Cognitive impairment among older adults living with HIV/AIDS and frailty

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Abstract

In 2014, 17% of newly diagnosed HIV infection cases in the United States were made in people over 50 years of age; actually, it is expected that in the near future this population group will be the most affected. This epidemiological change can be explained by the increased incidence of HIV infection in people over 50 years, but also by its higher prevalence due to treatment advances. As HIV infection has become a chronic one, new challenges have emerged. For instance, early-onset "geriatric syndromes," such as frailty, have been recognized in these patients. Frailty refers to a physiological state of vulnerability that increases the risk of adverse health-related outcomes. Frail individuals have higher risk of cognitive impairment; however, it is not known if early-onset frailty in those infected by HIV could also increase the risk of cognitive impairment in this already vulnerable population. The purpose of this review article is to describe, from an epidemiological point of view, the relationship between the changes promoted by HIV and the syndrome of frailty on cognitive function.

KEY WORDS: *Frailty. HIV. AIDS. Cognitive impairment. Aging.*

Introduction

Human immunodeficiency virus (HIV) infection and AIDS epidemiology has changed according to population aging[1]. According to US Centers for Disease Control and Prevention data, 17% of new cases of HIV infection in that country in 2014 corresponded to 50-year old and older people. Recently, the New York Medical Center reported that one out of every five new HIV-infection diagnoses was made in individuals older than 50 years[2]. This phenomenon has caused for the proportion of older adults diagnosed with HIV/AIDS to increase, which is the result of two main reasons: 1) an increased incidence of infection in this population that is not perceived as being at risk for sexually-transmitted infections, and 2) a drastic change in natural evolution of the disease, which has changed from being a disease that led to death to be a chronic disease[3], mainly owing to the use of highly active antiretroviral therapy (HAART). This way, for 2015, 50% of the population with HIV/AIDS was estimated to be 50 years' old or older, and to account for 15% of new diagnoses of infection with this virus in the American Union[4].

The majority of older adults that are HIV carriers do not suspect they are infected[5], and this is one of the reasons why the diagnosis is usually made at more advanced stages in comparison with younger patients[6], which favors the development of comorbidity, lower treatment adherence and early appearance of geriatric syndromes. In this sense, HIV/AIDS is an "accelerated aging" model, since affected people can develop different syndromes that are traditionally seen at old age, even up to 15 years earlier than in non-infected people[7]. These include "frailty", which has important repercussions on older adults' health.

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The frailty syndrome describes a state of great vulnerability and poor resilience, the higher incidence of which is closely related to the passage of time, and its presence increases the risk of health adverse outcomes, such as disability, mortality and cognitive impairment[8].

Just like frailty, cognitive function declination is an almost universal aging-related phenomenon[9]; however, HIV infection is also a condition that has been associated with the onset of cognitive changes. This way, a frailty, old age and HIV infection interaction is plausible, and it might favor a higher likelihood of cognitive impairment in people who suffer from them in comparison with those who don't have these problems. However, there is sparse information on the interaction of these three factors and the development of cognitive impairment. Therefore, the purpose of this review is to describe epidemiological evidence pointing at a possible relationship between HIV infection, frailty syndrome and cognitive changes in older adults.

HIV infection and aging

The human aging process results from an interrelation of genetic, biological, environmental and individual lifestyle factors[10]. HIV infection induces multiple changes in different organs and systems of the body, including the immune system, which is one of the most affected[11-13]. The virus promotes an inflammatory (C-reactive protein, interleukin 6, tumor necrosis factor alpha [TNF-a]) and procoagulant (fibrinogen, D-dimer) sustained response, which is related to viral load and is very similar to that described in non-VIH infected older people[14,15].

On the other hand, there is also high toxicity generated by HAART chronic use, which was been associated with HIV patients' body vital capacity reduction, which may cause a multi-system damage that favors further deterioration[16,17]. However, HAART early initiation and managing to maintain CD4+ T-lymphocytes normal counts have been associated with better life expectancy, very similar to that of the general population[18,19].

