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# Evaluation of aortic changes in elderly people autopsied with acquired immunodeficiency syndrome

## Aortic changes in elderly people with AIDS

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### Abstract

**Background:** To verify the distribution of the degree of fat deposits and percentage of collagen and elastic fibers in the intimal and medial layers of the aorta of elderly patients autopsied, with and without Acquired Immunodeficiency Syndrome (AIDS).

**Methods:** Twenty-six fragments of the aorta from elderly patients autopsied in the period from 1982 to 2014, were collected and, divided into two groups, being 13 with AIDS and 13 without AIDS. The intensity of the atherosclerosis was macroscopically evaluated in a semi-quantitative way. To quantify the elastic and collagen fibers, it was used the Leica Qwin Plus® software.

**Results:** In the comparison of the macroscopic intensity of atherosclerosis, the AIDS group ( $t = 0.6969$ ,  $p = 0.4992$ ). Regarding elastic fibers, there was a significant increase in the AIDS group ( $U = 115,800$ ;  $p < 0.0001$ ). Comparing the groups, there was a significant increase of the collagen fibers in the aortic layers in the AIDS group ( $U = 114,100$ ;  $p < 0.0001$ ).

**Conclusion:** The infection by the HIV influence in the amount of fibers in the extracellular matrix and the intensity of lipid deposit, demonstrating that it may be a risk factor to be considered for the development of atherosclerosis.

**Keywords:** Atherosclerosis, Acquired immunodeficiency syndrome, Elderly people, Aorta

### Background

According to the Ministry of Health, in Brazil there is more than 39 million people aged 50 years or more (Ministério da Saúde [homepage on the Internet] 2012). Considering the confirmation of the Human Immunodeficiency Virus (HIV), individuals in this age range are regarded elderly people (Center For Disease Control (CDC) [homepage on the Internet] 2002).

Described for the first time in 1981, Acquired Immunodeficiency Syndrome (AIDS), disease resulting from HIV infection, is a great problem of public health around the world, causing immunosuppression and consequently opportunistic infections and neoplasia (Center For Disease Control (CDC) [homepage on the Internet] 2002).

The number of elderly people coexisting with HIV has increased and some of the reasons related to such increase are the progressive cultural changes in society, with regard to sexuality, low adhesion to the use of condom, dissemination of drug therapy with antiretroviral drugs for AIDS and the progressive studies in the area that contributed for the reduction in the mortality rates

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of the contaminated individuals (Verolet et al. 2015; Serra et al. 2013; Frugoli and Magalhães Júnior 2011; Ray et al. 2010). Associated to this, in elderly people, the atherosclerosis presents higher indices of occurrence, due to the characteristics resulting from ageing and the exposure time to risk factors (Pires et al. 2004).

Atherosclerosis is a chronic cardiovascular disease (Ketelhuth and Hansson 2015) which affects blood vessels, mainly the medium and large caliber elastic arteries (Krause et al. 2007), such as the aorta. Its etiology is multifactorial with genetic and environmental influences (Perk et al. 2012). The injuries, resulting from this process, are related to an excessive fibrous and proliferative inflammatory response to different forms of aggression against the endothelium and the smooth muscle in the artery walls. A great number of growth factors, cytokines and vessel-regulator molecules participate in this process (Ross 1993).

In this context, the goal of this study was to analyze the intensity of atherosclerosis and the percentage of elastic and collagen fibers in the intimal and medial layers of the aorta artery of elderly patients autopsied, with and without AIDS. With this, the study aims to contribute for a better understanding of the association between the retrovirus and the arterial remodeling and the development of atherosclerosis, in elderly patients.

