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EDITORIAL

An Editorial. Aging with Human Immunodeficiency Virus Infection and the Impact of Long-term Anti-retroviral Therapy

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Introduction

The world is now well into the third decade of use of effective anti-retroviral therapy (ART) that provides sustained control of HIV-1 viremia (viral loads <200 copies of HIV RNA/microliter). With few exceptions, control of HIV in individual patients is predictable and long lasting. Only a short time ago, the prevailing opinion was that HIV infection 'physiologically aged' an individual by ten years or more compared to uninfected subjects and could lead to premature frailty.[1-4] Whereas these findings may have accurately characterized the untreated HIV-infected individual, they do not apply to those on ART. We discuss these concepts and show why they have not held up to scrutiny since clinical and cellular evidence contradict these statements. Theories about aging in HIV-positive patients arose in the early 2000's[5] about the time we began to study the course of HIV infection in our clinics, measuring frailty as well as obtaining and preserving blood samples from HIV- and healthy, age-matched control patients that allowed us to study cellular aging and immunity as well as the molecular features of HIV genes in viral quasispecies suppressed by ART.

One deleterious outcome of aging could be frailty, once believed to be an ineluctable outcome of aging HIV-infected patients. Most clinicians probably would not argue with a definition of frailty such as, "you'll know it when you see it." However useful this definition may be in practice, measurable parameters of frailty are needed to conduct a study. We chose to use a phenotypic measurement of frailty, the so-called Fried criteria[6] that are easily and rapidly obtained in the clinic at each visit.[7] The Fried method provides ordinate values for 5 functional aspects of health observed in aging individuals: shrinking weight, slowness, weakness in grip strength, low physical activity and exhaustion. The diagnosis of frailty using these criteria requires that any three of such measurements be abnormal.[8] There are many "surrogate measurements of frailty" for HIV patients, the most popular being the "frailty index" wherein one adds up diseases over a lifetime. This information can be obtained from the history and records. This information can be obtained from the history and records. However, directly observing our patients in the clinic and measuring for frailty gave us the clue that "frailty" was not permanent, and thus, decline was not inevitable as was held for the uninfected elderly.[9]

We found that frailty in HIV patients, with few exceptions, was transient (i.e., reversible), lessened with time due to increasing CD4 cell counts and suppressed viremia from use of antiretroviral drugs.[10]

Frailty in HIV patients is often a transient state.

We began our aging studies with 100 HIV-infected patients measuring Fried criteria on each individual along with standard laboratory tests. Eighty-one patients were not frail whereas, 19 were frail (~ 20% frail). Frailty in about one of five patients was observed in all our HIV clinical studies. Interestingly, community dwelling older adults have a frailty rate of 7%.[8,9] We found that CD4 counts <200 cells/mm^3 (indicative of AIDS) were associated with 9-fold increased odds of frailty relative to patients with a CD4 count >350 cells/mm^3 (odds ratio, 9.0, with 95% confidence interval).[10] Frailty was not dependent upon age, rather, it was associated with the immune status of the individual and often, the presence of opportunistic infections. For example, 7 frail patients were measured 6 months after the diagnosis of frailty: 2 died refusing therapy, 4 were no longer frail, and 1 patient remained frail.[10] In that study we concluded that frailty is common in HIV outpatients, often transient and associated with low CD4 counts. HIV patients, especially at younger ages, revert to their prefrail state if they remain adherent to anti-retroviral therapy. Thus, frailty in HIV was clearly unlike what occurs in the uninfected elderly in whom a stepwise decline in function was the predicted outcome.[5]

