

Dynapenia and quality of life in HIV-infected individuals

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ABSTRACT

The appearance of effective antiretroviral therapy (ART) has transformed the evolutionary profile of acquired human immunodeficiency virus (HIV) into a chronic disease, with increased life expectancy but complications related to its use, such as muscle weakness. **Objective:** Describe the occurrence of dynapenia and its relationship with quality of life in HIV infected individuals. **Methods:** This is a cross-sectional observational study, in which handgrip strength was evaluated with handgrip dynamometry. HIV-infected individuals aged ≥ 18 years and ability to have muscle strength measured were included. The diagnosis of dynapenia was determined by the literature for handgrip strength evaluation and body mass index (BMI). Short-Form Health Survey (SF-36) was used to evaluate the quality of life, and other variables such as time to use ART and the Charlson Comorbidity Index (CCI), as well as age, gender and weight were recorded. **Results:** The presence of dynapenia was 11.6% in the sample studied. There was an association of dynapenia with the variables age ($p = 0.0001$), presence of comorbidities ($p = 0.0001$), lower handgrip strength ($p = 0.0001$) and lower BMI ($p = 0.033$). The quality of life has been compromised in both the physical and mental domains. **Conclusion:** There is dynapenia in part of the individuals with HIV and its association with poorer quality of life was found, what suggests the necessity of screening and treatment of this often underreported health problem in this population.

Keywords: HIV Seropositivity, Muscle Weakness, Quality of Life

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INTRODUCTION

Since the initial description of Acquired Immunodeficiency Syndrome (AIDS) in the late 1970s, the history of human immunodeficiency virus (HIV) infection has been marked by several important therapeutic advances.¹ The morbidity and mortality of HIV infection have declined rapidly along with the implementation of these therapeutic strategies.² Nevertheless, the prevalence of HIV and AIDS continued to grow. Data from 2012 reveal that HIV was the fifth leading cause of mortality among young and middle-aged people in Brazil and worldwide.³

However, with the emergence of effective antiretroviral therapy (ART), the evolving profile of HIV infection has become a chronic disease, characterized by an increase in the life expectancy of patients under treatment, when compared with those who do not have access to ART, and by the appearance of complications related to the use of these drugs.⁴ This drug therapy, despite suppressing HIV replication, can cause side effects that affect activities of daily life and consequently the general quality of life of patients with AIDS.⁵

According to scientific literature, HIV-infected people undergoes skeletal muscle mass loss, which worsens with the progression of the disease and contributes to the reduction of strength and physical performance. This is because muscle mass depletion is associated with imbalances between excessive protein degradation and induced lipodystrophy concomitant with nutrient malabsorption. This phenomena result in decreased strength.⁶ This reduced muscle strength is defined as dynamapenia, and it is commonly studied in the elderly.⁷

It has been published that these muscular alterations seem to be a major cause of morbidity and mortality in these individuals⁸ and that all types of muscle complications due to HIV infection can still occur, particularly in untreated patients.⁹ Therefore, the correct management of ART is fundamental to the quality of life of people living with HIV / AIDS. Correct adherence to treatment is still a challenge, as the presence of side effects jeopardize its benefits.¹⁰ Early interventions such as adequate nutrition and strength training can help reduce the consequences of HIV.¹¹

OBJECTIVE

Due to the lack of research on the presence of dynamapenia in this population, the purpose of this study was to describe the occurrence

of dynamapenia and its relation with quality of life in HIV infected individuals in two infectious outpatient clinics.

METHODS

This is a cross-sectional observational study on dynamapenia and its impact on quality of life in 172 HIV-infected individuals, who are assisted at the Magalhães Neto Infectology Clinic and at the Specialized Diagnostic, Assistance and Research Center (CEDAP) located in the city of Salvador / Bahia, Brazil. The data collection started in December 2016 and lasted eight months.

The inclusion criteria of the study were HIV-infected patients with stable hemodynamic status, aged above 18 years, capable of understanding and executing simple external commands, with absence of dyspnea or any cardiorespiratory alteration that might interrupt the muscular strength tests. Exclusion criteria were patients who were pregnant and / or had ongoing infections.

