Liver damage of autopsied patients with acquired immunodeficiency syndrome and antirretroviral therapy effect

Lesão hepática de pacientes autopsiados com síndrome da imunodeficiência adquirida e o efeito da terapia antirretroviral

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ABSTRACT

Aim: To evaluate steatosis percentage and hepatic interstitial fibers of autopsied patients with Acquired Immunodeficiency Syndrome (AIDS), relating to the use of antiretroviral therapy (ART). Methods: 62 liver fragments from patients with and without AIDS autopsied from 1996 to 2017, matched by age (18-49), gender and race. These patients were divided in two groups: patients with AIDS (n=31) and patients without AIDS (n=31). Patients with AIDS were analyzed according to treatment on ART (n=15) or non-ART (n=16). In the histomorphometric analysis sections were made and stained with hematoxylin-eosin, picrosirius and reticulin for steatosis, type I and type III collagen analysis, respectively. Results: Patients with AIDS showed significantly larger steatosis percentage (26.05 vs 21.95%, p<0.001), type I collagen (1.63 vs 1.01%, p<0.001) and type III collagen (8.68 vs 7.83%, p<0.001). Patients with AIDS on ART showed significantly lower steatosis percentage (25.45 vs 26.36%, p<0.001) and type I collagen (1.52 vs 1.75%, p<0.001). Patients with AIDS on ART showed lower percentage of type III collagen (8.52 vs 8.77%, p<0.96), however it was not statistically significant. Conclusion:

AIDS increases in hepatocyte fat accumulation and steatosis and liver fibrosis. However, ART has a decreased beneficial role in hepatocyte fat accumulation and fibrosis development since the medication detains both processes.

Keywords: AIDS, autopsy, liver, antiretroviral therapy.

RESUMO
Objetivos: Avaliar o percentual de esteatose e fibras instersticias hepáticas de pacientes autopsiados com Síndrome da Imunodefiência Humana Adquirida (Aids) em relação ao uso da terapia antiretroviral (TARV). Métodos: 62 fragmentos de fígado de pacientes com e sem Aids autopsiados de 1996 a 2017 foram pareados por idade (18-49 anos), sexo e raça. Esses pacientes foram divididos em dois grupos: com Aids (n=31) e sem Aids (n=31). Os pacientes com Aids ainda foram analisados de acordo com o uso da TARV (n=15) e aqueles que não fizeram uso da TARV (n=16). Na análise histomorfométrica foram feitos cortes e corados em hematoxilina-eosina, picrosírius e reticulina para análise da esteatose, e dos colágenos tipo I e tipo III, respectivamente. Resultados: Pacientes com Aids apresentaram estatisticamente maior porcentagem de esteatose (26,05 x 21,95%, p<0,001), colágeno tipo 1 (1,63 x 1,01%, p<0,001) e colágeno tipo III (8,68 x 7,83%, p<0,001). Pacientes com Aids em uso de TARV apresentaram significativamente menor porcentagem de esteatose (25,45 x 26,36%, p<0,001) e colágeno tipo I (1,52 x 1,75%, p<0,001). Pacientes com Aids em uso da TARV apresentaram menor precentual de colágeno tipo III (8,52 vs 8,77%, p<0,96), porém sem diferença estatisticamente significativa. Conclusão: A Aids aumenta o acúmulo de gordura nos hepatócitos e contribui para a fibrose hepática. No entanto, o uso da TARV tem papel benéfico diminuindo o acúmulo de gordura e no desenvolvimento da fibrose, uma vez que a medicação detém os dois processos.

Palavras-chave: Aids, autópsia, fígado, terapia antirretroviral.

1 INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus, a retrovirus capable of invading immune system cells and causing immunodepression (CAO et al., 1992). Now it is recognized that liver plays a key role in HIV infection pathogenesis (GANESAN et al., 2019).

HIV is capable of entering and replicating inside Kupffer cells at the beginning of the infection. These cells express CD4, CCR5 and CXCR4 receptors that facilitates the linkage between the virus and hepatic cells, which favor the viral invasion into the hepatocytes (SVEGLIATI-BARONI, DE MINICIS, 2010; HONEYCUTT, 2016).

