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Review

The Aging of HIV: New Challenges and Perspectives

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ABSTRACT

The number of older adults living with HIV infection has increased significantly. Several similarities have been found between aging and HIV infection. Patients with HIV can present with premature complications that are often observed in chronological aging, they have been called Geriatric Syndromes (GS). Frailty syndrome, a pathological state of excessive vulnerability in old age, shares with HIV infection the phenomenon of immunodeficiency.

This article reviews the epidemiology of HIV in the elderly, and the impact of immunological aging on the development of negative outcomes known as geriatric syndromes in older adults living with HIV. Finally, the objective of this review is to provide a practical positioning based on scientific evidence, given the new challenges and perspectives of HIV infection in old age, proposing as a more appropriate strategy the establishment of a multidisciplinary vision that includes the support of geriatric medicine in the evaluation of the elderly patient with HIV.

Keywords: Older adults, HIV, Geriatrics syndromes, Frailty.

INTRODUCTION

By the end of 2013, over four million people who are older 50 years were living with HIV infection. It was estimated that by 2015 one-half of the individuals in the United States (US) with HIV was older than 50 years old. The increase observed in the last 20 years of elderly with HIV is largely due to the success of Highly Active Antiretroviral Therapy (HAART) [1,2].

The incidence is also a factor for this epidemiological transition. According to the Center for Disease Control and Prevention (CDC), almost 40% of all newly diagnosed HIV infections were in patients who are 50 years old and above. In the US, the cumulative number of AIDS cases reported to CDC in adults aged 50 years or older increased more than 10-fold from 16,288 in 1990 to over 1,70,000 by the end of 2013. As of 2011, 70% of adults living with HIV and receiving care within the national US Veterans Administration Healthcare System were 50 years of age and above. So, the percentage of older adults living with HIV infection (OALHIV) grew from 17.4% in 2001 to 36.2% in 2010 [3]. This change was so unexpected that American Society of Geriatric and the American Academy of HIV had to re-define "elderly" in the context of HIV infection as: all adults of 50 years and older are now considered elderly [4].

Thus, it is a priority to gain a better understanding of the interaction between age and HIV infection. Added to this, OALHIV present complications usually observed in aging: cognitive impairment, osteoporosis and fractures, disability, falls and frailty [5,6]. We must remember that aging from the biological point of view is characterized by the acceleration in the rate of irreparable physiological damage and its accumulation in the body [7].

But, has this transformed HIV into a chronic disease? It was about the effectiveness of the treatment. This success of drug therapy has led to new challenges related to the aging of HIV [8]. OALHIV have a higher prevalence of problems related to aging (cardiovascular disease, cancer, renal and cognitive impairment, among others) [9].

IMMUNOLOGICAL AGING: IMMUNOSENESCENCE

There are several similarities between aging and HIV infection at the immune level. These include damage to DNA, loss of DNA repair capacity and alterations in the mechanisms of immune system cells [10]. These changes can condition a chronic autoimmune activation (observed in both aging and HIV/AIDS) and that has been related to the appearance of atherosclerosis, decreased bone mineral density and sarcopenia [11]. Despite presenting a positive response to ART treatment, adults of any age with HIV apoptosis

have a greater susceptibility to develop many of the so-called geriatrics syndromes as frailty and cognitive impairment [12,13]. Both numerical loss and dysfunction of native CD4+ T cells are common features of immunosenescence and HIV infection [14]. The mechanisms that cause cellular damage and those that try to repair it contribute equally to cellular depletion and its regenerative abilities, which lead to the characteristic progressive proinflammatory state in old age [15].

Some of the intracellular and nuclear systems responsible for the promotion and suppression of cytokine production are the nuclear factor kappa B (NF-kB), sirtuins, and the fork head box O (FoxO) system. The key to aging of inflammatory origin is the way in which the senescent immune system converges with the different cell signaling pathways (NF-kB, sirtuins, FoxO), in order to produce its deleterious effects through reactions that in previous stages of life would favor survival while in old age predispose to the development of degenerative diseases that cause the functional decline characteristic of old age [16-21].

RISK IMMUNOPHENOTYPE

It is undeniable that aging and HIV-1 infection are associated with immunological changes with each other. It has been shown that chronic exposure to antigens causes alterations in the immune response associated with high morbidity-mortality in old age, independently of any other factor [22]. These changes were grouped and called "risk immunophenotype." It is characterized by low levels of B cells, increased levels of CD8+ /CD28- T cells, poor proliferative response of T cells, CD4+ /CD8+ <1 T ratio, and seropositivity to cytomegalovirus (CMV) [23].

