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High prevalence at computed coronary tomography of non-calcified plaques in asymptomatic HIV patients treated with HAART: a meta-analysis.

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ABSTRACT.

Introduction. Asymptomatic patients with human immunodeficiency virus (HIV) infection are at increased risk of vascular disease. Whether asymptomatic HIV patients have increased prevalence or structural differences in coronary artery plaques is not clear.

Methods. Pubmed, Cochrane and Google Scholar were searched for articles evaluating asymptomatic HIV patients evaluated with coronary computed tomography. The prevalence of coronary stenosis (defined as >30% and > 50%), of calcified coronary plaques (CCP) viewed as more 'stable' plaques, and of non-calcified coronary plaques (NCP) viewed as more 'vulnerable' plaques were the end points of interest.

Results. 9 studies with 1229 HIV patients and 1029 controls were included. No significant differences were detected about baseline cardiovascular risk profile. The prevalence of significant coronary stenosis >30% or >50% did not differ between HIV+ and HIV- patients (42% [37-44] and 46% [35-52] with an Odds Ratio [OR] of 1.38 [0.86-2.20] for >30% stenosis) and (15% [9-21] and 14% [7-22] with an OR of 1.11 [0.81-1.52]), respectively. The prevalence of calcified coronary plaques (CCP) (31% [24-32] and 21% [14-30] with an OR of 1.17 [0.63-2.16]) also did not differ among HIV+ and HIV- patients. On the contrary rates of NCP were >3-fold higher in HIV-positive patients [58% (48-60) and 17% (14-27) with an OR of 3.26 (1-30-8.18)], with an inverse relationship with CD4 cell count at meta-regression (Beta -0.20 [-0.35-0.18], p 0.04).

Conclusion. Asymptomatic HIV patients present a similar burden of coronary stenosis and calcified coronary artery plaques but significantly higher rates of non-calcific coronary plaques at computed tomography. The association between HIV infection,

reduced CD4 cell counts and higher prevalence on non-calcific coronary artery plaques may shed light into the pathogenesis in HIV-associated coronary artery disease, **stressing the importance of primary prevention in this population.**

INTRODUCTION.

Life expectancy of human immunodeficiency virus (HIV) patients dramatically increased thanks to highly active antiretroviral therapy (HAART)[1]. Physicians managing these patients are shifting towards a more global assessment of clinical conditions, with a particular attention of development of both clinical and subclinical cardiovascular disease[2,3].

HIV patients, actually, are exposed for many years to the continuous interaction between traditional risk factors, coronary HIV infection, immune-mediated response and the still debated effect of HAART[3,4].

In acute coronary syndrome (ACS) settings, this peculiar pathological pattern has led to a higher risk of coronary adverse events; several challenges have been identified in those patients, such as drug to drug interaction with new antiaggregants or statins and compliance to medications[4].

Consequently, primary care is becoming crucial, both to prevent subclinical impairment of systolic and diastolic dysfunction[5] and to reduce number of cardiovascular adverse events[3]. Even subclinical atherosclerosis has been related with risk for cardiovascular events in the general population[7,8], and particular for those presenting with non-calcified plaques due to a higher risk of rupture[9]. An increased use of coronary computed tomography (CCT) has been reported, both to measure coronary artery calcium (CAC) and to evaluate the prevalence and features of coronary plaques, in order to accurately address pharmacological and interventional strategies[10-12].

Some studies have found a higher prevalence of subclinical atherosclerosis in HIV-positive patients[13-15] but the results are not consistent. Consequently we performed a systematic review to understand the prevalence and the peculiarities of coronary plaques in asymptomatic HIV-positive patients.

METHODS.

The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[18] was followed during elaboration of the present analysis.

Search strategy and study selection.

Pertinent articles were searched in Medline, Cochrane Library, Biomed Central and Google Scholar in keeping with established methods[16] with Mesh strategy: ((coronary computed tomography) OR (CCT)) AND (hiv OR aids OR (human AND immunodeficiency AND virus)).

Two independent reviewers (F.DA, E.C.) first screened retrieved citations at the title and/or abstract level, with divergences resolved after consensus. If potentially pertinent, they were then appraised as complete reports according to the following explicit selection criteria. Studies were included if (i) investigating with CCT asymptomatic HIV and non HIV patients (ii) with more than 90% of patients treated with HAART. Exclusion criteria was (i) absence of non HIV controls.

