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REVIEW ARTICLE

Controversies of Arterial Hypertension in People Living with HIV on Antiretroviral Treatment

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Abstract

Introduction: Antiretroviral therapy (ART) in HIV carriers increased the life expectancy of this population, favoring the emergence of cardiovascular and metabolic diseases and cancer as the main causes of death.

Objective: to review the literature on the prevalence of arterial hypertension (AH) and associated factors in HIV carriers using ART.

Methods: The literature of the last ten years was been reviewed, using the PubMed, SciELO, IBECS and LILACS databases and the descriptors: *antiretroviral therapy highly active*; *acquired immunodeficiency syndrome; hypertension and HAART (highly active antiretroviral therapy)*. Review articles, case reports, letters to the editor, studies with HBV / HCV co-infected and experimental studies were been excluded.

Results: Nineteen studies were been selected, totaling 47,753 patients. The prevalence of HA ranged from 8.0% to 45.0%. The studies identified high body mass index, advanced age, male sex, smoking, high cholesterol, low HDL cholesterol, hypertriglyceridemia, diabetes mellitus, central obesity, family history of hypertension, previous cardiovascular event, time of HIV diagnosis, ART, time of ART use, ART with protease inhibitors (PIs) and CD4 ≥ 200 cells / ml as factors associated with HA. Multivariate analyzes reported associations with family history of HA, aging, various antiretroviral regimens, male gender, previous cardiovascular event, time of HIV diagnosis, central obesity, diabetes, metabolic syndrome, and time of ART.

Conclusion: The prevalence of AH in HIV patients varies widely according to the population studied. In these individuals, in addition to the association with classic risk factors, AH is also related to viral infection and the use of ART.

Keywords

Acquired Immunodeficiency Syndrome, Metabolic syndrome, Antiretroviral therapy, Prevalence, HIV/AIDS

Introduction

According to UNAIDS, in 2017, 36 million people in the world were living with HIV (PLWHA) and due to the rapid increase in antiretroviral therapy (ART) coverage, more than 20 million (54.0%) had access to adequate treatment. In Latin America in 2016, 58.0% of the population with HIV received ART [1].

The expansion of antiretroviral therapy markedly increased the life expectancy of PLWHA. On the other hand, the lengthening of life for a longer time facilitated the appearance of diseases related to increasing age, among which we can include cardiovascular and metabolic diseases and cancer, which now emerge as the main causes of death in this population [2]. In addition to this, HIV infection became a disease of chronic course, with uncertain long-term complications that justify the investigation of the effects of the same infection, as of the treatment on the health of the carriers [3].

The possible association between ART and arterial hypertension (AH) has been a focus of attention by the scientific community. However, several studies that have been published regarding the association, their results are controversial [4,5]. It is suspected that factors such as time of infection with HIV, time of ART use, exposure

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to different types of therapeutic regimens, and PIs may be considered risk factors for arterial hypertension [6-9]. A systematic review published on the subject points to classic risk factors for high blood pressure such as obesity, advanced age, smoking, among others, they behave in the same way in the person with HIV [5].

Given the above, the objective of this study was to review the literature of the last 10 years on the prevalence of arterial hypertension (AH) and associated factors, in patients living with HIV using ART.

Methods

A narrative review has been carried out using the data banks of Pubmed, *Scientific Electronic Library Online* (Scielo), IBECS and LILACS. The articles published in English, Portuguese and Spanish were included between 2010 and 2020. The descriptors were initially verified on the Virtual Health Library site (http://decs.bvs.br/) and at the *National Center for Biotechnology Information* (https://www.ncbi.nlm.nih.gov/mesh) and thus defined: antiretroviral therapy highly active (HAART); acquired immunodeficiency syndrome; hypertension and HAART (*Medical Subject Heading*).

Studies published in the last ten years were included that will address the issue of arterial hypertension and associated factors in patients with HIV /AIDS receiving ART. Review articles, Updates, case reports, letters to the editor, studies with HBV/ HCV co-infected patients, and experimental studies were excluded.

Results

The search returned 209 articles. After applying the filters by period, language, delimitation of studies in humans and abstracts, 91 articles were been excluded for having more than 10 years of publication and 61 for not meeting the inclusion criteria or being duplicated. 57 articles were selected, four were review articles and 34 with content irrelevant for the purpose of this study, including other diseases and HIV/HCV/HBV coinfection among others, 25 articles were included in this review totaling 41,306 patients (Figure 1).