The variables measured and collected included muscle strength, gender, age, weight and time of ART; this information was obtained from electronic medical records. The health-related quality of life (HRQoL) and the Charlson Comorbidity Index (CCI) of these individuals were assessed.

For measuring muscle strength, a dynamometry test was used to assess handgrip strength (HGS), as it is an easy way to measure muscle strength with reliable results in clinical practice. The handgrip dynamometry was obtained by measuring the maximum isometric force. To do so, individuals were asked to sit in a chair, with elbows flexed at 90 ° and to perform a maximum strength on a digital hand grip dynamometer (E Clearmodel eh10110 Santa Catarina, Brazil), with their dominant hand. Three measurements were conducted with an interval of one minute between them, and the highest measure was considered for the analysis. The criteria to define dynamapenia for men was BMI \leq 24 kg/m² and HGS \leq 29 kgf; BMI of 24.1 kg/m² to 28 and HGS \leq 30 kgf; BMI > 28 kg/m² and HGS \leq 32 kgf. For women the criteria was BMI \leq 23 kg/m² and HGS \leq 17kgf; BMI of 23.1 to 26kg/m² and HGS \leq 17.3kgf; BMI of 26.1 to 29 kg/m² and HGS \leq 18 kgf; BMI > 29 kg/m² and HGS \leq 21 kgf.¹²

The quality of life was assessed with the Short-Form Health Survey (SF-36) which is a multidimensional questionnaire with 36 items in eight domains of two main categories: physical (physical function, pain, general health and imitations due to physical health) and

mental (mental health, energy/fatigue, Social functioning and emotional well-being). This questionnaire presents a final score of zero to 100, with zero being the worst status of quality of life and 100 the best.^{13,14}

The Charlson Comorbidity Index (CCI) was also used in the study to assess the presence and the level of disease severity. The score for this index ranges from 0 to 6 for each clinical condition. In addition, for each decade of life from the age of 50, a weight is added to the index. Scores are classified into three groups: mild (CCI 1-2 points); moderate (CCI of 3-4 points); and severe (CCI \geq 5 points). The higher the score obtained, the greater the severity and risk of death of the individual.¹⁵

The methodology of this research was based on the study by Lédo et al.¹⁶ and was approved by the Ethics Review Board (ERB) of the Faculdade de Medicina da Universidade Federal da Bahia (UFBA) – Brazil (registration number: CAAE: 50509715.8.0000.5662). All participants signed the Informed Consent Form.

Initially, a descriptive analysis was conducted with the Statistical Package for Social Science (SPSS), version 20.0 for Windows. The covariance analysis (ANCONVA) with adjustments for age and the Chi-Square test were used to compare categorical variables between groups with and without dynamapenia, whenever the variables were normally distributed. The non-parametric Mann-Whitney test was used to compare the ART time, the CCI, and the SF-36 scores in the groups with and without dynamapenia. Pearson's correlation analysis was used to evaluate the linear association between HGS and age because of its normal distribution, Spearman's correlation with HGS and time ART use. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The sample consisted of 172 HIV-infected individuals, with mean age of 36 years, 72.6% of whom were male. Dynamapenia was observed in 20 individuals (11.6%) presented dynamapenia, from which 14 (70.0%) were male. In the comparison of numerical variables, there were significant differences in age, CCI, handgrip strength, weight and time of ART (Table 1).

When testing the association between age and the presence of dynamapenia, we observed that above 45 years of age, there was statistically significant higher percentage of individuals with dynamapenia (p=0.001). There was no statistical difference in the frequency of dynamapenia between the variables gender, race and use of ART (Table 2).

In the analysis of quality of life, for the domains of physical functioning, limitations due to physical health, pain, energy/fatigue and emotional well-being, patients with dynapenia

had lower means when compared to those without dynapenia. For general health, social aspects and mental health, there was no statistical difference (Table 3).

