Original article

Aging, neurocognitive impairment and adherence to antiretroviral therapy in human immunodeficiency virus-infected individuals

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A B S T R A C T

Background/objective: There is an increasing number of older patients with human immunodeficiency virus infection due to the success of antiretroviral therapy, the improved prognosis and life expectancy of patients, and the higher number of new infections among older individuals. The main objective of the present study was to compare the characteristics of older human immunodeficiency virus patients with those of younger patients.

Materials and methods: We conducted a cross-sectional study with human immunodeficiency virus-infected patients who were treated at the Specialized Care Service (Serviço de Assistência Especializada) for human immunodeficiency virus/AIDS in the city of Pelotas, South Brazil. Sociodemographic information as well as data on human immunodeficiency virus infection and treatment were collected. All participants underwent psychiatric and neurocognitive assessments, and their adherence to antiretroviral therapy was evaluated.

Results: A total of 392 patients participated in the study, with 114 patients aged 50 years and older. The characteristics showing significant differences between older and younger human immunodeficiency virus-infected patients included race/ethnicity, comorbidities, duration and adherence to antiretroviral therapy, currently undetectable viral load, and cognitive impairment. Compared to younger patients, older patients were at higher risk of exhibiting cognitive impairment [OR 2.28 (95% CI: 1.35–3.82, $p = 0.002$)] and of having increased adherence to antiretroviral therapy [OR 3.11 (95% CI: 1.67–5.79, $p < 0.001$)].

Conclusions: The prevalence of neurocognitive impairment remained high in human immunodeficiency virus-infected patients despite antiretroviral therapy. In the present

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study, the prevalence of this type of impairment was significantly higher in patients aged ≥50 years, most likely due to aging, human immunodeficiency virus infection, and a possible synergistic effect between these factors. Despite this higher prevalence, older patients exhibited higher rates of adherence to antiretroviral therapy and of undetectable human immunodeficiency virus viral load.

Introduction

With the advent of antiretroviral therapy (ART), the prognosis of human immunodeficiency virus (HIV)-infected individuals has dramatically improved. The evolution of this therapy into less complex regimens that are safer, easier to administer, and have fewer side effects allows for viral replication to be controlled indefinitely in most patients.[1,2] Despite the success of ART, which led to the reduction of HIV-related opportunistic diseases, HIV-infected individuals exhibit an increase in non-AIDS-defining illnesses that are typically related to aging, such as cardiovascular diseases, dyslipidemia, diabetes mellitus, cancer, liver diseases, renal diseases, bone disorders, and neurocognitive impairment (NCI).[3,4] Aging is accelerated in HIV-infected patients compared to non-HIV-infected patients, with subjects aged 50 years and above being considered elderly.[4–7] Several factors have been associated with the above-mentioned differences in aging, including chronic HIV infection, ART side effects, and accelerated aging of the immune system.[8–10]

NCI in HIV-infected patients has remained highly prevalent even after the advent of ART. In addition to changes associated with HIV (HIV-associated neurocognitive disorder – HAND),[11,12] other factors traditionally related to cognitive impairment are present in HIV-infected patients and have a significant association with cognitive impairment in this population. The contribution of aging to the persistence of NCI has driven growing interest in the study of patients using ART. Several reports have shown a higher prevalence of cognitive impairment among older HIV-infected patients compared to younger patients using ART.[13–16]

There has been an increase in the population of older HIV-infected adults due to increased number of new HIV infections at more advanced ages, the chronic nature of the infection, and increases in life expectancy.[17,18] Further studies are necessary to better understand this population. The objectives of this study were to (i) compare the characteristics of younger HIV-infected patients with those of the older patients; (ii) assess the prevalence of cognitive impairment in HIV-infected patients after the advent of ART; (iii) determine whether an association exists between cognitive impairment and aging among other factors; and (iv) compare ART adherence in HIV-infected patients aged ≤50 years with adherence of younger patients.