Table 1 shows the prevalence of AH and associated factors reported in the selected articles, showing a variation ranging from 12.7% in the study with the Ethiopian population to 45.6% in the Malaysian study. The majority (64.0%) of the studies were been done in Africa.

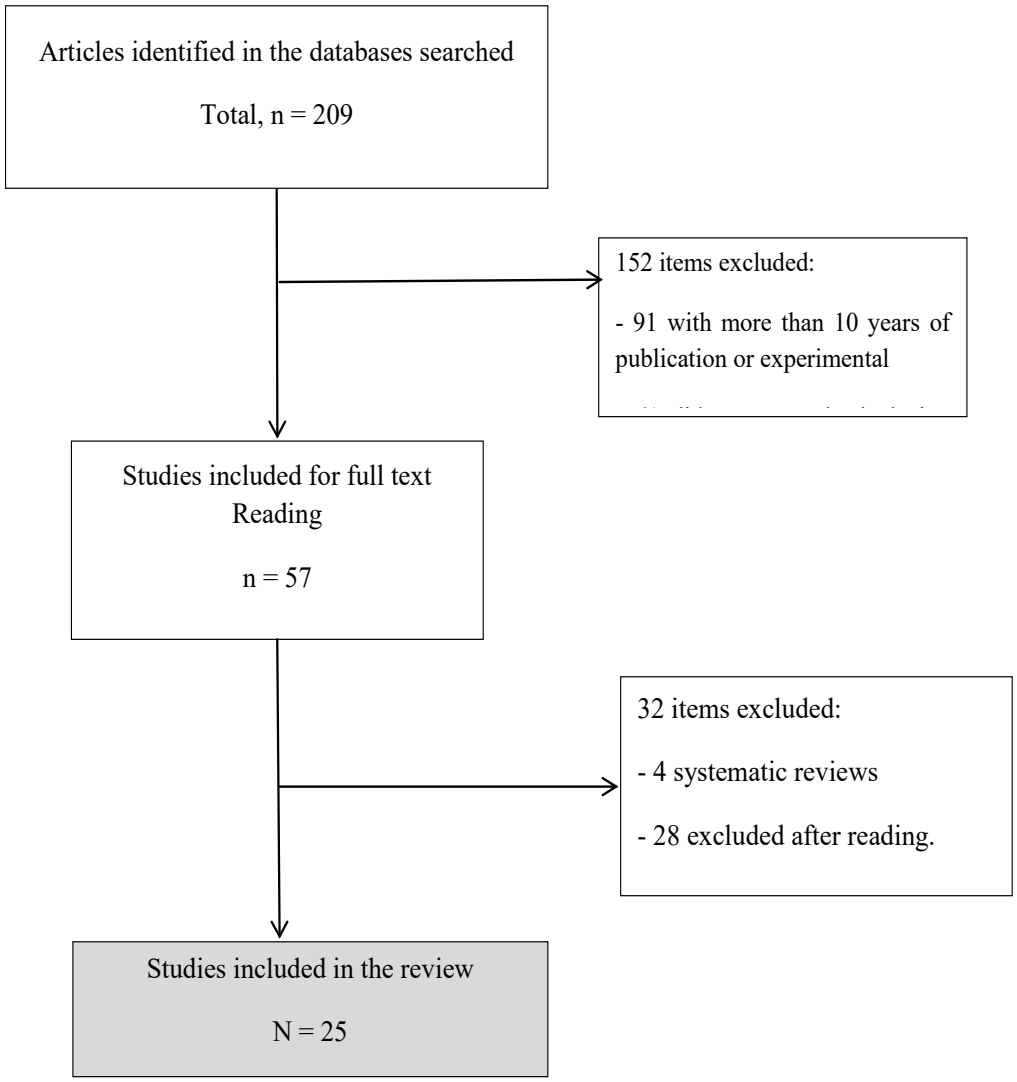

Figure 1: Study selection flowchart.

Table 1: Prevalence of arterial hypertension, and associated factors in bivariate analyzes and multivariate models, in HIV/AIDS carriers.

