

A PEER-REVIEWED ARTICLE

The aging process in HIV-infected patients: a comorbidity that needs more research

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A segment of the HIV-infected population is growing old, resulting in increasing instances of comorbid conditions due to the aging process. Numerous reviews in the literature relate to the aging of HIV-infected patients, most reporting on epidemiologic changes, the influence of antiretrovirals, T-cell count, and comorbidities in this group.^{5,6,12,13,18}

It is well known that aging brings significant comorbidities such as cognitive dysfunction, cardiovascular problems, coronary artery disease, cerebrovascular disease, and frailty syndrome, among other issues. The effect of HIV infection on the development of these problems is as yet unknown.^{1,3,4,7,14}

Research studies of issues beyond the epidemiological are scarce in this population. Numerous gaps exist in our knowledge about HIV and the aging/frailty syndrome in HIV-infected individuals has not been well defined. Outcomes related to the impact of antiretrovirals on the aging process and the characteristics of frailty syndrome in HIV-infected patients have not been studied in depth.

This article explores research options to evaluate the differences between chronological and biological age in HIV-positive patients, frailty syndrome in HIV-infected populations, the impact of antiretroviral therapy on the aging process of HIV-infected patients, the potential reversibility of frailty syndrome in HIV-positive populations with the use of antiretroviral therapy, and the potential delay of the aging process.

RESEARCH STUDIES IN AGING HIV-INFECTED PATIENTS

Epidemiological Studies

In a critical review of available literature, Martin *et al.*⁸ mentions that approximately 25% of HIV infections occur in the over-50 age group. The authors posit that HIV care in elderly patients is more complex due to comorbidities, lack of clear guidelines, absence of studies on interactions between antiretrovirals and other medications taken by this group, and the impending development of age-related or geriatric syndromes.

In a recent multicentric cross-sectional study conducted in Spain, Mothe *et al.*¹¹ described the clinical characteristics of patients over 70 years old with HIV infection. The majority of them were male (76%) with low CD4 counts at diagnosis (52%), compared to 34% of those in younger populations having low CD4 counts at the time of diagnosis. Dyslipidemia, hypertension, diabetes, cardiovascular disease, chronic renal failure, malignancies, and cognitive dysfunction were the most common comorbidities found. Interestingly, the authors found an average use of three drugs besides antiretrovirals.

In a study within the HIV Outpatient Clinic of the Interim Louisiana Public Hospital in New Orleans, 151 patients over 60 years of age were identified. The median age of this group was 61.8, and their baseline CD4 count was 404, with approximately 28% of patients having CD4 counts <200 /mm³. Hypertension, diabetes, dyslipidemia, hepatitis C, and depression were the most common comorbidities.¹⁷ The authors of this study found that diabetes and mobility problems were statistically significant issues in patients over 60 years of age.

Biologic versus chronologic aging in HIV-infected patients

Chronologic age and biologic age are two dynamic and individual variables in the continuum of the aging process. It is difficult to establish a common aging scale for

individuals and in the case of HIV-infected populations the presence of HIV factor might add another confounding variable. For the study in our clinic, the arbitrary cutoff age of 50 was chosen to identify elderly patients with HIV infection.

Coronary aging in HIV-infected patients has been studied by Guaraldi *et al.*,⁷ who evaluated 400 patients infected with HIV in a cross-sectional study. The patients underwent cardiac computed tomography imaging to identify coronary artery calcium. Interestingly, the authors found increased vascular age (approximately 15 years) compared to chronological age in 162 patients (40.5%). In a regression analysis, the authors also found that the only predictor of increased vascular age was an *increased* CD4 T-cell count. These results may have significant implications in view of the fact that antiretroviral therapy with a concomitant increase in CD4 count would heighten chances of increased coronary aging.

Ances *et al.*¹ studied the interactions between HIV infection and aging on brain function in 26 HIV-seropositive patients and 25 non-HIV-infected patients. The authors found no interaction between HIV infection and aging. It is worth noting that the functional brain demands in HIV-positive patients were equivalent to those of HIV-negative patients who were 15 to 20 years older.

These two studies mention the potential difference of 15 to 20 years between chronological and biological ages in HIV-infected patients. Other factors such as comorbidities, effects of antiretroviral therapy, and genetic predisposition may play significant roles in the final determination of the difference between chronologic and biologic aging in HIV-infected populations. These may be confounding factors that should be taken into account in research studies if a head-to-head analysis between chronologic and biologic ages is intended.

Frailty syndrome in the elderly HIV-infected

Frailty syndrome is frequently encountered in elderly populations. Frailty has been defined as a geriatric syndrome of increased vulnerability to environmental factors. Frailty has been considered synonymous with disability and co-morbidity, to be of high prevalence in old age, and to confer a high risk for falls, hospitalization, and mortality.^{2,3,4,6}

The inherent characteristics of frailty syndrome have not been studied in depth. Similarities and differences between general frailty syndrome and HIV-related frailty syndrome need to be established. The impact of antiretroviral therapy, immune reconstitution, and HIV viral load control should be evaluated in relation to the potential reversibility of HIV-related frailty syndrome.