Table 1. Mean comparison of continuous variables of patients with and without dynapenia (n=172), assisted at the Magalhães Neto Infectology Clinic and CEDAP Salvador / Bahia, Brazil, 2016-2017

	With dynapenia	Without dynapenia	p-value
	Mean (SD)	Mean (SD)	
Age (years)	50.5±13.8	39.6±12.2	0.0001
Charlson Comorbidity Index	1(0-2)*	0(0-1)*	0.0001
Handgrip strength (kgf)	20.6±7.2	36.1±9.9	0.0001
Weight (kg)	59.1±18.0	68.6±14.8	0.009
Height (m)	1.66±0.09	1.70±0.09	0.097
BMI (kg/m2)	21.3±5.9	23.6±4.	0.033
Time of ART (years)**	6.0(1.5-11.25)*	2.0(1.0-10.0)*	0.138

*Median (Interquartile interval 25%-75%); **N=71 patients; CEDAP, Centro Especializado em Diagnóstico, Assistência e Pesquisa; SD, standard deviation; BMI, body mass index, ART, antiretroviral therapy.

Table 2. Demography of HIV patients with and without dynapenia (n=172) assisted at the Magalhães Neto Infectology Clinic and CEDAP Salvador / Bahia, Brazil, 2016-2017

	With dynapenia	Without dynapenia	p-value
	N(%)	N(%)	
Age			
≤ 45 years	5 (4.8)	99 (95.2)	
>45 years	15 (22.0)	53 (88.0)	
Sex			0.775
Female	6 (12.8)	41 (87.2)	
Male	14 (11.2)	111 (88.8)	
ART			0.185
Yes	9 (8.9)	92 (91.1)	
No	11 (15.5)	60 (84.5)	
Ethnic			0.097
White	7 (21.8)	25 (88.2)	
Black	5 (12.8)	34 (87.2)	
Brown	8 (7.9)	93 (92.1)	

CEDAP, Centro Especializado em Diagnóstico, Assistência e Pesquisa; ART, antiretroviral therapy.

Table 3. Comparison of medians and interquartile intervals (25%-75%) of quality of life scores of patients assisted at the Magalhães Neto Infectology Clinic and CEDAP Salvador / Bahia, Brazil, 2016-2017

SF-36 domains	With dynapenia	Without dynapenia	p-value
Physical functioning	47.5(20-78.75)	90(65-100)	0.0001
Limitations due to physical health	0(0-43.75)	100(6.25-100)	0.0001
Pain	56.5(20-72)	74(61-90)	0.0002
General health	61(45-67)	67(47-82)	0.0490
Energy/fatigue	40(30-45)	45(35-63.7)	0.0420
Social functioning	68.75(50-96.9)	75(62.5-75)	0.3760
Emotional well-being	0(0-58.3)	100(0-100)	0.0030
Mental health	52(40-66)	48(36-67)	0.5100

CEDAP, Centro Especializado em Diagnóstico, Assistência e Pesquisa

In the analysis of linear association between the variables age and handgrip strength, an inverse and weak correlation ($r=-0.410$, $p=0.001$) was observed (Figure 1), as well as for handgrip strength and time of ART ($r=-0.404$, $p=0.001$), Figure 2.

DISCUSSION

This study identified dynapenia in some of the patients with HIV attended at an outpatient facility and a correlation of this comorbidity with poorer quality of life. Dynapenia is a word of Greek origin, which means "poverty of strength" initially regarded as an age-related loss of muscle strength.¹⁷ This information is relevant, since this problem is a predictor of functionality. The loss of muscle mass would be the probable contributing factor for this finding,¹⁸ agreeing with the publication by Lédo et al.¹⁶

Oliveira et al.¹⁹ demonstrated in one study that HIV infection is associated with decreased muscle strength in men when compared to groups of non-HIV infected controls. However, this lower muscle strength observed in men was not associated with a decrease in muscle mass. The presence of comorbidities and impairment of muscle activation may have played a role in the differences found and should be further investigated.²⁰

HIV infection is considered a chronic disease that is related to some degree of disability and physical impairment in affected patients.^{21,22} The physical consequences of HIV involve metabolic, neurological and structural, and inflammatory muscular abnormalities.¹⁹ In addition, the use of ART has been associated with mitochondrial dysfunction and motor impairment.²³ In the present study, of the 71 individuals (41.27%) who used ART, 15.5% presented dynapenia, corroborating with findings in the literature, what associates clinical symptoms such as myalgia and muscle weakness after the use ART.²⁰

It was also observed that, as the duration of antiretroviral therapy increases, muscle strength decreases. The same finding was observed when age was compared between the groups of patients with and without dynapenia. Moreover, in this study, higher ages was associated with a higher frequencies of dynapenia, although there was a weak inverse correlation between these variables.