The relationship between HIV and age has generated the concept of HIV-associated non-AIDS (HANA) conditions, which alternate with comorbidity in a common term. HANAs describe the multifactorial contribution of risk factors to the pathogenesis of concomitant diseases and, at the same time, they underscore that comorbidity clinical presentation is an intrinsic component of HIV-related disease in the HAART era. HANA conditions three pathogenic mainstays are: 1) HIV-related disease; 2) antiretroviral drugs toxicity; and 3) host-associated risk factors[20]. This biological process generates a higher number of chronic conditions that can occur simultaneously, such as cardiovascular disease, hypertension, renal impairment and diabetes, among others, which largely lower quality of life[7]. In addition, these conditions have shown higher prevalence at earlier stages of life in comparison with subjects without HIV of the same age[21]. Pluripathology is a risk factor for polypharmacy, which in turn increases the likelihood of toxicity and drug-drug interactions that may predispose to other conditions (arrhythmia, falls, depression, renal impairment, etc.)[22].

On the other hand, HIV-infected population is known to have high prevalence of addictions and use of drugs, both licit and illicit. An example is smoking (three-fold more common), which entails an increased risk for suffering acute myocardial infarction, lung cancer, emphysema or stroke. In addition, the use of other substances by these individuals, such as amphetamines and cocaine, has been implied in problems of memory, bone mineral loss and heart conditions, which in combination favors adverse outcomes[23]. In this sense, the increase of older population with HIV represents a challenge for the different world health systems, as they are dealing with populations at high risk for developing a large number of medical conditions driven both by age and the virus itself. Therefore, creating initiatives and actions that adapt to this population's needs and that include a delay in the development of geriatric syndromes is necessary.

Frailty in individuals with HIV

Frailty is a state of great vulnerability that increases the risk for developing adverse health outcomes and that is different from disability and comorbidity[8]. Although the consequences for health can be disastrous, it is a potentially reversible and preventable process[24]. The frailty concept –considered as a syndrome– applied to the HIV-infected individual was initially studied in the Multicenter AIDS Cohort (MACS), where the prevalence and expression of frailty was studied in a cohort of 1946 men (mean age, 53.8 years; 898 HIV+ with HAART use and 1048 HIV-) between 2007 and 2011. The investigators reported a phenotype that was similar to that described in older adults (frailty-like) in 477 patients, out of which 54% were HIV+[25]. Desquilbet et al.[26], with a sample of 2150 participants (mean age, 42 years, range, 37 to 47), reported a prevalence of frailty of 13.9%[26]. Terzian et al.[27], in a sub-analysis of the Women's Interagency HIV Study (WIHS) (a prospective cohort study started in 1994 in five cities of

the USA) with 1781 female participants (573 HIV- and 1206 HIV+), all younger than 50 years, demonstrated a prevalence of frailty of 8% in HIV- women in comparison with 12% in those who were HIV+, but it was even higher (20%) in those with CD4 T-lymphocyte count < 100 cell/mm^3 [27]. Onen et al.[28] cross-sectional analysis of the Study to Understand the Natural History if HIV and AIDS in the Era of Effective Therapy (SUN) (a cohort of 322 participants with HIV, mean age of 47 years and 79% men) determined a prevalence of frailty of 5% according to the Cardiovascular Health Study criteria.

The presence of frailty in the population with HIV has been inversely related to the use of HAART. Desquilbet et al.[29] reported a drop in the prevalence of frailty of more than one half (from 24 to 10.1%) after the introduction of HAART, which turned out to be one of the main protecting factors against the development of frailty[30-32]. However, there is a mismatch in the age of onset of this geriatric syndrome, since its prevalence in the 55-year old population with HIV appears to be similar to that reported in subjects older than 65 years without HIV; this observation reinforces the idea of frailty early onset in this population, probably owing to conditions promoted by the virus[30]. This way, the frequency of frailty syndrome among relatively young HIV-infected individuals appears to be similar to that reported by epidemiological studies that use to include 65-year old and older adults without infection[8,33]. In the light of this evidence, HIV infection appears to be a frailty-promoting factor in this population, regardless of people's age.

