AIDS Research and Therapy

REVIEW

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Brief communication: comorbidities and aging in people living with HIV

Laura Beatriz de Camargo Vicioli[1*†] and e Lenice do Rosário de Souza[1†]

Abstract

The main objective of the study was to assess the occurrence of non-aids-related comorbidities typical of aging in people living with HIV diagnosis 20 years ago or more and under treatment with antiretroviral drugs for a long time. The associations between the same age group in people living with HIV with reported ART use 20 + years and people living with HIV with reported ART use between two and five years in relation to the risk of comorbidities studied, there was a predominance of metabolic alterations in the 50–60 and 60 + age groups ($p < 0.003$). The conclusion was that exists a higher risk of comorbidities associated with people living with HIV for more than 20 years, but the length of treatment did not necessarily influence this risk.

Keywords HIV, TCD4 + cells, Comorbidities, Premature aging

Introduction

One of the main alterations found in people living with HIV (PLWHIV) is dyslipidemia and glycolytic metabolism, probably associated with antiretroviral therapy (ART), which leads to an increase levels of VLDL (*very low density lipoproteins*), LDL (*low density lipoprotein*), a significant decrease in HDL (*high density lipoprotein*), increases insulin resistance, glucose intolerance and diabetes *mellitus*. In addition to the action of antiretroviral drugs, dyslipidemia can occur due to the interaction of various factors, such as genetic predisposition, environmental issues or the host's own response to HIV, while the presence of diabetes *mellitus* in PLHIV is considered common after prolonged use of ART, being a factor favoring the development of insulin resistance [1–4]. Tenofovir has also been associated with bone mineral density (BMD) decrease and an increased number of bone fractures due to osteoporosis [5, 6]. Lima et al. [5, 7], observed that osteopenia and osteoporosis are associated with factors directly related to the virus itself, such as persistent activation of pro-inflammatory cytokines, especially tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1).

Guimarães et al. [8] in a study carried out in Brazil, showed that at least 7% of patients, before the implementation of ART, already had cardiovascular alterations, which were aggravated by the prolonged use of this therapy.

Currently, there have been a higher prevalence rate of cardiovascular diseases related to sedentary lifestyle and obesity in PLWHIV [9]. Another factor present in this population is the increase on the occurrence of cancers associated with the typical comorbidities of aging. Among age-related neoplasms, the most common are hepatocellular, laryngeal, lung, renal and penile carcinomas, prostate and colon adenocarcinoma and Hodgkin's lymphoma, among other types of lymphoma [10, 11]. Therefore, in addressing the growing burden of

†Laura Beatriz de Camargo Vicioli and Lenice do Rosário de Souza contributed equally to this work.

*Correspondence:
Laura Beatriz de Camargo Vicioli
laura.vicioli@unesp.br
[1]Department of Tropical Diseases, Paulista State University "Julio de Mesquita Filho" - Unesp, Botucatu, Brazil

age-related comorbidities among long-term HIV survivors is crucial for public health.

Methods

Study design

This was a retrospective cohort study which included 160 PLWHIV, of both sexes, treated at the "Domingos Alves Meira" Specialized Infectious Diseases Outpatient Service (SAEI-DAM) – Clinical Hospital Complex of the Faculty of Medicine (FMB) – Botucatu, SP, who were divided in two study groups. Group 1 (G1): 63 people who had been using ART for at least 20 years; and group 2 (G2): 97 people who had been using ART between two and five years. The inclusion criteria for both groups were having a diagnosis of HIV infection, regular outpatient and laboratory follow up at SAEI-DAM, having 18 years old or more, using ART and agreeing to take part in the study by signing the Free and Informed Consent Form.

Data collection

Data collection and the recruitment were carried out from November 8, 2021 to September 5, 2022 and included a short interview using a questionnaire to confirm demographic data, lifestyle habits and diagnosis of chronic diseases such as diabetes *mellitus*, systemic arterial hypertension, dyslipidemia, cardiovascular, bone and neoplastic diseases. Weight and height were used to calculate body mass index (BMI).