Compared to HIV-negative individuals, the population of HIV-positive patients with CD4+ T depletion and a strong viral load has high levels of inflammatory markers (IL-6), coagulation abnormalities and monocyte activation [24]. It is striking that with the increase in CD4+ T with HAART, geriatric syndromes seem to reverse. The analysis shows that there is no significant association between age and frailty when adjusted to the CD4+ T count, but there is an important association between age and the CD4+ T count. Regarding HAART, it has been observed that its use is a protective factor against fragility only if the CD4+ T count is normalized. With each year added to the treatment, the risk of frailty decreased by 20% [25].

GERIATRIC SYNDROMES AND HIV INFECTION

Chronic inflammation in the elderly conditions a state of organic vulnerability that is explained by the so-called geriatrics syndromes, which is defined as a condition that increases the risk of negative outcomes in older adults. Elevated levels of IL-6 in was associated with decreased muscle strength, gait velocity and greater disability for basic (BADL) and instrumental activities of daily living (IADL), compared to non-frailty. In addition, higher levels greater of IL-6 predicted the development of disability. The proteolytic and cytotoxic properties of TNFα and IL-6 generate cachexia and muscle wasting that determines the loss of strength and muscle mass [26-30].

Frailty is a condition that increases vulnerability to stress and has been associated with a damaged and dysfunctional homeostatic response. Functional complications of aging were identified as a priority area of research in HIV and aging for the first-time following observations of the high prevalence of the frailty syndrome in HIV-infected men in the MACS study (Multicenter AIDS Cohort Study) [31,32].

The functional impairment seen in HIV was initially reported in association with AIDS syndrome, observed most often in patients with high HIV-1 RNA or with CD4+ T<200 cell/mL. The disability associated with HIV infection was recognized since the beginning of the epidemic [33]. One of the first major studies that identified disability in adults living with HIV was published in the pre-HAART era. Disability for BADL and IADL was reported in 4% and 14% respectively. It has become clear since then that disability has a strong association with the presence of AIDS and with low CD4+ T levels, and with a reduced survival period [34].

FRAILTY SYNDROME

Linda Fried operationalized 5 components commonly recognized in frailty: slowing, weakness, decreased activity levels, exhaustion and weight loss, to validate one of the most commonly used diagnostic constructs in geriatrics [35].

To start talking about frailty and HIV, we must remember that geriatric syndrome is strongly associated with traditional markers of HIV disease, in particular the CD4+ T count (current and in nadir) and the presence of a detectable viral load [36].

In a cohort of intravenous drug users, HIV positive participants with advanced disease (defined as T CD4+ <350 cells/ml and detectable viral load) were more likely to be frailty compared to HIV negative participants or those without advanced disease [37]. The same finding was observed in the MACS analysis: HIV positive participants with a history of AIDS were more likely to be frailty. Thus, the sum of the presence of frailty and HIV increases the risk of death by 7 times [38]. A strong association was observed between HIV infection and frailty related phenotype of MACS. There is a greater probability to have this association in patients with low CD4 +T counts (<350 cells/mL), high viral load (>100,000 copies/mL), presence of AIDS, time of infection and of course age [39]. Comparing both ages of treatment, pre-HAART patients had a higher prevalence of frailty (24%) than in the post-ART period (10%) [40]. In the WIHS study, women with AIDS or with TCD4+ <100 cell/mL had a high prevalence of frailty (12% and 20% respectively vs. 8% and 7% without AIDS) [41].

Among intravenous drug users of the ALIVE study, 14.5% of patients with HIV had frailty compared to 11.4% of patients without HIV. This study also demonstrated an increase in the risk of death, independent of HIV infection, that is, exclusively due to the presence of frailty syndrome [42]. In all these studies a prevalence of frailty has been reported, between 5 and 33%.

Low CD4+ T cell count and high viral load are predictors of HIV frailty. An effective HAART plays a role in protecting against frailty, which underlines the importance of early treatment implementation [43].

ARE FRAGILITY, DISABILITY AND FUNCTIONAL IMPAIRMENT INTERCHANGEABLE MEASUREMENTS IN HIV?

A study compared the Short Physical Performance Battery (SPPB) against frailty phenotype in 359 people infected with HIV with HAART. Among the 27 people who were classified as frailty, less than half had a significant impairment in SPPB (<9 score) and

only 4 had a perfect score. On the contrary, of the 26 people with a SPPB score <9, only 3 were non-frail, and 13 were frail [44]. These results support the consensus that the frailty, functional impairment or disability constructs are complementary, but not interchangeable.

