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Atherogenesis: Diseases that May Affect the Natural History "Schistosomiasis and HIV Infection"

Carlos Teixeira Brandt ,
Emanuelle Tenório A. M. Godoi, André Valença,
Guilherme Veras Mascena and
Jocelene Tenório A. M. Godoi

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1. Introduction

Atherosclerosis is an endothelial dysfunction induced by elevated and modified low-density lipoproteins (LDL), free radicals, infectious microorganisms, shear stress, hypertension, toxins after smoking or combinations of these and other factors[1], which is characterized by decreased nitric oxide synthesis, local oxidation of circulating lipoproteins and their entry into the vessel wall[2]. Intracellularreactive oxygen species similarly induced by the multiple atherosclerosis risk factors lead to enhanced oxidative stress in vascular cells and further activate intracellular signaling molecules involved in gene expression[3].

Up regulation of celladhesion molecules facilitates adherence of leukocytes to the dysfunctional endothelium and their subsequent transmigration into the vessel wall.The evolving inflammatory reaction is instrumental in the initiation of atherosclerotic plaques and their destabilization. There are evidence[4] supporting a pathophysiological role of T cells, B cells and macrophages in the development of atherosclerosis in general[5].

2. Atherogenesis and cardiovascular diseases

Decades ago, the endothelium was considered just a barrier non thrombogenic, vascular control which was attributed primarily to the sympathetic nervous system and circulating vasoactive hormones. The discovery that the endothelium synthesizes important vasodila-

tors such as nitric oxide and prostacyclin, and vasoconstrictors such as endothelin, aroused great interestin endothelial function and role of vascular control, both in physiological processes and in pathological conditions. The model 'response to injury' of the endothelium explains more precisely this complex pathophysiological mechanism. In this model the endothelium is injured by hemodynamic stimulus, such as hypertension, or bychemical attack, such as in smoking, begins to operate in a manner dysfunctional. This endothelial dysfunction leads to compensatory responses that alter the normal homeostatic properties of the endothelium to a reduction in nitric oxide synthesis and an increase inpermeability of the endothelium which binds to LDL cholesterol in the vessel wall[6]. Adhesion molecules begin to be expressed on the surface of the endothelium will lead to attraction of monocytes and lymphocytes to the arterial wall[7].

LDL modified by oxidation is a major cause of injury to the endothelium. Many authors believe that LDL oxidation does not take place in the circulation, and therefore it must occur in the subendothelial space of the arterial wall. After being trapped in the artery wall, it is internalized by macrophages via the scavenger receptor surfaces of these cells which leads to the formation of foam cells. Inflammation mediators such as tumor necrosis factor α, interleukin-1 and macrophage colony-stimulating factor further increase the binding of LDL to the endothelium and smooth muscle and increase the transcription of the LDL receptor gene. Experimental studies in mice show that oxidized LDL (oxLDL) promotes atherosclerosis, however, clinical trials of antioxidants were not effective in reducing cardiovascular events[8],[9].Increased levels of oxLDL are presentin human gingival crevicular fluid compared to plasma of healthy individuals, indicating that oxLDL could be generated in inflamed extra-arterial tissues, transferred to the circulation, rapidly taken up into the arterial wall, and contribute to the perpetuation ofatherosclerosis[10].

Early 'fatty-streak' lesions consist of T cells and monocyte-derived macrophage-like foam cells loaded with lipids and after successive accumulation of apoptotic cells, debris and cholesterol crystals forms a necrotic core. Initial lesions most commonly developin places where laminar blood flow is altered, as in the bifurcations of the vessels, which interferes with the shear stress and adequate production of nitric oxide[11]. In these places, substances are produced by the endothelium that promote adhesion, migration and accumulation of monocytes and T cells. The flow changes, leading to a reduced shear stress, modifies the expression of genes such as intercellular adhesion molecule, platelet derived growth factor B chain[12],[13].

The mature atherosclerotic plaque shows in addition to cells, two distinct structural components: a lipid core, very dense, and fibrous cap that is its fibrotic component. The higher the fibrotic component less prone to disruption (less unstable) is the atherosclerotic plaque. The lipid core is highly thrombogenic. When it makes contact with the blood stream by rupture of the fibrous cap or endothelial erosion, occurring phenomena of platelet adhesion and aggregation, thrombin generation and fibrin, with underlying thrombus formation, which represents the common starting point of acute coronary syndromes[14].

