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## Impact of age on markers of HIV-1 disease

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### Abstract

Aging is a complicated process characterized by a progressive loss of homeostasis, which results in an increased vulnerability to multiple diseases. HIV-1-infected patients demonstrate a premature aging phenotype and develop certain age-related diseases earlier in their lifespan than what is seen in the general population. Age-related comorbidities may include the development of bone disease, metabolic disorders, neurologic impairment and immunosenescence. Age also appears to have an effect on traditional markers of HIV-1 disease progression, including CD4<sup>+</sup> T-cell count and viral load. These effects are not only a consequence of HIV-1 infection, but in many cases, are also linked to antiretroviral therapy. This review summarizes the complex interplay between HIV-1 infection and aging, and the impact that aging has on markers of HIV-1 disease.

### Keywords

aging; comorbidities; disease progression; HIV-1; neurocognitive impairment

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Aging is a complicated biological process involving numerous intricately linked intrinsic and extrinsic factors affecting different systems of the human body. Several unique medical comorbid factors are observed with increasing frequency with aging or senescence. In addition to the increased vulnerability to disease associated with advancing age, typical changes related to aging include changes in hearing, vision, bone strength and density and immune function. Because life expectancies are increasing, particularly in the developed world, the incidence of aging-related disease is expected to increase dramatically in the coming decades.

In a subset of the aging population in the developed world, treatment of individuals infected with HIV-1 has improved significantly since the introduction of combination antiretroviral therapy (ART), also known as HAART. Mortality and morbidity have decreased significantly and life expectancy has increased dramatically in this subpopulation as a result

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of HAART [1-4]. As a result, HIV-1 has become an epidemic that is increasingly affecting older adults. By 2015, it is estimated that approximately half of patients infected with HIV in the USA will be over the age of 50 years, making it paramount to understand the risk factors associated with aging and HIV-1 infection [5].

Although HAART has greatly improved mortality rates in infected patients when compared with no treatment or monotherapy, a large discrepancy in life expectancy persists between HIV-infected individuals and the general (noninfected) population. Studies have shown that a 20-year-old infected individual on HAART with a nadir CD4 count of between 100 and 200 cells/ $\mu$ l can expect to live approximately 42 years, which is only about two-thirds as long as the general population. This number increases to 50 years in those with a nadir CD4 count of greater than 200 cells/ $\mu$ l and falls to 32 years in those with a nadir CD4 count of less than 100 cells/ $\mu$ l [6-8]. Interestingly, despite these discrepancies, mortality resulting from AIDS-related illnesses has decreased dramatically. HIV-1-infected individuals are also at increased risk of non-AIDS-related illnesses traditionally associated with aging, including cardiovascular disease and neurocognitive decline. This has led to the concern that HIV-1-infected individuals may suffer from accelerated aging and neurocognitive impairment or comorbidities normally associated with advanced age much sooner than the general population.

### **Aging-related comorbidities within the HIV-1-infected population**

Aging is a complicated process involving several intrinsic and extrinsic factors intricately linked together, involving different systems of the human body. Common aging-related chronic conditions include diabetes, lipidemia, cardiovascular disease, immune dysregulation, changes in bone strength and density and neurologic impairment, including dementia syndromes such as Alzheimer's disease (AD) and vascular dementia. These diseases are progressive and are often treatable, but not curable, and often coexist within the aging population [9-11]. Prevalence of these diseases is increased among HIV-1-infected patients [12,13] and current research suggests that this may be the result of premature aging associated with HIV-1 infection [14,15]. Furthermore, the simultaneous presence of two or more of these aging-related diseases is more common among HIV-1-infected patients than in the general population when looking at a wide spectrum of ages [16]. Interestingly, the prevalence of multiple aging-related diseases among HIV-1-infected patients is equivalent to prevalence among members of the general population who are 10–15 years older [17-19]. This supports the notion that accelerated/premature aging in the HIV-1-infected population contributes to the increase in aging-related diseases.

### **Diabetes, dyslipidemia & lipodystrophy**

Diabetes is a serious metabolic condition that is increasing in prevalence in the elderly. By 2025, adults aged 60 years and older are expected to comprise approximately two-thirds of the diabetic population in developed countries [20]. Minority populations may be particularly affected [20]. With increased age comes the risk of more severe and chronic complications associated with diabetes [21]. In addition to a rise in the incidence of diabetes in the general aging population, the decreased mortality associated with controlled HIV-1 infection has led the incidence of diabetes to increase in this population. Some research has suggested that HIV-1 infection can cause islet B-cell dysfunction, leading to insulin-dependent diabetes in the absence of islet cell or insulin antibodies [22]. Although HIV-1 infection alone has not been strongly associated with an increased risk of diabetes, increasing age within this population has been associated with increased risk [23]. Increasing age, male sex, minority race and elevated BMI are all associated with increased risk of diabetes in the general population. The effect of these factors is more pronounced in the HIV-1-infected population; thus, their risk of diabetes is higher [23].

While a number of clinical factors have been associated with increased risk of diabetes in both the HIV-1-infected as well as the elderly population, an even greater association occurs between diabetes and the use of HAART (Figure 1). Long-term HAART treatment, which is largely responsible for the decreased mortality associated with HIV-1 disease, is also associated with an increased risk of diabetes. Early in the HIV-1 epidemic, when no treatment options were available and many patients rapidly developed AIDS, toxicity and efficacy assessments of new antiretroviral compounds were limited to identifying the most immediate problems and major concerns associated with these agents. Some abnormalities, including metabolic diseases, were considered to be secondary to the control of the severe immune deficiency affecting these patients [24,25]. However, as therapy regimens improved and the lifespan of HIV-1-infected patients increased, addressing the secondary toxicities and problems associated with these treatments has become increasingly important. Studies have now directly demonstrated that some antiretroviral compounds are associated with an induction of insulin resistance and onset of diabetes [26-28]. Risk of diabetes onset increases with the use of nucleoside reverse transcriptase inhibitors (NRTIs) and to a lesser extent with non-NRTIs [23,27]. Mitochondrial toxicity associated with the use of NRTIs likely plays a role; mitochondrial DNA (mtDNA) content is decreased with the use of compounds such as stavudine, zidovudine and didanosine [26,27,29,30]. However, the role of protease inhibitors (PIs) cannot be overlooked; PIs are rarely given alone and may play a role in the risk associated with NRTIs [23,27]. Indinavir and ritonavir in particular appear to interfere with insulin-stimulated glucose uptake, resulting in insulin resistance [31]. A cumulative dose effect from the actions of multiple compounds may explain the increased risk of diabetes onset.