## Methods

### Study design

This is a retrospective study approved by the Research Ethics Committee of the Federal University of Minas Gerais Triangle (CEP-UFTM) under the protocol number 1376. We used twenty-six cases, with more than 50 years old, autopsied at a hospital of Uberaba, Minas Gerais, Brazil, from 1982 to 2014. Two pathologists carried out the autopsy and the diagnosis of AIDS was made through the evidence of at least one of the defining diseases of the syndrome and by the cluster of differentiation 4 (CD<sub>4</sub>) count below 200 cells/mm<sup>3</sup>. Data relating to age, sex, cause of death and color were collected from the reports of the autopsies. Regarding the use of antiretroviral therapy, data were available from the pharmacy department. The fragments were retrieved from the archive of anatomical specimens of the Discipline of General Pathology.

Of the 141 segments analyzed, 13 were selected from patients who were 50 years of age or older who were diagnosed with AIDS and were viable for the analysis, independent of gender, color, cause of death or base disease. With the objective of pairing with the study group, 13 segments were collected and constituted the group without AIDS. Patients aged 50 years or older were considered elderly (Center For Disease Control (CDC) [homepage on the Internet] 2002; Cardoso et al. 2013; Favarato et al. 2016).

### Macroscopic analysis

The aorta fragments were evaluated with the help of a standardized scale of 12.0 cm. Each examiner measured the degree of fatty deposit on the non-millimetric scale, subjectively measuring one point on the scale. Next, with the help of a ruler, it was measured the distance between 0.0 cm and the point marked on the scale.

Consensually, the observers classified the atherosclerosis according to the degree of fatty deposit into mild, from 0.1 cm to 4.0 cm, moderate, from 4.1 cm to 7.0 cm, and severe from 7.1 cm to 12.0 cm. The degree of fatty deposit in the macroscopy was evaluated according to the classification into mild, moderate or severe (Fig. 1). From this criterion, the observers of this study described the atherosclerosis quantitatively. For this evaluation, the extension of the atheromatous plaques, presence of fibrosis and calcification, were considered (Ferraz et al. 2012).

### Morphometric evaluation

All fragments were subjected to histological processing, and then serial cuts of 4 µm thick were made for histochemical procedures.

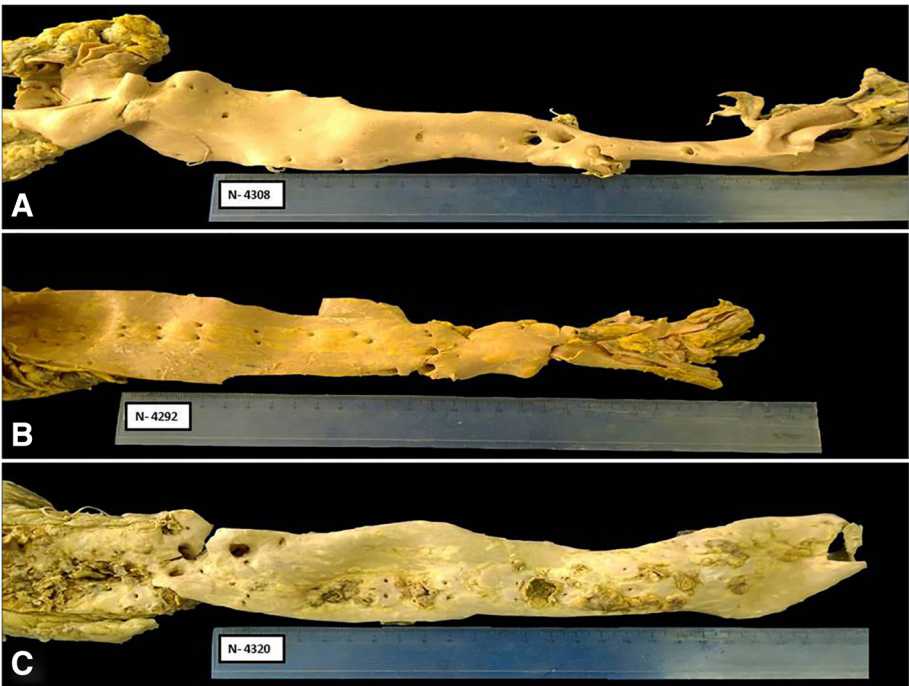
In the verhoeff stain, it was observed the elastic fibers in the intimal and medial layers of the abdominal portion of the aorta artery, viewed under common light and 40x objective with total magnification of 1250x. The picrosirius staining was used to quantify the collagen fibers in the intimal and medial layers of the abdominal portion of the aorta artery, examined under polarized light, with 40x objective and total magnification of 1250x, through four quadrants and subsequent division of 10 fields in both staining. The Leica Qwin Plus® software for morphometry made the analyses of the collagen and elastic fibers (Fig. 2).