Apart from traditional risk factors, numerous evidences have shown an association between atherosclerosis and genetic variants which should allow in the future, a new understanding of the molecular mechanisms of cardiovascular disease[15].

3. Schistosomiasis mansoni infection may affect the natural history of atherogenesis

Infections of Schistosoma mansoni, the adult worms significantly reduced atherogenesis in apolipoprotein E gene knockout (apoE(-/-)) mice. These effects occurred in tandem with a lowering of serum total cholesterol levels in both apoE(-/-) and random-bred laboratory mice and a beneficial increase in the proportion of HDL to LDL cholesterol. The serum cholesterol-lowering effect is mediated by factors released from S. mansoni eggs, while the presence of adult worms seemed to have little or no effect. High levels of lipids, particularly triacylglycerols and cholesterol esters, present in the uninfected livers of both random-bred and apoE(-/-)mice fed a high-fat diet were not present in livers of the schistosome-infected mice[16].ApoE-deficient mice chronically exposed to the eggs of Schistosomamansoni over a period of 16 weeks showed thattotal serum cholesterol and low-density lipoprotein (LDL) were reduced in egg-exposed ApoE-deficient mice fed a diet high in cholesterol compared to unexposed controls. However, exposure to eggs has no effect on atherosclerotic lesion size or progression in these animals. Macrophages isolated from egg-exposed mice had an enhanced ability to take up LDL but not acetylated LDL (acLDL). This suggests that schistosome eggs alone may alter serum lipid profiles through enhancing LDL uptake by macrophages, but these changes do not ultimately affect atherosclerotic lesion development[17].

Previous studies have shown that people infected with schistosomiasis have lower levels of serum cholesterol than uninfected controls. In human beings the first manifestations of cardiovascular disease from atherogenesis arise at an advanced stage of atherosclerosis. However, patients with hepatosplenic schistosomiasis mansoni have abnormal lipid peroxidation, with elevated erythrocyte-conjugated dienes implying dysfunctional cell membranes, and also imply that this may be attenuated by the redox capacity of antioxidant agents, which prevent accumulation of plasma malondialdehyde (MDA)[18]. These lipid metabolism changes affect the natural history of atherogenesis including the risk factors.

The alterations in the arterial wall occur during the subclinical period of atherogenesis, characterized by progressive thickening of the endothelium. This endocrine organ is responsible for physiological processes that are vital to vascular homeostasis[19].

When risk factors exist, endothelial thickening can be detected already in childhood, and can be predictive of cardiovascular events in adults[20]-[22]. Since the first anatomopathological description, several articles have been published associating ultrasound measurements (intima-media thickening – the identifiable portion of the endothelium) with cardiovascular diseases[23].

The accuracy, reproducibility and rapidity of Doppler ultrasound have made this method a powerful tool for early diagnosis, as well as in the monitoring of atheroscletrotic lesions and even when evaluating results in population studies[24].

There are already several well-established risk factors for atherosclerosis, such as hypertension, dyslipidemia, smoking and diabetes[25]. However, there are other factors which are still controversial as to the predictive value of findings. Among those factors, bacterial (*C. pneumoniae, H. pylori*), as well as viral (herpes simplex, Epstein-Barr) and parasitic (*T.cruzi, S.mansoni*) infections[26].

Schistosomiasis, an endemic disease in several regions in the world and with high prevalence in Pernambuco, Brazil, has been the target of research studies on disease prevention, clinical and surgical treatments to alleviate the effects of hypertension on the portal system, hypersplenism and child hypoevolutism[27],[28].

Important alterations have been demonstrated in the lipid profile of those who present with advanced disease[29]. Speculations are made as to whether those findings could influence the behavior of the intima-media complex. On the other hand, whether the lipid alterations in human hepatosplenic schistosomiasis mansoni (HSM) patients interfere with atherogenesis has been investigated[30].

The hepatic lesions in patients with hepatsplenic schistosomiasis mansoni produce changes in the lipid profile. There is a tendency toward normalization after surgical treatment of portal hypertension[31]. Since those changes are related to the extent of the lesion to endothelial cells, Doppler ultrasound is used to assess whether those HSM influence intima-media thickness in humans[32].

The relation of lipoproteins to atherosclerosis is known[30]. However, several years passed before an insight was achieved into the association between the biochemical findings and the structural lesions found in the wall, especially in the vascular endothelium. The participation of cells such as lymphocytes, macrophages and monocytes is decisive in the inflammatory component of that disease.