Although evidence suggests a direct connection between diabetes and HAART, there may also be an indirect mechanism involving lipoatrophy. HAART has been associated with fat redistribution syndrome (lipodystrophy) that may include both central fat accumulation (lipohypertrophy) and peripheral fat wasting (lipoatrophy) [32]. Changes in body fat redistribution are commonly accompanied by the development of insulin resistance [33-37]. In lipoatrophy, increased lipolysis reflects insulin resistance within adipose tissue. Lipolysis results in increased circulating free fatty acids, which reinforces insulin resistance in both the liver and skeletal muscles [35-37]. Visceral fat accumulation as seen in lipohypertrophy is also associated with an increase in cardiometabolic risk factors, including increases in triglyceride levels and a decrease in insulin sensitivity [38-43]. This holds true in both the HIV-1-infected population and the general population. Patients on HAART treatment that includes stavudine and/or didanosine have increased lipoatrophy compared with patients on regimens that do not include these agents, suggesting a connection between therapy-induced lipoatrophy and insulin resistance [26,28,35-37,44,45]. The connection between lipoatrophy and didanosine is more controversial, with some studies demonstrating no link [46]. A more severe metabolic syndrome includes lipodystrophy, severe dyslipidemia, and insulin resistance. This disorder – HAART-associated dyslipidemic lipodystrophy – is likely caused by antiviral therapy, which can include NRTIs and PIs. Dyslipidemia itself is characterized by abnormal lipid and lipoprotein profiles and occurs in a high proportion of HIV-1-infected patients, particularly those treated with PIs or certain NRTIs, including stavudine, zidovudine, didanosine, lamivudine and abacavir [18]. Dyslipidemia patients typically present with elevated serum triglycerides and total cholesterol levels, decreases in high-density lipoprotein (HDL) cholesterol and increases in low-density lipoprotein (LDL) and very low-density lipoprotein cholesterol levels. Prior to HAART, it was shown that HIV-1 caused dyslipidemia with declines in total cholesterol levels [47-49]. Untreated patients infected with HIV-1 have been shown to have not only low total cholesterol, but also lower levels of LDL and HDL in conjunction with elevated serum triglyceride levels [25,50,51]. Lower HDL levels have been connected to higher levels of HIV-1 RNA circulating in the periphery [52,53]. Following the introduction of HAART, it has been demonstrated that

therapy also plays a role in dyslipidemia. It has been hypothesized that the catalytic region that PIs target in the HIV-1 protease is homologous with two human proteins that regulate lipid metabolism. The homologies with these two proteins, CRABP-1 and LDL receptor-related protein, and the potential targeting of these two proteins by PIs may be the cause of the dyslipidemia and lipodystrophy with the associated insulin resistance in PI-treated patients [32,54-56].

The link between dyslipidemia, lipodystrophy and diabetes suggests that treatment regimens as well as HIV-1 infection itself may play a role in causing metabolic complications. The metabolic complications in patients not infected with HIV-1 are typically observed in an aging population, and are generally responsible for increased cardiovascular and hepatic disease. This suggests that these metabolic disorders, which are typically associated with aging, may present a premature aging phenotype, but at the same time may promote and participate in premature aging by linking to other aging-related diseases (Figure 1).

### **Immune dysregulation (immunosenescence)**

Immunosenescence typically occurs in individuals greater than 70 years old. It is a general term used to describe an age-related decline in immune competence marked by alterations in the overall function of the immune system [57]. Immunosenescence is characterized by an increase in the number of terminally differentiated effector memory CD8<sup>+</sup> T cells that are generally characterized by the inability to proliferate, the absence of CD28 expression, shortened telomeres, loss of telomerase activity and enhanced secretion of inflammatory cytokines [58]. The number of naive CD8<sup>+</sup> T cells also tends to decrease. In addition, the CD4<sup>+</sup>:CD8<sup>+</sup> T-cell ratio decreases, overall T-cell activation increases, T-cell proliferation and thymic involution are reduced and levels of many inflammatory mediators increase. Typically, immunosenescence in the elderly is associated with increases in susceptibility to cancer and infectious diseases, reduced effectiveness of vaccination, increased autoimmunity and widespread increases in, as well as dysregulation of, inflammation, which can lead to organ damage [58-63]. Immunosenescent phenotypes are generally accelerated by the presence of chronic infections, with CMV implicated most often in aging. The term 'immune risk phenotype' was coined to describe the combination of a high CD8<sup>+</sup> T-cell count and low CD4<sup>+</sup> T-cell count with poor proliferative response to concanavalin A as well as low percentages of B cells [64,65]. There was a 2-4-year decrease in survival rate observed in patients aged 85 years and older in Sweden involved in part of the OCTO study [66]. The definition was later revised to only include a CD4<sup>+</sup>:CD8<sup>+</sup> T-cell ratio and then revised again to include persistent CMV infection. The decrease in survival rate among patients exhibiting the immune risk phenotype was also observed in the NONA study, with included elderly patients not necessarily selected for good health [67].

With HAART resulting in a chronic type of HIV-1 infection, in which patients with well-controlled disease potentially live for several decades, immunosenescence is occurring in patients with controlled disease as well as in those with uncontrolled disease. The immunosenescence observed appears to be premature, occurring in younger HIV-1-infected patients compared with the general population (Figure 1). The phenotype is similar to that observed in older, noninfected people (Figure 2). However, new evidence suggests that premature aging may occur not only in the CD8<sup>+</sup> T-cell population, but also in specific subsets of naive CD4<sup>+</sup> T cells [68]. Patients who do not regain a normal CD4<sup>+</sup> T-cell population during therapy are more likely to demonstrate the immunosenescence phenotype, compared with those in whom CD4<sup>+</sup> T cells are restored [69-71]. Good thymic output of naive T cells correlates with a good immunological response to treatment. Studies suggest that premature aging phenotypes in both the CD8<sup>+</sup> and CD4<sup>+</sup> T-cell compartments predict faster clinical disease progression [72]. HIV-1-associated immunosenescence may thus contribute to long-term continued immunodeficiency as well as to premature aging-

associated diseases in infected patients [19,73]. Investigators are exploring ways to increase immune response to therapy, boost the naive T-cell production and either restore function to senescent immune cell populations or deplete these dysfunctional cells.

### Bone disease

The most common bone disease observed in the elderly is osteoporosis. Osteoporosis is classically defined as an imbalance between bone resorption and formation. Osteoporosis can develop in several ways, including excessive bone resorption, inadequate levels of new bone formation during remodeling or an interplay between these mechanisms [74]. Generally, bone regeneration is marked by bone resorption by osteoclasts and new bone formation occurring via osteoblasts. Peak bone mass usually occurs at approximately 30 years of age, after which bone density naturally declines because the rate of osteoclast resorption outpaces new bone formation by osteoblasts. The WHO classifies general bone health into three categories: normal, osteopenia and osteoporosis [75]. Dual-energy x-ray absorptiometry is used to assess bone health by measuring bone mineral density (BMD). In addition to age, factors increasing the risk of bone loss include female sex, race, lifestyle, diet, body size, menopause and hormone treatment. Osteoporotic bone is less dense, weaker and much more prone to fractures and breaks [76,77].