### Statistical analysis

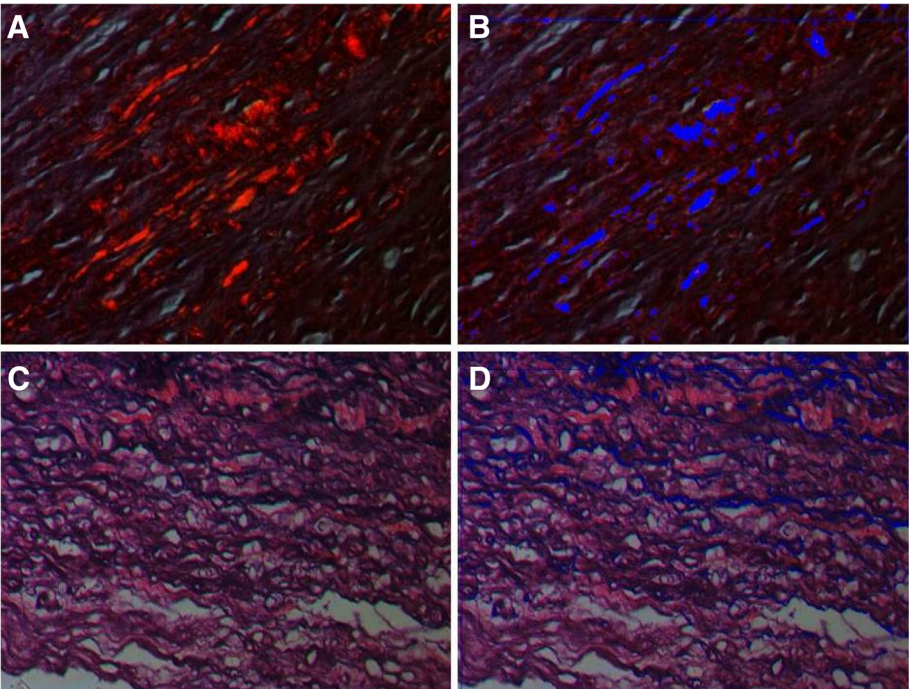
For the statistical analysis, it was elaborated a Microsoft Excel® spreadsheet. The information was analyzed using the software GraphPad Prism® 5. To verify the distribution of the variables, it was applied a Shapiro-Wilk and Kolmogorov-Smirnov statistical test. The t student test was used for normal distribution for the comparison of two groups and the Mann-Whitney test (U) was used for non-normal distribution for the comparison of two groups. As for the correlation, it was applied the Spearman (rS) for non-normal distribution. The differences were considered significant when significance level (p) was lower than 5% ( $p < 0.05$ ).

## Results

In the present study, 26 fragments of the abdominal aorta from elderly patients autopsied, with and without AIDS, were obtained and analyzed.



