



# THE IMMUNE SYSTEM, HIV, & AGING

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**TAG**  
Treatment Action Group

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Treatment Action Group (TAG) is an independent AIDS research and policy think tank  
fighting for better treatment, a vaccine, and a cure for AIDS.

TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information.  
We are science-based treatment activists working to expand and accelerate vital research and  
effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and  
policy makers to end AIDS.

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*Aging seems to be the only available way to live a long life.*

—Daniel François Esprit Auber (1782–1871)

### **Notes on version 2.0**

The first version of this report attempted to offer some reassurances about the extent to which the risk of aging-associated diseases can be elevated in people with HIV infection. After publication, concerns were raised that these statements could be interpreted as downplaying the importance of the interaction between HIV and aging, and diminishing the importance of the issue. We are particularly grateful to Jules Levin from the National AIDS Treatment Advocacy Project, who has led advocacy efforts on the topic of HIV and aging, for raising this point, which we have tried to address in this update.



# The Immune System, HIV, and Aging

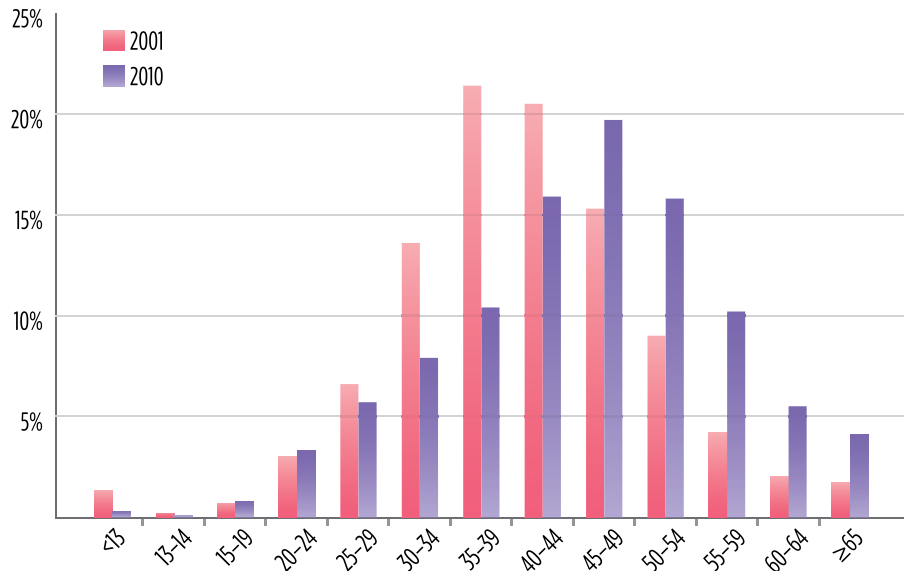
## Introduction

Little more than a decade ago, it was almost inconceivable that the issue of aging with HIV infection would emerge as an important concern. But it has now become clear that combination antiretroviral therapy (ART) can suppress virus replication for many years—likely for life—in most people who can access the drugs, and the opportunistic infections that were once the primary causes of illness have largely evanesced everywhere treatment is available. Morbidity and mortality from HIV infection has plummeted, and the survival of HIV-positive individuals is edging ever closer to that of comparable HIV-negative people.<sup>1,2</sup> With the specter of AIDS having finally been chased from the near horizon, attention has turned to health problems that may lie further down the road.

Looming largest are illnesses typically associated with aging. Examples include cardiovascular, kidney, and liver disease; bone loss and increased fracture risk; frailty; cognitive impairment; and cancer. Evidence is accumulating that the risk of these conditions is elevated in HIV-positive individuals and, in some cases, they may be occurring at a younger age, on average, than is typically observed among comparable HIV-negative populations.<sup>3</sup> As the proportion of older individuals living with HIV grows (see figure 1), there is an urgent need to understand how a broad array of factors may be contributing to this phenomenon; these factors include inflammation, immune dysregulation, polypharmacy, long-term drug toxicities, and coinfections and comorbidities that are disproportionately prevalent among people with HIV, such as hepatitis B and C, current or former substance-use disorders, stress, and depression.