HIV-1 infection is also a risk factor for bone loss or disease (Figure 1). Low BMD has been reported in studies involving both older [78-81] and younger [77,82-86] HIV-1-infected patients. Bone fracture rate is 30–70% higher in HIV-1-infected patients compared with uninfected controls [87-89]. The mechanism behind low BMD in HIV-1-infected patients is complex. Chronic HIV-1 infection appears to exacerbate osteoporosis risk factors, such as poor nutrition and weight loss. HIV-1-infected patients are also more likely to use tobacco and alcohol, which increase osteoporosis risk [85,90-92]. HIV-1 infection itself also appears to directly affect bone loss. HIV-1 proteins increase osteoclastic activity and promote osteoblast apoptosis [93]. Increases in TNF- $\alpha$ , an inflammatory cytokine commonly upregulated in HIV-1 infection, have also been shown to result in increased bone resorption by osteoclasts [94]. Studies have also shown that uncontrolled viremia may impact BMD; therapy-naive HIV-infected patients have a high prevalence of osteopenia [77,95]. The initiation of HAART may also induce a significant loss in BMD, regardless of the compounds used [92,96,97]; agents implicated include tenofovir- and atazanavir-ritonavir [92,98-102]. BMD appears to stabilize in patients receiving long-term, established HAART [90,91,103,104]. Vitamin D is important for cell growth, immunity and metabolism [105]. Vitamin D deficiency has been associated with decreased BMD and increased risk and severity of bone diseases. Current research also suggests that vitamin D deficiency may be linked to an increased risk of HIV-1 infection and enhanced disease progression. Research has suggested that vitamin D supplementation along with HAART may improve bone health in infected patients while simultaneously controlling HIV-1 replication, increasing CD4<sup>+</sup> T-cell counts, slowing the rate of HIV-1 disease progression, decreasing the risk of HIV-1-related neurocognitive decline and improving overall survival [105,106]. However, much more research is needed to fully understand the effects of vitamin D on infected individuals, the mechanisms involved and the concentrations to be used.

Risk factors for increases in bone loss in HIV-1-infected patients, including those on HAART, affect all age ranges. The prevalence of fractures in HIV-1-infected patients is 62% higher than in uninfected patients, again spanning all age ranges [87]. As the HAART-treated population grows older, bone disease may increase not only from disease, but also with age [12]. Recent studies have demonstrated significantly decreased BMD in postmenopausal HIV-1-infected women, as well as a higher level of bone turnover markers, further increasing the risk of fractures and breaks for these women [107]. Little is known about when to screen HIV-1-infected patients at risk for bone loss, and few studies have



assessed the efficacy of common treatments for bone loss in HIV-1-infected patients. Thus, studies assessing appropriate diagnosis and treatment options for bone loss in this growing population deserve strong emphasis.

### Neurologic impairment

Cognitive decline without dementia is common among older patients and is thought to be a component of normal aging (Table 1) [108]. Cognitive decline in the healthy elderly population typically involves problems with memory/learning, attention/working memory, language/lexical retrieval and visuospatial functioning. Decline in cognitive functioning may impair an older person's ability to perform instrumental activities of daily living, such as managing personal finances [108,109]. Underlying disease states unrelated to aging, such as HIV-1 infection, can also cause cognitive decline.

HIV-associated neurocognitive disorder refers to a wide variety of neurologic disorders from mild cognitive impairment to HIV-associated dementia (Figure 1) [110,111]. Drug treatment has substantially reduced HIV-associated dementia, but HIV-1-related neurocognitive disorders are an increasing problem in patients aged 50 years and older [112,113]. Results suggest that HIV-1-related neurocognitive disorders may be potentiated by common age-associated medical problems, including hypertension [114], hypercholesterolemia [115] and diabetes [116]. Evidence also suggests that HIV-1-related neurocognitive impairment occurs in conjunction with biomarkers commonly seen in patients with AD, with or without vascular comorbid factors such as  $\beta$  amyloid and total  $\tau$  [117,118]. An abundance of research shows the presence of neuropathological markers commonly seen in AD in individuals with HIV-1-related neurocognitive disorders [119]. In these studies, HIV-1-infected participants had decreased  $\beta$  amyloid and increased total  $\tau$  in cerebrospinal fluid (CSF). In one study, CSF samples were examined from three groups: HIV-1-infected patients with intact or impaired cognition and normal, uninfected control subjects [120]. HIV-1-infected patients with neurocognitive impairment had lower CSF  $\beta$  amyloid levels, comparable to levels in patients with mild AD. Total  $\tau$  was higher for AD patients, but lower than levels in HIV-1-infected subjects or normal, uninfected participants. Well-established dementia-related factors such as the ApoE  $\epsilon 4$  genotype also appear to contribute to HIV-1-related neurocognitive disorders. Thus, a variety of age-related cardiovascular risks may contribute to HIV-1 neurocognitive disorders. According to one model, age-related medical problems occurring in conjunction with HIV-1-related biologic substrates act synergistically and result in a higher incidence, or early emergence, of HIV-1-related neurocognitive disorders [121-124].

Recent research underscores a variety of important clinical and methodological factors in evaluating the origins and clinical course of neurocognitive problems in older patients with HIV-1 infection [125]. First, older patients typically present with longer disease duration and longer length of treatment with antiretroviral medications [112,113]. Also, some of these patients survived the period when appropriate pharmacological treatment was not yet available, and some were treated with therapies more toxic than compounds currently available. Their longer survival, coupled with the effects of HAART, poses a challenge for prospective research assessing the unique contribution of age to HIV-1-related neurocognitive deficits.

Several studies have examined age-related neurocognitive impairment in HIV infection (Table 1). Becker *et al.* described greater neuropsychological impairment in older compared with younger patients in a large cohort of HIV-1-infected patients, compared with a control (uninfected) population [116]. Twenty-three percent of older HIV-infected patients versus 9% of younger patients had evidence of dementia. The control group in this study, however, was younger than the HIV-1-infected cohort. Studies have also described age effects as they

relate to serostatus; neurocognitive test results were more variable among older than younger HIV-1-infected patients, and among older study participants not infected with HIV-1 [126]. An additional study reported age effects among older HIV-1-infected patients; however, this study lacked a comparable study group not infected with HIV-1 [127]. Another study showed worse cognitive impairment in older HIV-1-infected patients; however, in this study, the sample of older patients not infected with HIV-1 was quite small [128]. Finally, a study examining patients from the Hawaii Aging with HIV Cohort found no striking interaction between age and neurocognitive status [129]. This study carefully controlled for potentially confounding demographic variables. All of these studies illustrate important methodological factors in studying the relationships among age, HIV infection and neurocognitive function. They suggest that age might best be used as a continuous rather than a categorical variable and raise the question of whether age should be treated as a linear or nonlinear variable.