Frailty in the elderly is a function of aging and aging-related decline in organ systems where homeostatic reserves are exhausted.[13] It is estimated that perhaps 50% of individuals over the age of 85 years are frail whereas, in community dwelling individuals over the age of 65 years, prevalence is 7%.[6,8,9] In our studies, we have not found a relationship of frailty with age in HIV-infected individuals. For example, there was no significant difference between HIV-infected patients below or over the age of 50 years, the age at which HIV patients are considered "older".[5] Neither was there an increased incidence of frailty with each increasing decade of life. We found the opposite, i.e., individuals who took anti-retroviral therapy for the longest time period had the lowest incidence of frailty.[10] Anti-retroviral therapy actually protected against frailty! And to underscore the reversibility of HIV-frailty, as opposed to frailty in the elderly, we found that repeated exergaming (a computerized measurement of patients' balance, and coordination) had the potential to reverse some aspects of frailty.[11] In another study[12] of HIV-infected individuals (n=122), factors associated with sarcopenia (a hallmark of the uninfected frail elderly) such as decreased grip strength, slow walking and shrinkage were seen less frequently than exhaustion and low physical activity. For example, shrinkage or weight loss occurred in 65%, decreased grip strength occurred in 43%, and decreased gait speed in 39 % whereas, low physical activity occurred in 83% and exhaustion was present in 100% of the frail HIV patients.

Not surprisingly a major contribution to frailty was emotional/psychiatric disturbances. For example, documented psychiatric illness occurred in 31% of the patients irrespective of frailty status yet all frail HIV patients were depressed, 30% with Center for Epidemiologic Studies Depression Scale (CESD)[13] scores indicating mild to moderate depression and 70% with scores indicating a major depressive disorder.[12]In a follow up study,[12] we assessed 122 HIV patients using the 5-measure Fried criteria. The prevalence of frailty was again 19%. All frail patients reported exhaustion with CESD scores indicating depression; 70% were severely depressed. (Exhaustion is synonymous with depression as measured by the CESD scale). The next most common characteristic we found in frail HIV-infected patients was low physical activity (kcal expenditure/week), and the third characteristic, weight loss. Markers of sarcopenia such as decreased grip strength and decreased gait speed, hallmarks of frailty in the elderly, were the least common of the 5 criteria. Not unlike the previous

study, frailty was reversible: 6 frail patients returned for reassessment and only 2 were frail. We concluded that frailty in the HIV-infected patients is potentially reversible and strongly associated with depression and low physical activity, as opposed to frailty in the elderly which is associated with aging-related sarcopenia and is often irreversible.[12,14]

Effects of long-term ART therapy on cellular aging, immunosenescence, and viral genotypes.

The HIV-1 envelope variable region 3 (V3 region) gene harbors the major pathogenic regions of HIV, important in infectivity.[15,16] It is important as well for the association of gp120 on the cell surface with gp41, virus neutralization, replication efficiency, utilization of the coreceptor, and host cell tropism.[16] HIV-infected individuals on long-term ART control viremia and improve CD4 T cell counts but still harbor residual HIV. Consequently, we[16] focused on determining whether there was much variability within the viral genome in the V3 region of HIV isolates from 25 HIV-infected older patients on long-term ART looking for evidence of possible evolution of the infecting virus during the long period (4-30 years) of viral suppression by ART. It was found that there was little evidence of heterogeneity among nucleotide amino acid sequences in the V3 region, most isolates demonstrated the R5 phenotype even though the V3 region sequences maintained all the functional domains for biological activity as well as the epitopes for neutralizing antibody although there was variation in the cytotoxic T lymphocyte (CTL) epitopes.[16] Similar findings were also found[17] in another important HIV-1 accessory gene, vpr that encodes a multifactorial protein involved in viral replication and pathogenesis, especially in non-dividing and resting target cells.

We also looked at host factors such as immunity and aging of T cells in patients on long-term ART.[18] Surprisingly, it was found that HIV-infected patients manifested less cellular "aging" as well as robust T cell immunity counter to the hypothesis of aging in HIV-infected patients.[1-4] Evidence was adduced for immunological reconstitution, including reduction in terminally differentiated T cells and improvement in ratios of naïve to memory cells. In other words, there was a phenotypic shift from older to younger T cells, avoiding terminal differentiation. In addition, there were increased naïve $CD4^+$ T cells and the $CD4^+$ T cells showed improved functions by producing cytokines, including IL-2, IL-10 and IFN-γ. This was considered an indication of a reduction of exhausted/senescent T cells with improvement in the ratios of naïve to memory cells and also the function of T cells in HIV-infected patients. This was ascribed to suppression of viremia and improvement of CD4 T cell counts from long-term ART.[18] These findings and others, yet to be discussed, moved us to declare that ART alone was sufficient to control HIV-infection and restore many cellular functions.[19]