In our study, subjects with dynapenia had a higher CCI, with a statistically significant

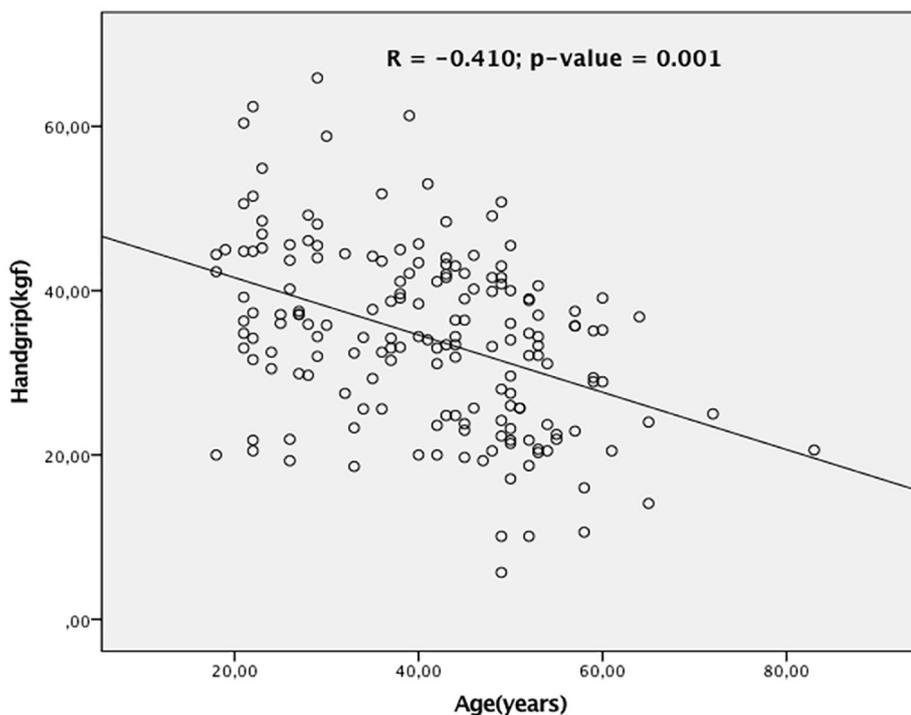


Figure 1. Correlation between handgrip strength (kgf) and age (years), n=172, Salvador 2016-2017.

