Published in final edited form as:

Immunol Res. 2010 December ; 48(1-3): 59–71. doi:10.1007/s12026-010-8167-9.

A Challenge for the Future: Aging and HIV Infection

Tammy M. Rickabaugh¹ and Beth D. Jamieson¹

¹UCLA AIDS Institute and Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, California, USA 90095

Abstract

Older individuals (≥ 50 years of age) are increasingly becoming a new at-risk group for HIV-1 infection and, together with those surviving longer due to the introduction of anti-retroviral therapy (ART), it is predicted that more than half of all HIV-1-infected individuals in the U.S. will be greater than 50 years of age in the year 2015. Older individuals diagnosed with HIV-1 are prone to faster disease progression and reduced T-cell reconstitution despite successful virologic control with anti-retroviral therapy (ART). There is also growing evidence that the T-cell compartment in HIV-1⁺ adults displays an aged phenotype and HIV-1-infected individuals are increasingly diagnosed with clinical conditions more commonly seen in older uninfected persons. As aging in the absence of HIV infection is associated with alterations in T-cell function and immunosenescence, the combined impact of both HIV-1 infection and aging may provide an explanation for poorer clinical outcomes observed in older HIV-1-infected individuals. Thus, the development of novel therapeutics to stimulate immune function and delay immunosenescence is critical and would be beneficial to both the elderly and HIV-1 infected individuals.

Keywords

HIV; ART; CD4⁺ T-cells; CD8⁺ T-cells; IL-7; TAT2; aging

Introduction

The devastating AIDS pandemic has directly affected the lives of millions of individuals over the last three decades. Currently there are approximately 33.4 million HIV-infected individuals worldwide, with about 1.9 million residing in the United States (1,2). The face of the pandemic has evolved over time. Historically the age group most at-risk for HIV infection was individuals 20–40 years of age. In 2006, individuals aged 50 and older made up 15.5% of all new HIV/AIDS diagnoses, in comparison to only 7.5% of all AIDS diagnoses in 1982, designating this age group as one of the newest at-risk demographics (3). Compounding this, anti-retroviral therapy (ART) has extended the life of persons living with HIV. In 2006, 25% of individuals living with HIV/AIDS were aged 50 and over, an increase of 17% from 2001 (3). By 2015, it is predicted that greater than half of all HIV-1-infected individuals in the US will be older than 50 years of age (4,5). Thus, the face of HIV/AIDS in the U.S. is increasingly becoming an older one, resulting in many challenges for the care and treatment of these individuals.

Aging in the absence of HIV infection is associated with a significant decrease in immune function resulting in a poor response to immunization and an increased risk of morbidity and mortality from pathogen exposure in comparison to younger individuals (6–8). Thus, it is

not surprising that HIV-1-infected persons over the age of 50 exhibit more rapid disease progression and an increased likelihood of developing AIDS while receiving ART (9,10). Despite a positive response to ART, HIV-1 infected adults display an increased susceptibility to frailty (11), non-Hodgkin's lymphoma (12), anal and cervical carcinomas (13,14), and osteoporosis (15,16). Many of these clinical manifestations are more commonly observed in uninfected individuals of advanced age (17,18) and, in HIV-1 infection, several are associated with a decrease in CD4⁺ T-cell number (11,12,19). As loss of naïve CD4⁺ T-cells is characteristic of both immunosenescence and HIV-1 infection (20–22), and dysfunctional naïve CD4⁺ T-cells also increase with both age and HIV-1 infection (23), we hypothesize that premature aging of the naïve CD4⁺ T-cell compartment in HIV-1 infection may play a role in the development of age-inappropriate diseases in HIV-1⁺ individuals and contribute to poorer clinical outcomes observed in the older HIV⁺ population. Therefore, as a UCLA AIDS Institute laboratory whose current focus is on immunological aging, we have sought to elucidate the effects of both age and HIV infection on the naïve CD4⁺ T-cell compartment. In this review we will discuss various studies, including our own, that address the effect of aging and HIV infection on naïve CD4⁺ T-cells, the total CD8⁺ T-cell compartment, and the development of therapeutics to improve immune function in both HIV infected persons and the elderly.

Impact of aging on naïve CD4⁺ T-cells

The thymus, the organ responsible for T-cell differentiation and education, involutes with age (24–26). Thymic atrophy is characterized by a replacement of thymopoietic tissue with fatty tissue, resulting in an average shrinkage in size from 70 g in infants to 3 g in elderly individuals (24). This involution led to speculation that thymopoiesis may not occur in the elderly. The amount of thymopoiesis can be determined by the number of recent thymic emigrants (RTE) in the periphery. RTE are naïve T-cells that are enriched in T-cell Receptor Excision Circles (TRECs) which are formed during T-cell receptor rearrangement in the thymus (25). We found evidence of RTE in the peripheral blood of elderly persons (>65 years of age), although at a much lower rate than in younger individuals (25). Due to the reduced levels of thymic output, it was surprising that we (27) and others (25,28) had observed only a moderate decrease in the number of peripheral naïve CD4⁺ T-cells with aging.

Recently, Kimmig, et al. demonstrated that naïve CD45RA⁺CD4⁺ T-cells could be further subdivided into two distinct subpopulations using the cell surface marker CD31 (29), which has aided in further elucidating the effect of aging on naïve CD4⁺ T-cells. CD31, also known as platelet/endothelial cell adhesion molecule (PECAM-1), is expressed on endothelial cells, many different hematopoietic cells, and most human CD34⁺ hematopoietic progenitor cells (30). The CD31 molecule contains two immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (31) which play a role in protection against cell death and influence cell-survival pathways in a variety of other systems (32–38). Although the function of CD31 on CD4⁺ T-cells is not yet clear, CD31 expression on T-cells is correlated with RTE. CD4⁺ T-cells defined as CD45RA⁺CD27⁺CD31⁺CD4⁺ (CD31⁺CD4⁺) are enriched in RTE, contain between 8 (29) and 12 (27) fold higher numbers of TREC than CD45RA⁺CD27⁺CD31[−] CD4⁺ T-cells (CD31[−]CD4⁺), and are therefore considered to be the least differentiated naïve CD4⁺ T-cell subset (Figure 1). We found that CD31⁺CD4⁺ T-cells stimulated *in vitro*, in the absence of IL-7, lose the CD31 marker after three rounds of replication (27), supporting the hypothesis that the CD31[−]CD4⁺ subset is the proliferative offspring of CD31⁺CD4⁺ T-cells. Evidence of clonal expansions of naïve CD31[−] CD4⁺ T-cells in HIV-1-infected individuals that are similar to those in the effector/memory CD4⁺ T-cell pool also suggests that CD31[−]CD4⁺ T-cells are the naïve subset which are recruited into the effector/memory pool in response to antigen (39)(Kilpatrick, et al. unpublished results).

