors were not significa ntly associated with the outcome after adjustment, aOR values were still > 1.0, suggesting that associations might remain.

Thus, the final model was made to include age, sex, BMI, hypertension, HCV coinfection, HDL, triglycerides, nadir CD4 and, in turn, INSTI use or raltegravir use. In this model, age, sex, HDL-c, nadir CD4 and raltegravir use maintained their association with IMT-PF (Table 4).

Dividing the people with IMT-PF into two classes, IMT > 1.00–1.20 mm and presence of plaques, the analyses were performed using a multinomial regression model. For univariate analysis, the associated variables were age, sex, BMI, hypertension, diabetes, angina, acute myocardial infarction, HDL-c, triglycerides, nadir CD4 < 200 cells/μL, HIV infection duration, previous nonnucleoside reverse transcriptase inhibitor (NNRTI) use, current INSTI use and current raltegravir use. After adjusting for age and sex, BMI, hypertension, diabetes, HCV coinfection, low HDL-c, increased TGL, nadir CD4 < 200 cells/μL, previous NNRTI use, current INSTI use and current raltegravir use were associated with IMT > 1.00–1.20 mm and/or presence of plaques.

Thus, all these factors were included in the complete model (INSTI and raltegravir use were alternatively included). Age, sex, TGL and nadir CD4 were significantly associated with pathological findings (Table 5).

TABLE 5 Adjusted odds ratios (OR) and 95% confidence interval (95% CI) for intima-media thickness (IMT) > 1.00–1.20 mm and plaques (multinomial regression model)

	IMT > 1.00–1.20 mm			Plaques		
Parameter	**aOR**	**95% CI**		**aOR**	**95% CI**	
Age (by 1 year)	1.06	1.04	1.08	1.09	1.07	1.12
Female (ref. male)	0.52	0.31	0.87	0.55	0.31	0.97
BMI (kg/m^2) (ref. 18.6–25.0)						
≤ 18.5	0.48	0.11	2.16	1.20	0.36	3.93
> 25.0–30.0	1.04	0.69	1.56	1.57	1.04	2.37
> 30.0	1.25	0.64	2.42	1.85	0.99	3.46
Hypertension (ref. N)	1.28	0.88	1.87	1.30	0.88	1.90
Diabetes (ref. N)	0.72	0.38	1.35	1.27	0.74	2.16
HCV coinfection (ref. N)	1.44	0.99	2.10	1.30	0.88	1.92
Low HDL-c [ref. ≥ 40 (M) ≥ 50 (F) mg/dL]	1.23	0.82	1.85	1.68	1.11	2.53
Triglycerides ≥ 150 mg/dL (ref. < 150 mg/dL)	0.91	0.62	1.34	1.66	1.13	2.46
Nadir CD4 < 200 cells/μL (ref. ≥ 200 cells/μL)	1.23	0.86	1.75	1.81	1.25	2.62
Past NNRTI use (ref. N)	1.12	0.77	1.63	0.68	0.44	1.04
Current INSTI use (ref. N)	1.16	0.76	1.76	1.41	0.94	2.11
Current raltegravir use (ref. N)	1.64	0.97	2.77	1.48	0.87	2.50

Note: PLWH with normal IMT represented the control group. All variables significantly associated with IMT > 1.00–1.20 mm or presence of plaques in the age- and sex-adjusted analyses were included in the model.

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; HDL-c, high density lipoprotein cholesterol; INSTI, integrase strand transferase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

DISCUSSION

As previously seen, PLWH are at higher risk of CVD than the general population [1, 2]. In particular, chronic inflammatory processes are activated and atherosclerosis is accelerated in PLWH [7, 10, 11]; this is the reason why cardiovascular disease is one of the most common non-AIDS events with overall increased morbidity and mortality. Although the mechanisms involved remain elusive, endothelial activation due to the chronic inflammation could be the keystone of this phenomenon in which proinflammatory cytokines [7], pro-angiogenic haematopoietic and endothelial progenitor cells [10], circulating CD40 ligand and Dickkopf-1 [11] could be involved.

Carotid IMT and presence of plaque have been shown to predict cardiovascular events in large studies [12, 13]. Also, in asymptomatic people without CVD, carotid IMT and plaque assessment are more likely to revise Framingham Risk Score than coronary artery calcium score. [14]. Furthermore, common carotid blood flow velocity was independently associated with future CVD using colour-duplex ultrasound and Doppler spectral analysis [15]. In clinical practice, evaluation of the carotid artery by ultrasonography is a very useful, simple and safe method to detect and prevent CVD indirectly. 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 CVD of between 6% and 20%. [16].