Frailty and cognitive impairment

In spite of the difficulties to find a universal definition of frailty, there is a consensus that this state is the cause of multiple adverse outcomes, including a poor quality of life, greater disability, more hospitalizations, higher probability to be institutionalized and higher risk of dying[8,34]. The mechanisms that link cognitive impairment and frailty might be associated with endothelial dysfunction within a proinflammatory environment with increased oxidative stress[35]. On the other hand, aging-associated atherosclerotic processes, which can even produce cerebrovascular events, are interrelated with frailty by means of a series of factors such as inflammation, procoagulant processes and fibrinolytic systems[37], which places frailty expression as a possible prodromal stage of vascular-cause cognitive impairment. Frailty is related to multiple chronic conditions and functional deterioration, which requires a larger amount of energy; thus, this condition might explain why mitochondrial metabolism produces higher quantities of free radicals. At the same time, this increase in the production of free radicals can also activate nuclear factor kappa B pathway, which in turn leads to inflammation[36]. Frailty most popular phenotype is the one proposed by Fried et al.[8], which has demonstrated its validity in the prediction of health-adverse outcomes; however, the most important criticism to this phenotype is that its five components are of physical nature, and other potential components that are also usually affected by aging have therefore been proposed. Accumulation of deficits over time ("frailty index") is one of them, which weighs the presence of multiple common problems at old age (such as functional status, comorbidity or psychosocial factors) and, the higher the problem accumulation, the higher the risk for adverse outcomes[37]. However, cognitive function changes (an almost universal phenomenon that occurs with aging) have been inconsistently included in frailty definitions. In recent years, understanding of the relationship between frailty and the development of cognitive impairment has improved.

Frail adults often have poorer performance in cognitive tests they undergo. For example, in a study on the association between frailty and cognitive impairment conducted in 155 older adults without dementia (mean age of 67.4 ± 5.4 years), those who were frail had poorer performance in different neurocognitive tests, such as the mini-mental state examination (MMSE) and the Montreal Cognitive Test (MoCA). In this study, frailty measured with the Edmonton Frail Scale had a negative and statistically significant correlation with the degree of cognitive performance, as shown with the used tests (MMSE: $r = -0.622$, $p < 0.001$; MoCA: $r = -0.687$, $p < 0.001$), which indicates that cognitive performance declines as frailty increases[38].

Frailty has been associated with the development of different degrees of cognitive impairment. Boyle et al.[39] reported the relationship between a frailty scale (measured in the grip strength, gait velocity, body mass index and extenuation components) and the development of mild cognitive impairment in 761 subjects (mean age, 79 ± 7.1 years). During the 12-year follow-up, 40% developed mild cognitive impairment, and the risk for it increased by up to 63% for each unit of increase in the frailty scale (hazard-ratio [HR]: 1.63; 95% confidence interval [CI]: 1.27-2.08)[39]. Another cohort study with a 4-year follow-up carried out in a French population (6030 participants; mean age, 74.1 ± 5.2 years; 61.2% females) showed that frailty was a risk factor for dementia. However, risk was statistically significant only in those people with poor cognitive

performance (but not dementia) at study enrollment, regardless of their physical status (HR: 4.98; 95% CI: 2.17-11.41; p < 0.001)[8]. On the same token, Samper-Ternent et al.[40] reported, with information of 1370 65-year old and older participants (mean age, 73.2 ± 4.8 years) from the Hispanic Established Population for the Epidemiological Study of the Elderly (H-EPESE), that those who were classified as frail at study inclusion were at higher risk for cognitive impairment in comparison with those who were not frail, after 10 years of follow-up (odds ratio [OR]: 1.27; 95% CI: 1.07-1.52)[40]. These observations point at frailty as a state that drives to cognitive impairment, although the pathophysiological pathways have not been clearly elucidated. Probably some inflammatory mechanisms are implicated in the relationship of both problems, as well as vascular changes, which can favor cognition impairment. This statement results from the conclusions of two epidemiological studies that point at frailty as a risk factor for vascular-type dementia[41,42]. One of them included 5248 participants (from 65 to 95 years) and focused on the study of the relationship between this geriatric syndrome and the incidence of vascular-type dementia. After 7 years of follow-up, those subjects who were frail at study inclusion and had no dementia, were at higher risk for developing vascular dementia (HR: 2.73; 95% CI: 1.05-7.13) even after adjusting for multiple confounders; this study concluded that frailty is a major risk factor for the development of this type of dementia[41]. The same finding was replicated by an Italian study with a mean follow-up of 3.5 years, where frailty was found to be a risk factor for vascular-type dementia as well, even after adjustment for potential confounders (HR: 2.68; 95% CI: 1.16-7.17)[42]. In the light of these results, frailty expression has been considered to be a prodromal stage of vascular dementia, which is supported by the results of a study that shows that vascular changes, such as carotid intima-media increased thickness, as well as carotid lumen increased diameter (as shown by Doppler ultrasound), are more common in frail than non-frail individuals[43].