**Fig. 1** Macroscopy of 10% formaldehyde-fixed aortas in elderly patients with or without autopsied Aids in HC / UFTM, from 1982 to 2014. **a** Aorta showing a small amount of lipid stretch marks in all arterial extension, the intensity of atherosclerosis being classified as mild **b** Aorta showing atheromatous plaques in all arterial extension, the intensity of atherosclerosis being classified as moderate. **c** Aorta showing fibrous and atheromatous plaques with calcifications, the degree of atherosclerosis being classified as severe



**Fig. 2** **a** Histological section stained with picosirius seen under polarized light, 1250x final increase, evidencing a greater amount of birefringent collagen fibers. **b** Quantification of collagen fibers, stained by picosirius by Leica Qwin Plus® software, evidenced by the blue area. **c** Histological section stained with verhoeff seen under common light, 1250x final increase, showing a greater amount of elastic fibers, evidenced by the blackened coloration. **d** Quantification of elastic fibers, stained by verhoeff by Leica Qwin Plus® software, evidenced by the blue area

Data relating to age, sex and color, were described in Table 1.

With regard to the classifications of cause of death, data were presented in Table 2.

According to the use of antiretroviral therapy, the results are described in Table 3.

In the comparison of the macroscopic intensity of atherosclerosis, the AIDS group presented higher intensity when compared to the non-AIDS group ( $t = 0.6969$ ,  $p = 0.4992$ ) (Table 4).

In relation to elastic fibers, there was a significant increase in the group with AIDS compared to that without AIDS ( $U = 115,800$ ;  $p < 0.0001$ ) (Fig. 3).

Comparing the groups, there was a significant increase of the collagen fibers in the intimal and medial layers of the aorta in the AIDS group compared to that without AIDS ( $U = 114,100$ ;  $p < 0.0001$ ) (Fig. 4).

Evaluating the percentage of elastic fibers in the intima and medial layers of the aorta artery with age, there was a negative correlation ( $rS = -0.0438$ ;  $p = 0.3182$ ) in the AIDS group.

Analyzing the group with AIDS, there was a positive correlation between the advancing age and the increase of collagen fibers in the intima and medial aortic artery layers ( $rS = 0.0387$ ;  $p = 0.3776$ ).

In the evaluation of the percentage of elastic fibers with age, there was a positive and significant correlation ( $rS = 0.1507$ ;  $p = 0.0006$ ) in the group without AIDS.

In the non-AIDS group, the correlation between collagen fiber percentage and age was negative and significant ( $rS = -0.1725$ ;  $p < 0.0001$ ).

All the graphs of correlation analysis are showed on Fig. 5.

## Discussion

The present study compared through the semi-quantitative and morphometric methods, the intensity of atherosclerosis and the percentage of elastic and collagen fibers in the intimal and medial layers of the aorta artery of autopsied elderly people with and without AIDS.

**Table 1** General characteristics of the sample of 26 elderly people, with and without Aids, autopsied in the period from 1982 to 2014

General characteristics	Elderly with AIDS n (%)	Elderly without AIDS n (%)
Mean age (min-máx)	57,38 (51–68)	63,38 (53–77)
Gender		
Male	10 (76,92%)	8 (61,54%)
Female	3 (23,08%)	5 (38,46%)
Skin color		
White	11 (84,62%)	8 (61,54%)
Non white	2 (15,38%)	5 (38,46%)

n = total number; min = minimum; max = maximum

**Table 2** Distribution of the cause of death of elderly people, with and without Aids, autopsied in the period from 1982 to 2014

Cause of death	Elderly with AIDS n (%)	Elderly without AIDS n (%)
Cardiovascular	3 (23,08%)	7 (53,85%)
Non cardiovascular	10 (76,92%)	6 (46,15%)
Total	13 (100%)	13 (100%)

n = total number

The life expectancy for the patients with HIV, after starting the use of anti-retroviral therapy increased considerably (Kramer et al. 2009). Despite the increase in the life expectancy and greater exposure of elderly people contaminated to risk factors for cardiovascular diseases, we verified that in the group with AIDS, the cause of death was predominantly infectious (76.92%) and in the group without AIDS, the majority was related to cardiovascular events (53.85%).