N°	Author/ Year	Country	N	Prevalence AH	Associated variables in the bivariate analysis with AH.	Associated variables in multivariate models with AH
1	Arruda, et al. [10]	Brazil	958	25.6%	High TG, male sex, high BMI, CD4 count ≥ 200 cells / ml.	
2	Bernardino, et al. [34]	Spain	310	39.0%	Central obesity, ART, family history of AH, advanced age and CD4 count ≥ 200 cells/ ml.	Family history of AH OR = 2.24 (p = 0.027), age increase OR = 1.08 (P < 0.001), number of different antiretroviral regimens OR = 1.2 (p = 0.001), and female gender OR = 0.27 (p = 0.02).
3	Malaza, et al. [39]	South Africa	14198	27.9%		Obesity in men OR = 2.99 95% CI (2.00-4.48), in women OR = 1.64 95% CI (1.39-1.92) and obesity (BMI > 30) for men OR = 1.53 95% CI (1.14-2.06).
4	Mateen, et al. [11]	Uganda	5563	27.9%	Black ethnicity, DM, high BMI, CD4 count ≥ 200 cells/ ml, older age, and time of HIV/AIDS illness.	
5	Krauskopf, et al. [14]	United States	2390	22.0%	Smoking, high cholesterol, older age, and ART based PIs	
6	Nuesch, et al. [35]	Switzerland	10361	25.0%	Smoking, high total cholesterol, older age, and ART based PIs	
7	De Socio, et al. [12]	Italy	1182	29.3%	Age ≥ 50 years, BMI ≥ 25 kg/ m2, family history of CVD, previous cardiovascular event, central obesity, metabolic syndrome, diabetes, time of HIV diagnosis (years) and time of exposure to ART.	Age ≥ 50 years OR = 1.94 95% CI (1.46-2.56); men vs. women OR = 1.63 95% CI (1.18–2.26); BMI ≥ 25 kg/m^2 OR = 2.52 95% CI (1.91–3.33); family history of CVD OR = 1.58 95% CI (1.18-2.12); previous cardiovascular event OR = 3.14 95% CI (1.65-5.99); central obesity OR = 1.42 95% CI (1.03-1.97); Metabolic Syndrome OR = 5.67 95% CI: (4.16-7.73); DM OR = 2.66 95% CI (1.65-4.27); time to HIV diagnosis (years) OR = 1.20 95% CI (1.05-1.36) and time to ART OR = 1.22 95% CI (1.08-1.36).
8	Hejazi, et al. [18]	Malaysia	340	45.6%		Male gender OR = 3.03 95% CI (1.18 - 7.79) and BMI OR = 1.26 95% CI (1.03 - 1.55).
9	Ogunmola, et al. [31]	Nigeria	403	19.0%	Obesity	Obesity (p < 0.05)
10	Peck, et al. [29]	Tanzania	150	28.7%		Age OR = 1.07 95% CI (1.04-1.09), current alcohol consumption OR = 0.13 95% CI (0.02-0.99), high BMI OR = 1.09 95% CI (1.03- 1.15) and CD4 count ≥ 200 cells/ml OR = 4.33 95% CI (1.51-12.40)
11	Antonello, et al. [13]	Brazil	1009	22.5%	Older age, smoking, cocaine use, obesity, diabetes, dyslipidemia, and viral load < 50 copies/ml	Age > 40 years and prevalence of HA = 1.99 95% CI (1.17 - 3.34).
12	Dimala, et al. [20]	Cameroon	200	28.5%	Advanced age, male sex, smoking, obesity, ART, and HIV infection over 30 months	Male gender OR = 2.77 95% CI (1.09 - 7.03) and obesity OR = 2.75 (1.09 - 6.91)
13	Menanga, et al. [7]	Cameroon	53	43.2%	HDL low cholesterol and high total cholesterol.	
14	Nsagha, et al. [9]	Cameroon	160	29.4%	ART and ART time.	