Hypertension, dyslipidemia, diabetes and smoking constitute risk factors already largely associated with atherogenesis. The interfaces of atherosclerosis with infections are very complex. This is due to the mechanisms used by the infectious agents and the different forms of response from the host organism. Infection and inflammation induce an acute phase response, which, in turn, leads to alterations in lipids and proteins. These changes initially protect the host from the deleterious effects of bacteria, viruses and parasites; however, if extended, they could contribute to atherogenesis[33].

Changes take place in the metabolism of total and HDL cholesterol and in their reverse transport over the course of an infection. The responses are not fully understood, but lipopolysaccharides (LPS) and cytokines are known to reduce total cholesterol serum levels and produce various effects in rodents[34].

The incidence of coronary artery disease and stroke is higher in patients with chronic infections. Some lesions are supposedly produced by the infectious agent itself, as in the case of

C. pneumoniae and *Cytomegalovirus*, while other lesions seem to be induced by humoral mechanisms, as in the case of H. pylori and chronic urinary, respiratory and oral infections[35].

Since atherosclerosis itself is an inflammatory disease, and given that infections induce a proatherogenic change in lipoproteins, a cycle is started that tends to aggravate the atherosclerotic lesions[36].In certain instances of bacterial infections, beneficial effects can be found from the alterations in lipoprotein metabolism. The conjugation of LPS to lipoproteins protects animals from hypotension, LPS-induced fever and death.

Regarding parasite infestations, complex mechanisms are triggered, since both the direct action of the parasite and immune reactions induced by its presence have been demonstrated[37].

Atherosclerosis-resistant rats developed early atherosclerotic plaques when infested with *T.cruzi*, while rats that were susceptible to atherosclerosis sustained fewer atherosclerotic lesions when infested with *S. mansoni*. On the basis of those findings, it is postulated that infection by *S. mansoni* may produce a protective effect against atherosclerosis[38].

The IMT has been study in infectious processes[39]. The attempt to identify early markers of atherosclerosis has been the object of several studies. The ankle-arm index, which has been used since the 1970's to assess blood flow to the lower limbs, has been introduced in the armamentarium of cardiologists and atherogenesis experts as a marker of diffuse atherosclerosis[40].

Brachial artery distensibility, coronary flow reserve, pulse wave analysis, pulse wave velocity and plethysmography have also been used to detect endothelial dysfunction and also considered to be risk markers for cardiovascular disease[16].

Some authors have proposed the validation criteria of surrogate markers for clinical analysis. They established three conditions for validity: the first is that the marker should be more sensitive and more readily available than clinical conclusions, in addition to being easy to assess, preferably through noninvasive methods. Second, the causative relationship between the marker and the clinical conclusions should be established on epidemiologic and pathophysiological bases, as well as clinical studies. It is a prerequisite that patients with and without vascular disease exhibit differences in the marker readings. Third, in intervention studies, expected clinical benefits (benefit assessment) should be anticipated from changes observed in the markers. This last argument implies that the development of markers is not only a matter of time/cost. Moreover, other diagnostic methods for measuring IMT such as the transesophageal echocardiogram, intravascular ultrasound and magnetic resonance imaging, in addition to being more expensive and more invasive, are not appropriate for screening[21],[41].

The Doppler ultrasound scan with an automatic calibrator becomes minimally sonographer-dependent. Normal limits for IMT measurements have been established as between 0.4 mm and 1.0 mm, whereas those above 1.5 mm are interpreted as a plaque. The results are immediately ready for printout or to be saved on an HD or CD-ROM for occasional and future

comparisons. Questions that might be raised concerning loss of sensitivity with this type of equipment have already been addressed in a comparison with conventional machines[42].

The carotid artery ensures easy access to the examiner; for its anatomy, as it is a superficial artery and follows a more or less straight path along the cervical segment, in addition to being a vessel with abundant elastic fibers that respond promptly to hemodynamic "stress"[23].

A study with populations at difference ages showed that IMT increases at a rate of [IMTmm = 0.009 x age+0.35], i.e., it is a biological phenomenon that can be quantified[30].

The means for IMT values of common and internal carotids are higher among patients with some risk factor (hypertension, age and smoking). This pattern occurs in normal subjects and patients with hepatosplenic schistosomiasis mansoni clinical and surgical treated, but this phenomenon is not observed in these patients without any treatment[43]. These findings lend support to the hypothesis that hepatosplenic schistosomiasis mansoni may be a protective factor against atherogenesis[30].

