



Scientific Letter

Archi-Prevaleat Project. A National Register of Color-Doppler Ultrasonography of the Epi-Aortic Vessels in Patients Living with HIV

Keywords: HIV; Endothelial wall; Color-Doppler ultrasonography; Vascular lesions.

Published: March 1, 2020

Received: December 19, 2019

Accepted: February 14, 2020

Citation: Martini S., Ferrara S., Bellacosa C., Celesia B.M., Taccari F., Di Filippo G., Tartaglia A., Gaeta G., Maggi P. Archi-prevaleat project. A national register of color-doppler ultrasonography of the epi-aortic vessels in patients living with HIV. *Mediterr J Hematol Infect Dis* 2019, 11(1): e2020018, DOI: <http://dx.doi.org/10.4084/MJHID.2020.018>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

To the editor.

Persons Living with HIV (PLWH) are at higher risk of cardiovascular disease (CVD) than the general population. Carotid ultrasound is a non-invasive diagnostic tool, aimed at the assessment of vascular anatomy and function. Our present aim is to generate a National Register of color-Doppler ultrasonography (Archi-Prevaleat) to better evaluate the characteristics of vascular lesions in PLWH on a large number of data. The project involves Italian Centers in which the examination is performed by specifically trained physicians. The Register is based on an on-line platform (<http://www.archiprevaleat.com/>) aimed at collecting data regarding Intima Media Thickness (IMT) and plaques in patients routinely submitted to the examination. The register will generate a number of retrospective, non-interventional observational studies. Our preliminary data show a considerably high percentage of patients with IMT and strong evidence of plaques. However, it is noteworthy that clinicians tend to submit to this investigation their patients at higher CV risk. Considering that this diagnostic tool is particularly useful in patients at intermediate risk, this will prompt to extend the investigation to all patients, to proactively prevent CVD.

The introduction of effective antiretroviral (ARV) regimens have produced a profound impact on the natural history of HIV infection, leading to a dramatic decrease in its mortality and a considerable increase in the life expectancy of Persons Living with HIV (PLWH). Nevertheless, these patients still appear to be at higher risk of a number of co-morbidities, such as cardiovascular disease (CVD) than the general population.^{1,2} Measurement of carotid IMT with color-Doppler ultrasonography is a non-invasive, sensitive and highly reproducible technique aimed at the assessment of vascular anatomy and function, and for identifying and quantifying atherosclerotic lesions,

even at a very early stage. It is a well-validated research tool and is widely used in clinical practice.³

This technique allows measurement of a variety of parameters including intima-media thickness (IMT), arterial diameter, the presence of plaque, blood flow, and velocity measurements.

Carotid IMT and presence of plaque have been shown to predict cardiovascular events in large studies.^{4,5} Also, in low-risk subjects, initial screening by IMT and plaque assessment is likely to provide useful information for the detection of subclinical atherosclerosis.⁶ Furthermore, common carotid blood flow (CBF) velocity was independently associated with future cardiovascular disease (CVD) using color duplex ultrasound and Doppler spectral analysis.⁷ In clinical practice, evaluation of the carotid artery by ultrasonography is a handy, simple, and safe method to detect and prevent CVD indirectly. In preventive medicine, IMT measurement is especially important for subjects with intermediate CV risk, i.e., for subjects with a 10 year risk of CV disease between 6% and 20%.⁸

PREVALEAT (PREmature VAScular LESions and Antiretroviral Therapy) is an ongoing multicenter, longitudinal cohort study involving several Italian centers since 1998, aimed to the evaluation of cardiovascular (CV) risk in HIV-infected patients using color-Doppler ultrasonography.⁹⁻¹² The cohort produced, in the years, several studies in this field. Considering that this technique is, at present, widely diffused among the Italian HIV outpatient facilities, our present aim is to generate a National Register of color-Doppler ultrasonography (Archi-Prevaleat) to better evaluate the characteristics of vascular lesions in PLWH, on a large number of data. This ongoing project involves, at present, nine Italian Centers in which the ultrasonographic examination is performed by specifically trained physicians during a Continuing Medical Education stage previously organized by the

coordinating Center (Bari). Periodical follow-up meetings were held using images and filmed reports aimed at the comparison and standardization of the technique. The Register is based on an on-line platform (<http://www.archiprevaleat.com/>) aimed at collecting data regarding patients routinely submitted to the examination for the first time and at all the subsequent follow-up examinations.