Materials and methods

This study was a cross-sectional study that recruited adult HIV-infected individuals diagnosed according to the protocol of the Brazilian Health Ministry. These patients were receiving care at a Specialized Center (Serviço de Assistência Especializada – SAE) for HIV/AIDS in the city of Pelotas, South Brazil, in 2015. Patients with a previous neurological disease and/or psychotic disorder were excluded from the study.

All patients treated at the SAE were invited to participate in the study, and those who agreed signed the informed consent form. The present study was approved by the Ethics Committee. Participants completed a sociodemographic questionnaire and underwent psychiatric and neurocognitive assessments. The instrument used for psychiatric assessment was the International Neuropsychiatric Interview (MINI – Plus). The neurocognitive assessment was performed using the following instruments: Grooved Pegboard Test, Color Trails Test (CTT) parts 1 and 2, Finger Tapping Test, Montreal Cognitive Assessment, and the International HIV Dementia Scale (IHDS). The cutoff point for the latter was a score of 10 or less. All of the assessments were performed within the SAE premises.

Laboratory data and clinical features were abstracted from the patients' medical records. Collected information included stage of HIV infection, use of ART, duration of treatment, time of diagnosis, CD4 counts and viral load, and comorbidities. HIV viral load was considered undetectable when less than 50 copies/mL.

Adherence to ART was measured by self-reporting and the filling of prescriptions at the pharmacy over the previous three months. The patients who reported to have not forgotten a single dose of medication in the past three days and who regularly filled the ART prescription at the SAE pharmacy over the past three months were considered adherent.

Except for the IHDS, there are no standardized cutoff points for the other neurocognitive assessment instruments in Brazil. Therefore, the scores of the remaining instruments (MoCA, CTT-1 and CTT-2, Finger Tapping Test, and Grooved Pegboard Test) were distributed into quartiles. To obtain higher specificity, the individuals who (i) scored in the upper quartile in at least three of the five instruments used, and (ii) reached the IHDS cutoff point were considered positive for NCI.

Evidence of cognitive impairment was also evaluated by the Instrumental Activities of Daily Living (IADL) scale, as standardized by the Clinical Protocol and Therapeutic Guidelines for the Management of HIV Infection in Adults of the Brazilian Health Ministry.

Sociodemographic and clinical data were subjected to descriptive analysis by calculating frequencies of categorical variables, and the means and standard deviations of continuous variables among patients aged 50 years or more and compared to those aged less than 50 years.

Multiple logistic regression was used to analyze the independent association of age with NCI adjusted for prespecified

factors of interest (age, gender, race/ethnicity, education level and cumulative years on ART), in addition to factors with a p-value ≤ 0.2 in univariate analysis. The analyses were performed using SPSS software (version 21).

A possible independent association of age and adherence to ART was also tested using multiple logistic regression.

Results

A total of 392 patients participated in the study, 114 of whom were aged 50 years or more with a mean age of 56.7 years, ranging from 50 to 82 years.

Tables 1 and 2 show a comparison of the characteristics of older and younger patients. The characteristics with significant differences included race/ethnicity, comorbidities (diabetes mellitus, hypertension and dyslipidemia), use of ART, adherence to ART, duration of ART use, currently undetectable viral load, and cognitive impairment (according to the IHDS and the combination of the IHDS and other instruments). Older patients exhibited a higher prevalence of diabetes mellitus, hypertension and dyslipidemia. ART use was more common among patients aged 50 years or more, as was the duration of ART and the rate of patients with undetectable viral loads.

There was no difference in the prevalence of depression among the patient groups. The prevalence of NCI according

Table 1 – The characteristics of HIV-infected patients aged <50 years and ≥50 years.