ART may also have neurocognitive effects. One study attempting to define the effects caused by therapy examined patients taking stavudine or didanosine, both of which are linked to mitochondrial toxicity, versus zidovudine or lamivudine, which are thought to be less toxic. These studies found decreased concentrations of brain *N*-acetylaspartate in patients taking stavudine or didanosine in frontal white matter, a common marker of HIV-1-associated neurocognitive impairment [130]. This finding would be compatible with compromised mitochondrial integrity. A second issue involves whether newly evolved neurocognitive impairment in older HIV-1 patients was accompanied by prior monotherapy versus dual therapy. The impact of these treatment regimens in older patients with emerging neurocognitive deficits requires further investigation. Third, the issue of cognitive reserve should be considered. In the literature on dementia, cognitive reserve is viewed as a mechanism that either delays onset of cognitive disabilities or limits the severity of cognitive disabilities over illness duration [131]. The impact of cognitive reserve in older patients with HIV-1 disease has not been examined.

Studies have suggested that factors that increase risk for dementia, including smoking, dyslipidemia, hypertension and diabetes mellitus, are increased in the HIV-1-infected population and can be associated with greater cognitive impairment in these patients [114,132]. Comorbid cardiovascular diseases, including hypertension and hypercholesterolemia, are associated with impaired performance on neurocognitive testing [115]. In a large cohort of HIV-1-infected patients, subclinical atherosclerosis, measured by carotid intima-media thickness (a proxy for cerebrovascular compromise), was related to slower performance on tests assessing psychomotor operations [133]. In another study, researchers employed diffusion tensor imaging to study brain alterations in HIV-infected individuals with or without cerebrovascular risk factors [134]. Diffusion-weighted MRIs assessing fractional anisotropy and mean diffusivity were obtained. Abnormal glucose metabolism was associated with lower fractional anisotropy in the caudate nucleus and hippocampus. However, effects were mitigated when scores were adjusted for age and education. It is likely that HIV-1 infection conveys risk to the integrity of subcortical nuclei. However, understanding the specific effects of illness related to cerebrovascular disease will require more detailed studies.

## Effects of aging on markers of HIV-1 disease progression

Numerous factors linked to progression of HIV infection (Table 2) have been previously reviewed [135]. These factors include immunologic, virologic, host and viral genetic and host-specific factors, such as age, sex and mode of transmission. Understanding these factors and defining the parameters that affect disease progression will facilitate the development of new therapeutic agents and improve treatment decision-making. These 'markers' include

classical factors such as CD4<sup>+</sup> T-cell count and HIV-1 viral load (VL) measurements. Age itself is an important predictor of HIV-1 disease progression. HIV infection progresses to AIDS more rapidly in older than in younger patients, and mortality is much higher in older patients who develop an AIDS-defining illness [136].

### Viral load

VL measurements (HIV-1 viral RNA quantification from peripheral blood) have long been used as a prognostic marker of HIV-1 disease progression [137-139]. In many patients, VL and CD4<sup>+</sup> T-cell count are inversely related, as are VL and survival time [140,141]. Disease progression is considerably increased in patients with HIV-1 RNA levels >100,000 copies/ml, regardless of CD4<sup>+</sup> T-cell count. Extensive research has demonstrated that, unlike CD4<sup>+</sup> T-cell counts, HIV-1 RNA levels from later time points may be better indicators of disease progression, with a stable viral set-point not being reached until after 1 year of infection. Treatment efficacy and response to therapy are strongly linked to baseline VL levels. Levels greater than 150,000 copies/ml correspond to a 1.5-fold increased likelihood of treatment failure (meaning the ability to decrease the VL to <50 copies/ml).

Studies have shown that older patients present with higher VL measurements at diagnosis (Table 2) [142-144]. Regarding virological response to HAART treatment, many studies have found no difference between younger and older patients [145-155], whereas others have found a better response in older patients [149,156-164]. The better virologic response observed in older patients may reflect better adherence to HAART [154,161,165,166], but this has not always been the case [156].

### CD4<sup>+</sup> T-cell counts

CD4<sup>+</sup> T cells are important mediators of the specific immune response to infection and are a primary target of HIV-1 infection. As infection progresses, the number of CD4<sup>+</sup> T cells declines, restricting the ability of the immune system to respond to other invading pathogens (Figure 2) [167]. To date, the CD4<sup>+</sup> T-cell count is the most significant and the most utilized predictor of disease progression [168-174], and the overall treatment protocol is usually initiated in response to a decline in CD4<sup>+</sup> T-cell count [137]. In the past, in resource-rich settings, a CD4<sup>+</sup> T-cell count of approximately 350 cells/ $\mu$ l was the treatment threshold, whereas in resource-limited settings, 200 cells/ $\mu$ l was the treatment threshold. This lower threshold is thought to double the risk for disease progression [170]. However, current thinking suggests that treatment should either be initiated when the CD4<sup>+</sup> T-cell count reaches 500 cell/ $\mu$ l, or that treatment should be given to every infected individual, regardless of CD4<sup>+</sup> T-cell count. In addition to determining when to start HAART treatment, CD4<sup>+</sup> T-cell count has been used to monitor the efficacy of treatment regimens [137,175].

Both age and HIV-1 infection have been shown to independently induce changes in the number and function of CD4<sup>+</sup> T cells (Figure 2 & Table 2). In elderly HIV-negative patients, immunosenescence leads to a decrease in CD4<sup>+</sup> T-cell counts [15,176-178]. Thymic involution, which occurs with aging, results in a decreased ability to replace CD4<sup>+</sup> T cells that are depleted by HIV-1 infection [179-181]. In addition to the decreased ability to replace CD4<sup>+</sup> T cells, HIV-1 infection is associated with a decreased capacity for the growth of T-lymphocyte precursor cells [182]. Although the number of memory CD4<sup>+</sup> T cells increases with age, their ability to respond to primary pathogens decreases [183-186]. Studies have shown that older patients present with lower CD4<sup>+</sup> T-cell counts at diagnosis [187,188]. Thus, immunologic recovery may be less robust in older HIV-positive patients than in younger patients. A recent study involving 1956 patients showed an inverse relationship between CD4<sup>+</sup> T-cell recovery and patient age on multivariate analysis [189]. Although many studies concur with these results and suggest a decline in CD4<sup>+</sup> T-cell count



and in CD4<sup>+</sup> T-cell response to HAART treatment with increasing age [70,147-149,153,154,156,157,189-195], controversy continues regarding this observation. A recent study examining 101 elderly HIV-1-infected patients and 202 matched, younger HIV-1-infected patients showed a similar rate of response in the two groups with respect to CD4<sup>+</sup> T-cell increases following the initiation of HAART [152]. Other studies support this finding [145,150-152,155,159-161,164,196,197]. However, greater compliance among older patients may explain these results [154,161,165,166].