Utilizing CD31, CD45RA and CD27 to identify naïve CD4⁺ T cells, we and others discovered a significant age-related decline in the proportion and absolute number of CD31⁺CD4⁺ T-cells, consistent with the decline in thymic function, whereas the CD31⁻CD4⁺ subset only moderately declines with age (27–29). This data is supported by a longitudinal study of uninfected individuals followed over an average time span of 12–20 years (27). In the absence of significant contribution of CD31⁺CD4⁺ T-cells by the thymus and a decrease in CD31⁺CD4⁺ T-cells in the periphery, the CD31⁻CD4⁺ subset appears to maintain the naïve CD4⁺ T-cell compartment in aging (27,28).

In addition to the loss of CD31⁺CD4⁺ naïve T-cells, other evidence of aging in the naïve CD4⁺ T-cell compartment includes shorter telomere lengths in CD45RA⁺CD28⁺CD4⁺ naïve T-cells in the elderly (40). Telomeres are located at the ends of chromosomes and consist of highly repetitive tracts of DNA (41). Their main function is to protect the ends of the chromosome from loss of critical coding sequence during strand replication (42) and, unless telomerase is active in the cell, the length of the telomere is shortened with each cellular replication (43). Once telomeres shorten to a critical length, also known as Hayflick's limit (approximately 5 Kb), the cell enters senescence and can no longer proliferate (43). We observed significant telomere shortening with age in both CD31⁺ and CD31⁻ naïve CD4⁺ T-cell populations (27). A significant decrease in TREC number in CD31⁺CD4⁺ T-cell subset in older individuals (27,29) also suggests a proliferative history of these cells and further suggests a limited capacity to respond to neo-antigens, despite maintaining TCR diversity that would allow recognition of a diverse assortment of neo-antigens (27). This is of significant concern because CD4⁺ T-cells are known to be key players in adaptive immune responses by providing essential support for germinal center formation as well as antigen specific B-cell proliferation and differentiation (44). CD4⁺ T-cells also provide help for CD8⁺ T-cell responses, most notably in chronic diseases such as HIV-1 infection, and are required for the maintenance of CD8⁺ T-cell memory after acute infections (45). Functional alterations in CD4⁺ T-cells appear to influence their ability to support efficient antibody responses and may contribute to diminished CD8⁺ T-cell responses, a phenomenon observed during chronic HIV infection (45,46). Aging of the T-cell compartment is associated with hyporesponsiveness to stimulation, reduced IL-2 production, alterations in signal transduction, and decreased proliferative capacity (20,47), but the observation that this may be true of the least differentiated naïve CD4⁺ T-cell subset is novel and provides a partial explanation for poor responses to vaccines and increased susceptibility to infectious diseases and neoplasms reported for older adults (6–8). We are currently assessing T-cell receptor signaling and proliferative capacity of both CD31⁺ and CD31⁻ naïve CD4⁺ T-cell subsets of uninfected adults of various ages to further explore the mechanisms behind diminished T-cell responses to antigen seen with age. In light of this data, aging of the naïve CD4⁺ T-cell compartment independent of HIV-1 infection has grave implications for older HIV-1⁺ individuals, both those that are living longer with HIV and those infected at an older age.

Effects of HIV-1 infection on the naïve CD4⁺ T-cell compartment

Many of the age-related clinical diagnoses seen in HIV-1-infected individuals are correlated with decreased CD4⁺ T-cell numbers, suggesting an important role for CD4⁺ T-cells in protection against these diseases. Despite better virological control when taking ART, older individuals demonstrate less CD4⁺ T-cell reconstitution than younger ART-treated HIV-1⁺ individuals (48). The loss of effector/memory CD4⁺ T-cell number and function contributes to immunodeficiency in HIV-1⁺ individuals (49), but understanding the role of naïve T-cells in HIV infection is becoming increasingly vital to understanding HIV pathogenesis. Various studies have shown that naïve CD4⁺ T-cells, defined as CD45RA⁺ and CD62L⁺, are lost fairly early in HIV-1 infection in both children and adults (21,22) due in part to increased

recruitment of naïve cells into the memory pool (50) and to decreased survival of naïve CD4⁺ T-cells due to direct HIV-1 infection (51,52). As an additional insult, HIV-1 infection appears to cause thymic involution and atrophy (53), leading to an age-inappropriate decrease in thymopoiesis (54–56). Notably, we previously demonstrated that the loss of naïve CD4⁺ T-cells precedes the loss of T-cell homeostasis and progression to AIDS (51) suggesting the importance of this compartment in delaying HIV disease progression.

To better understand the effects of HIV-1 on the naïve CD4⁺ T-cell compartment, we are currently conducting a detailed study of both CD31⁺ and CD31[−] subsets of naïve CD4⁺ T-cells, in younger and older HIV-1 infected individuals. In a nested case-control study examining samples from HIV-1-infected men one year prior to an AIDS diagnosis, we demonstrated that CD31 expression was significantly lower on the naïve cells of HIV-1-infected men who progressed to AIDS in one year in comparison to infected men who took 5 years or more to progress (39). This data implies a significant increase in proliferation of CD31⁺CD4⁺ T-cells in response to HIV-1 infection and further suggests that CD31⁺CD4⁺ T-cells play an important role in protection against HIV-1 disease progression. Supporting the notion of increased peripheral proliferation of this subset, we have data demonstrating that both CD31⁺ and CD31[−] naïve CD4⁺ T-cell subsets of HIV-1-infected adults have telomere lengths similar to those of uninfected individuals two to three decades older in age (Rickabaugh, et al., manuscript in preparation). Thus, HIV-1 infection results in premature phenotypic aging of even the least differentiated of the naïve CD4⁺ T-cells. As naïve CD31⁺CD4⁺ T-cells of HIV-1⁺ individuals appear to be impaired in their ability to proliferate and enter the cell cycle (57), we are currently investigating the correlation between telomere length and possible functional defects of these two subsets in younger and older HIV-1⁺ participants.