In the macroscopic evaluation of the aorta, we can observe that the AIDS group had higher atherosclerosis intensity than the non-AIDS group. In the literature, a study performed through autopsy analysis reports on endothelial dysfunction in HIV-positive individuals, such as multiple vessel lesions and muscle cell hyperplasia (Chan et al. 2009), with endothelial dysfunction due to increased lipids in the vessel leads to the entry of lipoproteins in the intima layer forming lipidic streaks, an initial manifestation of atherosclerosis (Xavier 2013; Hansson 2009).

In the group with AIDS, elastic fibers and collagen fibers showed a significant increase when compared to the group without AIDS. With the progression of AIDS, the components of the extracellular matrix are altered, which causes an increase in collagen fibers, elastic fibers, laminin, fibronectin and proteoglycans (Paiva et al. 1996; Leng SX Yang and Walston 2004; De Lima Pereira et al. 2007). Moreover, it is demonstrated that the disease is associated with a higher percentage of collagen fibers, related to the greater activation of the immune system in a chronic way and with local inflammation (Shacker et al. 2005; Estes et al. 2007).

In the evaluation of the percentage of elastic fibers in the intima and medial layers of the aorta with age, the

**Table 3** Distribution of use of antiretroviral therapy in elderly patients with Aids autopsied in the period from 1982 to 2014

Use of antiretroviral therapy	Elderly patients with Aids n (%)
Yes	1 (7,69%)
No	11 (84,62%)
Without data	1 (7,69%)
Total	13 (100%)

n = total number



**Table 4** Centimeters of atherosclerosis in aorta patients in each group

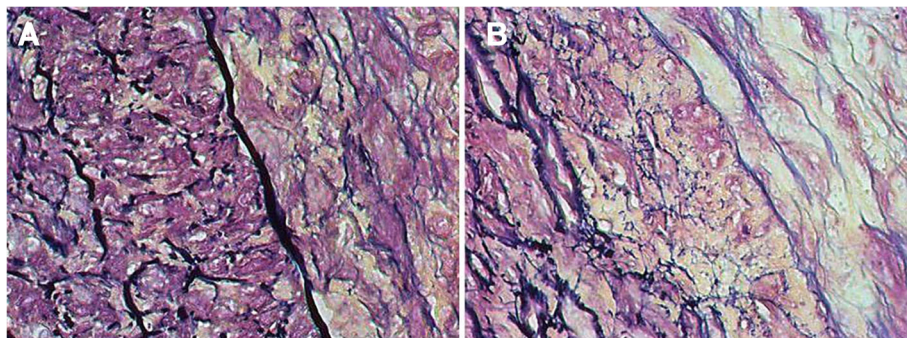
Patients	Aids	Scale (cm)	Macroscopic classification of atherosclerosis
N-3939	Yes	4.5	Moderate
N-4098	Yes	4.5	Moderate
N-4103	Yes	1.8	Mild
N-4157	Yes	5.6	Moderate
N-4178	Yes	11.9	Severe
N-4196	Yes	11	Severe
N-4253	Yes	2.8	Mild
N-4292	Yes	11.8	Severe
N-4318	Yes	6.3	Moderate
N-4207	Yes	7	Moderate
N-4277	Yes	8	Severe
N-4061	Yes	4.5	Moderate
N-4121	Yes	3.5	Mild
N-4223	No	4.4	Moderate
N-3502	No	8.4	Severe
N-3510	No	5.1	Moderate
N-3566	No	5.4	Moderate
N-3570	No	9.3	Severe
N-3865	No	1.9	Mild
N-3923	No	4.1	Moderate
N-3996	No	8.5	Severe
N-4012	No	2.5	Mild
N-4308	No	3.6	Mild
N-3633	No	10.6	Severe
N-4099	No	4.2	Moderate
N-3672	No	6	Moderate

AIDS group showed a negative correlation and the group without AIDS, a positive and significant correlation. Due to the AIDS patients, were more marked with the effects of atherosclerosis, changes in the amount of elastic fibers occur due to the damages suffered in the extracellular matrix of the disease (Kurtz and Oh 2012), in the atherogenesis the action of enzymes promote the degradation of elastic fibers and, with ageing, decreased elastin synthesis (Wachi 2011). Other aggravating factors are calcifications that occur in atherosclerotic plaques, that may affect from fibers, due to calcification of elastin, which results in complete degradation (Bobryshev 2005).

