Chapter 2
Pathophysiology of HIV/AIDS

Julian Falutz

Key Points

- Inflammaging describes the increase in inflammation-driven chronic illnesses that exist in older adults.
- In seropositive patients the effects of chronic immune activation and chronic inflammation contribute to incomplete CD4 recovery and limit overall immune reconstitution.
- Human immunodeficiency virus (HIV) positive older patients are generally less likely to attain the same degree of post-HAART immune recovery than younger patients, regardless of better adherence to drug therapy.
- Chronic stimulation of the immune system occurs by various on-going elements including life-long exposure to environmental antigenic stressors, persistence

J. Falutz, MD, FRCP(C)
Director, Comprehensive HIV & Aging Initiative, Chronic Viral Illness Service, Division of Infectious Diseases, Senior Physician, Division of Geriatrics, McGill University Health Centre, Montreal, QC, Canada
e-mail: julian.falutz@mhc.mcgill.ca

G. Guaraldi et al. (eds.), *Managing the Older Adult Patient with HIV*, DOI 10.1007/978-3-319-20131-3_2,
© Springer International Publishing Switzerland 2016

of non-curable infections (eg, cytomegalovirus [CMV] and herpes viruses), and increase in age-related gastrointestinal microbial translocation.
- Chronic immune activation contributes to development of accelerated age-related immunosenescence, typically observed in patients with HIV.

2.1 Immunodeficiency, Immune Activation, and Chronic Inflammation

HIV infection causes progressive immunodeficiency by specifically targeting CD4+ cells of the monocyte/macrophage lineage. This leads to both functional impairment and destruction of target cells [1]. Untreated seropositive patients develop a profound CD4 cytopenia (normal CD4 count in uninfected adults is >600–800 cells/μL) and dysregulation of both cellular and humoral immunity, resulting in disruption of immune homeostasis parameters. The serum HIV viral load (HIV-VL) is often increased to very high levels, up to several million copies per mL in some untreated patients. All currently available highly active antiretroviral therapy (HAART) regimens effectively reduce HIV viral replication to below the level of detection of currently available assays (<40 copies/mL) within several months of starting therapy. This results in a variable and slowly progressive immune recovery (defined as the return of the absolute number of CD4+ T cells towards, but rarely to, normal levels) but only limited immune reconstitution (the re-establishment of normal quantitative relationship between CD4 and CD8 T cells) [1]. However, the usual extent of immune recovery significantly reduces the risk of developing typical AIDS-related complications. Higher levels of CD4 recovery, particularly to levels >500 cells/mL, are associated with a lower risk of developing AIDS. This relationship informs the clinical scenarios faced by aging patients with HIV.

Older patients with HIV are more likely to present with significant immunosuppression or AIDS-related complications.

This is most likely due to the clinical reality that HIV is considered less often in the differential diagnosis of common HIV-related symptoms. Older patients' baseline CD4 counts are also usually lower at the time of initial clinical presentation, due to both a delay in making a timely diagnosis of HIV and to the possible effect of accelerated age-related immunosenescence that may occur in patients with HIV [2].

Although the evidence remains controversial, after beginning HAART older patients are generally less likely to attain the same degree of post-HAART immune recovery than younger patients, and their plateau CD4 counts are also lower [3]. This may be related to their starting HAART at lower CD4 levels. As a result, they remain at higher risk of developing AIDS-related complications. The survival of older patients after developing AIDS is also less than that of younger patients [4]. However, after starting HAART, older patients achieve an undetectable HIV-VL as often as younger patients [3]. Furthermore, they are more likely than younger patients to maintain an undetectable HIV-VL over time, and this is likely due to better adherence to drug therapy [5].

Persistent immune activation is a key feature in patients responding to HAART. This phenomenon refers to processes involving cell activation and proliferation, suggested by increased levels of inflammatory cytokines, monocytes, activated T cells, and coagulation parameters [6]. Patients with untreated HIV infection have laboratory evidence of an activated immune state even in the absence of concurrent infectious or malignant complications [1]. HAART reduces these increased activation markers, but rarely to pre-HIV infection levels [7].

Several factors predispose to persistent immune activation, including:

- low-level HIV replication [6], which occurs in treated patients with undetectable HIV-VL and is a strong stimulus to chronic immune activation;
- thymic dysfunction leading to impaired T cell maturation [8];
- co-infection with specific viruses such as hepatitis B and C, human papillomavirus (HPV), and CMV [6]; and
- microbial translocation.