### Monocyte-macrophage populations

In comparison to the adaptive immune response, less is known about the effects of age on the innate immune response. The proper functioning of blood monocytes and tissue-resident macrophages is paramount in controlling inflammation, and these cell populations play a large role in the development of age-related inflammatory conditions [198]. Studies have demonstrated a large increase in the minor population of CD14<sup>+</sup>CD16<sup>+</sup> monocytes displaying a mature phenotype in older patients [199,200]. This cell population has been shown to be increased in untreated HIV-1-infected individuals [201,202] and is thought to play a major role in trafficking HIV to the brain [203-206]. Macrophages in older patients have decreased levels of activation, as demonstrated by a decrease in the expression of MHC class II HLA-DR activation molecules (Figure 2) [199,207]. Activation of macrophages is key for the proper functioning of these cells. The microbicidal capacity of macrophages also appears to diminish with age. This is reflected in weakened respiratory bursts, decreases in reactive nitrogen and oxygen intermediates and decreased capacity to complete phagocytosis [208-210]. Similar changes in function occur in response to HIV-1 infection. This functional change has been shown to be mediated by Nef and is related to the decrease in CD4<sup>+</sup> T cells (Table 2)[211,212].

However, not all age-related effects on monocytes and macrophages have been associated with a decrease in function (Figure 2). Older patients have elevated basal plasma levels of IL-6, a proinflammatory cytokine that can be secreted by both monocytes and macrophages. Increases in IL-6 have been considered a risk marker for the development of atherosclerosis [213]. Elevated levels of IL-6 are also detected in younger HIV-1-infected patients compared with healthy control patients [214]. Other proinflammatory responses observed in older patients include increases in high-affinity p55- and p75-soluble TNF- $\alpha$  receptor levels [215,216]. These receptors have also been shown to be elevated in HIV-1-infected patients and are linked to both immune activation and disease progression [217,218]. These factors remain elevated even after 6 years of undetectable VL [219]. These studies suggest that the phenotype of innate immune functioning observed in older patients matches the phenotype detected in response to HIV-1 infection and may play a role in the accelerated aging effects reported in younger HIV-1-infected patients.

### Mitochondrial effects

Aerobic respiration in eukaryotes occurs in the mitochondria, which are involved in the primary energy-yielding reactions within the cell. Mitochondria produce 92% of cellular ATP and play critical roles in calcium regulation, thermogenesis and apoptosis [220]. Within the cell, mitochondria exist as a highly dynamic network that is actively remodeled through fission and fusion events [221]. The mitochondrial genome has been shown to reside within the matrix. Unlike the multichromosome configuration of nuclear DNA, which contains both introns and exons, the human mitochondrial genome is intronless, circular and approximately 16,569 base pairs in size [222]. Depending on cell type, circular mtDNA copies can range from 1000 to 8000 per cell [223]. The entire mitochondrial genome is dedicated to energy production, and each copy codes for 13 electron transport chain protein subunits necessary for oxidative phosphorylation (the process of converting ADP to ATP).

The rest of the mitochondrial genome includes two ribosomal RNA genes and 22 transfer RNAs that provide translational machinery.

Mitochondria maintain an electrical membrane potential ( $\Delta\Psi_m$ ) that is dependent on oxidative phosphorylation. In the coupled state,  $\Delta\Psi_m$  is maintained at a resting potential between  $-180$  and  $-200$  mV due to the serial reduction of electrons within the inner membrane [224,225]. This electrical potential is required for the import of mitochondrial proteins from the cytosol. It is also necessary for ATP transport out of the mitochondria and is coupled to the activity of the mitochondrial permeability transition pore, which has been shown to regulate the exchange of metabolites and ions such as calcium (involved in apoptosis) [226-228].

During aging and in response to HIV-1 infection and HAART treatment, virtually all aspects of mitochondrial function may be impaired (Table 2) [229,230]. Due to the direct impact of NRTIs, mtDNA deletions and mutations have been examined as a potential cause of HIV-1- and HAART-related pathologies. During aging, mutations in mtDNA, in the form of large deletions, accumulate in a variety of tissues [230]. The most recent examination of this issue, in the aging primate liver, showed increased mtDNA lesions and increased oxidative stress in mononucleocytes with age [231]. In addition, mice bearing a defective allele of the mtDNA polymerase- $\gamma$  exhibit a premature aging phenotype [232]. In the case of HIV and HAART, the NRTIs directly inhibit DNA polymerase- $\gamma$ , although the ability of the enzyme to distinguish and remove these compounds from the nascent DNA chain varies [233,234]. Attempts to quantify the impact of NRTIs on the mitochondrial genome in the clinic have taken several forms. In most cases, peripheral blood cells have been examined, in the hope that mitochondrial changes in this cell population would reflect changes associated with pathologies related to mitochondrial dysfunction, such as lipodystrophy and metabolic changes. Results have been conflicting, with some studies reporting a decline in mtDNA content and others failing to find such an association, as previously reviewed by Curran and Ribera [235]. Possible causes for variation between multiple studies include heterogeneous patient genetic backgrounds and the fact that lipodystrophy is almost certainly a multifactorial syndrome. Indeed, a recent study found that patients harboring a polymorphism at *E1143* of the polymerase- $\gamma$  gene have a fourfold higher risk for the development of lipodystrophy while on ART [236]. Haplogroups of mtDNA were associated with differences in metabolic response to ART in an independent study [237], although the development of lipodystrophy was not related to mitochondrial haplogroups in a separate study [238]. Individuals probably vary in susceptibility to the influence of a specific therapy on the mitochondrial genome, and the rate of expansion for mitochondrial mutations also appears to vary. A variation in mitochondrial mutations during aging has long been recognized [239,240]. The variability in the rate of expansion of mtDNA mutations in individuals on HAART was demonstrated in a recent report examining mtDNA deletions and the expression of cytochrome C oxidase subunits in individual muscle fibers [241]. Thus, an individualized approach to the issue of mitochondrial toxicity in ART will be needed to resolve the problems faced in the clinic.

## Conclusion

Aging within the context of HIV-1 disease is a complicated and expanding area of research. Age-related diseases such as bone disease metabolic disorders, cardiovascular diseases, and immunologic dysregulation are linked to HIV-1 infection in various ways. HIV-1 infection can lead to a premature aging phenotype, and disease and treatment effects are different in patients who are infected at older ages. The effects of age on HIV-1 infection and markers of HIV-1 disease progression are controversial. The literature varies on the effects age has on VL and on CD4<sup>+</sup> T-cell counts in older HAART-treated patients. More research is needed to

completely elucidate the effects age has on HIV-1 disease and how best to treat these patients.

## Future perspective

Studies on the impact of HIV-1 infection and age on each other have often been discrepant or did not account for possible confounding factors. With regard to the effects of age on CD4<sup>+</sup> T-cell count and VL, comparing the overall mortality of older versus younger patients may be most useful. A study examining 788 patients (253 older and 535 younger) showed that in patients not receiving HAART, the hazard rate for death for older patients was twice that observed in younger patients. However, after the initiation of HAART, mortality was reduced by 72% among the older patients, and this reduction increased with HAART usage until there was no statistical difference between the two groups [160]. These results suggest that deferring treatment in older patients, as well as failing to diagnose infection, may adversely impact survival. Failing to diagnose infection in older patients is especially problematic. Older patients are less likely to be tested for HIV-1 infection and are more likely to be misdiagnosed than younger patients [242-246]. There is a misperception that older patients are less at risk for HIV infection, and many of the symptoms, including fatigue, frailty and increased illness, may be misattributed to increased age itself. Thus, older patients are typically diagnosed much later in the course of infection than younger patients.