The laboratory data included the serum levels of total cholesterol and its fractions (HDL, LDL and VLDL), fasting glycemia, urea, creatinine, CD4+/CD8+T lymphocyte counts, determinations of plasma HIV viral loads and bone densitometry scans. The Framingham score was calculated to assess cardiovascular risk.

Data analysis

It was carried out a descriptive data analysis, obtaining frequencies and percentages for sociodemographic variables. The mean, standard deviation, median, minimum and maximum values were calculated for the quantitative variables.

Table 1 Time on ART as a risk factor for comorbidities in relation to G1 *vs* G2. Botucatu, Brazil, 2022

Outcomes	OR	95%CI		p-value
Intermediate/high cardiovascular risk	1,045	0,976	1,118	0,2
Diabetes *mellitus*	1,094	1,007	1,188	0,033
Dyslipidemia	1,043	0,972	1,12	0,23
Bone changes	1,002	0,937	1,072	0,94
Neoplasms	0,921	0,838	1,013	0,09

ART: Antiretroviral therapy; OR: *oddis ratio*; 95%CI: 95% confidence interval. *Logistic regression analysis (G1 *vs* G2); (G1): 63 people who had been using ART for at least 20 years; and group 2 (G2): 97 people who had been using ART between two and five years

Comparisons of means between groups were made using the *student's t-test* in the case of symmetrical data. In the case of asymmetry, associations between groups were made using the chi-square test.

Considering each comorbidity as a response variable, a logistic regression model was adjusted for time and groups (G1 vs. G2) as explanatory variables, obtaining a risk or protective factor for each comorbidity.

Results and discussion

In G1, there was a predominance of females (54.0%), and in G2, there was a predominance of males (70.1%). The average ages for G1 and G2 were 57.7 years (range 39–83) and 39.7 years (range 21–71), respectively.

In the logistic regression analysis of time on ART, the variables and groups (G1 vs. G2) were evaluated to determine the risk of the comorbidities studied, as shown in Table 1.

When evaluating the same age groups in relation to metabolic changes, intermediate/high cardiovascular risk and bone changes such as osteopenia and osteoporosis, differences were observed between the groups, as shown in Table 2.

Despite the successful use of early ART to control viremia, reduce the risk of disease progression and prevent transmission of the virus, metabolic complications have been reported over time in PLHIV, such as dyslipidemia, diabetes *mellitus*, bone changes, among others, with the possible causes being older drugs in the classes of non-nucleoside reverse transcriptase inhibitors and protease inhibitors, which have resulted in long-term consequences, fat accumulation and a high mortality rate, according to Stires et al. [12].

Based on the data obtained in this study, people who had been diagnosed and treated for longer had a higher occurrence of the comorbidities assessed and not associated with the virus, such as cardiovascular risk, dyslipidemia, diabetes, hypertension, bone changes and neoplasms. All of these may be related to various factors, the chronic HIV disease and the ART, age, genetic, family and environmental. In this regard, Vos et al. [13], in a study of an African PLWHIV, did not relate greater cardiovascular risk to therapy.

In the present study, among individuals under treatment with ART during 20 years or more, there was a greater risk of developing cardiovascular diseases, dyslipidemia, bone changes and neoplasms, with no differences in relation to the length of treatment. As for the risks of systemic arterial hypertension and diabetes *mellitus*, they were similar in both groups, with a relationship with treatment time only for diabetes. According to Ouyang et al. [14], PLHIV in the long term can develop diabetes due to chronic inflammatory process, intestinal dysbiosis and insulin resistance related to certain therapeutic regimens.