GERIATRIC ASSESSMENT IN OALHV

One of the pillars on which geriatric medicine rests is undoubtedly the prevention of functional decline and the maintenance of autonomy. As we mentioned the limitations in functionality are powerful predictors of disability and death.

What is the proper way to measure frailty in OALHIV? Even at this time when the majority of HIV positive patients with access to treatments undergo prolonged immune reconstitution and suppression of the detectable viral load, there is no consensus on which tool to measure frailty is the most successful.

It is likely that-as in geriatrics medicine- the best scale will depend on the clinical context in which it is used, either as a convenient screening tool or as part of a more complete evaluation.

Evaluation scales are likely to include measurements of chronic viral co-infections or some laboratory data well known for their influence on HIV (viral load, CD4+ T count). Although these factors may contribute to vulnerability in OALHIV, they could represent something else in addition to the frailty that has been identified in populations of HIV-positive elderly [45].

However, there are few published studies in which frailty is assessed by the phenotype or fragility index in OALHIV. On the other hand, our research group is a pioneer in the study of frailty in old age in Latin America. The frequency of frailty in one of our first studies was reported in 14%. Variations in the definition of frailty limit comparisons between study populations; however, this study is also the first to describe the subtypes of the frailty profile in OALHIV [46,47].

The measurement of functional impairment, disability or frailty in the clinical evaluation of people infected with HIV is necessary for understanding current needs and for establishing a long-term prognosis, now that the infection has become chronic and that the largest group of HIV patients is over 50 years old.

The tools to evaluate function, malnutrition, disability and frailty are already commonly used in clinical and research settings in geriatrics and gerontology, our proposal is that they should have a similar application in HIV care and research.

The VACS index has been extensively studied. It was originally designed to assess health status and as a predictor of mortality in patients with chronic HIV disease. The index has shown association with various health problems common to old age and frailty: inflammation, muscle weakness, cognitive impairment and mortality [48]. Changes in the VACS Index reflect response to antiretroviral therapy more completely than do isolated changes in CD4 cell count and HIV-1 RNA. As in the development of the VACS index, we must consider a tool that is simple, cost-effective, that requires a minimum of time and effort on the part of doctors, and that provides a valid evaluation of the results of interest [49].

In this context, a series of considerations are proposed for the development, use and interpretation of functional and frailty evaluations (**Figure 1**).

