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HIV Infection-Associated Frailty: The Solution for Now Is Antiretroviral Drugs: A Perspective

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Abstract

This Perspective article provides a new view of frailty as it relates to HIV-1 infection. We discuss new findings and where our research is going.

Keywords

frailty, HIV-1 infection, antiretroviral drugs, immune function recovery, CD4 count and CD8 T cells

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What Do We Already Know about This Topic?

Frailty was a common complication of HIV infection, particularly in AIDS patients. Frailty can be measured in different ways. There is a phenotype of frailty that changes to a non-frail state with improvement of the immune deficiency associated with HIV infection.

How Does Your Research Contribute to the Field?

We have shown that years of anti-retroviral therapy can return frail patients to a non-frail state. In addition, prolonged anti-retroviral therapy restores cellular function and numbers of cells adversely affected by HIV. Recently we demonstrated a marked improvement in aging markers in HIV patients on long-term anti-retroviral therapy.

What Are Your Research's Implications toward Theory, Practice, or Policy?

It is anticipated that anti-retroviral therapy now being administered at the time of diagnosis, cure of hepatitis C and use of current HIV therapies with fewer side effects will diminish the incidence and prevalence of frailty associated with HIV infection.

Introduction

Frailty related to HIV-1 infection is rapidly becoming a specter of the past, joining another ogre, disfiguring lipodystrophy, as grim historical footnotes to the HIV epidemic in the United States. Frailty is a syndrome with a generally accepted phenotype consisting of unintentional weight loss, weakness, exhaustion, slow walking speed, and low physical activity.[1] With the advent of the latest antiretroviral therapy (ART), in particular, the integrase inhibitors combined with powerful tools to test for drug resistance, it is possible to control HIV infection in all patients. This leap forward in health care of HIV-infected individuals rivals the events of late 1995 and 1996 when 3-drug regimens unfolded on the scene. Now, for example, in our clinics with over a thousand HIV-infected individuals, 91% of them consistently have viral loads <20 RNA copies/mL and many of those with durable viral load suppression attend clinic only once a year. This, in spite of the fact, that many

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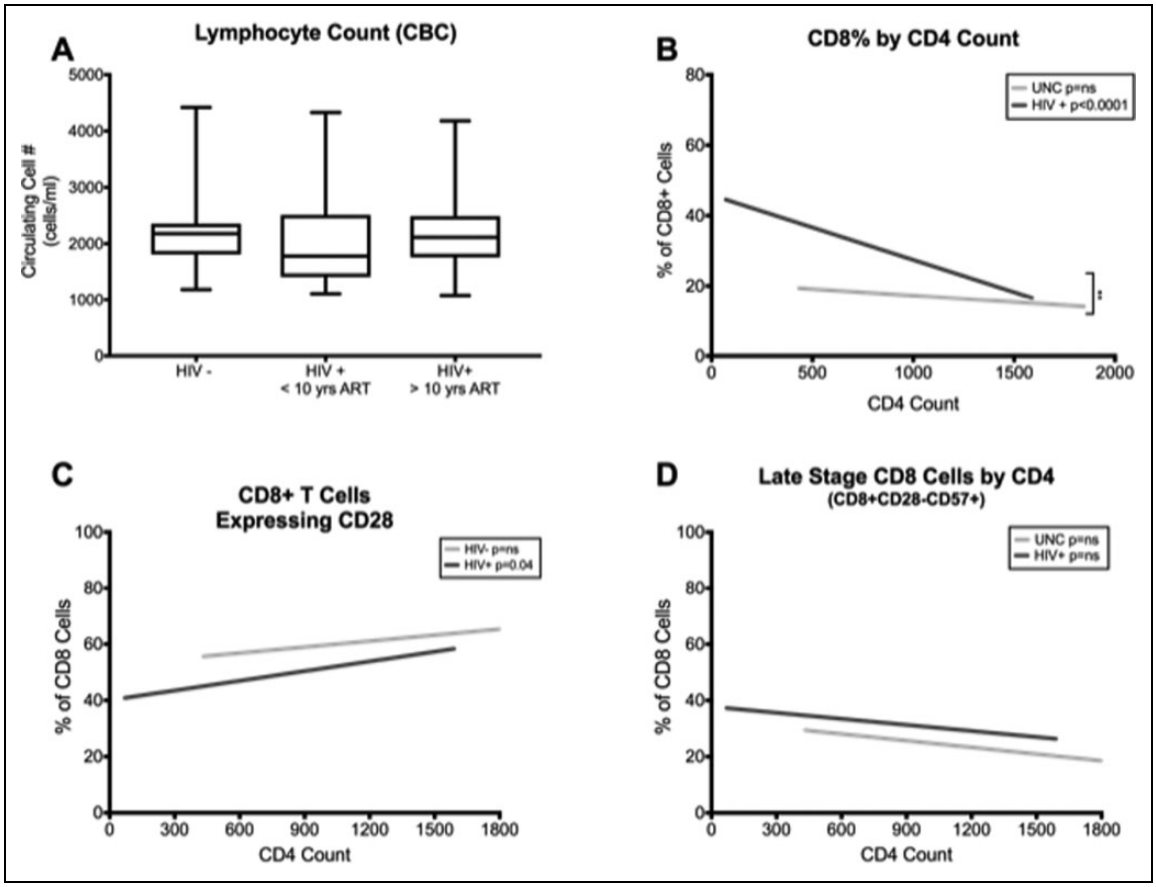