Microbial translocation refers to the process by which intestinal microbial products enter the systemic circulation. Initial HIV infection affects the gut-associated lymphatic tissue (GALT) leading to epithelial injury and extensive CD4 T cell depletion. HAART does not completely reverse this injury and results in incomplete restoration of the initial severe histologic and immune disruption. Partial restoration of the GALT permits passage of biologically active products, including lipopolysaccharide (LPS), to the bloodstream, resulting in the activation of monocytes/macrophages, B and T cells, plus coagulation factors [9]. Microbial translocation also occurs to a lesser degree in normal aging [10], itself considered to represent a state of chronic immune activation, although to a much more limited extent than that caused by HIV.

Chronic immune activation interacts with and predisposes to chronic inflammation. Chronic inflammation is also associated with increased levels of cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-1β, and acute phase reactants that act in a positive feedback manner to attract further immune system components. Physiologic aging is also accompanied by low-grade inflammation leading to a chronic increase in inflammatory mediators [11]. In the general population these factors may contribute to an increase in age-related diseases such as atherosclerosis, dementia, diabetes, cancer, and sarcopenia. This pro-inflammatory state may also occur if the normal mechanisms that turn off the otherwise effective immune response are defective or inefficient.

The term ‘inflammaging’ was coined almost 15 years ago to describe the tripartite interaction between the up-regulated inflammatory response, the subsequent low-grade chronic inflammation, and the increase in inflammation-driven chronic illnesses that exists in older adults [12]. This process incorporates neuro-endocrine activation via a chronically stimulated hypothalamic–pituitary–adrenal axis, so that glucocorticoid hypersecretion functions as the major counteractive response, but is associated with its own long-term toxicities [13]. A similar scenario may be active in treated HIV disease [14].

2.2 HIV and Immunosenescence

Chronic immune activation and the related state of chronic inflammation also contribute to the development of immunosenescence, a term describing the changes in immune parameters that occur in normal aging [15]. These have been studied mostly in persons older than 80 years of age who are more prone to infections, have decreased responses to routine vaccines, and are at increased risk of disorders in which chronic inflammation plays a pathogenic role [16]. Genetic signals affect immune parameters via an impact on diet, age-related thymic involution (resulting in decreased thymic hormones required for normal T cell maturation) [15], and rates of telomere shortening [17], which are themselves possibly modifiable by lifestyle factors. Immunosenescence affects multiple components of innate immunity including neutrophils, natural killer (NK) cells, monocytes/macrophages, dendritic cells, and impacts markers of cellular senescence on T cell and B cell lymphocytes [16–18].

Age-related changes in immune parameters are mostly related to chronic stimulation of the immune system by various factors. These include life-long exposure to environmental antigenic stresses, persistence of non-curable infections (CMV and herpes viruses), and increase in age-related gastrointestinal microbial translocation. These stimuli lead to:

1. expansion of the pool of terminally differentiated senescent memory CD28– T cells that release the pro-inflammatory cytokines IL-6 and TNF-α, further contributing to chronic inflammation [16, 17];
2. reduction of the pool of naïve T cells capable of responding to new antigenic stimuli [17]; and
3. an inverted T-helper/T-suppressor cell ratio (normally greater than 1.0–1.5).

The inverted T cell ratio was shown to predict short-term morbidity and mortality in the prospective Swedish OCTO and NONA studies of community-dwelling octogenarians and nonagenarians [19]. The inverted CD4/CD8 T cell ratio has been referred to as the immune risk phenotype (IRP), and has been associated with poor health-related outcomes [20].

Immune dysfunction changes that occur in response to untreated HIV infection, and to a lesser extent in patients on HAART, are similar to those that occur in normal aging. On this basis, treated HIV has been described as a state of accelerated immunosenescence [21]. Immune changes that occur to a variable degree in both untreated and treated patients with HIV include [22–24]:

- a low CD4/CD8 ratio;
- low numbers of naïve T cells;
- low T cell proliferation potential;
- expanded CD8+/CD28− numbers;
- reduced T cell repertoire;
- increased IL-6 production;
- reduced thymus function;
- reduced T cell telomere lengths;
- expanded CMV-specific CD8 T cells; and
- reduced vaccine responses.

These similarities between immunosenescence-related changes in people with HIV and older seronegative adults is further supported by the finding that young patients with HIV and severe immunosuppression have naïve T cell numbers comparable to healthy seronegative persons of more than 80 years of age [19]. Rates of telomere shortening in terminally differentiated CD8+/CD28− cells of young patients with HIV are also similar to those in healthy seronegative centenarians [25]. Levels of a known biomarker of aging, cyclin-dependent kinase inhibitor 2A (CDKN2A), a cell senescence mediator, are increased in treated younger patients, suggesting that increased biologic aging may occur in these patients [26].