It is important to emphasize that the reported elevations in risk for aging-associated diseases among people with HIV (compared with similar HIV-negative counterparts) are variable; there are inconsistencies between studies and as yet unresolved controversies regarding the extent to which HIV infection is an independent risk factor for specific illnesses. So while there is cause for vigilance and concern—particularly at ages 50 and up—there is no reason to panic, and not all HIV-positive people are likely to face a significant additional hazard of aging-associated conditions. As a general recommendation, HIV-positive individuals should consider the lifestyle factors that are now known or expected to maximize health once a person reaches old age; these include daily exercise, a healthy diet, maintaining low blood pressure and cholesterol, and avoiding substance abuse and excess fat gain.

The purpose of this brief report is to outline current scientific knowledge regarding the immunologic connections between HIV and aging, and provide an introduction to some of the unresolved questions that are being addressed—or need to be addressed—by research.



**Figure 1. The age distribution of people living with HIV in the United States, based on the percentage of individuals in each age category in 2001<sup>4</sup> compared to 2010 (data from areas with confidential name-based reporting).**<sup>5</sup> The growth of the population of older individuals living with HIV is a global phenomenon. It is estimated that in sub-Saharan Africa there are 3 million people living with HIV who are 50 or more years old, more than 13 percent of the region’s total HIV cases.<sup>6</sup> Recent data from the Swiss HIV Cohort Study reveal similar trends in Europe.<sup>7</sup>

### The Debate over “Premature Aging” or “Accelerated Aging”

In recent years, there have been strenuous debates among researchers over whether HIV infection or antiretroviral therapy is associated with more rapid aging, with “premature aging” or “accelerated aging” being the scary-sounding terms most frequently bandied about in both scientific articles and related media stories. Outside of the field of HIV research, the best-described example of premature aging is a rare genetic condition named progeria, which affects children. As the endocrinologist Carl Grunfeld has pointed out, essentially nothing that has been described in HIV-positive people bears resemblance to the manifestations of progeria. Furthermore, the evidence for aging-associated diseases occurring at younger ages in individuals with HIV infection is, at this point, mixed and sometimes contradictory. The main point this report attempts to convey is that there is compelling evidence that untreated HIV infection causes the more rapid development of an aged immune system profile and that several of the features of an aged **immune system** (such as depleted naive cells and an inverted CD4:CD8 ratio) are the slowest to normalize when HIV replication is suppressed by treatment. Thus, in TAG’s opinion, one of the key questions is not whether HIV causes premature aging, but rather to what extent an aged immune-system profile contributes to the diseases of aging—both in HIV-positive people and the HIV-negative elderly.

## Aging and HIV Pathogenesis

One of the first reports associating age with prognosis of HIV infection was published in 1987: in a cohort of hemophiliacs, older age was significantly associated with more rapid progression to AIDS.<sup>8</sup> Over the subsequent two decades, this finding has been repeatedly confirmed in all populations.<sup>9,10,11,12,13,14,15</sup> It was also shown early on that age had an impact independent of CD4 T-cell count.<sup>16</sup> Parallels between the clinical manifestations of AIDS and aging—such as cognitive impairment, muscle wasting, and frailty—were also noted, suggesting to some researchers that the common basis was likely to be immunologic.<sup>17</sup> At that time, however, data on the immunologic changes that occur during natural aging and their links to health outcomes were scarce.

In recent years, a clearer picture of the role of the immune system in aging has begun to emerge. In broad strokes, the evidence suggests that there is a gradual attrition of immune-system resources caused in part by the many different infections an individual is exposed to over a lifetime, with chronic infections—those pathogens that are controlled rather than cleared from the body—playing a particularly prominent role. The key example is cytomegalovirus (CMV), which has been consistently associated with immune dysfunction and mortality (over two to six years of follow-up) among very old individuals.<sup>18</sup> A possible contribution from Epstein-Barr virus (EBV) infection has also been suggested.<sup>19</sup>

As the immune system becomes less competent in old age, it also seems to have to work harder, leading to a state of chronic inflammation that's been described as "inflamm-aging."<sup>20</sup> A particularly important advance in this field of research has been the identification of a cluster of factors that were strongly predictive of earlier mortality among an elderly (>85 years old) Swedish cohort known as the "immune risk profile" or "immune risk phenotype" (IRP – see box 1).<sup>21</sup> Ongoing research is now investigating whether the IRP also applies to other populations including those aged 60 and over.<sup>22</sup>