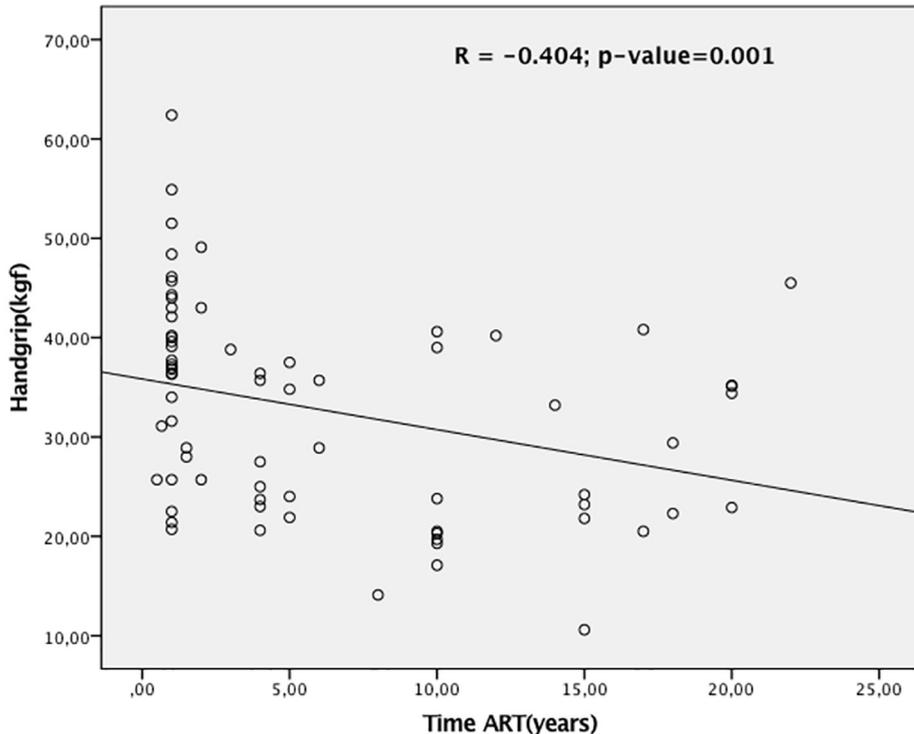


Figure 2. Correlation between handgrip strength (kgf) and time of ART (years), n=71, Salvador 2016-2017.

difference ($p=0.0001$) when compared to individuals without dynapenia. This finding agrees with studies that has shown that patients with HIV infection can often develop multiple complications, and comorbidities.^{24,25} HIV-infected patients also have an increased risk of poor physical function with unintentional weight loss, self-reported exhaustion, slow gait speed, low physical activity, and muscle weakness.²⁶ Reduced muscle strength in patients infected with HIV hinders performance in activities of daily life, which can greatly influence the functioning and social participation of the individual, compromising their HRQoL and generating a negative evolutionary cycle throughout their life.

When comparing the quality of life between both groups, we observed that patients with dynapenia had a poorer quality of life. The domains with the worst scores were physical function, limitations due to physical health, pain, energy/fatigue, and Emotional well-being, however no analysis of correlation between strength and these domains were conducted. Although the literature suggests that dynapenia may have a negative impact on health and quality of life, little is known about the repercussions of this condition in patients with HIV. Mariano et al.²⁷ identified a negative correlation between the diagnosis of handgrip strength decrease and quality of life according to two classification criteria and the SF-36 domains.

Also on quality of life of HIV-infected individuals of our study, when comparing the groups with and without dynapenia with reference to mobility aspects, such as functional capacity, physical limitation and pain, all these conditions were more affected in the dynapenia group, with a statistically significant differences between both groups. However, longitudinal studies should be conducted to confirm this finding, since in the literature it is non-existent, despite the possible correlation.

Bohannon et al.²⁸ reported associations of low handgrip strength in HIV-infected patients with future mortality, disability, functional decline and loss of independence, and a variety of disorders, commonly associated with decrease in muscle strength and also poor quality of life. However, even in the presence of these correlations, the present study did not evaluate the relationship between mortality and dynapenia, an

approach that should be evaluated in future studies. A positive association between quality of life of HIV-infected patients and the practice of physical exercise is already described in the literature, due to changes in lifestyle. These changes allow improvements in body composition, metabolic efficiency, joint mobility, posture, cognitive functions, perception of self-image and socialization, what seem to improve general function and satisfaction.²⁹ Therefore, comprehending these results for clinical practice is necessary, since the understanding of motor deficiencies associated with the infection can be addressed by specific interventions such as strength training and nutritional support.³⁰

Garcia et al.³¹ when evaluated the effects of combined training of HIV-infected patients, with 60-minute sessions of resistive exercises and aerobic training performed 3 times a week for 20 weeks, verified that this program managed to modify health-related variables. This program has also restored antioxidant mechanisms, proving to be beneficial for the quality of life of these patients.

Nevertheless, causal inferences was not possible to be addressed in our study given the cross-sectional design. Also the lack of a control group with healthy individuals made a more accurate comparison impossible. In addition, although expensive and sophisticated laboratory equipment could provide more accurate data for these individuals' overall muscle strength, such as the isokinetic dynamometer, when dealing with needy and outpatient populations, the handgrip dynamometer may be a better evaluation alternative. Thus, prospective follow-up longitudinal studies are suggested to better determine the impact of reduced muscle strength on quality of life and mortality, as well as on the associated factors of HIV-infected patients.