Fat accumulation in hepatocytes is a frequent alteration in HIV-infected patients that can be caused mainly by excessive alcohol consumption or metabolic changes. The first is called alcoholic liver disease (ALD) and the latter nonalcoholic fatty liver disease (NAFLD) (CARVALHEIRA, SAAD, 2006; PANDREA., et al., 2010).

HIV infection generates a systemic inflammatory process that causes some cytokines release that are capable of leading to insulin resistance and so contributing to NAFLD. This disease may be accompanied by steatohepatitis, an active inflammation that increases the liver fibrosis risk in which fibroblasts are stimulated to produce collagen because of the persistent cell damage contributing to cirrhosis onset (LEMOINE, SERFATY, CAPEAU, 2012; STERLING, SMITH, BRUNT, 2013; GANESAN et al., 2019).

Liver damage in these patients may also be aggravated by the use of antiretroviral therapy (NÚÑEZ, 2010) however despite the side effects ART promotes extraordinary changes in natural history of HIV infection by the benefits to patients.

In this study, liver fragments analysis of autopsy material enable the characterization of major liver damages in HIV monoinfected patients and implications of ART treatment on them.

2 MATERIAL AND METHODS

In a retrospective study, autopsy protocol and medical records of 31 patients with and 31 without AIDS autopsied by pathologists in General Pathology Discipline from Clinical Hospital of Triângulo Mineiro Federal University from 1996 to 2017, matched by age (18-49), sex and race. Besides, information about body mass index (BMI) and ART were obtained from medical records.

Patients with AIDS group were subdivided in two: group of patients on ART (n=15) and group of non-ART patients (n=16). HIV-infected patients with genetic liver disease, hepatic neoplasms, lymphomas, alcoholic cirrhosis and/or hepatitis B or C were excluded from the study.

Patients on ART for at least 3 months, even if irregular use, were included in the study. zidovudine (AZT), didanosine, stavudine, lamivudine, nelfinavir, efavirenz, indinavir were the drugs used in combination or isolated.

Liver sections were stained with hematoxylin-eosin (HE), picrosirius (PS) and reticulin (RET) and analyzed. HE stain was used to quantify steatosis percentage. Steatosis percentage was quantified by analyzing 60 fields per slide by light microscopy using Leica QWin Plus®15 (Cambridge, UK) with magnification of x40. The number of fields per slide evaluated was defined by calculating the average accumulated (WILLIAMS,1977). Optically empty vacuoles were traced by the observer to determine the steatosis percentage by analyzed field.

Images of 60 fields per slide of PS and RET stained sections were analyzed with a magnification of x40 for type I and type III collagen percentage in hepatic parenchyma, respectively. PS stained sections were examined using polarized light microscopy in which

collagen areas are yellow reddish, meaning positively birefringence. RET stained sections were examined by light microscopy in which type III collagen areas appear black. Leica QWin Plus®15 was used to quantify collagen in extracellular matrix to determine percentage per field area analyzed. Periportal space and Glisson capsule areas were excluded from collagen type I analysis.

A spreadsheet was elaborated in Microsoft Excel® and statistical analysis carried out in GraphPad Prism® 5.0. To verify the distribution of variables Kolmogorov-Smirnov statistical test was applied. The t student test was used for normal distribution and homogeneity of variances and values expressed as media and standard deviation (X±SD). Mann-Whitney test was used for normal or non-normal distribution and heterogeneity of variances and values expressed as median and minimum and maximum values (Med-Min-Max).

In the semi-quantitative evaluation of the morphological pattern and topographical distribution of steatosis, the chi-square (χ^2) frequency test was used. The differences were considered significant when significance value (p) was lower than 5% ($p < 0.05$).

Ethical aspects: This study was approved by the Triângulo Mineiro Federal University Research Ethics Committee (protocol number 2.555.429).

3 RESULTS

The age range in groups with and without AIDS was about 35 and there was a prevalence of white men. Regarding BMI, patients with AIDS showed malnutrition while patients without AIDS showed normal BMI and the difference between these values were significant (Table 1). This finding confirms nutritional alterations that are often seeing in patients with the syndrome.

AIDS patients showed significantly higher steatosis percentage, type I collagen and type III collagen (Table 2, Figure 1 A-F) compared to patients without AIDS. Both groups showed prevalence of macrovesicular pattern and steatosis topographic distribution in area 1 which means that optically empty vacuoles were localized predominantly in hepatic zone I but there was no significantly difference (Figure 2 A-B). However, this localization suggests an advanced NAFLD. According to medical records, about 90% of AIDS patients presented abusive or moderate alcohol consumption, contributing to liver fat accumulation.