4. HIV infection may affect the natural history of atherogenesis

Individuals infected with human immunodeficiency virus (HIV) have a different condition of life of the population free of infection with regard to morbidity and mortality from premature atherosclerosis and cardiovascular, and its related complications[44]-[47].

Atherosclerosis is a systemic disorder characterized by the formation of cholesterol plaques, especially at the level of the intima of the arterial wall. All arteries can be affected, but the clinical consequences are more important at the level of coronary and carotid arteries of the lower limbs (LL).

Arterial disease is chronic, along with coronary artery disease and ischemic stroke, one of three clinical manifestations of the same pathophysiological process: atherothrombosis. The classic risk factors of atherosclerosis are: smoking, hypertension (HTN), diabetes mellitus (DM), hypercholesterolemia, and obesidade[48]. Atherosclerosisisamajor cause ofmortality worldwidemobility, andlow life expectancyis mainly due to heart attack and stroke(CVA)[49]-[51].

The morbidity and mortality among HIV-infected individuals with advanced disease was very high until the advent of potent antiretroviral therapy (HAART), which produced an improvement in quality and increased expectation [52]-[55].

This therapy, however has been associated with a variety of adverse effects, which include metabolic changes such as changes lypodistrophy, insulin resistance, lactic acidosis and dislipidemia[46],[56]. All these changes are pro-atherogenic and its consequences are often fatal. The development of cardiovascular disease in HIV-infected individuals is related to endothelial dysfunction. This dysfunction and accelerated atherosclerosis is a

consequence of HIV itself that activates the endothelial directly or indirectly through production of citocinas[57].

There is evidence that both pathophysiological HIV to antiretroviral therapy may affect the profile lipídico[58],[59], insulina resistance[60],[61] and the response of vasodilatação[62]. The increased mortality in individuals with HIV due to cardiovascular events in young patients, often without classic risk factors for atherosclerosis, is cause for concern and the subject of new studies[44],[46].

Antiretroviral therapy is associated with pro-atherogenic metabolic abnormalities such as metabolic syndrome, type II diabetes, abnormal distribution of body fat, these conditions also associated with arterial disease coronariana[63],[64]. Some studies suggest that class of drugs known as protease inhibitors (PI) can be associated with premature atherosclerosis and cardiovascular events, vasculares[47]. It is not clear, but what is the real contribution of ART in HIV and increased risk of cardiovascular disease.

The measurement of intima-media complex (IMT) by ultrasonography (USG) is a noninvasive marker of early atherosclerosis and may reflect the increased overall cardiovascular risk and is associated with increased risk of acute myocardial infarction (AMI) and / or AVC[65]-[67].

The IMT can be used as a predictor of atherosclerotic disease in coronary arteries independently of classical risk factors: age, sex, smoking, hypertension, dyslipidemia, diabetes and family history of coronary artery disease (CAD). IMTcan be consideredas a markerfor the evaluation ofatherosclerosissubclínica[68]-[70].

The study using IMT has been performed in patients with acquired immunodeficiency syndrome (AIDS) in the investigation of risk factors for atherosclerosis as an early marker, but there are few studies prospectivos[71],[72].

In AIDS patients the automatic measurement of MIC performed in right and left common carotid, with software determining produces the following measures: average, maximum and minimum (Figure 1). In this same place three manual measurements can be performed. Thus, it is possible to calculate the arithmetic mean of the measure in manual right and left common carotid and the maximum and minimum extent (Figure 2). In the right and left internal carotid it can be performed as manual. The gold standard can be represented by the mean of automatic measurements from the right common carotid (RCA) and left common carotid (LCA)[73],[74]. We have measured population of 50 years AIDS patients, the MIC was considered thickened if > 0.8 mm[75] was considered the presence of a thickening demonstrated plate when WCC > 1.5mm[73],[76].