CONCLUSION

Dynapenia was found in part of the patients included in our study and an association of this comorbidity with poorer quality of life was found, especially in the physical functioning domains, limitation due to physical health, pain, energy/fatigue and limitations due to emotional

aspects. This finding suggests patients with HIV/AIDS need proper screening and treatment of this commonly under-reported public health problem. Also, performing proper muscle strengthening exercises can help improve muscle strength in these individuals.

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REFERENCES

1. Authier FJ, Chariot P, Gherardi RK. Skeletal muscle involvement in human immunodeficiency virus (HIV)-infected patients in the era of highly active antiretroviral therapy (HAART). *Muscle Nerve*. 2005;32(3):247-60. DOI: <http://dx.doi.org/10.1002/mus.20338>
2. Ippolito G, Galati V, Serraino D, Girardi E. The changing picture of the HIV/AIDS epidemic. *Ann N Y Acad Sci*. 2001;946:1-12. DOI: <http://dx.doi.org/10.1111/j.1749-6632.2001.tb03899.x>
3. A ONU e a resposta à AIDS no Brasil. Brasília: UNAIDS; 2013.
4. Authier FJ, Gherardi RK. Muscular complications of human immunodeficiency virus (HIV) infection in the era of effective anti-retroviral therapy. *Rev Neurol (Paris)*. 2006;162(1):71-81.
5. Patil R, Shimpi A, Rairikar S, Shyam A, Sancheti P. Effects of fitness training on physical fitness parameters and quality of life in human immunodeficiency virus-positive Indian females. *Indian J Sex Transm Dis*. 2017;38(1):47-53. DOI: <http://dx.doi.org/10.4103/0253-7184.196886>
6. Dudgeon WD, Phillips KD, Carson JA, Brewer RB, Durstine JL, Hand GA. Counteracting muscle wasting in HIV-infected individuals. *HIV Med*. 2006;7(5):299-310. DOI: <http://dx.doi.org/10.1111/j.1468-1293.2006.00380.x>
7. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. *Front Physiol*. 2012;11(3):260. DOI: <http://dx.doi.org/10.3389/fphys.2012.00260>
8. Roubenoff R. Acquired immunodeficiency syndrome wasting, functional performance, and quality of life. *Am J Manag Care*. 2000;6(9):1003-16.
9. Chariot P, Bignani O. Skeletal muscle disorders associated with selenium deficiency in humans. *Muscle Nerve*. 2003 Jun;27(6):662-8.
10. Melchior R, Nemes MIB, Alencar TM, Buchalla CM. Desafios da adesão ao Tratamento de pessoas vivendo com HIV / Aids no Brasil. *Rev Saúde Pública* 2007; 41 (Supl. 2): 87-93.
11. De Carvalho BF, Policarpo S, Moreira AC. Nutritional status and quality of life in HIV-infected patients. *Nutr*