The group on ART showed significantly lower steatosis and type I collagen percentage (Table 2), showing benefit to the liver in the studied group. However, there was no significantly difference in the steatosis morphological pattern and topographical distribution (Figure 2 C-D) and there was prevalence of macrovesicular pattern and greater presence of optically empty

vacuoles in area 1. Regarding collagen III, group with ART showed lower percentage yet with no significantly difference (Table 2).

4 DISCUSSION

This study verified the prevalence of white men in both patients with and without AIDS groups. Epidemiological data demonstrated prevalence of men in HIV-infected individuals in the last years. These statistics prevails until the present day, in which the number of men with the disease is still greater when compared to the number of women, however having predominance in the age range of 15 to 24 years (BRASIL, 2022).

BMI analysis showed that patients with AIDS had a close value to malnutrition state, evidencing that this group commonly has nutritional problems such as progressive weight loss, changes in body composition and micronutrient deficiency. Weight loss is one of the earliest and most obvious clinical manifestations of the disease and may occur in all stages of HIV infection (OCKENGA et al., 2006).

Patients with AIDS presented higher percentage of hepatic steatosis, which corroborates the literature data that shows a higher prevalence in HIV positive individuals when compared to general population (SILVA et al., 2019; REZENDE et al., 2023). A study of liver biopsies from monoinfected patients demonstrated a prevalence of 55% of NAFLD in this group (MORSE et al., 2015).

The explanation for this may have several factors, including the direct action of the virus itself, metabolic diseases, alcohol abuse and lipodystrophy that are often associated with this group (SVEGLIATI-BARONI, DE MINICIS, 2010).

During acute HIV infection, inflammatory response promotes interleukin release such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), which are capable of interfering in lipid metabolism. These interleukins stimulate lipogenesis in adipocytes and therefore generating a greater offer of fatty acid to the liver and contributing directly to fatty accumulation in hepatocytes (VENHOFF et al., 2007). In addition, the virus is capable of interacting with the sterol regulatory element binding protein 1 (SREBP-1), a receptor that stimulates lipogenesis and causes changes in insulin signaling. Since this receptor is related to insulin resistance, it has also relation to a greater fatty acids synthesis and retention in the hepatocytes (LEMOINE SERFATY, CAPEAU, 2012; ARMAH et al., 2010; LEMOINE, INGLIZ, 2012; SILVA et al., 2019). Therefore, in this study, we considered that the patients with AIDS presented NAFLD

Another aggravating factor in this group is the frequent alcohol consumption that is higher in infected people when compared to the general population. A study including 715 HIV-infected patients showed that 33% had frequent alcohol consumption, impairing not only adherence to ART but also contributing to increased hepatotoxicity and consequently increased morbidity and mortality (HENDERSHOT et a., 2009; SHERMAN, THOMAS, CHUNG, 2014; SETH; SHERMAN, 2019). Medical records showed that 90% of patients presented alcohol consumption and the results confirm the previous evidence, therefore in this study hepatocyte fat accumulation was certainly aggravated by alcohol consumption.

Regarding the macrovesicular pattern and the topographical distribution of steatosis predominantly in area 1, no reports were found in the literature directly justifying the relationship of these findings with HIV infection. Macrovesicular steatosis is typically associated with a long-standing disorder of hepatic lipid metabolism, the most common histological change being frequently associated with alcoholic hepatitis, leading to the development of fibrosis and cirrhosis (BACON et al., 1994; VALLET-PICHARD, MALLET, POL, 2012; LOMBARDI et al., 2016). Therefore, we believe that the inflammatory reaction caused by the viral action contributed to the prevalence of the macrovesicular pattern and to a more advanced degree, justifying the greater distribution of optically empty vacuoles around the portal space. Even with the adherence to ART, it was not possible to see difference in the pattern and topographic distribution of steatosis.

The higher percentage of type I collagen is directly related to hepatic fibrosis increase, another common liver damage in HIV positive patients, is also responsible for the direct action of the virus, such as steatosis itself contributing to the increase of collagen fibers in the extracellular matrix of the liver (LEMOINE SERFATY, CAPEAU, 2012; LI VECCHI et al., 2012). A study revealed that 14.3% of monoinfected patients developed hepatic fibrosis and 5.2% developed cirrhosis, in the absence of other viral comorbidities and alcohol consumption (LUI et al., 2016), corroborating as reported in previous studies the direct participation of the virus with the progression to the liver fibrosis (SILVA, et al.,2019).