While the identification of the IRP among elderly individuals has been very influential in aging research, the studies so far involve small European cohorts, with much of the research performed over a decade ago using less sophisticated immunologic tests than are now available. It is uncertain if the IRP is similarly predictive of morbidity and mortality in other settings across the globe. Limited studies on the African continent suggest that background levels of immune activation are higher, while naive T-cell counts and CD4:CD8 ratios are lower;<sup>23,24,25</sup> it will be important for future research to explore whether this associates with shorter life expectancy, and how geographic variability intersects with HIV infection and aging.

These advances in aging research have highlighted numerous striking parallels with the pathogenesis of HIV infection (see box 1), and offer a new lens through which to view prior research findings. Evidence of the chronic strain placed on the immune system by the presence of HIV was documented before the virus was even identified; the first AIDS case reports included data showing elevated levels of T-cell activation as measured by the activation marker CD38 (then known as T10).<sup>26</sup> A researcher from the University of California, Los Angeles, Janis Giorgi, went on to show that CD38 expression on CD8 T cells was a strong predictor of the pace of disease progression,<sup>27</sup> a seminal finding that has been consistently confirmed in subsequent independent studies.<sup>28,29</sup> It has also been shown that the elevated levels of T-cell activation in people with untreated HIV are accompanied by increases in pro-inflammatory cytokines, such as IL-6, TNF- $\alpha$ , and alpha interferon.<sup>30</sup> So while the end stage of HIV infection is characterized by immune deficiency, it is preceded by a gradual erosion of immune system resources caused by chronic activation, a process that may have parallels with the newly described role of CMV in exacerbating immune decline in very old HIV-negative individuals.

Because the impact of HIV infection on the immune system mirrors that of aging in many respects, it is possible that manifestations suggestive of accelerated aging in HIV-positive people relate entirely to the virus. However, there are many other potential contributors. Antiretroviral drugs have a range of well-described toxicities that could conceivably play a role, such as damage to the energy-producing mitochondria in cells (a potential side effect of nucleoside reverse transcriptase inhibitors, or NRTIs),<sup>31</sup> elevations in levels of cholesterol and triglycerides (caused by some protease inhibitors),<sup>32</sup> the development of central abdominal obesity (which may be source of IL-6 and other inflammatory cytokines<sup>33</sup>) and insulin resistance (to which both NRTIs and protease inhibitors can contribute).<sup>34</sup> In addition, there are risk factors that may be more prevalent among HIV-positive people, such as current or former substance-use disorders, smoking, stress, depression, and sleep disturbances.<sup>35,36,37,38</sup>

**Box 1: Immune System Alterations in Aging and HIV Infection**

Immune Risk Profile (IRP)	HIV Infection
Inverted CD4:CD8 ratio Decreased proliferative responses and IL-2 production by T cells Increased levels of CD8+ CD28-negative T cells (senescent cells) Elevated levels of pro-inflammatory cytokines CMV infection	Inverted CD4:CD8 ratio Decreased proliferative responses and IL-2 production by T cells Increased levels of CD8+ CD28-negative T cells (senescent cells) Elevated levels of pro-inflammatory cytokines Narrowing of the T-cell repertoire Shortened telomeres in T cells
<b>Other Age-Associated Immune System Alterations</b>	
Narrowing of the T-cell repertoire Shortened telomeres in T cells	



## Immune Senescence Research in HIV

Immune senescence is used as a general term to describe the immunologic profile seen in the elderly. The word senescent is also applied to cells of the immune system that show signs of age-related dysfunction. Although the link between immune senescence and health outcomes came to light only relatively recently (and remains somewhat controversial), researchers have been investigating the phenomenon in people with HIV for many years.

In the mid-1990s, Rita Effros from the University of California, Los Angeles, first reported evidence that CD8 T cells were reaching a state known as replicative senescence in people with HIV.<sup>39</sup> Replicative senescence means that the cells have divided so many times that they can divide no more, rendering them dysfunctional and unable to perform their important duty of surveilling for, and eliminating, pathogen-infected cells (this role accords CD8 T cells their common name: “killer T cells”).