Characteristics	<50 years $n = 278$	≥50 years $n = 114$	p^a
Age (mean, SD)	37.15 (7.9)	56.76 (7.1)	
Gender (n, %)			
Male	124 (44.6)	51 (44.5)	1.0
Race/ethnicity (n, %)			
White	166 (59.7)	74 (64.9)	0.05
Non-white	112 (40.3)	40 (35.1)	
Education level (n, %)			
0–7 years	215 (77.4)	83 (72.9)	0.73
≥8 years	63 (22.6)	31 (27.1)	
Comorbidities (n, %)	75 (27.0)	76 (66.7)	<0.001
Use of ART (n, %)			
First-line	164 (58.9)	63 (55)	0.01
More than one ART	78 (28.6)	45 (40)	
Not using	36 (12.5)	6 (5)	
Duration of ART (years) (mean, SD)	5.3 (4.2)	6.4 (4.9)	0.03
Current CD4 count ≤200 (n, %)	41 (13.3)	15 (13.2)	0.91
CD4 nadir ≤200 (n, %)	104 (37.4)	45 (39.4)	0.41
Time of diagnosis (years) (mean, SD)	7.7 (8.5)	7.2 (5.4)	0.61
Adherents (n, %)	149 (53.5)	80 (70.3)	0.03
Current VL < 50 (n, %)	160 (57.5)	94 (82.4)	<0.001
Depression (n, %)	71 (25.7)	24 (21.3)	0.34

CD4 (cells/mm³), cluster of differentiation 4; VL (copies/mL), viral load; ART, antiretroviral therapy; SD, standard deviation; p^a values are calculated with X^2 test or Fisher exact test.

Table 2 – Neurocognitive impairment and age.

	<50 years $n = 278$	≥50 years $n = 114$	$^a p$
[b]IHDS (n, %)	139 (53.5)	73 (63.7)	0.008
[b]IHDS + [c]other tests (n, %)	81 (29.1)	61 (53.2)	<0.001
IHDS (mean, SD)	9.44 (1.9)	8.51 (2.3)	0.006
Score IADL (n, %)			0.45
≤7	0	0	
8/20	157 (56.6)	59 (52.3)	
≥21	121 (43.3)	55 (47.5)	

IHDS, International HIV Dementia Scale; IADL, instrumental activities of daily living.

[a] p-Values are calculated with X^2 test or Fisher exact test.
[c] Other test = grooved pegboard, finger-tapping, color trials 1 and 2 and MoCa.
[b] IHDS = IHDS score ≤10.

to the IHDS and the combination of the IHDS and other instruments was significantly higher in older patients. The education level was similar in both patient groups.

The association of an age ≥50 years with NCI remained significant after adjusting for gender, race/ethnicity, education level, current CD4 count, nadir CD4 count, and duration of ART [OR 2.28 (95% CI: 1.35–3.82, $p = 0.002$)]. In addition to age, other factors shown to be associated with cognitive impairment in the multivariate analysis were education level and nadir CD4 count (Table 3).

For patients using ART, adherence to treatment was significantly higher among older patients. This association remained significant after adjusting for gender, education level, nadir CD4 count, duration of treatment, depression, and presence of NCI [OR 3.11 (95% CI: 1.67–5.79, $p < 0.001$)].

Discussion

Despite the dramatic reduction in AIDS-related neurological disorders that has occurred since the advent of ART, NCI is still observed in HIV-infected patients and is a significant problem in the management of these patients. Several factors have been associated with cognitive impairment, including advanced age, lower education level, cardiovascular risk factors, CD4 nadir count, the most recent CD4 count and viral load.[11,15,19–23]

HIV frequently causes encephalopathy. Subcortical structures are mostly affected, leading to NCI, including deficits in attention, learning, memory, information processing speed, and problem solving skills.[24] In 2007, the HAND criteria were revised and classified into three conditions: asymptomatic NCI, mild neurocognitive disorder, and HIV-associated dementia (HAD). This nomenclature is referred to as the Frascati criteria.[25] Some studies have suggested that advanced age is associated with a higher prevalence of HAD. Valcour et al.[26] compared patients older than 50 years with younger patients, finding that the risk of developing HAD was increased by 3.26 (1.32–8.07)-fold in older patients compared to younger patients after adjusting for education level, race, drug addiction, the use of ART, viral load, and CD4 count. In the present study, the risk of exhibiting cognitive impairment was increased by 2.28 (1.35–3.82)-fold in older HIV-infected patients compared

Table 3 – Multivariate analysis, cognitive impairment outcome.