One of the mechanisms by which the virus leads to increased collagen fibers, as found in this study, is the ability of HIV to infect the stellate cells. These cells function as a central mediator in hepatic fibrosis, because when infected they change their phenotype, becoming highly proliferative, contractile and fibrogenic, producing predominantly type I collagen, characteristic of the cirrhotic liver (HONG et al., 2009; BRUNO et al., 2010).

HIV infection in stellate cells induces secretion of monocyte chemoattractant protein 1 (MCP-1), a proinflammatory cytokine that attracts monocytes and lymphocytes, contributing

to local inflammation and consequently to fibrosis evolution. In addition, the gp10 protein present in the viral envelope is capable of inducing hepatocyte apoptosis and direct activation of hepatic stellate cells (TUYAMA et al., 2010).

HIV-infected patients showed a significant increase in type III collagen. These fibers are abundant in hepatic stroma and are often found associated with type I collagen therefore, we believe that the collagen III increase occurs due to mechanisms similar as type I collagen, and the inflammatory response caused by the viral infection is responsible for this, since viral infection leads to an imbalance between the synthesis and deposition of the extracellular matrix (FRIEDMAM, 2003; SCHIERWAGEN, et al. 2013).

Kupffer cells are also targets of HIV and therefore can be infected and contribute to hepatic disease progression, including steatosis and fibrosis. In the latter, when activated the cells produce inflammatory and profibrogenic cytokines that in turn activate stellate cells which are the main source of liver fibrosis (BALAGOPAL et al., 2009; ROCKSTROH et al.,2014; TSUCHIDA, FRIEDMAN, 2017).

Introduction of ART still presents itself contradictory regarding hepatic lesions because are capable of causing metabolic and mitochondrial diseases worsen hepatic steatosis and fibrosis (MAGGI et al., 2015 ROCKSTROH et al.,2014; CROXFORD et al.,2016; MOHR., et al 2018). However, there are studies that defend its beneficial role, mostly those related to factors that worse steatosis progression and hepatic fibrosis such as coinfections and alcohol abuse (BENHAMOU et al., 2001; SULKOWSKI et al., 2000). And in this study ART was beneficial.

5 CONCLUSION

In conclusion, AIDS causes important liver damage that affects both extracellular matrix and different cells and components of the organ. The virus was associated with higher hepatic steatosis and fibrosis. However, ART showed a beneficial role by reducing hepatocyte fat accumulation and fibrosis development since the medication detains both processes.

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Tables

Table 1. Demographic variables of 62 autopsied patients with and without AIDS

		With AIDS (n=31)	Without AIDS (n=31)
Age (X±SD)[1]		35.35±7.03	35.64±7.71
BMI (kg/m²) - Med (Min-Max)		19.71 (13.60-33.79)	24.89 (16.32-38.30)
Gender (%)	Men	16 (51.61)	16 (51.61)
	Women	15 (48.39)	15 (48.39)
Race (%)	White	18 (58.06)	18 (58.06)
	Not White	13 (41.94)	13 (41.94)