The evidence for senescence derived from an assessment of the length of telomeres in CD8 T cells. Telomeres are specialized caps that protect the ends of each chromosome and guard against degradation of the DNA when chromosomes are copied during cell division (telomeres are commonly compared to aglets, the protective caps at the end of shoelaces that prevent fraying). Over the course of multiple cell divisions, telomeres shorten, and Effros’s paper reported that telomeres in CD8 T cells with a history of division sampled from people with HIV (in the pre-HAART era) were of similar length to comparable CD8 T cells sampled from people ages 100 years or older.

Effros also showed that the loss of expression of a cell surface molecule, CD28, serves as a marker for CD8 T-cell replicative senescence.<sup>40</sup> These findings were consistent with multiple independent studies documenting the accumulation of CD8 T cells lacking CD28 (CD28-negative) in HIV infection, in both adults and children.<sup>41,42</sup> The presence of these cells is viewed as cause for concern because in addition to their impaired ability to proliferate, they have a propensity to produce high levels of pro-inflammatory cytokines.<sup>43,44</sup>

Another key parallel between HIV infection and natural aging involves the loss of naive immune cells. The major cells of the adaptive immune system—CD4 T cells, CD8 T cells, and B cells—are each divided into two vast pools in the body: naive cells, which have not yet encountered an antigen to respond to, and memory cells, which are descendants of naive cells that met an antigen and responded to it sometime in the past. As people age, naive cell numbers decline, and memory responses specific to the many different pathogens that are encountered over a lifetime accumulate. Research has revealed a more rapid depletion of naive CD4 T cells, CD8 T cells, and B cells in people with HIV compared with HIV-negative controls.<sup>45,46,47</sup> More recently, it has been reported that the decline in the number of naive cells represents an even closer parallel between HIV and aging than the accumulation of senescent CD8 T cells.<sup>48</sup>

There are multiple mechanisms by which HIV causes this acceleration in the loss of immunologic naïveté. The ongoing replication of the virus persistently activates naive cells, causing them to differentiate into memory cells (and thus removing them from the naive pool).<sup>49</sup> Chronic immune activation is associated with a type of scarring damage to lymph tissue called fibrosis, which has been shown to limit the production of factors needed to maintain naive T-cell numbers<sup>50</sup> (lymph tissue fibrosis has not been well studied in HIV-negative individuals, but available evidence suggests it is more prevalent among those aged over 60<sup>51</sup>). The virus also contributes to the exhaustion of hematopoietic stem cells (HSCs), which give rise to naive T cells and B cells in cell-making factories located in the bone marrow. Circulating HSC levels in people with HIV resemble those from HIV-negative people over 75 years old.<sup>52</sup>

After T cells are produced in the bone marrow, they travel to the thymus (hence the “T” in their name), an organ located behind the breastbone that essentially acts as a training camp. The output of naive T cells by the thymus dwindles rapidly after childhood through a natural process called thymic involution, and gradually slows to a trickle by old age. HIV infection compounds this effect of aging, impairing the function of the thymus from the earliest stages of infection onward.<sup>53</sup> The diminution of naive cells and increase of memory cells specific for chronic infections (which occur during both aging and HIV infection) lead to a less diverse T-cell repertoire (diverse meaning having T cells capable of responding to many different antigens).<sup>54,55,56</sup>

It is not only the cells of the adaptive immune system that are affected. Studies have begun to look at components of the innate immune system, finding that monocytes in men with HIV ages 45 or under are similar to those from HIV-negative individuals over 65, displaying impaired function and shortened telomeres.<sup>57</sup>

Two additional features now known to be associated with immunologic aging were documented in people with HIV, initially in the first published case reports on people with AIDS,<sup>26</sup> before being thoroughly documented among the HIV-negative elderly: the inversion of the CD4:CD8 ratio (normally around 2:1, but typically <1 in untreated HIV infection), and a loss of CD4 T-cell functionality, particularly the ability of T cells to proliferate in response to stimulation and produce the cytokine interleukin-2 (IL-2).<sup>58</sup>