Regarding neurocognitive impairment in HIV infection, a variety of methodological and scientific issues must be considered. First, for this population, an age cutoff demarcating younger versus older patients may be arbitrary and could be less optimal than treating age as a continuous variable. The patient's premorbid neurocognitive status should be assessed if possible. Cognitive reserve may have protective effects. Genetic factors such as *APOE* status have been shown to convey risk for mild cognitive impairment in middle-aged and older patients not infected with HIV-1 [247]. There is no reason why a similar situation would not exist for HIV-1-infected patients. Operationally defining cerebrovascular risk with tools such as the Framingham Stroke Risk Index has been shown to predict both the presence and subtype of mild cognitive impairment in patients without HIV-1 infection [247]. These measures could be similarly useful in older HIV-1-infected patients. Regarding possible links between mitochondrial effects and neurocognitive decline, the challenge is to identify parameters that will reflect differences in mitochondrial function/biogenesis/homeostasis in specific regions of the brain in individuals. This might permit quantifying an individual's relative susceptibility to specific therapies. This information would allow a relative assessment of the risk of cognitive decline.

In conclusion, HIV-1 infection and aging itself both appear to play important roles in the increased morbidity and mortality of older HIV-1-infected patients. A complex interplay occurs between these factors and HIV-1 infection and subsequent immune dysregulation. HIV-1 infection also appears to cause a state of premature aging, in which infected patients not only develop disorders and diseases that are typically thought of as age-related, but also present with immune dysfunction similar to that observed in elderly uninfected patients. These conditions include neurocognitive impairment, bone disease, diabetes and other metabolic disorders and cardiovascular diseases, among others. In addition to occurring earlier, these conditions also appear to be more aggressive and progress more rapidly in HIV-1-infected patients when compared with the general population [110]. Many HIV-1-infected patients suffer from more than one of these conditions associated with accelerated aging, known as polyopathy. Polyopathy is also seen in elderly individuals as part of the general population, but it has been shown to occur approximately 15 years earlier in HIV-1-infected patients. These conditions, both singly and combined as polyopathologies, appear to be exacerbated not only by HIV-1 infection itself, but also by treatment. To date,

the most explored hypotheses for premature aging include the development of mitochondrial toxicity and immunosenescence [68,248]. Although research does suggest a significant role for HAART in premature aging, the benefits of HAART are incontrovertible, and the link between aging-related phenotypes and HIV-1 infection (in the absence or presence of HAART) means that we should focus on the early diagnosis and treatment of infected patients. We hope that early control of VL and CD4<sup>+</sup> T-cell counts will help to minimize the premature onset of age-related diseases. Finally, developing next-generation compounds for HIV-1 treatment with decreased toxicity continues to be a high priority to minimize the relationship between HIV-1 infection and aging-related morbidities.

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## Executive summary

### Aging-related comorbidities within the HIV-1-infected population

- The prevalence of multiple aging-related diseases in HIV-1-infected patients is equivalent to their prevalence in uninfected patients who are 10–15 years older.
- Diabetes incidence is increased in HIV-1-infected patients, with increasing age being associated with increasing risk, and HAART use demonstrating an even greater association with diabetes.
- The link between HAART and diabetes may indirectly involve peripheral fat wasting (lipoatrophy) and abnormal lipid and lipoprotein profiles (dyslipidemia).
- Premature aging occurs not only in the CD8<sup>+</sup> T-cell population, but also in specific subsets of naive CD4<sup>+</sup> T cells.
- Immunosenescence associated with HIV-1 contributes to long-term immunodeficiency and premature aging diseases.
- HIV-1 proteins, as well as some inflammatory mediators upregulated by HIV-1 infection, have been shown to increase osteoclast activity and promote osteoporosis.
- Appropriate screening times and treatment efficacy for bone loss in HIV-1-infected patients need to be assessed in this growing population.
- A growing body of research demonstrates that neuropathological markers normally associated with Alzheimer's disease are also present in HIV-1 neurocognitive diseases.
- Traditional risk factors for dementia, including smoking, dyslipidemia, hypertension and diabetes, are increased in HIV-1-infected patients and can be associated with greater cognitive impairment.

### Effects of aging on markers of HIV-1 disease progression

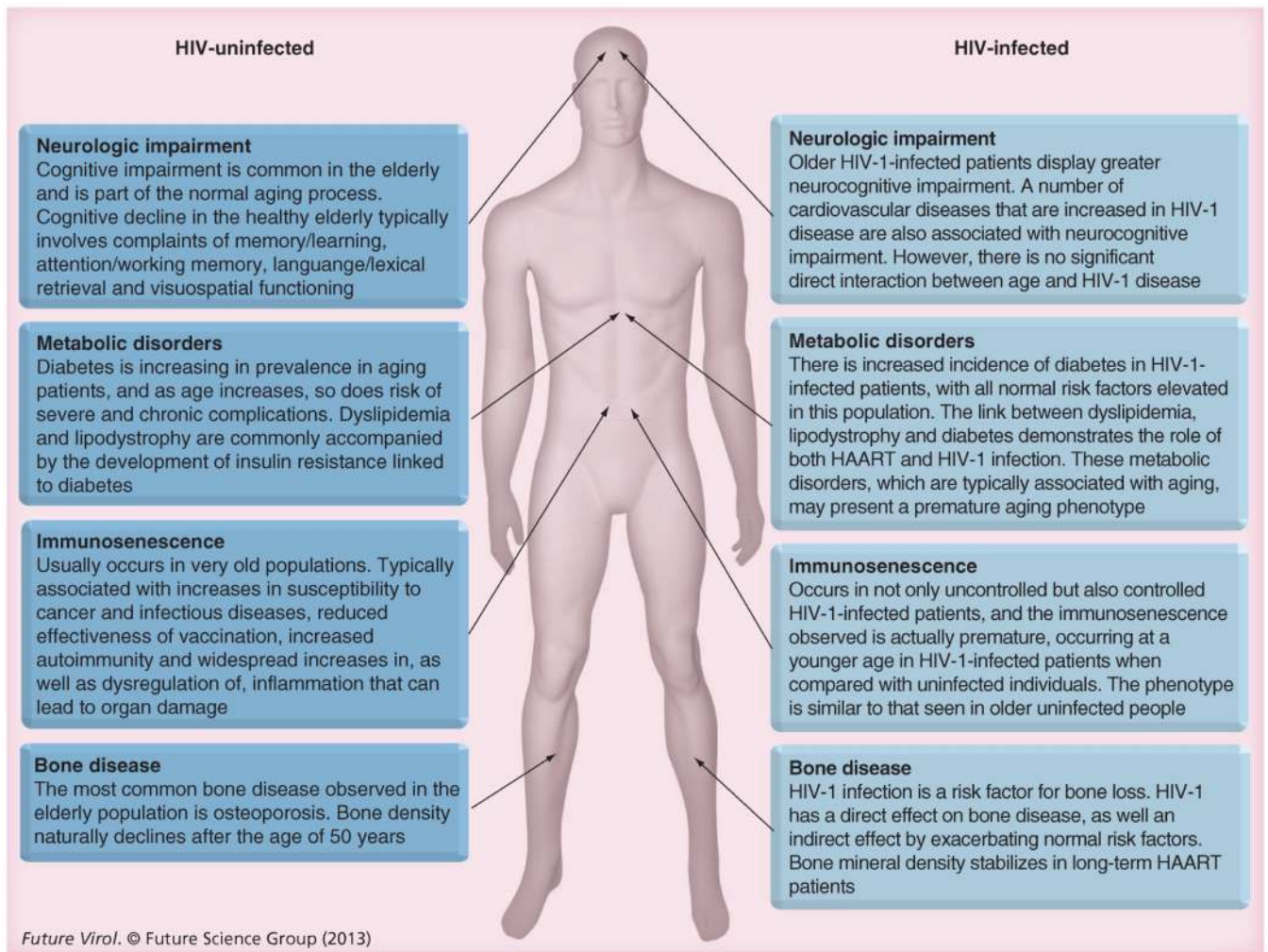
- Controversy exists with regard to virological response to HAART, with some studies finding no difference between younger and older HIV-1-infected patients and others finding a better response in older patients.
- Studies have demonstrated an inverse relationship between CD4<sup>+</sup> T-cell count and patient age; however, this finding is controversial, with other studies demonstrating no connection between age and response to HAART with regard to CD4<sup>+</sup> T-cell count.
- The increased virologic response observed in some older HIV-1-infected patients, as well as the result of no change between younger and older HIV-1-infected patients with regard to CD4<sup>+</sup> T-cell response, may be the result of increased adherence to HAART.
- HIV-1 infection results in decreased function of macrophages, as is seen with aging.
- HIV-1 infection, as well as increasing age, result in an increase in basal plasma levels of IL-6, as well as increases in p55- and p75-soluble TNF- $\alpha$  receptor.