Frailty is a risk factor for cognitive impairment, especially of that of the vascular type. Early identification of this geriatric syndrome might be useful in an effort to modify its possible evolution towards individual cognitive status decline.

Cognitive impairment in people with HIV

The introduction of HAART has radically modified vital and functional prognosis of HIV-infected people. In this sense, one benefit observed in the HIV+ population has been an improvement in their cognitive status, since in the pre-HAART era usually they progressed towards impairment. However, this good result has not been consistent, since 50% of HIV+ patients still have neurocognitive disorder associated with the virus (known as HAND)[44].

The central nervous system (CNS) is particularly affected by HIV, and the damage has been demonstrated both at its structure and function. One study that reported brain histopathology findings of 390 HIV-infected subjects, carried out at the San Diego Medical Center of the California University, showed great alterations of this organ, with HIV-associated encephalitis and opportunistic infections being the conditions that most affected the CNS[45]. There is no particular area of the encephalon that is specifically harmed by HIV; however, some areas can be more affected than others, such as the temporal white matter (especially the hippocampus) and the parietal cortex[46]. The HIV Neurobehavioral Research Center reported the impact of HIV infection-associated cognitive impairment on daily life functions in a sample of 267 HIV+ participants (mean age of 39.3 ± 7.5 years and mean education level of 13.6 years). The cognitive domains that were most compromised in HIV-infected subjects were shown to be those associated with learning, executive functions/abstraction, attention/working memory and motor functions (Table 1). On the other hand, less compromised areas were those associated with information-processing speed, verbal functions and deferred memory[47]. Studies conducted with magnetic resonance have shown flow alterations in microstructures around the white matter in brains of HIV-infected individuals (e.g. mean dispersion increase and anisotropic fraction reduction)[48]. Specifically, the presence of these changes in brain microstructures has been associated with psychiatric (major depressive disorder, anxiety, etc.) and neurologic conditions (neurocognitive disorders, delirium or HAND) in HIV-infected persons[49,50].

HIV is a neurotropic virus that lodges in the immune system, promoting the production of neurotoxic substances such as quinolinic acid and some excitatory amino acids (L-cysteine, glutamate, arachidonic acid, free radicals and TNF-α, among others). These factors, originating from macrophages and possibly astrocytes, contribute to neuronal damage, especially to the damage of dendrite synapses and inducing their apoptosis. HIV introduction into monocytes via gp120 triggers a series of events that start with the

Tabla 1. Studies demonstrating cognitive function impairment with aging, frailty and HIV infection