Intima Media Thickness (IMT) of common and internal carotid for both left and right sides is registered. A minimum of three measurements are requested: on the common carotid artery: 1 cm before the carotid bifurcation and at the carotid bifurcation; on the internal carotid: 1 cm after the carotid bifurcation and 2 cm after the carotid bifurcation. An IMT of >1 mm is considered pathological. Atherosclerotic plaques, if present, are described. All relevant images are photographed and properly archived.

The register will generate retrospective, non-interventional observational studies, planned by the panel of specialists involved in the project during periodical meetings.

The following parameters will be evaluated at the first visit and at the subsequent control visits, every 6 to 12 months:

1) IMT of common and internal carotid for both left and right sides: ultrasonography of the epi-aortic vessels is performed using a power colour-Doppler instrument with 7.5 MHz probes. We evaluate the characteristics of the intima, together with the pulsation index, the resistance index, the minimal speed, the peak speed and mean speed. A minimum of three measurements are requested: on the common carotid artery: 1 cm before the carotid bifurcation and at the carotid bifurcation; on the internal carotid: 1 cm after the carotid bifurcation and 2 cm after the carotid bifurcation. An intima media thickness (IMT) of >1 mm is considered to be pathological. Atherosclerotic plaques, if present, are described. All images are photographed and properly archived.

2) Data regarding independent risk factors for CVD (family history, smoke, active drug addiction, alcohol consumption) are collected at baseline and re-evaluated every 12 months.

3) HIV viral load, CD4+ cell counts, total serum cholesterol, LDLc, HDLc, glycemia, triglycerides, body mass index (BMI) are recorded at every control.

Moreover, during the study, periodical meetings will be held using filmed reports and/or images in order to obtain comparison and standardization of the techniques.

We have enrolled until now 159 patients who performed color-Doppler ultrasonography in the participating Centers. Demographic data of the enrolled patients, metabolic data, and result of the color-Doppler ultrasonographic investigation are summarized in **Table 1**.

Table 1.

ARCHIPREVALEAT DATA	
Numbers of patients	159
% of patients >50 years old	52.2 % (83/76)
Male/Female	124/35
Caucasians/Other etnies	155/4
Risk Factors for HIV infection	
MSM (Men sex with men)	MSM 53 (33.3%)
PWID(Persons with intravenous drug)	PWID 17 (10.6%)
HETERO(Heterosexual)	HETERO 62 (38.9%)
OTHER(Other risk factor)	OTHER 27 (16.9%)
CDC CLASSIFICATION: C	C: 35 (22 %)
CD4+, cell/ μ L mean \pm SD	696 \pm 355
PI based regimens	53/159 (33.3%)
% of patients with multiple comorbidities (> 1)	13.2% (21/159)
History of CV disease	11/159 (6.9%)
Diabetes	12/159 (7.5%)
Triglycerides (mg/dl) mean \pm SD	170.05 \pm 153.58
Cholesterol mean (mg/dl) \pm SD	189.88 \pm 48.76
HDL mean (mg/dl) \pm SD	43.6 \pm 13.7
LDL mean (mg/dl) \pm SD	117 \pm 38.2
% of Statin treatment	15% (24/159)
Overall % of carotid lesions (IMT and/or plaques)	40.41% (59/146)
% of IMT at Left carotid bulb	22.6% (33/146)
% of IMT at Right carotid bulb	13.6% (20/146)
% of IMT at Left carotid	12.6% (14/111)
% of IMT at Right carotid	11.7% (13/111)
% of Total Left Plaques	25.34% (37/146)
% of Total Right Plaques	19.8% (29/146)

In our cohort, 52% of patients were over 50 years old; females were 28.2%; 13% showed multiple comorbidities, and 6,9% had a history of CV disease. 22% of the patients were in group C of the Center for Diseases Control (CDC) – Atlanta 1993; 33.3% of the patients received an antiretroviral treatment based on protease inhibitors (PIs).

The overall percentage of patients with carotid lesions (IMT and/or plaques) was 40.41% (**Figure 1**). In detail, the prevalence of IMT has been 22.6% at the left carotid bulb, 13.6% at the right carotid bulb, 12.6 % at left internal carotid, and 11.7% at the right internal carotid. We have observed a total of 25.34 % of plaques at the left carotid and a total of 19.86% of plaques at the right carotid. A higher prevalence of plaques has been identified in the bulb section on both sides. (**Table 1** and **Figure 1**).