We also see significant loss of CD31[−]CD4⁺ T-cell numbers with HIV-1 infection (39), which does not occur in older uninfected individuals. In addition, we found that the TCR repertoire of CD31[−]CD4⁺ T-cells appears to be less heterogeneous in HIV-1-infected individuals in comparison to uninfected individuals (39)(Kilpatrick, et al. unpublished results), indicative of clonal expansions within this subset similar to what is seen in the effector/memory pool. As a small percentage of CD31[−]CD4⁺ T-cells also expressed the activation marker CCR5, CD31[−]CD4⁺ T-cells of HIV-1-infected individuals phenotypically resemble cells in transition between naïve and effector/memory, and may have a decreased ability to respond to a variety of neo-antigens. As we and others have shown that the CD31[−]CD4⁺ T-cell subset is important for maintenance of the naïve CD4⁺ T-cell compartment with age (27,29) and is thought to be the main subset recruited into the effector/memory pool (39), this deficit in CD31[−]CD4⁺ T-cell number and loss of ability to respond to antigen would be detrimental to immunological defense against HIV-1 infection and other pathogens. The impact would be particularly significant for older HIV-1⁺ individuals whose naïve CD4⁺ T-cell compartment would be adversely affected by both age and HIV-1 infection, offering a partial explanation for rapid disease progression and reduced CD4⁺ T-cell reconstitution observed in this population.

Changes in the CD8⁺ T-cell compartment with aging

As with the CD4⁺ T-cell compartment, thymic involution during aging results in a significant loss of naïve CD8⁺ T-cells which is also strongly associated with immunosenescence (53,58). Accompanying the loss of naïve CD8⁺ T-cells is an expansion of memory CD8⁺ T-cells which exhibit phenotypic changes, such as loss of CD27 and CD28 expression and changes in CD45RA and CD45RO expression patterns (53). The CD28 receptor in particular is critical for proper activation through the T-cell receptor, eliciting proliferation and differentiation of T-cells (59). Indeed, the proliferative capacity of

CD28⁻CD8⁺ T-cells is significantly diminished in experiments using TCR dependent and TCR independent pathways of stimulation (60). CD28⁻CD8⁺ T-cells also exhibit a diminished capacity to undergo apoptosis in response to superantigenic stimulation (61) and were shown to have shorter telomere lengths in uninfected older individuals (62), both of which are characteristics of senescent cells. Thus, it is not surprising that irreversible loss of CD28 on T-cells is the most significant genetic and phenotypic change correlated with replicative senescence (62) and that clonal expansions of CD28⁻CD8⁺ T-cells are used clinically to predict mortality risk in the elderly (62,63).

Effects of HIV-1 infection on the CD8⁺ T-cell compartment

HIV-1 infection is also associated with a significant loss of naïve CD8⁺ T-cells and an expansion of memory CD8⁺ T-cells (21,53). One study found that HIV-1 infection of young adults, 18–30 years of age, reduced naïve CD8⁺ T-cell numbers to values generally found in uninfected adults 20–30 years older, although the decrease seen in older HIV-1-infected individuals was not significant in comparison with age-matched uninfected controls (53). Phenotypic changes in expression levels of CD27 and CD28, reminiscent of changes observed with aging, are evident during chronic HIV-1 infection (53). Lower expression of CD28 on CD8⁺ T-cells, as well as CD4⁺ T-cells, is associated with faster HIV-1 disease progression and is correlated with a diminished response to immunization in HIV-1 infected individuals, highlighting the immunological importance of the CD28 co-stimulatory molecule in controlling HIV-1 (64–67). As with aging, the CD28⁻CD8⁺ T-cell subset is also expanded during chronic HIV-1 infection, even in younger HIV-1⁺ individuals (68). In a cross-sectional study, Rita Effros and Janis Giorgi found that peripheral CD28⁻CD8⁺ T-cells constitutes approximately 65% of the total CD8⁺ T-cell pool in both HIV-1-infected participants and older uninfected individuals (60). Notably, Effros, et al. and others, demonstrated that the telomere length of CD28⁻CD8⁺ T-cells was significantly shorter than other subsets of T-cells from the same individual and shorter than CD28⁻CD8⁺ T-cells within age-matched uninfected controls (60,69).

Thus, CD28⁻CD8⁺ T-cells of HIV-1-infected persons appear to have an extensive proliferative history and display a replicative senescent phenotype. The accumulation of senescent cells combined with a significant loss of naïve CD8⁺ T-cells, suggests that HIV-1 prematurely ages the CD8⁺ T-cell compartment. These changes are also thought to contribute to “immune exhaustion” seen in chronic HIV-1 infection (70). Altogether, these alterations greatly compromise the ability of the CD8⁺ T-cell compartment to offer immunological protection against HIV-1 and other antigens. As with the dual effect of aging and HIV-1 infection in the naïve CD4⁺ T-cell compartment, older HIV-1 infected individuals would be especially impacted by these immunological changes in the CD8⁺ T-cell compartment, and these immunological alterations are likely to contribute to poorer clinical outcomes observed in this population.

Promising therapeutics to improve immune function in HIV-1 and aging

Recent studies have shown that naïve T-cells are critical for immune protection in both the elderly and HIV-1⁺ individuals. Thus, there has been extensive research aimed at improving adult thymopoiesis and T-cell reconstitution to boost immune function. The first T-cell growth factor used in clinical trials of AIDS patients was IL-2. Unfortunately, the results of these trials were not consistent and patients experienced toxicity during treatment (71). Clinical studies in AIDS patients using human growth hormone (HGH) and insulin growth factor 1 (IGF1) increased thymic volume in children, but only modestly improved T-cell function (72). A more promising therapeutic, interleukin-7 (IL-7), is a potent T-cell cytokine that enhances both thymic-dependent and thymic-independent means of T cell

reconstitution. In the thymus, IL-7 plays a key role in lymphocyte development and survival, and promotes the differentiation and proliferation of CD4⁺CD8⁻, CD4⁺, and CD8⁺ thymocytes (73,74). In the periphery, IL-7 is thought to be a critical regulator of T-cell homeostasis and has been shown to be required for homeostatic proliferation of both naïve and memory CD4⁺ and CD8⁺ T-cells (75–78). Following bone marrow transplantation in mice, pharmacologic administration of IL-7 improved T-cell regeneration (79,80) and a separate study demonstrated that administration of IL-7 in athymic mice resulted in a significant increase in functional immune responses (81), suggesting that pharmacological administration of IL-7 can stimulate both thymic function and improve the quality of immune responses from T-cells in the periphery. In a clinical trial aimed at treating cancer patients with refractory tumors, treatment with recombinant human IL-7 (rhIL-7) preferentially expanded naïve T-cells, suggesting that IL-7 may be a promising therapeutic for improving T-cell reconstitution in HIV-1 infection (82). A recent phase I/IIa clinical trial evaluated the safety and efficacy of rhIL-7 therapy in HIV-1-infected participants. All participants had low CD4⁺ T-cell counts regardless of successful virologic control with c-ART and were subjected to repeated administration of rhIL-7 over 48 weeks. Despite evidence of decreased signaling through the IL-7 receptor on CD4⁺ T-cells of HIV-1-infected individuals (23), administration of rhIL-7 resulted in a significant peripheral increase in both naïve and central memory CD4⁺ and CD8⁺ T-cells that was sustained with subsequent treatment (83). Even 45 weeks after the last dose of rhIL-7 CD4⁺ T-cells were shown to be significantly higher than before rhIL-7 therapy (83). These expanded T-cells respond to TCR stimulation and produced intracellular cytokines in response to polyclonal and antigen-specific stimulation (83). In contrast to the acute toxic effects seen with IL-2 therapy, rhIL-7 therapy in this study appeared to be well tolerated overall and had the added benefit of improving both CD4⁺ and CD8⁺ T-cell mediated immunity.