Table 2 Associations between age group and comorbidities of 160 people living with HIV, Botucatu-SP, Brazil, 2022

Age group	Variables	G1			G2			
		Total	N	%	Total	N	%	p-value
40 to 50	Metabolic changes	12	7	58,3	25	7	28,0	0,16
	Intermediate/high cardiovascular risk	12	1	8,3	25	4	16,0	0,90
	Bone changes	12	4	33,3	25	0	0,0	0,013
51 to 60	Metabolic changes	29	20	69,0	16	5	31,3	0,03
	Intermediate/high cardiovascular risk	29	8	27,6	16	7	43,8	0,44
	Bone changes	29	16	55,2	16	5	31,3	0,22
More than 60	Metabolic changes	23	20	87,0	4	1	25,0	0,04
	Intermediate/high cardiovascular risk	23	16	69,6	4	2	50,0	0,85
	Bone changes	23	19	82,6	4	2	50,0	0,42

G1: 63 people living with HIV who have been taking antiretroviral therapy for at least 20 years; G2: 97 people living with HIV who have been taking antiretroviral therapy for between two and five years; Total: Total number of patients for each age group

N: Number of patients with each comorbidity

*Chi-square test

The same authors showed that in people with diabetes, metformin can improve the composition of the intestinal microbiota, thereby reducing the inflammatory process and the risk of developing comorbidities not associated with HIV/AIDS.

In a systematic review, Mohan et al. [15] demonstrated that mitochondrial dysfunction is the most common underlying mechanism used by HIV itself and by most antiretroviral regimens to cause inflammation, insulin resistance and dyslipidemia. Another finding was that protease inhibitors are in fact the most harmful class of antiretroviral drugs, due to their ability to initiate high toxicity in the host's metabolism, leading to the development of metabolic syndrome.

With regard to bone changes, there was a predominance of osteoporosis among the participants in this study with 20 years or more of treatment and osteopenia among those with up to five years of ART, although it was not possible to relate the treatment time factor to these comorbidities. A study by Dong et al. [5] found a high prevalence of osteoporosis in PLWHIV for a long time, but it was associated not only with ART, but also with the age, body mass index and lifestyle habits of the participants. Aguilar et al. [16] showed that PLWHIV have osteoporosis and osteopenia at an earlier age than those without the infection.

Another study carried out by Tasca et al. [17] in 2021, which assessed people living with HIV with and without the use of ART in relation to the prevalence of comorbidities not related to the viral agent itself, showed a predominance (53.2%) of osteopenia/osteoporosis both in the group that had been on treatment for 10 years and in the group without treatment, the latter being associated with the chronic inflammatory process caused by HIV itself, leading to bone mineral loss.

In the present study, when evaluating metabolic alterations, cardiovascular risk and bone changes in relation to the same age in both groups, it was possible to observe a predominance of metabolic alterations, such as diabetes *mellitus* and dyslipidemia, among the age groups of 50 to 60 years and 60 years old or more. It should be noted that this factor was independent of the time of diagnosis and time of treatment of the participants analyzed. On the other hand, people who had been diagnosed and on ART for less than five years showed greater cardiovascular risk and bone changes in the 48 to 55-year-old age group.

Among the limitations encountered during the development of this study, the difference in age between the individuals in the two groups was striking, which may have been directly related to the results obtained in this study. Another limiting factor was the failure to evaluate the specific ART regimens in the two study groups, especially in G1, due to the difficult of a more accurate analysis of the many therapeutic regimens used over the years.

Conclusion

This study showed that there is a higher risk of comorbidities not associated with HIV in people with more than 20 years of diagnosis and under ART treatment, but it was not possible to relate the diseases to the length of treatment as a risk for their development.

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Author contributions

L.B.C.V and L.R.S wrote the main manuscript text and L.B.C.V prepared all the tables in the manuscript. L.B.C.V carried out data collection. L.B.C.V, L.R.S and J.E.C performed statistical data analysis. L.B.C.V and L.R.S developed the study methodology.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

The questionnaire and Methodology of this study were approved by Universidade Estadual Paulista "Júlio de Mesquita Filho' Human Research Ethics Committee Botucatu-SP (Faculty of Medicine), with approval number 52625821.2.0000.5411. The datasets generated and/or analyzed during the current study are not public available due to [REASON WHY DATA ARE NOT PUBLIC] but are available under reasonable request accesing the Author.

Competing interests

The authors declare no competing interests.

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