The ankle-brachial index (ABI) is a simple, noninvasive, high predictive value for peripheral artery disease and has significant association with risk of cardiovascular mortality. It is a good method to be safe, reproducible, low cost, outpatient use and validated in the general population. Early diagnosis of atherosclerosis identifies people at high risk for cardiovascular events and thus provides effective treatment and control of factors risco[55].
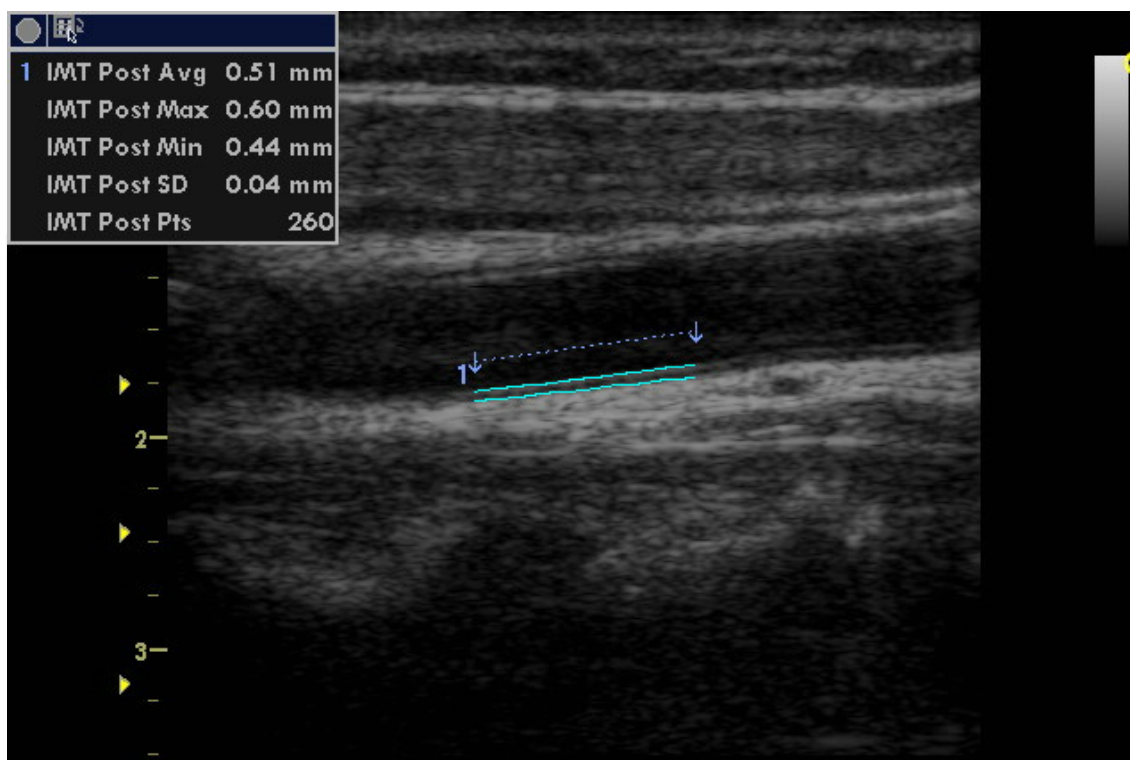
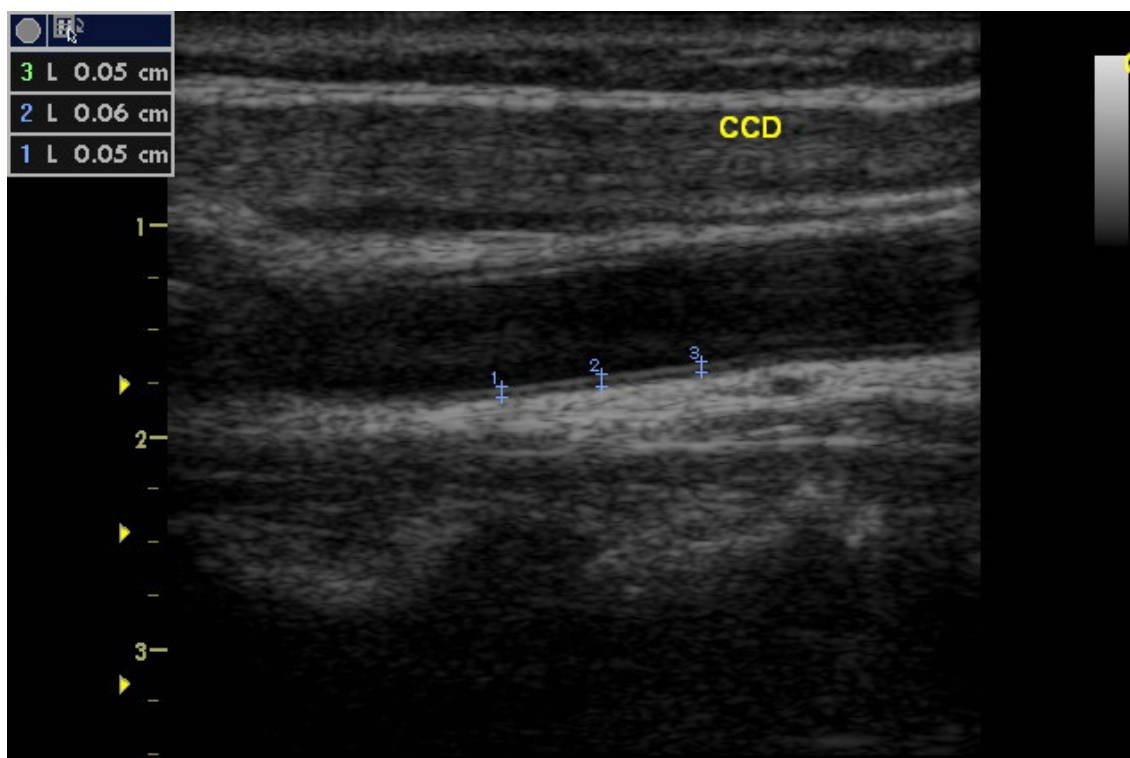**Figure 1.** Medida automática do CMI em CCD