12. Hosp.2017; 34(4):923-33.
12. Wasserman P, Segal-Maurer S, Rubin SD. High prevalence of low skeletal muscle mass associated with male gender in midlife and older HIV-infected persons despite CD4 cell reconstitution and viral suppression. *J Int Assoc Provid AIDS Care*. 2014;13(2):145-52. DOI: <http://dx.doi.org/10.1177/2325957413495919>
13. Campolina AG, Bortoluzzo AB, Ferraz MB, Ciconelli RM. Validation of the Brazilian version of the generic six-dimensional short form quality of life questionnaire (SF-6D Brazil). *Cien Saude Colet*. 2011;16(7):3103-10. DOI: <http://dx.doi.org/10.1590/S1413-81232011000800010>
14. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF36 (Brasil SF-36). *Rev Bras Reumatol*. 1999; 39(3):143-50.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83. DOI: [http://dx.doi.org/10.1016/0021-9681\(87\)90171-8](http://dx.doi.org/10.1016/0021-9681(87)90171-8)
16. Lédo APO, Neves JS, Martinez BP, Neto MG, Brites C. Sarcopenia em uma amostra de indivíduos infectados HIV atendidos a nível ambulatorial. *Rev Pesq Fisioter*. 2017;7(3):351-358.
17. Manini TM, Clark BC. Dynapenia and aging: an update. *J Gerontol A Biol Sci Med Sci*. 2012;67(1):28-40.
18. Raso V, Shephard RJ, Rosário Casseb JS, Silva Duarte AJ, D'Andréa Greve JM. Handgrip force offers a measure of physical function in individuals living with HIV/AIDS. *J Acquir Immune Defic Syndr*. 2013;63(1):e30-2.
19. Oliveira VH, Wiechmann SL, Narciso AM, Webel AR, Deminice R. Muscle strength is impaired in men but not in women living with HIV taking antiretroviral therapy. *Antivir Ther*. 2018;23(1):11-19. DOI: <http://dx.doi.org/10.3851/IMP3159>
20. Erlanson KM1, Schrack JA, Jankowski CM, Brown TT, Campbell TB. Functional impairment, disability, and frailty in adults aging with HIV-infection. *Curr HIV/AIDS Rep*. 2014;11(3):279-90. DOI: <http://dx.doi.org/10.1007/s11904-014-0215-y>
21. HIV Neuromuscular Syndrome Study Group. HIV-associated neuromuscular weakness syndrome. *AIDS*. 2004;18(10):1403-12. DOI: <http://dx.doi.org/10.1097/01.aids.0000131309.70451.fe>
22. Grau JM, Masanés F, Pedrol E, Casademont J, Fernández-Solá J, Urbano-Márquez A. Human immunodeficiency virus type 1 infection and myopathy: clinical relevance of zidovudine therapy. *Ann Neurol*. 1993;34(2):206-11. DOI: <http://dx.doi.org/10.1002/ana.410340217>
23. Arnaudo E, Dalakas M, Shanske S, Moraes CT, DiMauro S, Schon EA. Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy. *Lancet*. 1991;337(8740):508-10. DOI: [http://dx.doi.org/10.1016/0140-6736\(91\)91294-5](http://dx.doi.org/10.1016/0140-6736(91)91294-5)
24. Currier JS, Havlir DV. Complications of HIV disease and antiretroviral therapy. *Top HIV Med*. 2009;17(2):57-67.
25. Chu C, Pollock LC, Selwyn PA. HIV-associated complications: a systems-based approach. *Am Fam Physician*. 2017;96(3):161-9.

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26. Baranoski AS, Harris A, Michaels D, Miciek R, Storer T, Sebastiani P, et al. Relationship between poor physical function, inflammatory markers, and comorbidities in HIV-infected women on antiretroviral therapy. *J Womens Health (Larchmt)*. 2014;23(1):69-76. DOI: <http://dx.doi.org/10.1089/jwh.2013.4367>
 27. Mariano ER, Navarro F, Sauaia BA, Oliveira Junior MNS, Marques RF. Força muscular e qualidade de vida em idosos. *Rev Bras Geriatr Gerontol*. 2013;16(4):805-11. DOI: <http://dx.doi.org/10.1590/S1809-98232013000400014>
 28. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. *J Geriatr Phys Ther*. 2008;31(1):3-10. DOI: <http://dx.doi.org/10.1519/00139143-200831010-00002>
 29. Medeiros RCDSC, Medeiros JA, Silva TALD, Andrade RD, Medeiros DC, Araújo JS, et al. Quality of life, socioeconomic and clinical factors, and physical exercise in persons living with HIV/AIDS. *Rev Saude Publica*. 2017;51:66
 30. Cava E, Yeat NC, Mittendorfer B. Preserving healthy muscle during weight loss. *Adv Nutr*. 2017;8(3):511-9. DOI: <http://dx.doi.org/10.3945/an.116.014506>
 31. Garcia A, Fraga GA, Vieira RC Jr, Silva CM, Trombeta JC, Navalta JW, et al. Effects of combined exercise training on immunological, physical and biochemical parameters in individuals with HIV/AIDS. *J Sports Sci*. 2014;32(8):785-92. DOI: <http://dx.doi.org/10.1080/02640414.2013.858177>