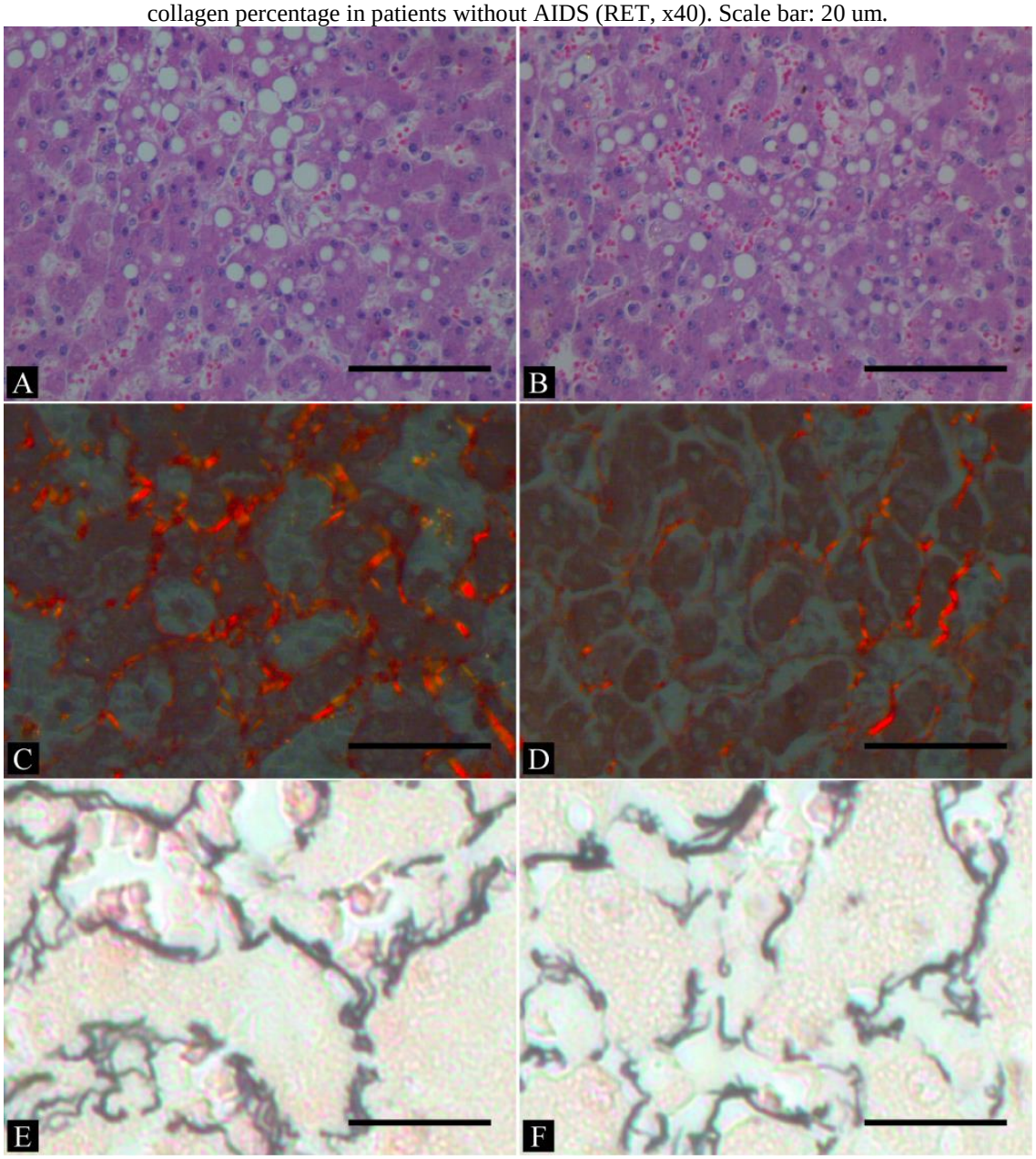
[1](X±SD): media and standard deviation.
Fonte: Elaborado pelo autor, 2023

Table 2. Hepatic variables of 62 autopsied patients with and without AIDS, 15 patients on ART and 16 with no therapy.

	Steatosis (%)	Collagen fibers (%)	Type III collagen (%)
		Med (Min-Max)	
With AIDS	26.05 (1.53-85.42)	1.63 (0.00-9.39)	8.686 (0.65-25.21)
Without AIDS	21.95 (1.73-84.86)	1.01 (0.00-28.75)	7.83 (0.22-25.93)
	T^1=146400	T^1=131000	T^1=153900
	p<0.0001	p<0.0001	p<0.0001
On ART	24.66 (1.53-61.39)	1.52 (0.00-8.13)	8.52 (0.65-25.21)
Non-ART	27.38 (2.64-85.42)	1.75 (0.00-9.39)	8.77 (0.75-25.01)
	T^1=353900	T^1=389400	T^1=431500
	p<0.0001	p<0.0002	p<0.9676