Figure 2. Medida manual do CMI em CCD

The reduction of the ABI values below 0.9 is associated with a significantly increased cardio-vascular risk, particularly by acute myocardial infarction and ischemic stroke, independent of other factors[77],[78]. The increase in ABI (> 1.3) is due more to changes in arterial compliance than the stenosis, which would be responsible for a decrease in ABI. The high prevalence of high ABI in patients with HIV may be mediated by the involvement of vascular elasticity as well as the formation of atheromatous plaques. A meta-analysis of six retrospective studies the ABI has been studied in patients with HIV. The populations were selected with varying criteria and there was no consensus about the risk factors responsible for abnormal ABI. The increased prevalence of ABI was higher than in the general population. In the population with HIV/AIDS remains whether the high prevalence of altered ABI is associated with increased incidence of cardiovascular events.

We selected 70 cases with HIV in use antirratrovirais (ARV) for at least five years of service reference in the State of Pernambuco and 70 controls without HIV, matched by sex and age, which were assessed by automatic measurement of carotid IMT in and ABI. It was taken into account the classical risk factors of atherosclerosis, anthropometric measurements and treatment with protease inhibitors (PI). We performed the analysis of homogeneity of groups. The groups were homogeneous at the 95% confidence.

The ABI was raised in a single patient in the case group (0.7%) and no change in the control group ABI. The WCC was not thickened in any individual. There was no statistically significant difference between case and control groups with respect to the ABI and the WCC, even when considering the type of treatment. There was no significant difference between the groups regarding presence of atheromatous plaques in the common carotid.

Maggi et al. evaluating patients with HIV and advocate the hypothesis that CMI is thickened more in the HIV group, which use the IP protocol is the cause of the thickening and that the lesions found in these patients are similar to arteritis and substantially different from atherosclerotic plaques[66],[69],[71],[72]. The present study does not confirm this hypothesis of thickening CMI in patients with HIV. In 70 patients there was no thickening in the common carotid, while also presenting the same classic risk factors for atherosclerosis, including having more hypercholesterolemia and hypertriglyceridemia than the control group. One possible explanation for the lack of thickening of the WCC in this population is the fact that the patients are young (mean 40.5 years), having long-term treatment (mean 8.16 years), have fewer risk factors than other atherosclerosis studies and found to be clinically stable (84% had an undetectable current CV with current median CD4 670.57) with less aggression endothelium.

It can be concluded that HIV-infected individuals do not run a higher risk of atherosclerosis than the control population, taking into consideration the classical risk factors of atherosclerosis and the specific characteristics of HIV-infected patients.

The result of this study is essential because as the population was very young, phase detection of atherosclerotic disease earlier period can be after cutting realized. The follow-up of a cohort for a new sectional assessment later is very important for early detection of atherosclerosis in HIV patients on antiretroviral therapy.

Author details

Carlos Teixeira Brandt, Emanuelle Tenório A. M. Godoi, André Valença,
Guilherme Veras Mascena and Jocelene Tenório A. M. Godoi

Federal University of Pernambuco, Pernambuco, Recife, Brazil

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