15	Sander, et al. [15]	Uganda	426	26.3%	High BMI and CD4 between 200 to 350 cells/cc.	Age OR = 1.08 95% CI (1.04 - 1.12) and high BMI OR = 1.15 95% CI (1.05 - 1.26).
16	Rabkin, et al. [17]	South Africa	175	37.7%	Smoking, ART, high BMI and family history.	
17	Dimala, et al. [28]	Cameroon	100	38.0%	Male gender and older age.	Age > 40 years OR = 2.29 (p = 0.001); male sex OR = 3.08 (p = 0.004) and obesity OR = 2.48 (p = 0.014).
18	Divala, et al. [25]	Malawi	952	23.7%	Advanced age, duration of ART greater than 24 months, overweight, obesity and proteinuria	Age between 45 - 54 OR = 4.50 95% CI (2.55 - 7.95), Age greater than 55 years OR = 7.46 95% CI (4.02 - 13.84), Obesity OR = 3, 67 95% CI (1.56 - 8.64) and proteinuria 2+ OR = 8.25 95% CI (1.25 - 54.44).
19	Okpa, et al. [22]	Nigeri	112	19.5%	Older age, overweight, obesity, and family history of AH	
20	Rogalska-Płońska, et al. [38]	Poland	417	28.0%	Older age, male, BMI > 30, high LDL, fasting hyperglycemia and high TG.	Age ≥ 50 years OR = 12.8 95% CI (4.26 - 38.75), male sex OR = 1.86 95% CI (1.05 - 3.30), BMI > 30 OR = 11.34 95% CI (1.22 - 104.89) and time of HIV infection +10 years OR = 1.86 95% CI 1.14 - 3.04)
21	Ataro, et al. [21]	Ethiopia	425	12.7%	Advanced age, increased abdominal circumference, increased waist / hip ratio, hyperglycemia, ART ≥ 5 years, total cholesterol ≥ 200 mg/dl, LDL cholesterol greater than 130 mg/dl, BMI ≥ 25 and drinking alcohol	Increased waist/hip ratio OR = 4.6 95% CI (1.6 - 13.3), Glycaemia ≥ 126 OR = 3.5 95% CI (1.1 - 11.4), ART ≥ 5 years OR = 2.3 95% CI (1.1 - 5.1), Cholesterol total ≥ 200 OR = 3.9 95% CI (1.3 - 1.9), current CD4 < 500 cells/cc OR = 2.7 95% CI (1.3 - 5.6) and drink alcohol OR = 3.4 95% CI (1.5 - 8.1)
22	Ngu, et al. [26]	Cameroon	311	24.8%	Central overweight and obesity.	Age > 45 years OR = 1.56 95% CI (0.89 - 2.74), Overweight OR = 1.76 95% CI (0.92 - 3.40), central obesity OR = 1.62 95% CI (0.82 - 3.18) and family history of AH OR = 0.64 95% CI (0.37-1.10)
23	Chireshe, et al. [24]	South Africa	600	29.9%	Older age, alcohol consumption, overweight, smoking, longer duration of ART and family history of hypertension	Participants aged 60 years and older and those who had been on ART between 5 and 10 years OR: 8.77 95% CI (3.28 - 23.47)
24	Pangmekeh, et al. [23]	Cameroon	315	36.4%	Use of ART and ART including Tenofovir/ Lamivudine/Efavirenz	Use of ART OR = 3.86 95% CI (1.98 - 7.50)
25	Vargas-Pacherrez, et al. [27]	Brazil	196	41.8%	Older age, overweight, increased abdominal circumference, family history of AH, AIDS-defining disease, HIV diagnosis > 12 years, > 2 ART regimens and ART based on PIs.	Age OR = 1.09 95% CI (1.04 - 1.13), overweight OR = 4.20 95% CI (1.84 - 9.61), increased abdominal circumference OR = 2.77 95% CI (1.12 - 6.89), family history of AH OR = 2.94 95% CI (1.25 - 6.89) and use of more than 2 ART regimens OR = 3.84 95% CI (1.31 - 11.30)

OR: Odds Ratio; BMI: Body Mass Index; AH: Arterial Hypertension; HDL: High-Density Cholesterol; LDL: Low-Density Cholesterol; ART: Antiretroviral Therapy, PIs: Protease Inhibitors; DM: Diabetes Mellitus; CVD: Cardiovascular Disease; MS: Metabolic Syndrome; TG: Triglyceride; AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus.

Table 1 shows that among the bivariate analyzes, older age was identified, high body mass index, male sex, smoking, high cholesterol, low HDL cholesterol, hypertriglyceridemia, diabetes mellitus, central obesity, family history of hypertension, cardiovascular event previous time, time of diagnosis of HIV, ART, time of ART use, ART based PI and CD4 ≥ 200 cells/ml as factors associated with AH. In the final column of the same table, it is also observed that the multivariate analyzes reported associations with HA in people living with HIV to family history, aging, use of several antiretroviral regimens, male gender, previous cardiovascular event,

time of diagnosis of HIV, central obesity, diabetes, metabolic syndrome, and ART time.