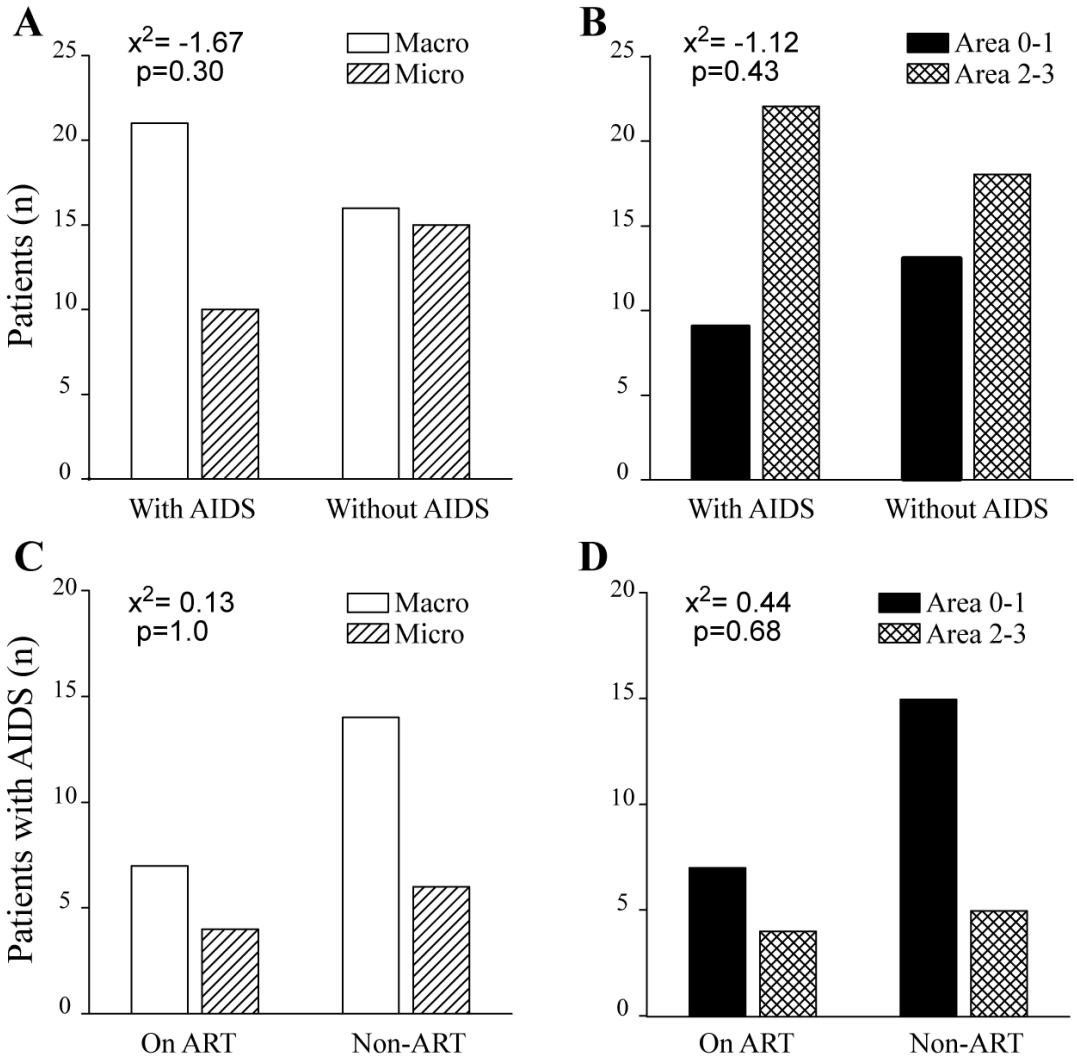
T^1: Mann-Whitney test.
Fonte: Elaborado pelo autor, 2023

Figure 1. Hepatic steatosis percentage, type I and type III collagen III percentage analysis of autopsied patients with and without AIDS. A) Higher hepatic steatosis percentage in patients with AIDS (HE, x20). B) Lower hepatic steatosis percentage in patients without AIDS (HE, x20). C) Higher collagen fibers percentage in patients with AIDS (PS, polarized light, x40). D) Lower collagen fibers percentage in patients without AIDS (PS, polarized light, x40). E) Higher type III collagen percentage in patients with AIDS (RET, x40). F) Lower type III collagen percentage in patients without AIDS (RET, x40). Scale bar: 20 um.



Fonte: Elaborado pelo autor, 2023

Figure 2. Hepatic steatosis morphological pattern (A) and topographic distribution (B) of 31 autopsied patients with AIDS, 31 without AIDS, 15 on ART (C) and 16 with no therapy (D).



Fonte: Elaborado pelo autor, 2023