Funciones cognitivas	Aging	Frailty	HIV
Orientation		Macuco (2012)[66] Age range: 65-69, 70-74, 75-79, ≥ 80 Orientation in time MMSE: Beta (SD): -50.80 (17.55); $p < 0.004$; R^2: 0.0230 Kruskal-Wallis	Marie Van Dyk (2015)[69] Young (mean 42.59; SD: 6.29) vs. older age (mean: 59.56; SD: 6.98) Orientation 0.038 (0.01) 0.003, ANCOVA
Attention and concentration	Junqué (1990)[59] Young (mean: 25.0; SD: 4.2) vs. older adults (mean: 70.3; SD: 5.3) Reaction time-motor response Sternberg paradigm, F = (1, 44) = 49.4; $p < 0.001$ MANOVA Saithouse (1995)[61] Young 20.9 years (SD: 3.8), older age (66.8 years; SD: 5.0) Response time Reaction time task, F = (1, 77) = 88.77; SEM = 46,09 l ANOVA Carlson (1995)[60] Young (mean: 68.8; 17-22), older age (mean: 68.8; 62-75) Reading time 12 readings, 125 words: F = (1.62) = 79.90; SEM = 44.13 ANOVA		Marie Van Dyk (2015)[69] Young (mean: 42.59; SD: 6.29) vs. older age (mean: 59.56; SD: 6.98) Visual search D-KEFS – TRAILS: F (1,37) = 4.47; p = 0.04 ANCOVA García-Torres (2015)[70] HIV- 46.86 years (SD: 4.26) vs. HIV+ 46.36 years (SD: 8.82) Attention/working memory Digits U = 52.00; p = 0.032*; °d = 0.917 Mann-Whitney's U; °p-value; Cohen's °d
Memory	Kinugawa (2013)[63] Young (21-45 years), middle-aged (48-62 years), older adults (71-83 years) Episodic memory Novel test; T = 3.72; $p < 0.001$ ANOVA (post hoc Holm-Sidak method) Bowles (1985)[65] Young (Mean = 21 years, SD = 3, 18-27) and older adults (72 years, SD = 4) Semantic memory Word retrieval task: F (1, 85) = 4.968, $p < 0.05$ ANOVA (two-way) Verhaeghen (1997)[64] Age range (18-92) Episodic memory Meta-analysis: $r_+ = -0.33$ Correlation coefficient (Hedges and Olkin).	Macuco (2012)[66] Age range: 65-69, 70-74, 75-79, ≥ 80 years Immediate memory MMSE: Beta (SD): 56.02 (15.58); $p < 0.001$; R^2: 0.0559 Kruskal-Wallis test Boyle (2010)[68] Age: 77.9 years (SD: 7.21) vs. 81.0 years (SD: 6.30) Episodic memory 7-test neuropsychological battery: -0.039 (0.01); $p < 0.001$ Proportional risk models Boyle (2010)[68] Age: 77.79 (SD: 7.21) vs. 81.0 years (SD: 6.30) Semantic memory †3-test neuropsychological battery: -0.026 (0.01); $p < 0.004$ Proportional risk models	Marie Van Dyk (2015)[69] Young (mean: 42.59; SD: 6.29) vs. older age (59.56; SD: 6.98) Memory Total HVLT-R, F (1,37) = 10.42; p = 0.003 ANCOVA García-Torres (2015)[70] HIV- 46.86 (SD: 4.26) years vs. HIV+ 46.36 years (SD: 8.82) Memory/learning TAVEC t(26) = °2.84; °p = 0.009†; d = 1.077 Student's t; °p-value, Cohen's d°

(Continue)

Tabla 1. Studies demonstrating cognitive function impairment with aging, frailty and HIV infection *(Continued)*

Funciones cognitivas	Aging	Frailty	HIV
Language			Marie Van Dyk (2015)[69] Young (mean: 42.59; SD: 6.29) vs. older age (mean: 59.56; SD: 6.98) Verbal fluency Letter Fluency, F (1,37) = 9.35; p = 0.004 ANCOVA Marie Van Dyk (2015)[69] Young (mean: 42.59; SD: 6.29) vs. older age (mean: 59.56; SD: 6.98) Letter Fluency, F (1,37) = 7.93; p = 0.003 Fluency (3-min time) ANCOVA
Executive functions	Verhaeghen (1997)[64] Age range 20-79 years Meta-analysis r_+ = -0.27 Working memory Correlation coefficient (Hedges and Olkin) Kinugawa (2013)[63] Young (21-45 years), middle-aged (48-62 years), old adults (71-83 years) Working memory Novel test; T° = 48; °p° = 0.001 ANOVA (post hoc Holm-Sidak method) Salthouse (1989)[62] Age range: 20-79 years Working memory Paper-folding task, R^2: 0.119, F (1, 117) = 21.41; SEM = 123.95; p < 0.01. Multiple regression (hierarchical)	Langlois (2012)[67] Age: robust 70.25 years (SD: 5.57) vs. frail 74.26 years (SD: 6.06) Executive functions Wechsler Adult Intelligence Scale (WAIS-III): 0.42 (0.83) vs. -0.47 (0.84); p < 0.001 MANCOVA Boyle (2010)[68] Age: 77.79 (SD: 7.21) vs. 81.0 years (SD: 6.30) Working memory 3-test neuropsychological battery: -0.033 (0.01); p < 0.003 Proportional risk models	Marie Van Dyk (2015)[69] Young (mean: 42.59; SD: 6.29) vs. older age (mean: 59.56; SD: 6.98) Grooved Pegboard, F (1, 37) = 5.29; p = 0.027 Psychomotor speed and dexterity ANCOVA Marie Van Dyk (2015)[69] Young (mean: 42.59; SD: 6.29) vs. older age (mean: 59.56; SD: 6.98) Psychomotor speed D-KEFS – TRAILS: F (1, 37) = 5.51; p = 0.024 ANCOVA García-Torres (2015)[70] HIV- 46.86 years (SD: 4.26) vs. HIV+ 46.36 years (SD: 8.82) Executive functions Stroop color, t(26) = -2.79; °p = 0.010*; d = 1.07 Student's t, p-value; Cohen's d García-Torres (2015)[70] HIV- 46.86 years (SD: 4.26) vs. HIV+ 46.36 years (SD: 8.82) Motor skills Tapping, t(25) = -2.82; °p = 0.009†; d = 1.08 Student´s t; °p-value; Cohen's d°