In a prospective study, Onen *et al.*¹⁴ evaluated 445 persons with a mean age of 41.7 years, 71% male, 63% African American, with a mean 8.4 years of HIV diagnosis. Frailty prevalence was 9%. The authors used Fried's frailty scale for evaluation of these patients (Fried *et al* constructed an index that comprises five physical features: weakness, low grip strength, low energy, slow gait speed, and low activity levels. Frailty is defined by the presence of three or more criteria and pre-frailty is defined as the presence of one or two criteria). They concluded that unemployment, a greater number of comorbid conditions, past opportunistic illnesses, a higher depression severity score, receipt of antidepressants, and lower serum albumin were independent predictors of frailty. They further determined that HIV infection was associated with a premature presentation of frailty.

Desquilbet *et al.*³ investigated the relation between HIV and the prevalence of frailty-related phenotype (FRP). The authors defined FRP based on the definition of Linda Fried's frailty index. Subsequently, they assessed the prevalence of frailty among HIV-non-infected individuals followed in the Multicenter AIDS Cohort Study (MACS) between 1994-2004 (to which a total of 1,977 individuals contributed 12,155 visits). Finally, the authors evaluated the association between FRP and HIV infection before the era of antiretrovirals (during which 245 HIV-infected patients contributed to 691 visits). They found that HIV infection was strongly associated with FRP prevalence and that the FRP

prevalence for 55-year-old men infected with HIV for less than four years was similar to that of HIV-uninfected men over 65 years old.

The relation between FRP and progressive deterioration of the immune system in HIV-infected men before and after the appearance of highly active antiretroviral therapy was studied in 1,046 HIV-infected men from 1994 to 2005. CD4-T cell count and plasma HIV-RNA viral load were evaluated as predictors of FRP. The authors found that adjusted prevalence of FRP remained low for CD4-T cell counts >400. After 1996, CD4-T cell count was the only factor independently associated with FRP. The authors concluded that CD4-T cell count predicted the development of FRP among HIV-infected men, independent of antiretroviral use. Finally, the study suggests that the deterioration of the immune system in HIV-infected individuals contributes to the systemic physiologic dysfunction of frailty.^{3,4} These findings may have interesting implications for the prevention of frailty syndrome in HIV populations.

POTENTIAL RESEARCH STUDIES IN THE ELDERLY

Numerous areas exist for potential research studies in elderly HIV-infected patients but this article will concentrate on two main areas: the influence of HIV on the aging process through the determination and difference, if any, between chronologic and biologic aging, and frailty-syndrome prevalence and characteristics of HIV-infected populations.

Biologic aging scale in HIV-infected patients

There is a need for randomized control trials comparing the aging process in non-HIV-infected and HIV-infected populations. Fortunately, a significant number of biologic aging scales that have already been applied to non-HIV aging groups may also be applied to HIV-infected groups.

One possibility is age grouping HIV-infected patients into comparable non-HIV-groups studying the aging of the two groups by comparing and contrasting the aging processes and their characteristics. The scale used should be validated. Mitnitski *et al.*¹⁰ proposed that accumulation of deficits might be used as a proxy of measure of aging. A well-known scale is Rockwood's accumulation deficits, a 92-item scale.⁹ The authors subsequently validated a study in which 40 of the 92 were used as proxies for evaluation of the aging process.^{9,10}

Studying the aging process in HIV-positive patients is important because it could be studied from an HIV perspective and then compared to the general aging process. The potential delay of the aging process with the use of antiretroviral therapy would be an exciting prospect if substantiated.

Frailty syndrome in HIV-infected populations

The applicability of general frailty indices depends on the scale utilized. In a cross-sectional analysis, Cigolle *et al.* compared three models of frailty (deficiencies in function, index of health burden, and biological syndrome) based on the Health and Retirement Study, in which a total of 11,113 adults aged 65 and older were studied. According to at least one model, 30.2% of respondents were frail; 3.1% were frail according to all three models. The authors conclude that different models of frailty might capture different groups.²

The frequency of frailty syndrome in the HIV-infected population has already been determined by certain groups. It is well known that older age groups may have higher frequencies. The characteristics of the process (onset point, clinical and serological markers, contributing factors, role of the HIV virus, and reversibility) have not been studied in depth.

One possible way to study frailty syndrome in HIV-infected patients would be to compare its frequency to non-HIV infected populations across different age ranges. This could be achieved by using the gold standard utilized in general populations (general

frailty index) and subsequently applying the same index to HIV-positive patients. Rockwood *et al.*¹⁵ recommended the use of accumulation of deficits as a proxy for evaluation of frailty.^{15,16}

Another possible way to study frailty in HIV-positive patients is to develop a new HIV-frailty index. This new index might be compared to the “gold standard” already applied to this population. The differences between the two, if significant, might reveal the fact that HIV infection *per se* is a contributing factor to frailty. It is well known that certain HIV-infected patients may already be frail without clinical manifestations, and the only way to detect these problems may be with the use of serum markers of frailty. In HIV-infected patients, other factors such as cognitive dysfunction/dementia, bone loss, severe immunosuppression (CD4 cell count <200), and vitamin D deficiency may play a significant role in the development of frailty.

The importance of the study of frailty syndrome is that this syndrome might be reversible up to a certain extent in this population, in contrast to what usually happens in non-HIV-infected patients in whom this problem is irreversible. The application of preventive measures and the treatment options for frailty syndrome in HIV-infected patients have not been studied in depth.

Trials are needed to compare these two processes between HIV-infected and non-HIV-infected populations. Details of the aging process and its potential delay, as well as details of frailty syndrome and its potential reversibility, could be elicited from these studies.❖

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