Characteristics	Crude model		Adjusted model	
	OR (95% CI)	p	OR (95% CI)	p
Gender[a]				
Female	1		1	
Male	1.15 (0.99–2.20)	0.06	0.75 (0.43–1.32)	0.32
Age (years)[a]				
<50	1		1	
≥50	2.04 (1.59–2.63)	0.001	2.28 (1.59–2.63)	0.002
Race/ethnicity[a]				
White	1		1	
Non-white	1.71 (1.04–2.83)	0.05	1.22 (0.98–2.03)	0.08
Education level (years)[a]				
0–7	6.72 (3.98–11.32)	<0.001	6.06 (3.98–11.32)	<0.001
≥8	1		1	
CD4 nadir[b]				
≤200	2.77 (1.57–4.89)	<0.001	2.78 (1.47–5.25)	0.02
>200	1		1	
Current CD4[b]				
≤200	1		–	
>200	0.64 (0.39–1.37)	0.27	–	

[a] Adjusted for gender, age, race/ethnicity, education level.
[b] Adjusted for duration of HIV infection, CD4 nadir, current CD4, initial VL, current VL, use of HAART, gender, age, race/ethnicity, education level.

to younger patients. The instruments used in the present study primarily allowed for assessing impairment of cognitive functions of the subcortical structures; however, it is not possible to state that this cognitive impairment is secondary to HIV activity on the central nervous system. For the diagnosis of HAND, the causes of cognitive impairment that are traditionally related to cognitive deficit and aging need to be ruled out.

Older patients have a higher risk of exhibiting neurocognitive disorders for causes that are traditionally associated with aging. Cognitive functions become impaired with aging, and age is an important risk factor for most of the neurodegenerative disorders that result in dementia. Recent longitudinal studies have shown that the worst cognitive deficits and neurological impairment in older individuals living with HIV result from (i) pathophysiological mechanisms related to HIV infection of the nervous system, (ii) aging-related factors,[27–29] and (iii) a synergistic interaction between HIV and aging.[30,31] The study by Seider et al.[30] reported significant decline in verbal memory of older HIV-infected patients. The cognitive performance of HIV-infected patients aged 50 and 60 years was similar to that of HIV-negative individuals aged 70 and 80 years, respectively. The present study showed an increased prevalence of cognitive impairment in HIV-infected patients, which is in agreement with the literature.[11,12] Furthermore, a higher prevalence of cognitive impairment was found in HIV-infected patients aged 50 years and above compared to younger HIV-infected adults, a result that is in line with other published studies.[13–16]

The prevalence of cognitive impairment is higher in older individuals in the general population, regardless of the HIV status. The main causes of dementia are Alzheimer's disease and vascular dementia. According to international data, the prevalence of Alzheimer ranges from 4.7 to 8.7% in individuals over 60 years of age,[32] and the prevalence of vascular dementia ranges from 1.2 to 4.2% in individuals over 65 years of age.[33,34] In addition to these causes of dementia, mild cognitive impairment (MCI) in also present in older individuals, affecting primarily individuals older than 65 years. The prevalence of MCI ranges from 3 to 22%,[35,36] depending on the population studied and the criteria used for its definition. Brazilian studies estimate that the prevalence of cognitive and functional impairment in older individuals is between 16 and 19.9%.[37–39] In our study, the prevalence of cognitive impairment in HIV-infected patients aged ≥50 years was 53.2%, which is higher than that reported in the literature, especially considering that the mean age of our sample was 57 years and the age considered in studies in non-infected populations is >60 years of age. The extent to which cognitive impairment is (i) secondary to HIV, (ii) secondary to other diseases (e.g., Alzheimer's disease and vascular dementia) or (iii) the result of a synergetic action of HIV with age-related factors that lead to cognitive impairment is not well understood. Comorbidities, such as diabetes, hypertension, and dyslipidemia, were more prevalent in older patients of the present study, as expected. The contribution of chronic HIV infection and the use of ART to these increased prevalence in HIV-infected patients could not be assessed in this study.