- Virtually all aspects of mitochondrial function may be impaired during aging and in response to HIV-1 infection and HAART treatment.
- Mice bearing a defective allele of the mitochondrial DNA polymerase- $\gamma$  exhibit a premature aging phenotype, and nucleoside reverse transcriptase inhibitors have also been shown to directly inhibit DNA polymerase- $\gamma$ .

#### Future perspective

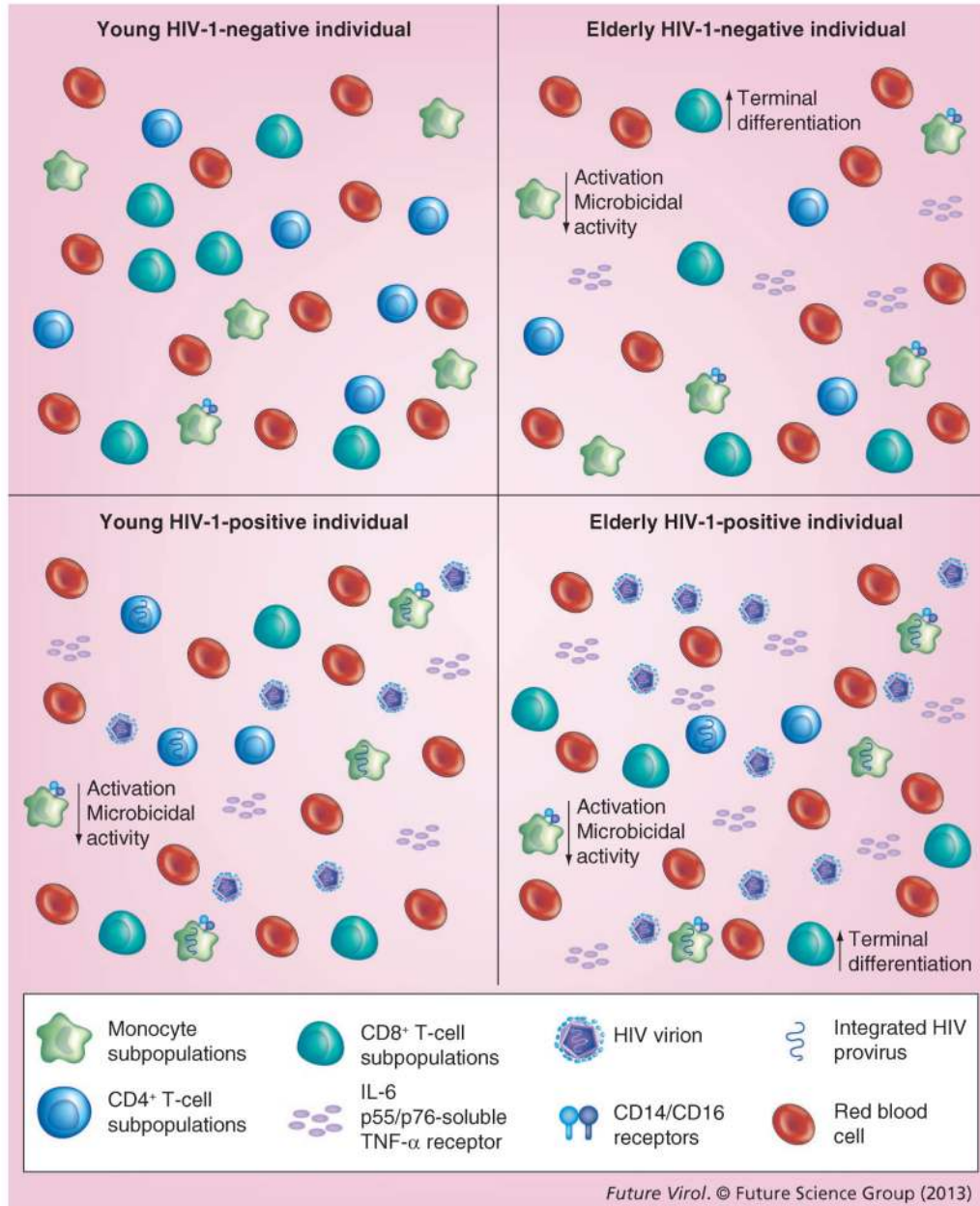
- The impact of mortality of older HIV-1-infected patients in comparison with younger HIV-1-infected patients may be more beneficial with regard to determining the effect of age on both CD4<sup>+</sup> T-cell count and viral load.
- Age cutoff, premorbid neurocognitive status, genetic factors, cardiovascular risk and mitochondrial risks must be considered in the assessment of age-related neurocognitive impairment in HIV-1.
- Continued production of next-generation compounds for HIV-1 treatment with decreased toxicity should be a high priority.