Data extraction

Two unblinded independent reviewers (G.B.-Z, F.DA, and E.C.) abstracted the following data on pre-specified forms: authors, journal, year of publication, location of the study group, baseline features, type and timing of antiretroviral therapy, and protocols of CCT. The prevalence of coronary stenosis (more than 30% and more than 50%), of

calcified coronary (CCP), of non-calcified coronary plaques (NCP) and of Coronary Artery Calcification Score (CAC) more than 0 were the end points of interest.

Internal validity and quality appraisal

Unblinded independent reviewers (G.B.-Z, F.DA, and E.C.) evaluated quality of included studies on pre-specified forms. Modifying the MOOSE items to take into account the specific features of included studies,[15-18] we separately abstracted and appraised study design, setting, data source, as well as risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias). For the quality assessment of the selected studies we used the Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis[19].

Data analysis and synthesis

Continuous variables are reported as mean (standard deviation) or median (range). Categorical variables are expressed as n/N (%). Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). **Meta-regression analysis for the impact of traditional risk factors and HIV features on the primary end point was performed with random effect with Comprehensive Meta-Analysis after computation of the event rate.** All confidence intervals were of 95%). Standard hypothesis testing was set at the two-tailed 0.05 level.

RESULTS.

217 studies were first screened at abstract level, and after evaluation 9 studies with 1229 HIV patients and 1029 controls were included[20-28]. (see Figure 1)**. Eight studies out of nine were prospective: eight were performed in the USA and one in Europe.**

Baseline features of the included patients are reported in Table 1. HIV patients were more frequently of male gender, with higher rates of diabetes mellitus and of hypertension in the included studies, but without significant differences.

Concerning immunovirological variables these patients had been on HAART for 8.3 (8-9) years, with a CD4+ T lymphocyte cell count of 529/mm^3 (525-571) and a CD4+ nadir of 201 cells/mm3 (181-257). 52% (51-53) have been exposed to Protease Inhibitors (PI), 94% (81-96) to nonnucleoside reverse-transcriptase inhibitors (NNRT) and 46% (43-47) to nucleoside reverse-transcriptase inhibitors (NRTIs).

In all studies, included patients were asymptomatic and only in the study of D'Abramo et al[20], they were included after a positive ergometric test. Protocols and definitions of CCT were consistent among all studies (Table A, Appendix web only).

Prevalence of significant coronary stenosis (>30%) did not differ between HIV+ and HIV- patients [42% (37-44) and 46% (35-52) with an Odds Ratio (OR) of 1.38 (0.86-2.20)]. Similarly prevalence of coronary stenosis above 50% (15% 9-21 and 14% 7-22 with an OR of 1.11 [0.81-1.52]), of calcific coronary plaques (31% 24-32 and 21% 14-30 with an OR of

1.17 [0.63-2.16] and of CAC above zero (43% [39-48] and 46% [26-56] with an OR of 0.88 [0.43-1,79] did not differ among HIV+ and HIV- patients (see Figures 2 and 3). On the contrary rates of NCP were significantly higher in HIV-positive patients [58% (48-60) and 17% (14-27) with an OR of 3.26 (1-30-8.18)].

At meta-regression analysis for coronary stenosis above 30% active smoking habit increased the risk (Beta 0.02 0.01-0.03, p<0.001) in HIV+, Immunologic status and HAART therapy showed a neutral effect. Moreover, CD4 cell counts was inversely related to the risk of non-calcific plaque (the higher CD4 cell counts the lower the prevalence, Beta -0.20 -0.35-0.18 p 0.04). (see Tables 3 and 4, Figure 5).

At funnel plot analysis, low selection bias was noted (Figure A).

DISCUSSION

This is the first paper reporting a pooled analysis of data about CCT scan in asymptomatic HIV patients. The main findings are: 1) HIV-infected patients present higher rates of NCP compared to similar cohorts of HIV-negative subjects 2) NCP prevalence and degree were positively associated with worse immunovirological parameters, suggesting that disease stage contributes to cardiovascular instability.

NCP represent an early stage of atherosclerosis, resulting to be more prone to rupture and thrombus formation compared than calcified ones, potentially leading to ACS. These observations were already reported in series of patients evaluated by CCT as well in ACS patients undergoing angiography followed by grayscale and radiofrequency intravascular ultrasonography (IVUS)[30,31] and were also consistent with pathological studies reporting that plaque more prone to rupture show a thin cap fibro atheroma and necrotic core with an overlying thin fibrous cap[32,33].