First time, we must recognize that the tools used in the clinical

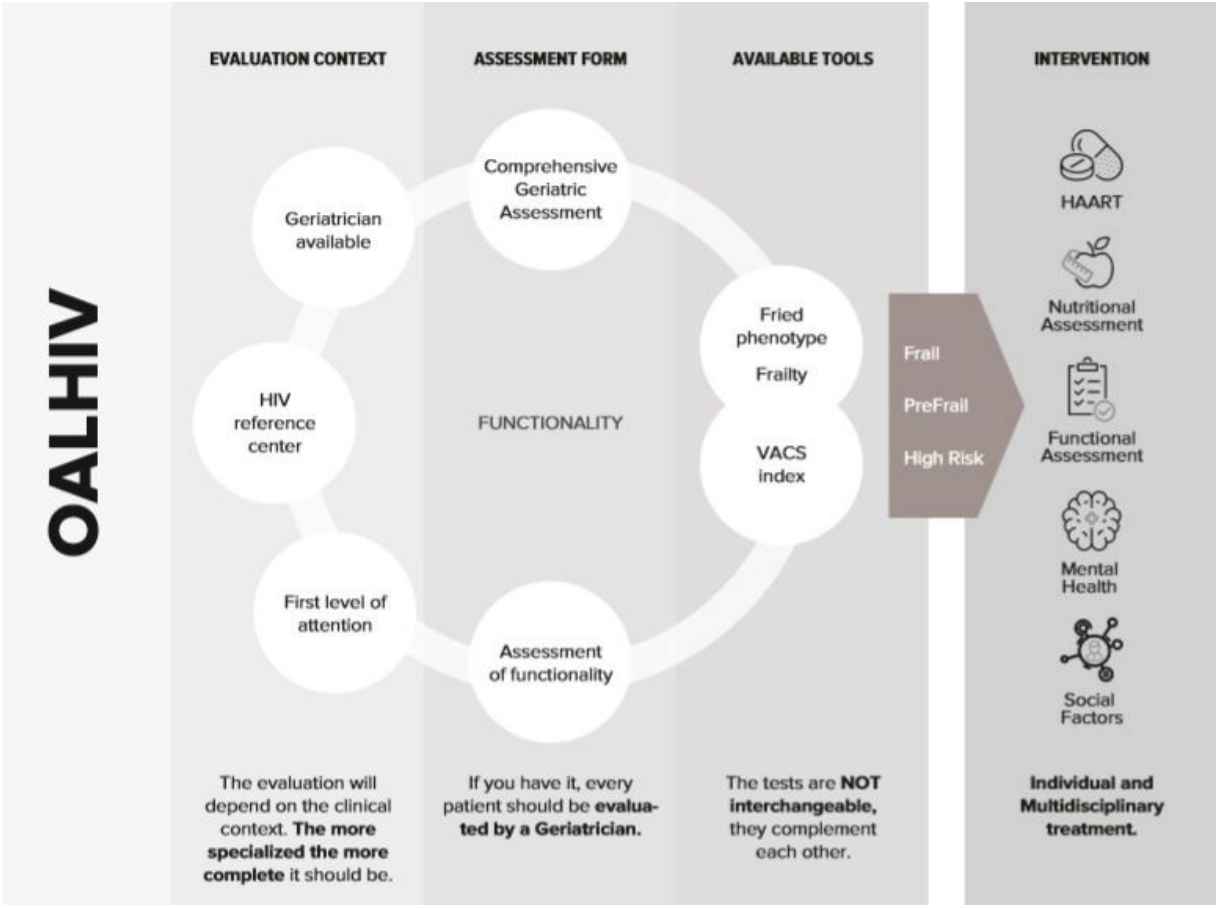

Figure 1: Proposed strategy for frailty in OALHIV.

area and in the field of research may be different. In this sense, interest in a particular outcome will be decisive in the choice of the tool. If the need is the evaluation of a patient in a nursing home or in an asylum, an assessment of the disability for BADL and IADL should be used.

On the other hand, if it is a research study designed to understand the pathophysiology of weakness during aging in patients with HIV, a standardized and objective measurement of strength without the influence of the environment (for example, grip strength) it would be a more suitable tool [50].

Second time, it should be taken into account if the tools can predict outcomes specifically in the context of HIV infection, or if the more general tools should be implemented. For example, as described above, in previous studies that used the Fried frailty phenotype or a fragility-like phenotype (e.g. VACS), frailty OALHIV was consistently associated with a count of low CD4+ T, high viral load and depressive symptoms. In this way a tool to identify frailty that includes-unlike frailty syndrome-specific HIV factors (CD4+ T and viral load) or depressive symptoms could be a more specific and sensitive predictor of vulnerability among OALHIV [51].

Third time, in the standardization of the tools it is necessary to include the criteria of application and interpretation so that the results can be compared in different contexts with relative ease. It is important to highlight that the tools to evaluate and measure the function, disability and frailty should be tested and validated as predictors of relevant outcomes (e.g. hospitalization, morbidity and mortality) in OALHIV. The evaluation of the frailty validated in the Cardiovascular Health Study was developed to predict hospitalizations, institutionalization and mortality in the general population over 65 years of age and seems to have a special utility as a prognostic tool in adults over 80 years [52].

For these reasons we suggest that-with the intention of predicting similar outcomes- it is absolutely necessary to validate this tool in the HIV-infected population even younger and with different comorbidities to the elderly population in which it has been traditionally used.

For example, in an intervention trial of a new HAART agent or a therapy to decrease immune activation or inflammation, a change in gait velocity would provide a clinically relevant, low-cost measure, easily obtainable from both benefit and damage from an investigational therapy [53,54].

In those over 70 who age with HIV, social isolation is very common. Many adults have moved away from their own family and have had friends who have already died. These events bring with them a relevant series of clinical and economic implications (for example, recognition of depression, need for community support services) [55].

CONCLUSION

As the focus of the HIV therapeutic strategy has shifted to the management of chronic non-infectious comorbidities in a growing and complex population, the promotion of measures that allow maintaining the abilities of an individual to remain independent is growing importance.

The identification of the most appropriate tools for the outcomes of interest and the validation and standardization of the tools in a population of HIV-infected adults of middle age and older, will improve the usefulness of functional and fragility evaluations in any clinical context.

The openness to the integral approach based on the promotion of the functionality provided by geriatric medicine is important for the care of the population that has aged carrying the HIV virus. So, it is essential that the infectologist specialized in HIV work shoulder to shoulder on all fronts (clinical, teaching and research) with specialists in old age: geriatricians.

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