Despite the higher prevalence of NCI, adherence to ART was higher in older patients than in younger patients in the present study. Older patients used ART longer and had a higher rate of undetectable viral loads, which is consistent

with better adherence. The above-mentioned higher prevalence of adherence among older HIV-infected patients is in agreement with several studies, suggesting that patients of the age-range tended to adhere more promptly to treatment than younger patients.[40–43] A recent meta-analysis[43] showing that older HIV-infected patients had a lower risk of non-adherence reinforces this finding. Older patients generally have a higher prevalence of factors associated with non-adherence; however, paradoxically, older patients with HIV are more likely to adhere to treatment. Perhaps these patients have been able to maintain ART for a longer period of time due to different factors, such as higher tolerability, and thus are less likely to experience complications that result from severe immunodeficiency and that are responsible for higher short-term mortality.

Among psychiatric disorders, depression is frequently diagnosed in HIV/AIDS patients, with a prevalence ranging between 12% and 66%.[19,44–49] In Brazil, studies estimate a prevalence between 32% and 34%.[19,46] The study by Passos et al. in the city of Pelotas, Rio Grande do Sul State, Brazil, revealed a high risk of suicide (34.1%).[47] Notably, our study found an increased prevalence of depression both in older and younger patients, with no significant difference between the groups. Published studies comparing the prevalence of depression among older and younger HIV-infected patients have reported discordant results.[48,49]

The present study has some limitations. First, the sample of patients aged 50 years and older was small, reducing the power to detect possible associations of cognitive impairment with factors present among older patients. Second, the instruments for measuring cognitive impairment are not yet fully validated in Brazil, with the exception of the IHDS.[50] Nevertheless, the prevalence found in our study was similar to the prevalence reported in other studies.[19,21] Another limitation is the evaluation of adherence to ART. Specifically, the use of self-reporting and the short evaluation period (three months) of the filling of ART prescriptions at the pharmacy may have resulted in an overestimation of adherence. However, there was a significant association between adherence and an undetectable viral load, reinforcing the validity of the methodology.