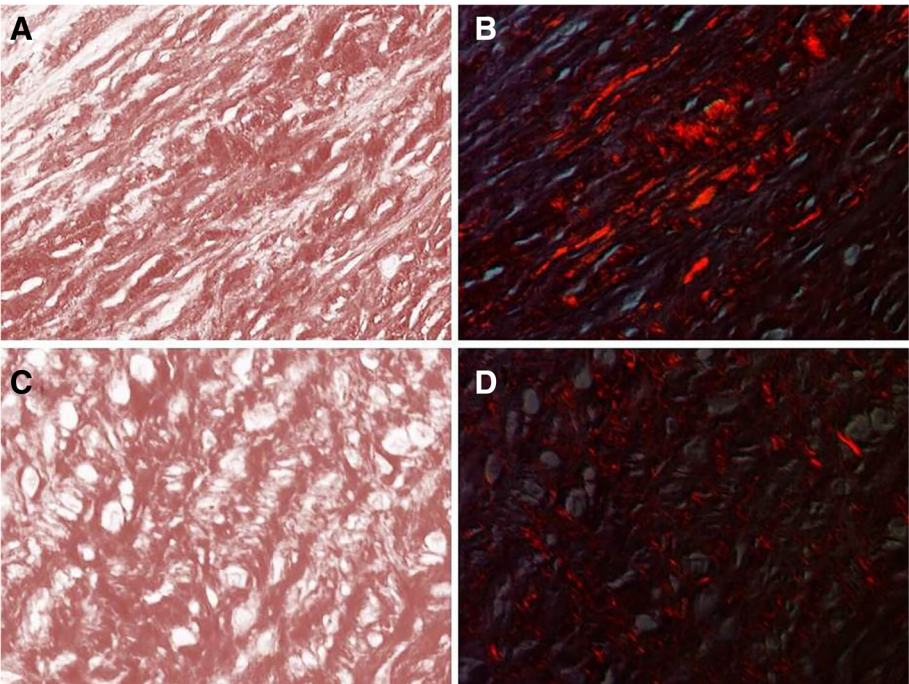
There was a positive and significant correlation between the increase in the percentage of collagen fibers and the advancing age of patients with AIDS. The vascular remodeling initiated by the inflammation, when in the presence of HIV, can be linked to the infection itself or metabolic factors associated (Ho and Hsue 2009). The event is triggered by activation of the endothelial cells and increased expression of collagen (Crowe et al. 2010). This group had a higher intensity of atherosclerosis, with the formation of atherosclerotic plaques triggers an inflammatory process that involves the smooth muscle cells of the intimal layer secreting collagen, elastic fibers and proteoglycans for the extracellular matrix (Insull 2009).

The non-AIDS group demonstrated a negative and significant correlation between aging and collagen fibers. The results corroborate with a literature that shows that with aging there is loss of collagen fibers as a consequence of the synthesis reduction and increase of its degradation (Chung et al. 2001).