**Figure 1. HIV-1 infection initiates a premature aging response**

Normal aging-related disease states that are observed in the elderly occur at much younger ages in HIV-1-infected patients. These disease states include enhanced neurologic decline, metabolic/cardiovascular diseases including dyslipidemia, lipodystrophy and diabetes, immune system dysfunction and bone disease. HAART also seems to play a role in premature aging.



**Figure 2. Immune regulation in response to aging and HIV-1 infection**

As an individual ages, immune competence declines and changes occur in the overall function of the immune system. With aging, the number of terminally differentiated CD8<sup>+</sup> T cells increases, while their ability to proliferate decreases and CD28 expression decreases. There are also fewer naive CD8<sup>+</sup> T cells. Aging also decreases the number and function of CD4<sup>+</sup> T cells. This decrease has also been shown to lead to a decrease in the overall CD4<sup>+</sup>:CD8<sup>+</sup> T-cell ratio. HIV-1 infection itself also induces changes in the overall number and function of CD4<sup>+</sup> T cells, increasing the number of terminally differentiated CD8<sup>+</sup> T cells and decreasing the ability of CD8<sup>+</sup> T cells to proliferate. Even though the number of CD4<sup>+</sup> T cells decreases, the number of memory CD4<sup>+</sup> T cells increases; however, these memory cells are less able to respond to pathogens. Blood monocytes and tissue macrophages typically have a decreased level of activation in older, uninfected patients.

Large increases have also been shown in CD14<sup>+</sup>/CD16<sup>+</sup> receptors on mature monocytes in the elderly. This was similar to what was observed in younger HIV-1-infected patients. Within both the older uninfected population, as well as HIV-1-infected patients, macrophages appeared to have diminished microbicidal capability. However, not all aging-related changes have centered on a loss of function. IL-6 cytokine levels increase with aging, as well as independently with HIV-1 infection. p55- and p75-soluble TNF- $\alpha$  receptor levels also increase. These levels all increase further in HIV-1-infected patients as they age.

**Table 1**  
**Neurologic complications associated with aging and HIV-1 infection**

Observation	Issues	Ref.
Older HIV <sup>+</sup> patients display greater neurocognitive impairment	Utilized large cohorts of HIV <sup>+</sup> and HIV <sup>-</sup> patients, but uninfected control group was younger than HIV <sup>+</sup> group	[116]
Age effects seen in older HIV <sup>+</sup> patients as compared with younger HIV <sup>+</sup> patients	Lacked young and old HIV <sup>-</sup> control groups	[127]
Differential decline in cognitive impairment with increasing age in HIV <sup>+</sup> patients	Sample of older HIV <sup>-</sup> patients was small	[128]
No significant interaction between age and neurocognitive impairment	None. Well-controlled study using a well-established cohort	[129]
Decreased concentrations of <i>N</i> -acetylaspartate in frontal white matter suggest mitochondrial toxicity	Only looked at four antiretroviral compounds	[130]
Cardiovascular diseases, including dyslipidemia, hypertension and diabetes, associated with neurocognitive impairment in HIV <sup>+</sup> patients, and greater neurocognitive score		[114,115,132]
Diffusion-weighted MRI found an association between abnormal glucose metabolism and lower fatty acid in caudate nucleus and hippocampus	Effects were mitigated with age and education adjustment	[134]

**Table 2**  
**Markers of HIV-1 disease progression are affected by age**

Marker	Young HIV-1-negative individual	Elderly HIV-1-negative individual	Young HIV-1-positive individual	Elderly HIV-1-positive individual
Viral load	Not applicable	Not applicable	Efficacy of and response to therapy is strongly linked to baseline viral levels [140,141]	Typically present with higher viral loads at time of diagnosis [142-144] Some studies show no difference between younger and older patients with regard to response to HAART [144-155], while others show increased response to therapy in older patients [149,156-164]
CD4 count	Normal CD4 <sup>+</sup> T-cell counts and cellular function	Age induces changes in the number, proportion and function of CD4 <sup>+</sup> T cells [176]	HIV-1 infection is associated with decreased capacity for replication of T-cell precursor cells [182] Respond well to HAART with CD4 T-cell rebound [183-186]	Older patients present with lower CD4 <sup>+</sup> T-cell counts at the time of diagnosis [187,188] Some studies show a decrease in response to HAART in older patients [70,147-149,153,154,156,157,189-195], while others show no difference [145,150-152,155,159-161,164,196,197]
Monocytes and macrophages	Normal cell counts and proper functioning of blood monocytes and tissue macrophages	Decreased levels of activation in older patients, with decrease in MHC class II HLA-DR [198,199,207] Increase in the minor CD14 <sup>+</sup> CD16 <sup>+</sup> cell population [199,200] Decreased microbicidal activity [208-210] Increase in basal levels of IL-6 and p55-soluble TNF- $\alpha$ receptor, as well as p75-soluble TNF- $\alpha$ receptor [213,215,216]	Increase in the minor CD14 <sup>+</sup> CD16 <sup>+</sup> cell population [199,200-202] Decreased microbicidal activity [208-212] Increase in basal levels of IL-6 and p55-soluble TNF- $\alpha$ receptor, as well as p75-soluble TNF- $\alpha$ receptor [213,215,216]	Decreased levels of activation in older patients, with decreases in MHC II HLA-DR [198-200] Increase in the minor CD14 <sup>+</sup> CD16 <sup>+</sup> cell population [199,200-202] Decreased microbicidal activity [208-212] Increase in basal levels of IL-6 and p55-soluble TNF- $\alpha$ receptor, as well as p75-soluble TNF- $\alpha$ receptor [213,234,235]
mtDNA	Maintains normal functioning and does not yet begin to accumulate the large deletions associated with older age	Large deletions accumulate in a variety of tissues [230] Direct correlation between the amount of mtDNA lesions [231] Mice bearing a defective allele of the mtDNA polymerase- $\gamma$ exhibit a premature aging phenotype [232]	HAART has been shown to directly inhibit DNA polymerase- $\gamma$ [233,234] Patients harboring a polymorphism at E1143 of the polymerase- $\gamma$ gene have a fourfold higher risk for the development of lipodystrophy while on HAART [236] Haplogroups of mtDNA were associated with differences in metabolic response to antiretroviral therapy in an independent study [237], although the development of lipodystrophy was not related to mitochondrial haplogroups in a separate study [238]	HAART therapy has been shown to directly inhibit DNA polymerase- $\gamma$ [234,235] Patients harboring a polymorphism at E1143 of the polymerase- $\gamma$ gene have a fourfold higher risk for the development of lipodystrophy while on HAART [236] Haplogroups of mtDNA were associated with differences in metabolic response to antiretroviral therapy in an independent study [237], although the development of lipodystrophy was not related to mitochondrial haplogroups in a separate study [238]

mtDNA: Mitochondrial DNA.