Analyzing different factors related to IMT, it appeared a high incidence of carotid lesions in patients with high levels of Triglycerides (36%), high levels of Cholesterol (34%). About the low CD4 count, only 5.6% of enrolled patients had < 200 CD4 with IMT in 33% of them. In every case, patients historically

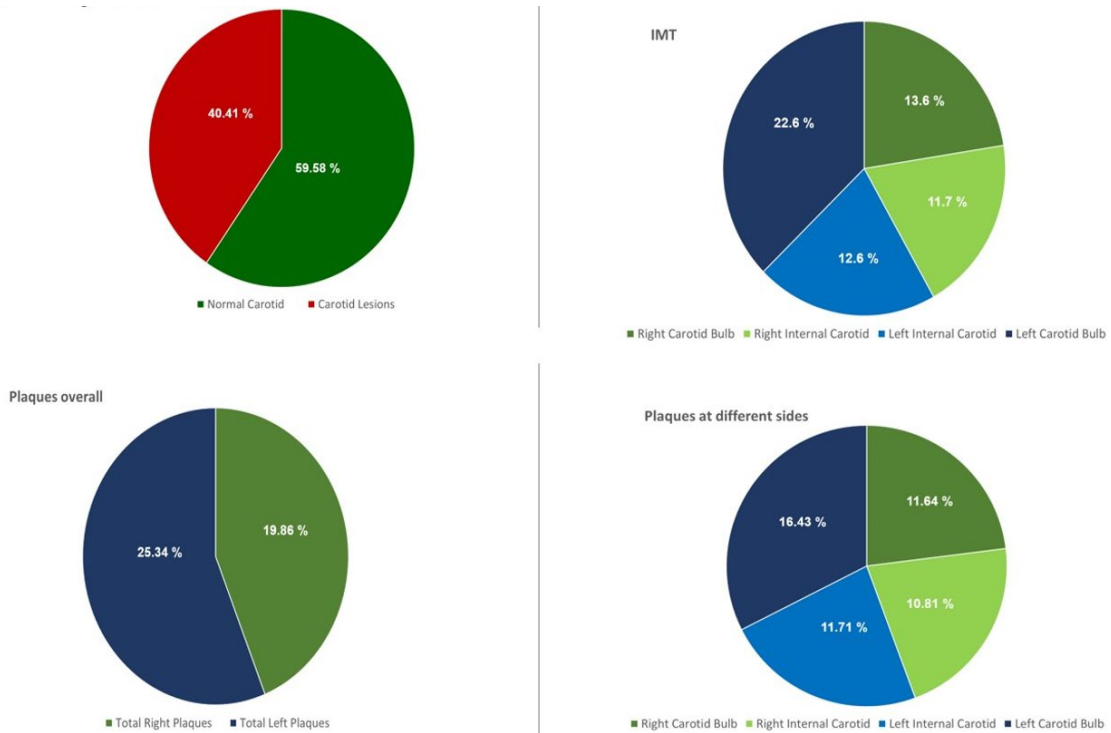


Figure 1. Percentage of Carotid lesions overall.