Our data show that the current overall percentage of PLWH with carotid impairments, either IMT or plaques, remains high (30.2%). In fact, in spite of the great improvement of ARV therapies, including the general amelioration of the quality of life among PLWH and the increase of their life expectancy, this percentage does not show substantial improvement in recent decades compared with our previous observations. In fact, 35.2% of PLWH were observed to have carotid lesions in 2000 [4], 31.7% in 2004 [5], and, in 2017, in a prospective study on advanced naïve PLWH, a population at higher risk of CV disease, the lesions were observed in 38.7% after 1 year of ARV therapy [7]. In all these studies, people treated with protease inhibitors (PIs) showed a significantly higher percentage of lesions, which was in line with data deriving from the D:A:D cohort [17]. It can be hypothesized that if in the past the increased CV risk of PLHW was due to the HIV-related inflammation, nowadays the vascular damage is sustained by the increase in the average age and the higher incidence of age-related comorbidities, despite the advent of new antiretrovirals that are more effective in controlling the infection and the

consequent inflammation. In our experience, several classic risk factors (older age, male sex, overweight, hypertension, high systolic blood pressure, high blood glucose, diabetes, previous myocardial infarction, low HDL-c and high triglycerides) play a central role in carotid impairments. Not unexpectedly, people with liver and kidney disease are at increased risk of carotid impairments. Variables related to HIV infection (HIV infection duration and CD4 cell nadir) still exerted a role; in our previous experience, CDC classification [4] and CD4 cell count [5] were significantly related to epi-aortic impairments. In the present study, the outcome of the naïve condition was protective, although the number of such patients was very low.

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

Considering the role of ARV therapies, in contrast to our previous papers where the role of PIs constantly emerged [4, 5, 7], our present study provided evidence that carotid lesions were related only to current use of raltegravir. Also, by analysing IMT and plaques separately, the role of the current use of raltegravir emerged for both. Although this datum should be taken with caution, considering that it could suffer fo a number of channeling biases difficult to fully adjust, this is consistent with recent evidence showing that INSTIs can determine weight gain in PLWH [18, 19]; moreover, a study in 2018 [20] described an increase in waist circumference in patients treated with raltegravir use. On the other hand, a correlation between short-term weight gain, subsequent risk of cardiovascular disease and diabetes has been found in the D:A:D: cohort [21]. The reason we only observed this correlation for raltegravir may lie in the fact that the sample size of people treated with elvitegravir or dolutegravir in our cohort is smaller, and dolutegravir approval is more recent than raltegravir. It was also observed that previous use of NNRTIs was associated with a lower risk of plaques. This seems concordant with a body of evidence that confirmed over time the cardiovascular safety of this class of antiretrovirals [22–24]. However, despite the high prevalence of IMT abnormalities in the cohort, the prevalence of clinical CVD is low. This could indicate that in our cohort there is currently good global control of overall CV risk factors, thanks to better management of modifiable traditional risk factors and less use of antiretrovirals related to CV development.

The main strengths of the present study are the large number of PLWH involved and the fact that the cohort involves centres from all the national territory. The major limitation is that, at present, only cross-sectional data are available.

In conclusion, in our experience, colour-Doppler ultrasonography could play a pivotal role in identifying and quantifying atherosclerotic lesions in PLWH, even at a very premature stage, and should be included in the algorithms of comorbidity management of these people. In light of our experience, we propose the realization of a larger registry of echoic images deriving from all national territories; this could represent an important source of data, which will allow us to better track the CV risk of PLWH and to evaluate the modifications over time of the role of the different risk factors, both traditional ones and those related to HIV infection, and also the impact of the new and old ARV regimens on CV risk.

AUTHOR CONTRIBUTIONS

PM designed the study, carried out analyses, interpreted the data and wrote the manuscript. AC and YS analysed and interpreted the data. CM and LG acquired the data and reviewed the manuscript. EDR performed the statistical analysis. BMC, SF, RB, GDiF, FT and AC collected the data from the participant centres.

FUNDING INFORMATION

The project has been partially supported by a Gilead Sciences Medical Grant.

CONFLICTS OF INTEREST

The authors declare that there is nothing to disclose regarding conflict of interest with respect to this manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Paolo Maggi https://orcid.org/0000-0002-8772-0136
Elena Delfina Ricci https://orcid.org/0000-0001-5279-0444

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How to cite this article: Maggi P, Ricci ED, Muccini C, et al. Subclinical atherosclerosis as detected by carotid ultrasound and associations with cardiac and HIV-specific risk factors; the Archi-Prevaleat project. *HIV Med*. 2022;1-9. doi:10.1111/hiv.13448