Further studies with patients on long-term ART extended these findings. For example,
patients on long-term ART showed immune restoration, including improvement in IFN-γ production by $CD4^+$ T-cells in response to HIV-specific and non-specific stimuli and reduction in HIV-specific $CD8^+$ T-cell response.[20] Also, HIV-specific CD8 T-cell responses wane in patients with suppressed viremia and improved functional CD4 T-cell counts, whereas it persists at higher levels in those who fail to restore their CD4 T-cell counts. HIV-specific IFN-γ produced by $CD4^+$ T cells remains unchanged with increasing age of patients whereas, HIV-specific $CD8^+IFN\text{-}\gamma^+$ T-cells decreased with increasing age of patients but still higher than uninfected individuals. Immune recovery appears to correlate strongly with increased CD4 T-cell counts.[19]

Since HIV-infected individuals with undetectable viral load and improved CD4 T cell counts due to long-term ART may continue to experience some level of inflammation and immunosenescence, the proinflammatory and anti-inflammatory cytokines were measured in 173 HIV-infected adults (from 22

to 81 years on long-term ART) compared to with 92 healthy, aging individuals.[21] The median levels of TNF-α, IFN-γ, IL-1β, IL-6, and IL-10 were higher ($p<0.001$ to <0.0001) and IL-17 trended lower in HIV-infected individuals than healthy controls (although IFN-γ, IL-1β, and IL-10 were within normal limits[22]). Nevertheless, HIV-infected, aging adults with undetectable viral load and restored CD4 T cell counts due to long-term ART still produce higher levels of both proinflammatory and anti-inflammatory cytokines compared with healthy controls, suggesting some level of inflammation. It has been noted that ART reduces cytokine levels within a year of beginning ART,[23] and it should be noted that our patients had been on ART for years. Furthermore, the meaning of a reduction in IL-17A in the HIV-infected subjects is uncertain as it may synergize with TNF-a to facilitate intestinal epithelial release of HIV.[24] However, improvement of IL-17A levels in our HIV patients due to ART[22], although not to the levels in healthy controls, is still likely to control and prevent the release of residual HIV from intestinal mucosal cells.

In our most recent clinical study, [25] we recruited long-term patients on ART, measuring frailty with a novel device validated for frailty. Measurements were performed using a sensor-based upper extremity method called, Frailty Meter (FM) (Frailty Meter™, Biosensics, Newton, MA)[26,27] that measures weakness, slowness, rigidity, and exhaustion. Thirty-seven (37) community-dwelling people living with HIV were measured for frailty using the sensor-based frailty meter. An immunological profile of the patients' $CD4^+$ and $CD8^+$ T-cell expression of cell surface proteins and cytokines was performed as well (n = 20). Phenotypic frailty prevalence was 19% (7/37) and correlated weakly with the number of past medical events accrued by the patient (r = 0.34, p = .04). There was no correlation of frailty with age, sex, prior AIDS diagnosis or HIV-1 viral load, or IFN-γ expression by $CD4^+$ or $CD8^+$ T-cells. Furthermore, there were more immune competent ($CD28^+$ $CD57^-$) cells than terminally differentiated/exhausted/senescent ($CD28^-$ $CD57^+$) T cells. Although frailty in people living with HIV on long term, suppressive ART does not correlate with aging or T cell markers of exhaustion or immunosenescence, it may still occur later in life similar to the uninfected elderly. Further work is needed.

Conclusion.

What has been learned is that…

1. When HIV infection is treated with effective, suppressive ART, "premature physiologic aging" manifested by frailty is prevented.

2. Over time effective ART significantly improves the damage that HIV infection caused to cellular immune function and premature senescence or "aging" of immune cells.

3. Phenotypic frailty in HIV-infected individuals (~20% incidence) is measurably different from frailty in non-infected community living elderly over the age of 65 years (~7% prevalence). The latter is characterized by sarcopenia. The former (caused by HIV) is transient and related to diminished immunity (e.g., AIDS), opportunistic infections, clinical depression and exhaustion.

4. Suppressive ART has changed the outlook for HIV infection in countries once besieged by frail, dying individuals.[28] ART is the most important component in tackling the HIV pandemic and recent evidence suggests that the most rapid and efficient tool to implement ART is Telemedicine.[29]

Conflict of Interest:

None

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