Note: Author name, publication year, compared groups, neuropsychological tests used, cognitive domain assessed, outcomes and statistical test used are presented.

*Logical Memory, immediate and delayed recall of the East Boston Story, Word List Memory, Word List Recall, and Word List Recognition.

†A 15-item version of the Boston Naming Test, Verbal Fluency, and a 15-item reading test.

‡Digit Span Forward, Digit Span Backward and Digit Ordering.

Tabla 2. HIV-associated neurocognitive disorder (modified from Antinori A et al.[58])

Diagnosis	Criteria
Asymptomatic neurocognitive impairment	Impairment on at least two cognitive domains assessed by means of a neuropsychological test standardized by gender, age and level of education (at least one standard deviation and without functional deterioration)
Mild neurocognitive impairment	Impairment on at least two cognitive domains assessed by means of a neuropsychological test standardized by gender, age and level of education (at least one standard deviation; slight interference with daily life activities)
HIV-associated dementia	Severe impairment on at least two cognitive domains assessed by means of a neurocognitive test standardized by gender, age and level of education (at least two standard deviations), with marked impact on daily functions

production of TNF-α and interleukin 1b, which in turn activate astrocytes, which release glutamate and nitric oxide radicals, which in turn react with superoxide and generate neurotoxic molecules; in addition, nitric oxide can activate extracellular matrix metalloproteases that favor neuronal damage and ultimately proteolysis, which causes direct damage at the CNS[51].

On the other hand, a relationship has been demonstrated between the degree of disease progression and cognitive impairment severity. Therefore, the prevalence of cognitive impairment, for example, at stage C, was higher in the pre-HAART era (52%) and lower after this therapy became available (45%)[52].

In 1991, the American Academy of Neurology AIDS Task Force proposed the nomenclature and diagnostic criteria for HIV-1-infection neurological manifestations. Years later, after HAART implementation, they were adapted and the inclusion of the term "asymptomatic neurocognitive impairment" was suggested to identify those individuals not displaying overt cognitive impairment, but who showed abnormal performance in standard neuropsychological tests. In order to enable establishing the diagnosis of HIV-associated neurocognitive disorders, changes to these criteria were proposed, also introducing functional performance assessment as a parameter of HIV-related neurocognitive disorder progression (Table 2). In this sense, it is recommended that HIV patient neurocognitive evaluation should take the following functions into account: attention/working memory, information-processing speed, verbal memory, learning, verbal fluency, executive functions and motor function, the results of which should consider subjects' age and level of education and agree with existing regulatory data[53]. HIV-associated neurocognitive disorders are often the consequence of viral replication in the CNS, which per se is already compromised by an inflammatory response, but that in the past few years has been attenuated thanks to HAART.

The presence of neurocognitive problems in HIV patients has other clinical implications. Those subjects with some degree of impairment might have lower treatment adherence and more disability for their daily activities, in addition to the loss of their working activities, deterioration of quality of life in general and increased risk of death. Since HIV-related cognitive damage is a risk factor for adverse outcomes on infected individuals' health and quality of life, systematic cognitive evaluation of these patients should be considered in order to enable the implementation of opportune intervention measures according to their needs.