Current intensive research efforts are focused on the development of pharmacological agents to curtail the effects of organismal aging. In particular, we and others (84,85) are interested in treatments to prevent, or even reverse, telomere shortening with the goal of minimizing the accumulation of senescent cells with age and/or chronic infections or diseases. Telomerase is a cellular reverse transcriptase responsible for adding telomeric DNA to the ends of the chromosome (86–88) and telomerase activity is thought to lessen the effects of oxidative stress, extensive proliferation in response to antigen, and normal cellular aging on telomere length (89,90). Lymphocytes have the ability to upregulate telomerase during development and in response to activation (91). T-cells can also be stimulated *in vitro* to induce telomerase levels as high as levels seen in tumor cells, but this effect is transitory and is generally not maintained for longer than 3 weeks (92). As either induction of telomerase, or maintenance of sustained telomerase activity, during cellular activation may prevent telomere shortening, some studies have focused on manipulating the activity of this enzyme to prevent immunosenescence.

The core enzyme of telomerase includes the human telomerase catalytic component (hTERT). Utilizing a gene therapy approach, Dagarag, et al. transduced CD8⁺ T-cells from HIV-1 infected individuals with hTERT, resulting in an increase in telomerase activity (93). The transduced cells exhibited stabilization of telomere length, a preservation of antiviral functions, and improved proliferative potential, demonstrating that it may be possible to delay or prevent senescence of CD8⁺ T-cells. Unfortunately, gene therapy approaches are fraught with criticism due to the inability to adequately control expression levels of transduced genes, and the risk of possible unintended side effects of gene transduction, rendering this a less than ideal means of therapeutic delivery *in vivo*. Fauce, et al., in collaboration with the biotechnology company Geron and our laboratory, implemented an alternative approach to activating telomerase. A screen of Chinese medicine plant extracts and compounds known to enhance immune function resulted in the discovery of TAT2

(cycloastragenol), a small molecule telomerase activator (84). We found that TAT2 transiently upregulated telomerase in cultured CD8⁺ T-cells of both uninfected and HIV-1⁺ individuals, with the largest increase observed in cells from individuals with AIDS (84). The increase in telomerase activity correlated with longer telomere lengths, improved immune effector function, and an increased capacity for cellular proliferation. Treatment with TAT2 also resulted in a significant reduction in viral replication in CD4⁺/CD8⁺ T-cell co-culture assays, and this effect was shown to be dependent on induction of telomerase activity (84). However, any reagent that increases telomerase activity also poses a risk of promoting the transformation of cells and increasing the proliferation of tumor cells. In this study TAT2 did not increase constitutive telomerase activity of a Jurkat T-cell tumor line, nor did it alter the rate of EBV transformation of B-cells in culture or enhance HIV-1 production from CD4⁺ T-cells of HIV-1⁺ individuals. Therefore, TAT2 may be a promising therapeutic agent for the prevention or delay of immunosenescence in older uninfected individuals. As low levels of telomerase in HIV-1-specific CD8⁺ T-cells is associated with faster HIV-1 disease progression (94), TAT2 may have the potential to counteract the aging effects of HIV-1 on the T-cell compartment and delay the onset of AIDS.

Concluding remarks

Although debate continues about the extent of premature aging that occurs with HIV-1 infection (95), mounting evidence strongly suggest that the T-cell compartment of HIV-1-infected individuals exhibits an aged phenotype. The combined effect of aging and HIV-1 infection on T-cells poses an immense challenge for the clinical care of the growing population of older HIV-1-infected individuals. Given the similarities in alterations of the T-cell compartment with aging and HIV-1 infection (Figure 2), the development of therapeutics to improve thymopoiesis, enhance peripheral T-cell function, and prevent or delay senescence, may prove to be beneficial to both affected populations. As there are some differences in HIV-1 infection that are not seen in normal human aging (Figure 2), the mechanisms behind immunological aging may not be identical. To address these issues, the National Institute of Health (NIH) has identified pathogenesis and management of HIV infection as a high-priority research area (4). Further exploration of the mechanisms behind immunosenescence is imperative to the development of innovative treatments to improve the health and well-being of the elderly and HIV-1-infected individuals.

Acknowledgments

We wish to thank all the study participants, including those from the Multi-Center AIDS Cohort Study (MACS), for their contribution to this work. We also thank Dr. Rita Effros for many enlightening discussions on this subject matter and Dr. Catherine Brennan for careful reading of this manuscript and constructive criticism of the work. The research described in this review was supported by NIAID Grant 5RO1-AI-058845 and NIA Grant 1RO1-AG-030327 awarded to B.D. Jamieson. T.M. Rickabaugh was also supported by the National Institutes of Health under Ruth L. Kirschstein National Research Service Award, 5 T32 CA009120, from the National Cancer Institute.