Chronic CMV infection also contributes to immune dysfunction in both HIV and elderly patients. In very old people, being CMV seropositive contributes to expansion of the CD8+/CD28− T cell pool [27]. The overall T cell response to latent herpes virus infections in the elderly is important and represents up to 20 % of the total memory T cell compartment [28]. Patients with treated HIV disease and good immune recovery have a strong anti-CMV response [29]. Treated patients also have an inverse relationship between strong anti-CMV T cell responses and both lower total and naïve CD4+ T cell numbers [30]. Treated patients with HIV who are CMV negative have higher CD4+/CD8+ T cell ratios, are more likely to achieve normalization of their CD4+/CD8+ T cell ratios (>1.0) with HAART, and are less likely to have immunosenescence related markers [31]. Although CMV seropositivity in patients with treated HIV represents a latent infection, the anti-CMV drug, valganciclovir, may decrease CD8+ T cell activation markers in treated patients [32].

2.3 Evolving Clinical Profile

Regardless of the effects of chronic immune activation and chronic inflammation, which contribute to incomplete CD4 recovery and limit overall immune reconstitution [33], it is clear that AIDS-related morbidity and mortality in treated patients has declined dramatically since the introduction of HAART in the mid-1990s. Long-term survival has improved significantly in adherent patients with reliable access to ARVs, but remains overall at about two-thirds that of uninfected, age-matched controls [34]. However, the subset of patients on HAART who maintain an undetectable HIV-VL and CD4 count (>500 cells/mL) for over 5 years are predicted to likely achieve normal long-term survival [35]. The main predictor of the extent of immune recovery is the ‘nadir’ CD4 count, which refers to the lowest CD4 count a patient had prior to starting HAART. Nadir counts less than

200 CD4 cells/mL are associated with poor immune recovery [36]. As noted, this is relevant to understanding the clinical consequences of older patients' generally less robust response to effective HAART.

While the incidence of typical AIDS complications has decreased, complications continue to occur. However, the spectrum of clinical disorders has changed. These currently consist of generally common medical conditions and typically include [37]:

- cardiovascular disease;
- bone demineralization;
- metabolic disorders with associated body composition changes;
- distinct malignancies;
- certain hepato-renal diseases; and
- non-dementing cognitive dysfunction.

In treated HIV infection, ongoing low-grade HIV viremia and the resulting chronic immune response plays an important pathogenic role in the development of the major non-AIDS complications, including atherosclerosis, osteoporosis, neurocognitive decline, and the increasingly recognized geriatric frailty syndrome [38]. The clinical presentation and course, plus response to treatment of these conditions are broadly similar to that occurring in non-HIV infected persons. However, the risk of developing these complications is variable and appears to be related to a post-HAART plateau CD4 count <500 cells/mL [39]. This limited immune recovery is more likely to occur in older patients with HIV [40]. This helps to inform why aging patients with HIV with lower nadir and plateau CD4 cell counts will be faced not only with typical aging related comorbidities but may also have an increased risk of these complications occurring at a younger age. Evidence suggests that, at least for bone demineralization and cardiovascular disease, older (but not typical geriatric aged) patients do have an increased risk compared to younger patients with similar CD4 counts [41, 42].

References

1. Maartens G, Celum C, Lewin SR. HIV infection: epidemiology, pathogenesis, treatment, and prevention. Lancet. 2014;384:258–71.
2. Althoff KN, Gebo KA, Gange SJ, et al. CD4 count at presentation for HIV care in the United States and Canada: are those over 50 years more likely to have a delayed presentation? AIDS Res Ther. 2010;7:45.
3. Althoff KN, Justice AC, Gange SJ, et al. Virologic and immunologic response to HAART, by age and regimen class. AIDS. 2010;24:2469–79.
4. Brooks JT, Buchacz K, Gebo KA, Mermin J. HIV infection and older Americans: the public health perspective. Am J Public Health. 2012;102:1516–26.
5. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, Quesenberry Jr CP. Older age and the response to and tolerability of antiretroviral therapy. Arch Intern Med. 2007;167:684–91.
6. Hunt PW. HIV and inflammation: mechanisms and consequences. Curr HIV/AIDS Rep. 2012;9:139–47.
7. Keating SM, Golub ET, Nowicki M, et al. The effect of HIV infection and HAART on inflammatory biomarkers in a population-based cohort of women. AIDS. 2011;25:1823–32.
8. Ho Tsong Fang R, Colantonio AD, Uittenbogaart CH. The role of the thymus in HIV infection: a 10 year perspective. AIDS. 2008;22:171–84.
9. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med. 2006;12:1365–71.
10. Tran L, Greenwood-Van Meerveld B. Age-associated remodeling of the intestinal epithelial barrier. J Gerontol A Biol Sci Med Sci. 2013;68:1045–56.
11. Chung HY, Cesari M, Anton S, et al. Molecular inflammation: underpinnings of aging and age-related diseases. Ageing Res Rev. 2009;8:18–30.
12. Cevenini E, Monti D, Franceschi C. Inflamm-ageing. Curr Opin Clin Nutr Metab Care. 2013;16:14–20.
13. Giunta S. Exploring the complex relations between inflammation and aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm-aging, from robustness to frailty. Inflamm Res. 2008;57:558–63.

14. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. Immunity. 2013;39:633–45.
15. Larbi A, Franceschi C, Mazzatti D, Solana R, Wikby A, Pawelec G. Aging of the immune system as a prognostic factor for human longevity. Physiology (Bethesda). 2008;23:64–74.
16. Freund A, Orjalo AV, Desprez PY, Campisi J. Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med. 2010;16:238–46.
17. McElhaney JE, Effros RB. Immunosenescence: what does it mean to health outcomes in older adults? Curr Opin Immunol. 2009;21:418–24.
18. Caruso C, Buffa S, Candore G, et al. Mechanisms of immunosenescence. Immun Ageing. 2009;6:10.
19. De Biasi S, Pinti M, Nasi M, et al. HIV-1 infection and the aging of the immune system: facts, similarities and perspectives. J Exp Clin Med. 2011;3:143–50.
20. Wikby A, Ferguson F, Forsey R, et al. An immune risk phenotype, cognitive impairment, and survival in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans. J Gerontol A Biol Sci Med Sci. 2005;60:556–65.
21. Nasi M, Pinti M, De Biasi S, et al. Aging with HIV infection: a journey to the center of inflammAIDS, immunosenescence and neuroHIV. Immunol Lett. 2014;162:329–33.
22. Tassiopoulos K, Landay A, Collier AC, et al. CD28-negative CD4+ and CD8+ T cells in antiretroviral therapy-naive HIV-infected adults enrolled in adult clinical trials group studies. J Infect Dis. 2012;205:1730–8.
23. Dock JN, Effros RB. Role of CD8 T cell replicative senescence in human aging and in HIV-mediated immunosenescence. Aging Dis. 2011;2:382–97.
24. Papagno L, Spina CA, Marchant A, et al. Immune activation and CD8+ T-cell differentiation towards senescence in HIV-1 infection. PLoS Biol. 2004;2, E20.
25. Effros RB, Allsopp R, Chiu CP, et al. Shortened telomeres in the expanded CD28-CD8+ cell subset in HIV disease implicate replicative senescence in HIV pathogenesis. AIDS. 1996; 10:F17–22.
26. Pathai S, Lawn SD, Gilbert CE, et al. Accelerated biological ageing in HIV-infected individuals in South Africa: a case-control study. AIDS. 2013;27:2375–84.

27. Olsson J, Wikby A, Johansson B, Löfgren S, Nilsson BO, Ferguson FG. Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the Swedish longitudinal OCTO immune study. Mech Ageing Dev. 2000;121:187–201.
28. Brunner S, Herndler-Brandstetter D, Weinberger B, Grubeck-Loebenstein B. Persistent viral infections and immune aging. Ageing Res Rev. 2011;10:362–9.
29. Naeger DM, Martin JN, et al. Cytomegalovirus-specific T cells persist at very high levels during long-term antiretroviral treatment of HIV disease. PLoS One. 2010;5, e8886.
30. Appay V, Fastenackels S, Katlama C, et al. Old age and anti-cytomegalovirus immunity are associated with altered T-cell reconstitution in HIV-1-infected patients. AIDS. 2011;25:1813–22.
31. Barrett L, Fowke KR, Grant MD. Cytomegalovirus, aging, and HIV: a perfect storm. AIDS Rev. 2012;14:159–67.
32. Hunt PW, Martin JN, Sinclair E, et al. Valganciclovir reduces T cell activation in HIV-infected individuals with incomplete CD4+ T cell recovery on antiretroviral therapy. J Infect Dis. 2011;203:1474–83.
33. Rajasuriar R, Wright E, Lewin SR. Impact of antiretroviral therapy (ART) timing on chronic immune activation/inflammation and end-organ damage. Curr Opin HIV AIDS. 2015;10:35–42.
34. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One. 2013;8, e81355.
35. Rodger AJ, Lodwick R, Schechter M, et al. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. AIDS. 2013;27:973–9.
36. Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis. 2005;41:361–72.
37. Palella Jr FJ, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006;43:27–34.

38. Hearps AC, Martin GE, Rajasuriar R, Crowe SM. Inflammatory co-morbidities in HIV+ individuals: learning lessons from healthy ageing. Curr HIV/AIDS Rep. 2014;11:20–34.
39. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. AIDS. 2008;22:841–8.
40. Effros RB, Fletcher CV, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. Clin Infect Dis. 2008;47:542–53.
41. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. J Clin Endocrinol Metab. 2008;93:3499–504.
42. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;92:2506–12.