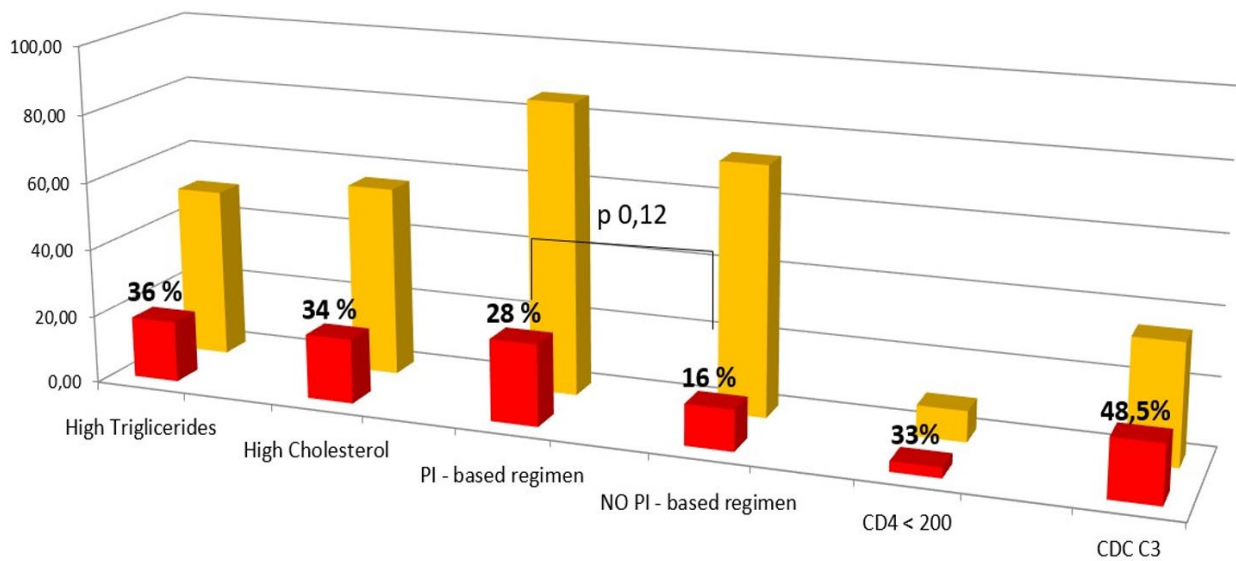


Figure 2. Percentage of Carotid lesions related to different factors.

classified as CDC C showed a high incidence of IMT (48.5%). About treatment, patients with a PI-based regimen, generally associated with high lipids and higher cardiovascular risk, showed IMT in 28% of cases, higher than patients treated with other antiretroviral regimens (16%). However, in this case, we have a trend of association between PI-based regimens and IMT but without statistical significance (p 0.12) (**Figure 2**).

As seen previously, HIV-infected individuals appear to be at higher risk of CVD than the general population. In HIV patients, chronic inflammatory processes are activated, and atherosclerosis is accelerated. Consequently, 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 seems to be the keystone of this phenomenon; proinflammatory cytokines,¹² pro-angiogenic hematopoietic and endothelial progenitor cells,¹³ circulating CD40 ligand, and Dickkopf-1¹⁴ could be involved.

In this setting, measurement of carotid IMT with color-Doppler ultrasonography plays a pivotal role in identifying and quantifying atherosclerotic lesions, even at a very early stage. A Register of echoic images deriving from all the National territory could represent

an important source of data able to produce a potentially continuous flux of information.

In our preliminary data IMT appears, as expected, associated above all with higher lipids levels, with CDC' C stage, and with the adoption of PI-based regimens.

Our Register shows a considerably high percentage of patients with IMT and strong evidence of plaques. However, it is noteworthy that the majority of the patients are over 50 years old; for the most part, they are males, with an advanced stage of HIV disease, treated with PIs-based antiretroviral regimens, and so considered at higher cardiovascular risk.^{12,15} These data highlight the fact that the clinicians tend to submit to this investigation their patients at higher risk of CV events; this, at present, hampers a reliable statistical comparison between groups, and represent the major

limitation of our study. On the other hand, this behavioral datum is crucial and should be modified with specific educational interventions. As we stated before, in fact, Archi-Prevalent Register is ongoing and includes periodical follow-up meetings of the involved physicians. For this reason, we feel that it could represent a valuable way to improve the awareness of the Italian specialists regarding this diagnostic tool and to ameliorate its utilization. Considering that this diagnostic tool is particularly useful in patients at intermediate risk, this will prompt to extend the investigation to all patients, to proactively prevent CVD, that, in association to aging, inflammation and dyslipidemia, will have a negative impact on good prognosis conquered by the advent of safer antiretroviral drugs.

S. Martini¹, S. Ferrara², C. Bellacosa³, B.M. Celesia⁴, F. Taccari⁵, G. Di Filippo⁶, A. Tartaglia², G. Gaeta¹, P. Maggi¹.

¹ Università della Campania, Luigi Vanvitelli.

² Università degli studi di Foggia.

³ Università degli Studi di Bari.

⁴ Università di Catania ARNAS Garibaldi.

⁵ Università Cattolica del Sacro Cuore.