References

1. UNAIDS/WHO. AIDS Epidemic Update: November 2009. Geneva, Switzerland: 2009.
2. UNAIDS/WHO. Epidemiological Fact Sheet on HIV and AIDS: United States of America 2008 Update. Geneva, Switzerland: 2008.
3. Center for Disease Control and Prevention. HIV/AIDS Surveillance Report 2006. Atlanta, Georgia: 2008.
4. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, Huebner RE, Janoff EN, Justice AC, Kuritzkes D, Nayfield SG, Plaeger SF, Schmader KE, Asworth JR, Campanelli, Clayton CP, Rada B, Woolard NF, High KP. Aging and infectious diseases: workshop on HIV infection and

- aging: what is known and future research directions. *Clin Infect Dis*. 2008; 47:542–553. [PubMed: 18627268]
5. Plankey MW, Ostrow DG, Stall R, Cox C, Li X, Peck JA, Jacobson LP. The relationship between methamphetamine and popper use and risk of HIV seroconversion in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr*. 2007; 45:85–92. [PubMed: 17325605]
 6. Effros RB. Long-term immunological memory against viruses. *Mech Aging Dev*. 2000; 121:161–171. [PubMed: 11164470]
 7. Herndler-Brandstetter D, Cioca DP, Grubeck-Loebenstein B. Immunizations in the elderly: do they live up to their promise? *Wien med Wochenschr*. 2006; 156:130–141. [PubMed: 16823527]
 8. Webster RG. Immunity to influenza in the elderly. *Vaccine*. 2000; 18:1686–1689. [PubMed: 10689149]
 9. Rosenberg PS, Goedert JJ, Biggar RJ. Effect of age at seroconversion on the natural AIDS incubation distribution. Multicenter Hemophilia Cohort Study and the International Registry of Seroconverters. *AIDS*. 1994; 8:803–810. [PubMed: 8086140]
 10. Darby SC, Ewart DW, Giangrande PL, Spooner RJ, Rizza CR. Importance of age at infection with HIV-1 for survival and development of AIDS in UK haemophilia population. UK Haemophilia Centre Directors' Organisation. *Lancet*. 1996; 347:1573–1579. [PubMed: 8667864]
 11. Desquilbet L, Jacobson LP, Fried LP, Phair JP, Jamieson BD, Holloway M, Margolick JB. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. *J Gerontol A Biol Sci Med Sci*. 2007; 62:1279–1286. [PubMed: 18000149]
 12. Engels EA, Pfeiffer RM, Landgren O, Moore RD. Immunologic and virologic predictors of AIDS-related non-hodgkin lymphoma in the highly active antiretroviral therapy era. *J Acquir Immune Defic Syndr*. 2010; 54:78–84. [PubMed: 20418723]
 13. D'Souza G, Wiley DJ, Li X, Chmiel JS, Margolick JB, Cranston RD, Jacobson LP. Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr*. 2008; 48:491–499. [PubMed: 18614927]
 14. Dorrucchi M, Suligoi B, Serraino D, Tirelli U, Rezza G. Incidence of invasive cervical cancer in a cohort of HIV-seropositive women before and after the introduction of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001; 26:377–380. [PubMed: 11317082]
 15. Thomas J, Doherty SM. HIV infection—a risk factor for osteoporosis. *J Acquir Immune Defic Syndr*. 2003; 33:281–291. [PubMed: 12843738]
 16. Fausto A, Bongiovanni M, Cicconi P, Menicagli L, Ligabo EV, Melzi S, Bini T, Sardanelli F, Cornalba G, Monforte A. Potential predictive factors of osteoporosis in HIV-positive subjects. *Bone*. 2006; 38:893–897. [PubMed: 16377270]
 17. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ*. 2009; 338:288–292.
 18. Cinti SK, Gandhi T, Riddell J. Non-AIDS-defining cancers: should antiretroviral therapy be initiated earlier? *AIDS Read*. 2008; 18:18–32. [PubMed: 18240449]
 19. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. *J Acquir Immune Defic Syndr*. 2009; 51:554–561. [PubMed: 19512937]
 20. Fulop T, Larbi A, Douziech N, Levesque I, Varin A, Herbein G. Cytokine receptor signalling and aging. *Mech Ageing Dev*. 2006; 127:526–537. [PubMed: 16530252]
 21. Roederer M, Dubs JG, Anderson MT, Raju PA, Herzenberg LA, Herzenberg LA. CD8 naive T cell counts decrease progressively in HIV-infected adults. *J Clin Invest*. 1995; 95:2061–2066. [PubMed: 7738173]
 22. Rabin RL, Roederer M, Maldonado Y, Petru A, Herzenberg LA, Herzenberg LA. Altered representation of naive and memory CD8 T cell subsets in HIV-infected children. *J Clin Invest*. 1995; 95:2054–2060. [PubMed: 7738172]
 23. Bazdar DA, Kalinowska M, Sieg SF. Interleukin-7 receptor signaling is deficient in CD4+ T cells from HIV-infected persons and is inversely associated with aging. *J Infect Dis*. 2009; 199:1019–1028. [PubMed: 19239367]
 24. Kuby, J.; Goldsby, RA.; Osborne, BA.; Kindt, TJ. *Immunology*. New York, NY: WH Freeman and Company; 2000.

25. Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF, Polis MA, Haase AT, Feinberg MB, Sullivan JL, Jamieson BD, Zack JA, Picker LJ, Koup RA. Changes in thymic function with age and during the treatment of HIV infection. *Nature*. 1998; 396:690–695. [PubMed: 9872319]
26. Aspinall R, Andrew D. Thymic involution in aging. *J Clin Immunol*. 2000; 20:250–256. [PubMed: 10939712]
27. Kilpatrick RD, Rickabaugh T, Hultin LE, Hultin P, Hausner MA, Detels R, Phair J, Jamieson BD. Homeostasis of the naive CD4+ T cell compartment during aging. *J Immunol*. 2008; 180:1499–1507. [PubMed: 18209045]
28. Kohler S, Wagner U, Pierer M, Kimmig S, Oppmann B, Mowes B, Julke K, Romagnani C, Thiel A. Post-thymic in vivo proliferation of naive CD4+ T cells constrains the TCR repertoire in healthy human adults. *Eur J Immunol*. 2005; 35:1987–1994. [PubMed: 15909312]
29. Kimmig S, Przybylski GK, Schmidt CA, Laurisch K, Mowes B, Radbruch A, Thiel A. Two Subsets of Naive T Helper Cells with Distinct T Cell Receptor Excision Circle Content in Human Adult Peripheral Blood. *J Exp Med*. 2002; 195:789–794. [PubMed: 11901204]
30. Watt SM, Williamson J, Genevieve H, Fawcett J, Simmons DL, Hatzfeld A, Nesbitt SA, Coombe DR. The heparin binding PECAM-1 adhesion molecule is expressed by CD34+ hematopoietic precursor cells with early myeloid and B-lymphoid cell phenotypes. *Blood*. 1993; 82:2649–2663. [PubMed: 7693043]
31. Newman PJ. Switched at birth: a new family for PECAM-1. *J Clin Invest*. 1999; 103:5–9. [PubMed: 9884328]
32. Bergom C, Goel R, Paddock C, Gao C, Newman DK, Matsuyama S, Newman PJ. The cell-adhesion and signaling molecule PECAM-1 is a molecular mediator of resistance to genotoxic chemotherapy. *Cancer Biol Ther*. 2006; 5:1699–1707. [PubMed: 17106245]
33. Gao C, Sun W, Christofidou-Solomidou M, Sawada M, Newman DK, Bergom C, Albelda SM, Matsuyama S, Newman PJ. PECAM-1 functions as a specific and potent inhibitor of mitochondrial-dependent apoptosis. *Blood*. 2003; 102:169–179. [PubMed: 12649141]
34. Bird IN, Taylor V, Newton JP, Spragg JH, Simmons DL, Salmon M, Buckley CD. Homophilic PECAM-1(CD31) interactions prevent endothelial cell apoptosis but do not support cell spreading or migration. *J Cell Sci*. 1999; 112(Pt12):1989–1997. [PubMed: 10343075]
35. Evans PC, Taylor ER, Kilshaw PJ. Signaling through CD31 protects endothelial cells from apoptosis. *Transplant*. 2001; 71:457–460.
36. Ferrero E, Belloni D, Contini P, Foglieni C, Ferrero ME, Fabbri M, Poggi A, Zocchi MR. Transendothelial migration leads to protection from starvation-induced apoptosis in CD34+CD14+ circulating precursors: evidence for PECAM-1 involvement through Akt/PKB activation. *Blood*. 2003; 101:186–193. [PubMed: 12393747]
37. Limaye V, Li X, Hahn C, Xia P, Berndt MC, Vadas MA, Gamble JR. Sphingosine kinase-1 enhances endothelial cell survival through a PECAM-1-dependent activation of PI-3K/Akt and regulation of Bcl-2 family members. *Blood*. 2005; 105:3169–3177. [PubMed: 15632208]
38. Noble KE, Wickremasinghe RG, DeCornet C, Panayiotidis P, Yong KL. Monocytes stimulate expression of the Bcl-2 family member, A1, in endothelial cells and confer protection against apoptosis. *J Immunol*. 1999; 162:1376–1383. [PubMed: 9973392]
39. Cao W, Jamieson BD, Hultin LE, Hultin PM, Effros RB, Detels R. Premature aging of T cells is associated with faster HIV-1 disease progression. *J Acquir Immune Defic Syndr*. 2009; 50:137–147. [PubMed: 19131896]
40. Pfister G, Weiskopf D, Lazurdi L, Kovaiov RD, Cioca DP, Keller M, Lorbeg B, Parson W, Grubeck-Loebenstien B. Naive T Cells in the Elderly: Are They Still There? *Ann New York Acad Sci*. 2006; 1067:152–157. [PubMed: 16803980]
41. Moyzis RK, Buckingham JM, Cram LS, Dani M, Deaven LL, Jones MD, Meyne J, Ratliff RL, Wu JR. A Highly Conserved Repetitive DNA Sequence, (TTAGGG)_n, Present at the Telomeres of Human Chromosomes. *PNAS*. 1988; 85:6622–6626. [PubMed: 3413114]
42. Greider CW. Mammalian telomere dynamics: Healing, fragmentation shortening and stabilization. *Curr Opin Genet Dev*. 1994:203–211. [PubMed: 8032197]

43. Harley CB. Telomere loss: Mitotic clock or genetic time bomb? *Mutat. Res.* 1991; 256:271–282. [PubMed: 1722017]
44. Swain S, Clise-Dwyer K, Haynes L. Homeostasis and the age-associated defect of CD4 T cells. *Semin Immunol.* 2005; 17:370–377. [PubMed: 15964201]
45. Sun JC, Williams MA, Bevan M. CD4+ T cells are required for the maintenance, not programming, of memory CD8+ T cells after acute infection. *Nat Immunol.* 2004; 5:927–933. [PubMed: 15300249]
46. Trimble LA, Shankar P, Patterson M, Daily JP, Lieberman J. Human immunodeficiency virus-specific circulating CD8 T lymphocytes have down-modulated CD3zeta and CD28, key signaling molecules for T- cell activation. *J Virol.* 2000; 74:7320–7330. [PubMed: 10906185]
47. Whisler RL, Newhouse YG, Bagenstose SE. Age-related reductions in the activation of mitogen-activated protein kinases p44mapk/ERK1 and p42mapk/ERK2 in human T cells stimulated via ligation of the T cell receptor complex. *Cell Immunol.* 1996; 168:201–210. [PubMed: 8640866]
48. Kirk JB, Goetz MB. Human immunodeficiency virus in an aging population, a complication of success. *J Am Geriatr Soc.* 2009; 57:2129–2138. [PubMed: 19793157]
49. Appay V, Rowland-Jones SL. Premature ageing of the immune system: the cause of AIDS? *Trends Immunol.* 2002; 23:580–585. [PubMed: 12464569]
50. Di MM, Sereti I, Matthews LT, Natarajan V, Adelsberger J, Lempicki R, Yoder C, Jones E, Chow C, Metcalf JA, Sidorov IA, Dimitrov DS, Polis MA, Kovacs JA. Naive T-cell dynamics in human immunodeficiency virus type 1 infection: effects of highly active antiretroviral therapy provide insights into the mechanisms of naive T-cell depletion. *J Virol.* 2006; 80:2665–2674. [PubMed: 16501076]
51. Chattopadhyay PK, Douek DC, Gange SJ, Chadwick KR, Hellerstein M, Margolick JB. Longitudinal Assessment of de Novo T Cell Production in Relation to HIV-Associated T Cell Homeostasis Failure. *AIDS Res Hum Retroviruses.* 2006; 22:501–507. [PubMed: 16796525]
52. Eckstein DA, Penn ML, Korin YD, Scripture-Adams DD, Zack JA, Kreisberg JFM, Roederer M, Sherman P, Chin PS, Goldsmith MA. HIV-1 actively replicates in naive CD4(+) T cells residing within human lymphoid tissues. *Immunity.* 2001; 15:671–682. [PubMed: 11672548]
53. Kalayjian RC, Landay A, Pollard RB, Taub DD, Gross BH, Francis IR, Sevin A, Spritzler J, Chernoff M, Namkung A, Fox L, Martinez A, Waterman K, Fiscus SA, Sha B, Johnson D, Slater S, Rousseau F, Lederman MM. Adult AIDS Clinical Trial Group 5015 Protocol Team, and Adult AIDS Clinical Trial Group 5113 Protocol Team: Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. *J Infect Dis.* 2003; 187:1924–1933. [PubMed: 12792869]
54. Aldrovandi GM, Feuer G, Gao L, Jamieson B, Kristeva M, Chen ISY, Zack JA. The SCID-hu mouse as a model for HIV-1 infection. *Nature.* 1993; 363:732–736. [PubMed: 8515816]
55. Jamieson BD, Douek DC, Killian S, Hultin LE, Scripture-Adams DD, Giorgi JV, Marelli D, Koup RA, Zack JA. Generation of functional thymocytes in the human adult. *Immunity.* 1999; 10:569–575. [PubMed: 10367902]
56. Withers-Ward ES, Amado RG, Koka PS, Jamieson BD, Kaplan AH, Chen ISY, Zack JA. Transient renewal of thymopoiesis in HIV-infected human thymic implants following antiviral therapy. *Nat Med.* 1997; 3:1102–1109. [PubMed: 9334721]
57. Luciano AA, Lederman MM, Valentin-Torres A, Bazdar DA, Sieg SF. Impaired induction of CD27 and CD28 predicts naive CD4 T cell proliferation defects in HIV disease. *J Immunol.* 2007; 179:3543–3549. [PubMed: 17785788]
58. Fagnoni FF, Vescovini R, Passeri G, Bologna G, Pedrazzoni M, Lavagetto G, Casti A, Franceschi C, Passeri M, Sansoni P. Shortage of circulating naive CD8(+) T cells provides new insights on immunodeficiency in aging. *Blood.* 2000; 95:2860–2868. [PubMed: 10779432]
59. Alegre MLK, Frauwirth A, Thompson CB. T-cell regulation by CD28 and CTLA-4. *Nat Rev Immunol.* 2001; 1:220–228. [PubMed: 11905831]
60. Effros RB, Allsopp R, Chiu C-P, Hausner MA, Hirji K, Wang L, Harley CB, Villeponteau B, West MD, Giorgi JV. Shortened telomeres in the expanded CD28⁻ CD8⁺ cell subset in HIV disease