Figure 1. HIV-positive patients (HIV+) on continuous ART with undetectable viral loads followed over 3 years (n = 110) compared to age-matched uninfected controls (HIV−; n = 75). **A**, The line in the box shows mean values of total lymphocytes for controls, patients on ART <10 years and >10 years, respectively. **B**, CD8 cells decline as CD4 count increase in number. **C**, CD8 cells expressing CD28 as CD4 count numbers increase. **D**, Late stage, terminally differentiated CD8 cells (expressing $CD28^{-}CD57^{+}$) in comparison to CD4 count numbers. ART indicates antiretroviral therapy.

individuals have numerous HIV mutations to antiretroviral drugs. To achieve the "undetectable" status, however, there must be a strong desire and commitment by patients to take ART, hence we do not at present have a 100% undetectable population. This is the nearest we have come yet to achieving a cure of this chronic disease.

Since people are living longer with HIV infection and simultaneously aging how can we say that the impact of frailty in HIV-infected patients is lessening? Two factors have a major effect on frailty in HIV infection. First, was our finding that the longer patients were administered ART, the less likely they were to be frail.[2] A second corollary was that HIV-related frailty was often transient and related to immune suppression. Improvement of patients' immunity with ART led to a nonfrail state thus, reversing frailty.[3] Our recent work has shed light on the issue of immune aging as it applies to HIV infection.[4] The old adage that HIV infection added perhaps as many as 10 to 15 years to an individual's age irrespective of their chronological age[5] likely no longer applies. We found that the longer patients took ART, the better the immune function of host cells, not only their CD4 count numbers but the entire immune repertoire of those responding to ART.[4] In a sense the patients were "getting younger," the markers we studied showed remarkable improvement approaching values of those of uninfected controls (specifically, there was a reduction in terminally differentiated markers and significant improvement in cytokine secretion in the presence of HIV-specific peptides).

We are currently studying specific immune aging markers in HIV-infected patients and once again we find improvement in infected patients on continuous, long-term ART. Our study was approved by the University of Arizona institutional review board. Informed and signed consent was obtained from all participants. There was a marked increase in numbers of overall lymphocyte counts comparable to those seen in healthy controls, and when measured by length of ART treatment, there was an increase in lymphocyte numbers in those on ART for greater than 10 years over those with 10 years of ART or less (Figure 1A). There was a reduction in the frequency of CD8 T cells with improving CD4 counts (Figure 1B). There was an increase in the expression of $CD28^{+}$ cells, including naive and central memory cells, and a decrease in $CD28^{-}CD57^{+}$ cells which are markers for terminal differentiation (Figure 1C and D). There is thus, an improvement in the quantity and quality of immune cells and a suppression of aging markers associated

with ART. These findings also measure a contributing factor to a normal, or nonfrail, state and that is a robust, functional immune system. Some of the measurements may be the long sought after biological markers of frailty. One difficulty that continues to bedevil aging investigators is the plethora of markers and a constantly changing consensus regarding the role or importance of a particular marker in the process of aging.