⁶ Università Federico II di Napoli.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Paolo Maggi. E-mail: p_maggi@yahoo.com

References:

- Maggi P, Di Biagio A, Rusconi S, Cicalini S, D'Abbraccio M, d'Ettore G, Martinelli C, Nunnari G, Sighinolfi L, Spagnuolo V, Squillace N. Cardiovascular risk and dyslipidemia among persons living with HIV: a review. *BMC Infect Dis*. 2017 Aug 9;17(1):551. <https://doi.org/10.1186/s12879-017-2626-z> PMID:28793863 PMCID:PMC5550957
- Rao SG, Galaviz KI, Gay HC, Wei J, Armstrong WS, del Rio C, Narayan KMV, Ali MK. Factors Associated with Excess Myocardial Infarction Risk in HIV-infected Adults: a Systematic Review and Meta-Analysis. *J Acquir Immune Defic Syndr*. 2019 Feb 20. <https://doi.org/10.1097/QAI.0000000000001996> PMID:30865179
- Schmidt-Trucksass A, Grathwohl D, Schmid A, 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. <https://doi.org/10.1161/01.ATV.19.4.1091> PMID:10195940
- 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. <https://doi.org/10.1161/01.CIR.0000120708.59903.1B> PMID:14993130
- 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. <https://doi.org/10.1056/NEJMoa1012592> PMID:21774709 PMCID:PMC3153949
- Naqvi TZ, Mendoza F, Raffi F, 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. <https://doi.org/10.1016/j.echo.2010.05.005> PMID:20554155
- Chuang SY, Bai CH, Cheng HM, et al. Common carotid artery end-diastolic velocity is independently associated with future cardiovascular events. *Eur J Prev Cardiol*. 2016;23:116-124. <https://doi.org/10.1177/2047487315571888> PMID:25691545
- 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* Volume 101, Issue 1, 4 January 2000, Pages E12-16. <https://doi.org/10.1161/01.CIR.101.1.e12>
- 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. <https://doi.org/10.1097/00002030-200011100-00001> PMID:11101050
- 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. <https://doi.org/10.1097/00002030-200404300-00010> PMID:15096805
- Maggi P, Volpe A, Bellacosa C, Pastore G, Perilli F, Lillo A et al. The role of immune reconstitution in the onset of subclinical atherosclerotic lesions. *J Acquir Immune Defic Syndr*. 2009 Dec 1;52(4):524-5. <https://doi.org/10.1097/QAI.0b013e3181b985c6> PMID:19901619
- Maggi P, Bellacosa C, Leone A, Volpe A, Ricci ED, Ladisa N, Cicalini S, Grilli E, Viglietti R, Chirianni A, Bellazzi LI, Maserati R, Martinelli

- C, Corsi P, Celesia BM, Sozio F, Angarano G. Cardiovascular risk in advanced naïve HIV-infected patients starting antiretroviral therapy: Comparison of three different regimens - PREVALEAT II cohort. *Atherosclerosis*. 2017 Aug; 263:398-404.
<https://doi.org/10.1016/j.atherosclerosis.2017.05.004>
PMid:28522147
13. Vecchiet J, Iachininoto MG, Capodimonti S, Nuzzolo ER, Falasca K, Martini M, Mancino P, Bianchi M, Leone AM, Ucciferri C, Larocca LM, Teofili L. Effect of antiviral therapy on pro-angiogenic hematopoietic and endothelial progenitor cells in HIV-infected people. *Thromb Res*. 2013 Mar;131(3):238-43.
<https://doi.org/10.1016/j.thromres.2012.12.007>
PMid:23290306
14. Falasca K, Reale M, Di Nicola M, Ucciferri C, Zecca IA, Santilli F, Pontolillo M, Liani R, D'Angelo C, Costantini E, Vecchiet J. Circulating CD40 ligand, Dickkopf-1 and P-selectin in HIV-infected patients. *HIV Med*. 2019 Nov;20(10):681-690.
<https://doi.org/10.1111/hiv.12789>
PMid:31424619
15. Ryom L, Lundgren JD, El-Sadr W, Reiss P, Kirk O, Law M, Phillips A, Weber R, Fontas E, d' Arminio Monforte A, De Wit S, Dabis F, Hatleberg CI, Sabin C, Mocroft A. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. *Lancet HIV*. 2018 Jun;5(6):e291-e300.
[https://doi.org/10.1016/S2352-3018\(18\)30043-2](https://doi.org/10.1016/S2352-3018(18)30043-2)