- implicate replicative senescence in HIV pathogenesis. *AIDS*. 1996; 10:F17–F22. [PubMed: 8828735]
61. Posnett DN, Edinger JW, Manalavan JS, Irwin C, Marodon G. Differentiation of human CD8 T cells: Implications for *in vivo* persistence of CD8⁺ CD28[−] cytotoxic effector clones. *Int Immunol*. 1999; 11:229–241. [PubMed: 10069421]
 62. Effros RB, Boucher N, Porter V, Zhu X, Spaulding C, Walford RL, Kronenberg M, Cohen D, Schächter F. Decline in CD28⁺ T cells in centenarians and in long-term T cell cultures: A possible cause for both *in vivo* and *in vitro* immunosenescence. *Exp Gerontol*. 1994; 29:601–609. [PubMed: 9435913]
 63. Wikby A, Johansson B, Olsson J, Lofgren S, Nilsson BO, Ferguson F. Expansions of peripheral blood CD8 T-lymphocyte subpopulations and an association with cytomegalovirus seropositivity in the elderly: the Swedish NONA immune study. *Exp Gerontol*. 2002; 37:445–453. [PubMed: 11772532]
 64. Brinchmann JE, Dobloug JH, Heger BH, Haaheim LL, Sannes M, Egeland T. Expression of costimulatory molecule CD28 on T cells in human immunodeficiency virus type 1 infection: Functional and clinical correlations. *J Infect Dis*. 1994; 169:730–738. [PubMed: 7907640]
 65. Valdez H, Smith KY, Landay A, Connick E, Kuritzkes DR, Kessler H, Fox L, Spritzler J, Roe J, Lederman MB, Lederman HM, Evans TG, Heath-Chiozzi M, Lederman MM. Response to immunization with recall and neoantigens after prolonged administration of an HIV-1 protease inhibitor-containing regimen. ACTG 375 team. AIDS Clinical Trials Group. *AIDS*. 2000; 14:11–21. [PubMed: 10714563]
 66. Choremi-Papadopoulou H, Gargalianos VP, Kordossis T, Iniotaki-Theodoraki A, Kosmidis J. Downregulation of CD28 surface antigen on CD4⁺ and CD8⁺ T lymphocytes during HIV-1 infection. *J Acquir Immune Defic Syndr*. 1994; 7:245–253. [PubMed: 7906302]
 67. Lange CG, Lederman MM, Madero JS, Medvik K, Asaad R, Pacheco C, Carranza C, Valdez H. Impact of suppression of viral replication by highly active antiretroviral therapy on immune function and phenotype in chronic HIV-1 infection. *J Acquir Immune Defic Syndr*. 2002; 30:33–40. [PubMed: 12048361]
 68. Borthwick NJ, Bofill M, Gombert WM, Akbar AN, Medina E, Sagawa K, Lipman MC, Johnson MA, Janossy G. Lymphocyte activation in HIV-1 infection. II. Functional defects of CD28[−] T cells. *AIDS*. 1994; 8:431–441. [PubMed: 8011246]
 69. Monteiro J, Batliwalla FM, Ostrer H, Gregersen PK. Shortened telomeres in clonally expanded CD28[−]CD8⁺ T cells imply a replicative history that is distinct from their CD28⁺CD8⁺ counterparts. *J Immunol*. 1996; 156:3587–3590. [PubMed: 8621891]
 70. Appay V, Almeida JR, Sauce D, Autran B, Papagno L. Accelerated immune senescence and HIV-1 infection. *Exp Gerontol*. 2007; 42:432–437. [PubMed: 17307327]
 71. Nelson BH. IL-2, regulatory T cells, and tolerance. *J Immunol*. 2004; 172:3983–3988. [PubMed: 15034008]
 72. Murphy WJ, Longo DL. Growth hormone as an immunomodulating therapeutic agent. *Immunol Today*. 2000; 21:211–213. [PubMed: 10877541]
 73. Akashi K, Kondo M, von Freeden-Jeffrey U, Murray R, Weissman IL. Bcl-2 rescues T lymphopoiesis in interleukin-7 receptor-deficient mice. *Cell*. 1997; 89:1033–1041. [PubMed: 9215626]
 74. von Freeden-Jeffrey U, Solvason N, Howard M, Murray R. The earliest T lineage-committed cells depend on IL-7 for Bcl-2 expression and normal cell cycle progression. *Immunity*. 1997; 7:147–154. [PubMed: 9252127]
 75. Tan JT, Dudl E, LeRoy E, Murray R, Sprent J, Weinberg KI, Surh CD. IL-7 is critical for homeostatic proliferation and survival of naive T cells. *Proc Natl Acad Sci USA*. 2001; 98:8732–8737. [PubMed: 11447288]
 76. Schluns KS, Kieper WC, Jameson SC, Lefrancois L. Interleukin-7 mediates the homeostasis of naive and memory CD8 T cells *in vivo*. *Nat Immunol*. 2000; 1:426–432. [PubMed: 11062503]
 77. Goldrath AW, Sivakumar PV, Glaccum M, Kennedy MK, Bevan MJ, Benoist C, Mathis D, Butz EA. Cytokine requirements for acute and Basal homeostatic proliferation of naive and memory CD8⁺ T cells. *J Exp Med*. 2002; 195:1515–1522. [PubMed: 12070279]