The population of HIV-infected individuals is aging. Therefore, studies aiming at understanding the behavior of HIV infection in this population are necessary. Most of the results that have been published to date have been conducted in high income countries, where the characteristics of the older patient population differ from those of the Brazilian population. The goal of the present study was to describe the characteristics of the patient population aged 50 years and older in a sample from South Brazil. Our results were similar to those from other international studies with respect to cognitive impairment and adherence to treatment.[14,15,43] Prospective studies with a larger sample of HIV-infected individuals at advanced age in Brazil are necessary to better understand the characteristics of this population, and the results will allow for improved management of these patients. Furthermore, the easy-to-apply instruments for the diagnosis of HAND need to be validated in Brazil in order to provide a more uniform diagnosis and evaluation of factors related to NCI in our country.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. New Engl J Med. 1998;338:853–60.
2. May M, Gompels M, Delpech V, et al. Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. Brit Med J. 2011;343:1–11.
3. Masiá M, Padilla S, Álvarez D, et al. Risk, predictors, and mortality associated with non-AIDS events in newly diagnosed HIV-infected patients: role of antiretroviral therapy. AIDS. 2013;27:181–9.
4. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med. 2011;62:141–55.
5. Guaraldi G, Orlando G, Zona S, et al. Premature age related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011;53:1120–6.
6. Bhatia R, Ryscavage P, Taiwo B. Accelerated aging and human immunodeficiency virus infection: emerging challenges of growing older in the era of successful antiretroviral therapy. J Neurovirol. 2012;18:247–55.
7. Cohen RA, Seider TR, Navia B. HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? Alzheimers Res Ther. 2015;7:2–10.
8. Cañizares S, Cherner M, Ellis RJ. HIV and aging: effects on the central nervous system. Semin Neurol. 2014;34:27–34.
9. Greene M, Justice AC, Lampiris HW, Valcour V. Management of human immunodeficiency virus infection in advanced age. JAMA. 2013;309:1397–405.
10. Van Baarle D, Tsegaye A, Miedema F, Akbar A. Significance of senescence for virus-specific memory T cell responses: rapid ageing during chronic stimulation of the immune system. Immunol Lett. 2005;97:19–29.
11. Sacktor N, McDermott MP, Marder K, et al. HIV-associated cognitive impairment before and after the advent of combination therapy. J Neurovirol. 2002;8:136–42.
12. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. AIDS. 2007;21:1915–21.
13. Brew BJ. Evidence for a change in aids dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of aids dementia complex. AIDS. 2004;18:75–8.
14. Valcour V, Paul R. HIV infection and dementia in older adults. Clin Infect Dis. 2006;42:1449–54.
15. Becker JT, Lopez OL, Dew MA, Aizenstein HJ. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. AIDS. 2004;18:11–8.
16. Wendelken LA, Valcour V. Impact of HIV and aging on neuropsychological function. J Neurovirol. 2012;18:256–63.
17. Stoff DM, Khalsa JH, Monjan A, Portegies P. Introduction: HIV/AIDS and aging. AIDS. 2004;18:1–2.
18. Joint United Nations Programme on HIV/AIDS. The Gap Report; 2016.
19. Troncoso FT, Conterno LO. Prevalence of neurocognitive disorders and depression in a Brazilian HIV population. Rev Soc Bras Med Trop. 2015;48:390–8.
20. Bhaskaran K, Mussini C, Antinori A, et al. Changes in the incidence and predictors of human immunodeficiency

virus-associated dementia in the era of highly active antiretroviral therapy. Ann Neurol. 2008;63:213–21.

21. Heaton RK, Clifford DB, Franklin DR, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010;75:2087–96.

22. Yakasai AM, Gudaji MJ, Muhammad H, et al. Prevalence and Correlates of HIV-Associated Neurocognitive Disorders (HAND) in Northwestern Nigeria. Neurol Res Int. 2015:1–9.

23. McCombe JA, Vivithanaporn P, Gill MJ, Power C. Predictors of symptomatic HIV-associated neurocognitive disorders in universal health care. HIV Med. 2013;14, 99-10.

24. McArthur JC, Haughey N, Gartner S, et al. Human immunodeficiency virus-associated dementia: an evolving disease. J Neurovirol. 2003;9:205–21.

25. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69:1789–99.

26. Valcour V, Shikuma C, Watters M, et al. Higher frequency of dementia in older HIV-1 individuals. The Hawaii aging with HIV-1 cohort. Neurology. 2004;63:822–7.

27. Sacktor N, Skolasky R, Selnes OA, et al. Neuropsychological test profile differences between young and old human immunodeficiency virus-positive individuals. J Neurovirol. 2007;13:203–9.

28. Becker JT, Maruca V, Kingsley LA, et al. Factors affecting brain structure in men with HIV disease in the post-HAART era. Neuroradiology. 2012;54:113–21.

29. Ances BM, Ortega M, Vaida F, Heaps J, Paul R. Independent effects of HIV, aging, and HAART on brain volumetric measures. J Acquir Immune Defic Syndr. 2012;59:469–77.