Discussion

This review showed that the prevalence of arterial hypertension (AH) in HIV carriers has a wide range from 8.0% to 45.0% [6-27], a result that will depend on the population studied. The prevalence of pre-hypertension was reporting in two studies 42.0% [8] and 34.0% [10].

Regarding the factors associated with AH in this population, the results can be divided into two groups, association with classic risk factors, such as age, family history of AH, obesity, among others, and those related to HIV infection and ART [14,15]. Many studies showed that patients with HIV behave in a similar way to those without infection, and regarding the association between HA and risk factors, they are already known.

Risso, et al. observed that the prevalence of AH in HIV-carriers under 40 years of age varied between 12.0-20.0%, yet it reaches a frequency of 35.0% to 41.0% in those over 40 years of age [6], demonstrating a positive association with age. Other studies corroborate these findings by demonstrating a higher frequency of AH in patients older than 50 years [12,14,15,18,28-30]. A positive association was also described between HA and body mass index [6,7,12,14,15,18,28-30], male sex [12,18,30-32], smoking, black ethnicity [14], hypercholesterolemia [14], lipodystrophy [14,33], hypertriglyceridemia [10,31], diabetes mellitus or hyperglycemia [11,12,15], increased abdominal circumference [12,34], low HDL cholesterol [7,28], family history for AH [17,34] independent of patients with or without HIV/AIDS and whether or not they are on ART.

Furthermore, several studies are favorable to the association between AH and HIV-infection or ART. Palacios et al, in a longitudinal study observed an increase in blood pressure after 48 weeks of ART [30]. Bernardino, et al. [34], studying PLWHA, in a hospital in Spain, reported a prevalence of 15.0% of AH with ambulatory monitoring and 39.0% of isolated AH and concluded that this last measure is useful for screening hypertensive patients in that population [34]. In those patients who switch to ART [7,9,17,34], time of HIV disease [11,28], type of antiretroviral treatment, especially those taking PIs [14] and have CD4 ≥ 200 cells/ml [9-11,34], were associated with AH [35]. Nüesch, et al. [35], reported an increase in systolic blood pressure with cumulative exposure to NNRI , PIs and triple treatments, in addition to the association with cardiovascular events [22,35] especially with Indinavir [36], Bloomfiel, et al. (2011) found that the period of exposure to PIs wasn't associated with high blood pressure [37], Ingjerd W, et al (2012) found that long exposure to ART (OR = 1.13, 95% CI, 1.03-1.24) and CD4 count ≤ 50 cells/ml (OR = 2.48; 95% CI 1.27-4.83) were independent factors of hypertension [31,33]. Ogunmola, et al. [31] comparing HIV positive patients and HIV patients in Nigeria, with and without ART and found a positive association between HA and ART [31].

By separately analyzing the articles that used multivariate analysis, it is possible to observe a positive association between arterial hypertension and the variables, family history of AH [12], aging [12,15,18,28,29,38], number of different antiretroviral regimens [34], male gender [8,18], previous cardiovascular event [12], family history of cardiovascular disease [12], time of diagnosis with HIV [12,38], central obesity [12,15,18,31,39], diabetes [12], metabolic syndrome [12] and time of ART [12].

It is worth highlighting that the associations of AH with the different therapeutic regimens, time of HIV-diagnosis and time of ART are closely related to age, which is an important risk factor for AH [40]. In other words, the longer the HIV carrier lives, the greater the exposure to ART and the greater the possibility of using different therapeutic regimens, being older, a fact that increases the risk of arterial hypertension. Furthermore, the age variable deserves special attention in this scenario before we can conclude on the relationships of HIV infection and its treatment with arterial hypertension [41].

Conclusion

In conclusion, the prevalence of AH in HIV/AIDS carriers is slightly higher when we compare those without infection and is associated with known classical risk factors. However, the results are controversial; there is evidence in favor of the association with factors related to HIV-infection and antiretroviral therapy, deserving to highlight the role of age in this relationship.

Ethics Approval and Consent to Participate

A research ethics committee of the Faculdade de Medicina da Bahia approved the project. No. 1,035,826.

Human and Animal Rights

No animals were used in this research.

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This study had no external funding sources.

Conflict of Interest

I declare no relevant conflict of interest.

Contributions for Authors

Conception and design of the research: Daniel Vargas; Data collection: Daniel Vargas; Analysis and interpretation of the data and Statistical analysis: Daniel Vargas; Writing of the manuscript: Daniel Vargas; Critical revision of the manuscript for important intellectual content: Daniel Vargas.

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