78. Seddon B, Tomlinson P, Zamoyska R. Interleukin 7 and T cell receptor signals regulate homeostasis of CD4 memory cells. *Nat Immunol.* 2003; 4:680–686. [PubMed: 12808452]
79. Abdul-Hai A, Or R, Slavin S, Friedman G, Weiss L, Matsa D, Ben-Yehuda A. Stimulation of immune reconstitution by interleukin-7 after syngeneic bone marrow transplantation in mice. *Exp Hematol.* 1996; 24:1416–1422. [PubMed: 8913288]
80. Bolotin E, Smogorzewska M, Smith S, Widmer M, Weinberg K. Enhancement of thymopoiesis after bone marrow transplant by in vivo interleukin-7. *Blood.* 1996; 88:1887–1894. [PubMed: 8781449]
81. Mackall CL, Fry TJ, Bare C, Morgan P, Galbraith A, Gress RE. IL-7 increases both thymic-dependent and thymic-independent T-cell regeneration after bone marrow transplantation. *Blood.* 2001; 97:1491–1497. [PubMed: 11222398]
82. Sportes C, Hakim FT, Memon SA, Zhang H, Chua KS, Brown MR, Fleisher TA, Krumlauf MC, Babb RR, Chow CK, Fry TJ, Engels J, Buffet R, Morre M, Amato RJ, Venzon DJ, Korngold R, Pecora A, Gress RE, Mackall CL. Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets. *J Exp Med.* 2008; 205:1701–1714. [PubMed: 18573906]
83. Levy Y, Lacabartz C, Weiss L, Viard JP, Goujard C, Lelievre JD, Boue F, Molina JM, Rouzioux C, Vettand-Fenoel V, Croughs T, Beq S, Thiebaut R, Chene G, Morre M, Delfraissy JF. Enhanced T cell recovery in HIV-1-infected adults through IL-7 treatment. *J Clin Invest.* 2009; 119:997–1007. [PubMed: 19287090]
84. Fauce SR, Jamieson BD, Chin AC, Mitsuyasu RT, Parish ST, Ng HL, Kitchen CM, Yang OO, Harley CB, Effros RB. Telomerase-based pharmacologic enhancement of antiviral function of human CD8+ T lymphocytes. *J Immunol.* 2008; 181:7400–7406. [PubMed: 18981163]
85. Effros RB. Telomerase induction in T cells: a cure for aging and disease? *Exp Gerontol.* 2007; 42:416–420. [PubMed: 17182206]
86. Blackburn EH. Telomerases. *Annu Rev Biochem.* 1992; 61:113–129. [PubMed: 1497307]
87. Greider CW. Telomeres, telomerase and senescence. *Bioessays.* 1990; 12:363–369. [PubMed: 2241933]
88. Hiyama K, Hirai Y, Kyoizumi S, Akiyama M, Hiyama E, Piatyszek MA, Shay JW, Ishioka S, Yamakido M. Activation of telomerase in human lymphocytes and hematopoietic progenitor cells. *J Immunol.* 1995; 155:3711–3715. [PubMed: 7561072]
89. Roth A, Yssel H, Pene J, Chavez EA, Schertzer M, Lansdorp PM, Spits H, Luiten RM. Telomerase levels control the lifespan of human T lymphocytes. *Blood.* 2003; 102:849–857. [PubMed: 12689947]
90. Bodnar AG, Kim NW, Effros RB, Chiu CP. Mechanism of telomerase induction during T cell activation. *Exp Cell Res.* 1996; 228:58–64. [PubMed: 8892971]
91. Weng NP, Palmer LD, Levine BL, Lane HC, June CH, Hodes RJ. Tales of tails: regulation of telomere length and telomerase activity during lymphocyte development, differentiation, activation, and aging. *Immunol Rev.* 1997; 160:43–54. [PubMed: 9476664]
92. Valenzuela HF, Effros RB. Divergent Telomerase and CD28 Expression Patterns in Human CD4 and CD8 T Cells Following Repeated Encounters with the Same Antigenic Stimulus. *Clin Immunol.* 2002; 105:117–125. [PubMed: 12482386]
93. Dagarag M, Evazyan T, Rao N, Effros RB. Genetic Manipulation of Telomerase in HIV-Specific CD8+ T Cells: Enhanced Antiviral Functions Accompany the Increased Proliferative Potential and Telomere Length Stabilization. *J Immunol.* 2004; 173:6303–6311. [PubMed: 15528369]
94. Lichterfeld M, Mou D, Cung TD, Williams KL, Waring MT, Huang J, Pereyra F, Trocha A, Freeman GJ, Rosenberg ES, Walker BD, Yu XG. Telomerase activity of HIV-1-specific CD8+ T cells: constitutive up-regulation in controllers and selective increase by blockade of PD ligand 1 in progressors. *Blood.* 2008; 112:3679–3687. [PubMed: 18728248]
95. Mascolini M. What speeds aging with HIV-and what can be done about it? Research Initiative-Treatment Action!. 2010:1–59.

Figure 1. Two naïve CD4⁺ T-cell subsets defined by CD4, CD45RA, and CD31

Peripheral blood mononuclear cells (PBMC) from an uninfected adult were stained with fluorescent antibodies to CD4, CD45RA, and CD31, and analyzed by flow cytometry (FACSCalibur™ flow cytometer, BD Biosciences Immunocytometry Systems). The plot shown is gated on CD4⁺ T-cells and shows the proportions of CD4⁺ T-cells that are CD45RA⁺CD31⁺, CD45RA⁺CD31⁻, CD45RA⁻CD31⁺, and CD45RA⁻CD31⁻. The two panels designated by the box depict the two naïve CD4⁺ T-cell subsets defined by the CD31 cell surface marker.

Figure 2. Similarities and differences in the T-cell compartment with aging and HIV-1 infection

The Venn diagram above depicts changes in the T-cell compartment as a result of either aging and/or HIV-1 on the T-cell compartment. The symbols indicate (↑) = increased, (↓) = decreased, or (↔) = stable proportion and number of T-cells.