What has been difficult to document in studies of HIV and frailty is the dynamic change occurring with patients on ART; every time one looks, the physical status seems to improve. For example, our first study of HIV and frailty published in 2013 (performed in 2010-2011) found a frailty rate of 19%.[1] This was using the very stringent criteria of Fried[1] and 7 of the patients had AIDS at the time of evaluation, and 6 months later, 4 of them were no longer frail.[2] Another medical triumph has occurred since our original publication and that is the ability to cure hepatitis C virus (HCV) infection. At one point, HCV was prominently associated with frailty in HIV infection and considered a major contributing factor to frailty. This is likely so for the reason that HCV alone contributes to the senescence of T cells.[6] In our study that had a frailty rate of 19% of 100 HIV-infected patients, the HCV prevalence was 32% (6 patients) in the frail group and 15% (12 patients) in the nonfrail group.[2] Now, almost all our long-term HIV-infected patients are cured of HCV infection and the prevalence of this disease has fallen in patients in the HIV clinic. So, this other viral scourge is decreasing in prevalence not only in the general public but in our HIV-infected patients as well.

In an effort to keep pace with these changes, we have decided to study our patients with a different tool to detect frailty. Although we regard the Fried method of measuring frailty[1] as the "gold standard" it cannot be performed on all patients and is time-intensive for the person administering the test.[7] We are now looking at a new methodology for assessing frailty. As opposed to testing for grip strength, energy, walking speed, physical activity, and/or unintentional weight loss per Fried, we are instead going to look at weakness, slowness, exhaustion, and flexibility of simple arm movements simultaneously with or without a cognitive challenge. The methodology involves use of a wireless device, The Frailty Meter[8] BioSensics LLC that detects frailty through a small, Bluetooth-supported motion sensor that attaches to the patient's wrist. The methodology has proven effective in assessing frailty by measurement of 20-second elbow flexion/extension activities and is ideal for use in a wide variety of settings as it is lightweight, mobile, and patients can complete the task while standing or sitting. Furthermore, the Frailty Meter is easy to use, incorporating software that is intuitive, an improvement over the previous technology we used to measure frailty.[9]

For the first time, we anticipate that we will be able to measure frailty during routine clinic visits and then follow the results over time. The patients will be interested in participating in something that is so simple and quick, even more so, something that will allow them to immediately see the results of their performance and discuss such information with members of the research team.

Declaration of Conflicting Interests

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References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001; 56(3):M146–M156.
2. Ianas V, Berg E, Mohler MJ, Wendel C, Klotz SA. Antiretroviral therapy protects against frailty in HIV-1 infection [published online October 04, 2012]. *J Int Assoc Provid AIDS Care*. 2013; 12(1):62–66. doi:10.1177/1545109712457241.
3. Rees HC, Meister E, Mohler MJ, Klotz SA. HIV-related frailty is not characterized by sarcopenia. *J Int Assoc Provid AIDS Care*. 2016; 15(2):131–134. doi: 10.1177/2325957414553848. Epub 2014 Oct 15.
4. Behrens NE, Wertheimer A, Klotz SA, Ahmad N. Reduction in terminally differentiated T cells in virologically controlled HIV-infected aging patients on long-term antiretroviral therapy. *PLoS One*. 2018;13(6):e0199101. doi: 10.1371/journal.pone.0199101. eCollection 2018.
5. Thurn M, Gustafson DR. Faces of frailty in aging with HIV infection. *Curr HIV/AIDS Rep*. 2017;14(1):31–37. doi: 10.1007/s11904-017-0348-x. Review.
6. Grady BP, Naniohy NM, van Baarle D. HCV monoinfection and HIV/HCV coinfection enhance T-cell senescence in injecting drug users early during infection. *Immun Ageing*. 2016;13:10. doi: 10.1186s12979-016-0065-0/.
7. Rees HC, Ianas V, McCracken P, et al. Measuring frailty in HIV-infected individuals, identification of frail patients is the first step to amelioration and reversal of frailty. *J Vis Exp*. 2013. doi: 10.3791/50537.
8. Frailty Meter™, Frailty Meter User's Manual Ver. 1.1 [package insert]. Watertown, MA: BioSensics LLC; 2018.
9. Veeravelli S, Najafi B, Marin I, Blumenkron F, Smith S, Klotz SA. Exergaming in older people living with HIV improves balance, mobility and ameliorates some aspects of frailty. *J Vis Exp*. 2016;(116). doi:10.3791/54275.