30. Seider TR, Luo X, Gongvatana A, et al. Verbal memory declines more rapidly with age in HIV infected versus uninfected adults. J Clin Exp Neuropsychol. 2014;36:356–67.

31. Morgan EE, Woods SP, Smith C, Weber E, Scott JC, Grant I. Lower cognitive reserve among individuals with syndromic HIV-associated neurocognitive disorders (HAND). AIDS Behav. 2012;16:2279–85.

32. World Alzheimer Report 2015: The Global Impact of Dementia. http://www.alz.co.uk/research/world-report-2015.

33. Hébert R, Brayne C. Epidemiology of vascular dementia. Neuroepidemiology. 1995;14:240.

34. Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54:S4.

35. Bischkopf J, Busse A, Angermeyer MC. Mild cognitive impairment – a review of prevalence, incidence and outcome according to current approaches. Acta Psychiatr Scand. 2002;106:403.

36. Busse A, Bischkopf J, Riedel-Heller SG, et al. Mild cognitive impairment: prevalence and predictive validity according to current approaches. Acta Neurol Scand. 2003;108:71.

37. Laks J, Batista EMR, Guilherme ERL, et al. Prevalence of cognitive and functional impairment in community-dwelling elderly. Importance of evaluating activities of daily living. Arq Neuropsiquiatr. 2005;63:207–12.

38. Hototian SR, Lopes MA, Azevedo D, et al. Prevalence of cognitive and functional impairment in a community sample from São Paulo, Brazil. Dement Geriatr Cogn Disord. 2008;25:135–43.

39. Lopes MA, Hototian SR, Bustamante SE, et al. Prevalence of cognitive and functional impairment in a community sample in Ribeirão Preto, Brazil. Int J Geriatr Psychiatry. 2007;22:770–6.

40. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133:21–30.

41. Barclay TR, Hinkin CH, Castellon SA, et al. Age-associated predictors of medication adherence in HIV-positive adults: health beliefs, self-efficacy, and neurocognitive status. Health Psychol. 2007;26:40–9.

42. Holodniy M, Hornberger J, Rapoport D, et al. Relationship between antiretroviral prescribing patterns and treatment guidelines in treatment-naive HIV-1 infected US veterans (1992–2004). J Acquir Immune Defic Syndr. 2007;44:20–9.

43. Ghidei L, Simone MJ, Salow MJ, et al. Aging, antiretrovirals, and adherence: a meta analysis of adherence among older HIV-infected individuals. Drugs Aging. 2013;30:809–19.

44. Bragança M, Palha A. Depression and neurocognitive performance in Portuguese patients infected with HIV. AIDS Behav. 2011;15:1879–87.

45. Kaharuza FM, Bunnell R, Moss S, et al. Depression and CD4 cell count among persons with HIV infection in Uganda. AIDS Behav. 2006;10:105–11.

46. Silveira MP, Guttier MC, Pinheiro CA, Pereira TV, Cruzeiro AL, Moreira LB. Depressive symptoms in HIV-infected patients treated with highly active antiretroviral therapy. Rev Bras Psiquiatr. 2012;34:162–7.

47. Passos SM, Souza LD, Spessato BC. High prevalence of suicide risk in people living with HIV: who is at higher risk? AIDS Care. 2014;26:1379–82.

48. Hinkin CH, Castellon SA, Atkinson JH, Goodkin K. Neuropsychiatric aspects of HIV infection among older adults. J Clin Epidemiol. 2001;54:44–52.

49. Eller LS, Rivero-Mendez M, Voss J, et al. Depressive symptoms, self-esteem, HIV symptom management self-efficacy and self-compassion in people living with HIV. AIDS Care. 2014;26:795–803.

50. Rodrigues RA, Oliveira RL, Grinsztejn B, Silva MT. Validity of the international HIV dementia scale in Brazil. Arq Neuropsiquiatr. 2013;71:376–9.