Previous CCT studies reported a higher prevalence of NCP in intermediate-risk asymptomatic patients, especially in those with significantly higher level of C-reactive protein, cholesterol (total and low-density lipoprotein) as well as a trend for a higher prevalence of diabetes mellitus[34]. Our analysis includes a young population (median age of 47 years) with a low prevalence of diabetes and a moderate prevalence of hyperlipidemia (11% and 27% respectively). Despite these characteristics, the prevalence of NCP was 3-fold higher compared with similar Framingham-based score non-HIV population (58% vs. 17%) and comparable to the one reported in recent study[35] by Park et al (NCP rate = 56%).

We reported a CAC score value higher than zero in less than half of subjects. Even if CAC score of zero was associated with very low risk of cardiac events, NCP plaque cannot be detected on non-contrast cardiac scans, used to measure CAC levels. **Previous studies utilizing CCT to estimate the extent of coronary artery disease in HIV patients assessed only CAC by scoring without explore directly the lumen caliber or plaques burden[36,37]. Although the CAC scoring is a well defined marker for atherosclerotic lesions and cardiac event risk in non-HIV population, it may not provide a reliable valuation of early atherosclerosis in young HIV patients in whom calcifications are absent: our finding demonstrate that a significant proportion of patients with coronary atherosclerosis may be missed using only calcium score criterion. Thus we stressed the additional value of adopting CCT over CAC scoring alone for the assessment of coronary tree in young HIV-positive patients; since CCP probably reflects advanced stable atherosclerosis while identifying NCP seem crucial in this group of patients.**

Additionally we reported a significant correlation between low CD4 cell counts and risk of NCP. The association between CD4 cell count and cardiovascular disease has already

been previously reported and it may be related to immune-dysfunction (immune activation and immune senescence) or to the prevalence of other infection potentially affecting endothelial cells (cytomegalovirus, HHV-8, and others)[38-40]. **Similarly, previous studies reported a low CD4+ count to be associated with a high prevalence of carotid artery plaques[41]: our findings strengthen these observations supporting the hypothesis of a systemic inflammatory dysregulation in HIV-positive patients.**

The only other variable that showed a positive interaction on the risk of coronary stenosis was active smoking status, accordingly to the higher risk of smoker-related comorbidities previously reported in HIV-infected than uninfected patient. Notably, these subgroup are actually an attractive target for a "multi-disease" screening since that recent studies are currently investigating the role of CT for lung cancer prevention in HIV-positive smokers even if with sparse results[42-44].

Clinical implications of present study may be of interest for physicians, cardiologists, infective disease specialists and general practitioners. **Plaque characteristics observed using CCT underline the vulnerable atherosclerotic pattern of HIV-positive subjects, suggesting the need of aggressive primary prevention programs in this specific population. These data highlight the importance of addressing modifiable cardiovascular risk factors to optimize long-term health in the setting of HIV infection comorbidities. Although not confirmed in randomized controlled trial, statins use may be crucial, for their effect on plaques stability. A parallel focus on smoking cessation is important, considering the interaction on the risk of coronary stenosis demonstrated from several studies. Furthermore several data report the underuse of aspirin in primary prevention[45] in high-risk HIV-positive patients despite heightened awareness regarding elevated cardiovascular risk, although the absence of randomized controlled trials may explain such conduct.**

Finally even if a CCT based approach for primary prevention has never been suggested to improve prognosis, these results may advise HIV physicians to evaluate and to focus on plaque characteristics in order to select appropriate primary prevention strategies.

LIMITATIONS

Our study shares several limitations. Unfortunately it was not possible to report about long-term follow-up or hard clinical events in this population. Moreover we do not have detailed data about HAART regimen and almost all patients are male making it impossible to appraise specific differences. **Third, we reported incidence of coronary stenosis more than 30% considering our aim to focus on plaques' features independentely from the percentage of stenosis.** Finally, the potential benefit by CCT needs to be weighted against its safety related to radiation exposure in asymptomatic young patients. Moreover as demonstrated in Table B, most of the included studies were of high quality, with an accurate definition of control population.

CONCLUSION

In this comprehensive meta-analysis, NCP was more prevalent and extensive in asymptomatic HIV-infected patients, especially in presence of lower CD4 cell counts. **This finding provides new details on the differences in atherosclerotic process in HIV-infected patients, stressing the importance of primary prevention in this population. On the other hand the use of CCT may be considered in the future, if supported by larger prospective studies, as a complementary tool to evaluate high risk patients, both for traditional cardiovascular risk factors as well for severity of HIV infection.**

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