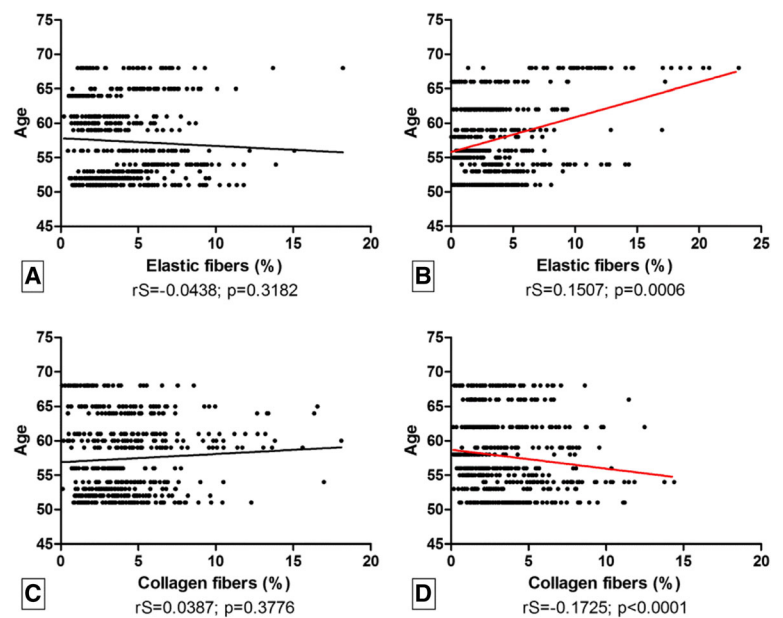
As the age increases, there is a greater exposure to risk factors related to the development of atherosclerosis, which may lead to arterial remodeling, one of which is the development of AIDS, as demonstrated in the literature and in the present study.



**Fig. 3** **a** Histological section stained with verhoeff seen under common light, 1250x final increase of an elderly patient with Aids, showing a greater amount of elastic fibers, evidenced by the blackened coloration. **b** Histological section stained with verhoeff seen under common light, 1250x final increase of an elderly patient without AIDS, showing a smaller amount of elastic fibers, evidenced by the blackened coloration



**Fig. 4** **a** Histological section stained with picrosirius seen under common light, 1250x final increase of an elderly patient with Aids. **b** Histological section stained with picrosirius seen under polarized light, 1250x final increase of an elderly patient with AIDS, evidencing a greater amount of birefringent collagen fibers. **c** Histological section stained with picrosirius seen under common light, 1250x final increase of an elderly patient without AIDS. **d** Histological section stained with picrosirius seen under polarized light, 1250x final increase of an elderly patient without AIDS, evidencing a smaller amount of birefringent collagen fibers



**Fig. 5** **a** Correlation between elastic fibers percentage and age in Aids group. **b** Correlation between elastic fibers percentage and age in non-Aids group. **c** Correlation between collagen fibers percentage and age in Aids group. **d** Correlation between collagen fibers percentage and age in non-Aids group

## Conclusions

Advances in the treatment of AIDS are progressively increasing the life expectancy among those infected by the virus, being a positive factor for public health. However, the findings in this study suggest that HIV infection may influence the greater development of arterial remodeling and consequently atherosclerosis, especially in the elderly population due to age being associated with atherogenesis due to the longer time of exposure to aggressors and aging processes.

## Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CD<sub>4</sub>: Cluster of differentiation 4; CEP-UFTM: Committee of the Federal University of Minas Gerais Triangle; CNPq: Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPEMIG: Fundação de Amparo à Pesquisa do Estado de Minas Gerais; HIV: Human Immunodeficiency Virus; p: Significance level; rS: Spearman test; U: Mann-Whitney test; UFTM: Triângulo Mineiro Federal University

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## Availability of data and materials

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

## Authors' contributions

Conception and design of study: MSO, VdPAT, MLdF. Acquisition of data: MSO, ACSdS, GKNdAF, BGST. Analysis and/or interpretation of data: MSO, GRJ, LAMdS. Drafting the manuscript: MSO, BGST, LFO, CLC, LSR, VdPAT, MLdFF, LSA. Revising the manuscript critically for important intellectual content: MSO, VdPAT, MLdFF. Approval of the version of the manuscript to be published: MSO, ACSdS, GKNdAF, GRJ, BGST, LAMdS, LFO, CLC, LSR, VdPAT, MLdFF. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais Triangle (CEP-UFTM) under the protocol number 1376.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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