The exacerbation of immunologic aging by HIV infection offers a potential explanation for the association between age and risk of disease progression described earlier. Older individuals start with an immune system that has already been eroded over time, so HIV compounds the aging-associated deficits that are already present.<sup>59</sup>

## Immune Senescence in the Era of Effective HIV Treatment

Suppression of HIV replication by ART typically leads to a rapid decline in immune activation, recovery of peripheral blood CD4 T-cell numbers, and reconstitution of key immune functions such as proliferative responses to opportunistic pathogens.<sup>60</sup> However, features of immune senescence can persist: recovery of naive T-cell numbers is slow (occurring over years) and depends on both age and the CD4 T-cell count at the time of therapy initiation.<sup>61,62</sup> Senescent CD8 T cells (and, although they do not accumulate to the same extent, CD4 T cells)<sup>63</sup> appear reluctant to fade away, although data are still very limited and more long-term studies are needed.<sup>64</sup> Levels of inflammation recede in parallel with immune activation, but typically remain above those seen in comparable HIV-negative individuals.<sup>65</sup> Underscoring the importance of age, the immune parameters of children on long-term ART much more closely resemble those of their HIV-negative counterparts, although activated and total CD8 T-cell counts remain slightly elevated, as does the proportion of memory CD4 T cells.<sup>66</sup>

### ART and Senescence

One of the longest studies to date on the impact of ART on senescent CD8 T cells was presented at the 19th Conference on Retroviruses and Opportunistic Infections (CROI) in March 2012. In a cohort of HIV-positive women followed for an average of 15.6 months after ART initiation, the researchers found that the proportion of senescent CD8 T cells declined by around five percent per year on average. Levels of senescent CD4 T cells were far lower, but did not decline significantly over the same period. The proportion of activated CD4 and CD8 T cells declined more precipitously (around 2% and 13% per year).<sup>67</sup>

In June 2012, a more comprehensive study of CD28-negative CD4 and CD8 T cells in HIV-positive men and women was published. In chronically infected individuals, after 96 weeks of treatment the proportion of CD28-negative CD4 and CD8 T cells declined by an average of 7.1% and 9.6%, but remained higher than in comparable HIV-negative controls (by 5.4% and 7.7%).<sup>68</sup>

Currently some of the strongest evidence that immune senescence can affect the health of individuals with HIV is indirect: older age and a variety of senescence markers are consistently associated with poor CD4 T-cell recovery despite HIV suppression, referred to as a discordant response or immunologic nonresponse.<sup>69,70,71</sup> Many studies have now shown that people in this situation face an elevated risk of illness compared with individuals with more robust CD4 T-cell gains.<sup>72,73,74,75,76,77,78,79</sup> These findings are paralleled by larger population-based assessments of life expectancy for people with HIV on treatment compared with their HIV-negative counterparts: a peripheral blood CD4 T-cell count of  $>500/\text{mm}^3$  is associated with a similar life expectancy, while a CD4 T-cell count of  $<500/\text{mm}^3$  correlates with an increased risk of death.<sup>80,81</sup> As an example, an analysis of 3,280 HIV-positive participants in two large clinical trials, all on treatment and with suppressed viral loads, found that there

were 28 deaths among individuals with CD4 T-cell counts of 350–499/mm<sup>3</sup>, whereas 16 deaths would have been expected in a comparable HIV-negative population. Among the larger group of participants with CD4 T-cell counts over 500/mm<sup>3</sup>, the number of deaths (34) exactly matched the expected mortality of the HIV-negative comparators.<sup>82</sup>

In line with these data, a recent long-term study of CD4 T-cell gains in people on ART followed for up to 12 years suggested that slower recovery in individuals over 50 years of age is reason enough to incorporate age considerations into HIV treatment guidelines.<sup>83</sup> In March 2012, the U.S. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* were updated to include a new section on caring for older people with HIV that explicitly recommends initiation of ART in individuals age 50 or older without regard to CD4 T-cell count “because the risk of non-AIDS related complications may increase and the immunologic response to ART may be reduced in older HIV-infected patients.”<sup>84</sup> The guidelines note, however, that this is a moderate recommendation based on expert opinion, informed by the current scientific literature on aging and HIV infection. An ongoing randomized controlled trial named START (Strategic Timing of Antiretroviral Treatment) is evaluating immediate versus delayed initiation of ART in a large population with a range of ages; results from this trial should provide clearer evidence regarding the risks and benefits of starting ART immediately in older individuals with HIV.