Cognitive impairment in individuals with HIV and frailty

Several studies have suggested that suffering from any form of HAND is associated with the frailty phenotype in HIV patients, as demonstrated in the MACS study. In a retrospective sub-analysis of this cohort, which included 505 participants (mean age 52 years, range from 32 to 69, and 36.9% with $\geq$ 16 years of education), 12.7% had asymptomatic cognitive impairment, 36.6% had symptomatic cognitive impairment, 12.9% had HIV-associated dementia and the rest had no impairment. It was established that those with some type of HAND had twice the risk to develop frailty (three of the five components proposed by Fried et al.[8]) (OR: 2.18; 95% CI: 1.05-4.54; p = 0.036), whereas in individuals who showed any HAND symptomatic form (either symptomatic cognitive impairment or HIV-associated dementia) the risk for developing frailty was up to 3-fold higher (OR: 2.99; 95% CI: 1.49-5.96; p = 0.002). In a second analysis adjusted by age, ethnicity, level of education, employment, CD4 load, smoking, use of marihuana, use of intravenous drugs and depression, the risk for the development of frailty was maintained among those who had HAND (OR: 2.2; 95% CI: 1.03-4.68; p = 0.042) or symptomatic HAND (OR: 2.8; 95%

CI: 1.37-5.75; p = 0.005). These results support the idea of a significant relationship existing between frailty and the presence of HAND; however, these findings have to be replicated in similar populations. With these results, it would appear necessary recommending systematic serial cognitive evaluations in individuals that are frail and that are infected with HIV[54].

The presence of cognitive impairment can be associated with functional impairment in HIV-infected individuals. This was shown in the Geriatric HIV Program: The Experience of an Urban Academic Center at One Year Follow-Up study, carried out at the Medical Center of Louisiana, in New Orleans. A total of 60 patients were evaluated in order to determine the presence of frailty-like syndrome (which considered the cognition, daily life basic and instrumented activities, nutritional status, depression, hearing loss, visual deficit and mobility); of them, only 20 entered the program (12 men and 8 women with a mean age of 63.5 years) and were divided into three subgroups according to their degree of frailty: mild (20%) when only one domain was compromised, moderate (50%) with two affected domains and severe (30%) with three or more involved domains. In this study, at one year follow-up, half the participants developed some type of cognitive impairments, and those with higher degree of frailty were the most affected, which supports the idea of a relationship between frailty intensity and the degree of cognitive impairment in individuals with HIV[55]. In the same sense, the study by the Hospital HIV Clinic and the San Francisco Veterans Affairs Medical Center Infectious Diseases Clinic (155 participants, 93.6% males, with a mean age of 57 years) showed the presence of frailty in 9% and cognitive impairment in 46.7%, which is a reflection of the high prevalence of both these conditions commonly seen in the elderly, but also among a relatively young HIV+ population[56]. Previous studies support the hypothesis that frailty syndrome can be observed in the HIV+ population regardless of age. This way, HIV+ patients are more prone to develop more health-adverse outcomes, including higher institutionalization, more hospital admissions and even higher probability of death. Since frailty is a state of risk for the development of cognitive impairment, it is plausible that the presence of frailty syndrome can promote a more accentuated or accelerated cognitive impairment in HIV-infected persons, in comparison with those fragile individuals without HIV infection. Frailty early identification in people with HIV can be useful to deliberatively investigate the presence of any type of cognitive impairment. This opens the possibility for the implementation of early interventions with the purpose to modify the course of frailty and avoid its disastrous complications. Owing to the paucity of scientific information, promoting studies better looking into the possible interaction of frailty and HIV infection with cognitive impairment, as well as other geriatric syndromes, early onset in younger populations is desirable.

Conclusions

HIV infection epidemiological change entails new challenges for health systems. Anatomical and physiological changes promoted by aging, together with the effects of HIV on the immune system, generate a state of increased vulnerability that has been shown to be related to the onset of frailty and its adverse outcomes, including cognitive impairment. However, the pathophysiological pathways implicated in these complications still remain to be determined. Both conditions' inflammatory mechanisms open the possibility for vascular alterations to be the cause of the compromise of cognitive function in frail subjects, just as observed in those without HIV. However, peculiarities of this chronic infection, as well as the presence of factors such as HAART or comorbidity in an increasingly older population, might play a fundamental role in cognitive impairment early or magnified onset in infected people. Treatment and health-associated preventive measures that are applied in older adults with frailty require to be extended to aging patients with HIV, since their efficacy and impact on this already vulnerable population is not known. Doing it might reduce the presence of HIV-associated cognitive alterations.

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