In terms of more direct associations between immune senescence and health outcomes in people with HIV, data are only beginning to emerge. Rita Effros’s research group has reported that higher proportions of CD28-negative CD8 T cells were associated with faster disease progression among men in the Multicenter AIDS Cohort Study (MACS),<sup>85</sup> but this was a retrospective analysis involving stored samples, and prospective studies are needed. A study involving 115 women age 40 or older in the Women’s Interagency HIV Study (WIHS) found a significant association between the proportion of both activated and senescent CD8 T cells and the presence of carotid artery lesions,<sup>86</sup> a harbinger of cardiovascular disease. Again, however, this involved looking back at samples collected at a single time point—referred to as a cross-sectional analysis—and prospective research is required to gain a clearer understanding of the associations. The study authors nevertheless state: “collectively, these observations are consistent with a model in which HIV infection results in immune activation, accelerated immunologic aging, and the premature onset of CVD [cardiovascular disease].” They also point out that in HIV-negative people, CMV has been shown to contribute to cardiovascular disease via similar mechanisms.<sup>87</sup>

Another study, this time in men, has found that several immunosenescence parameters—including lower naive CD4 and CD8 T cells, and higher proportions of CD28-negative T cells—are linked to the development of Kaposi’s sarcoma (KS) despite HIV suppression by antiretroviral therapy.<sup>88</sup> The KS in these cases resembles the generally benign “classic” form described in the HIV-negative elderly<sup>89</sup> as opposed to the aggressive form previously seen in AIDS. While more research is needed, the findings suggest that the aging of the immune system may be a risk factor for classic KS that is shared by some younger individuals with HIV and older HIV-negative persons.

## Inflammation

Some of the most important and influential data on the links between inflammation and health outcomes in people with HIV were obtained by the Strategies for Management of Antiretroviral Therapy (SMART) trial, which set out to investigate whether intermittent, CD4-guided ART could be as effective as continuous treatment. The trial enrolled 5,472 individuals who were randomly assigned to either a “drug conservation” arm (in which ART was started when the CD4 T-cell count fell below 250/mm<sup>3</sup> and interrupted when it exceeded 350/mm<sup>3</sup>) or a “viral suppression” arm in which ART was taken continuously. The median age of the participants was 43 in the drug conservation arm and 44 in the viral suppression arm, and the median time on ART prior to enrolling was six years for both groups.

The results from SMART, which were published in the *New England Journal of Medicine* in 2006, were unequivocal: intermittent ART was associated with a doubling in the risk of illness or death.<sup>90</sup> The researchers were somewhat surprised to note that few (~8%) of the illnesses that occurred were opportunistic infections; rather, the main contributors were major cardiovascular, renal, and hepatic disease—conditions more commonly associated with aging (aging researcher Russell Tracy has pointed out that these outcomes resemble those documented in a large study of HIV-negative individuals over 65<sup>91</sup>). Notably, over the average of 18 months of follow-up, these events occurred in only a small minority of participants: there were 120 cases of opportunistic disease or death among the 2,720 participants in the intermittent arm versus 47 among 2,752 people in the continuous arm. For major cardiovascular, renal, and hepatic disease there were 65 events and 39 events, respectively.

To probe the basis for these results, the SMART trial researchers collaborated with Lewis Kuller, a scientist at the University of Pennsylvania who has many decades of experience investigating the links between inflammation and disease, particularly the diseases of aging. Kuller looked at a suite of blood markers linked to inflammation and coagulation abnormalities in SMART trial participants and assessed whether there were associations with the trial outcomes. The results showed that high levels of a substance involved in blood coagulation, D-Dimer, and the cytokine IL-6 were strongly predictive of mortality.<sup>92</sup> Interruption of ART was linked to increased levels of both these biomarkers, which have also been linked to cardiovascular disease and mortality in HIV-negative individuals.<sup>93,94,95,96</sup> A subsequent analysis compared levels among SMART trial participants to a comparable HIV-negative cohort and demonstrated that they were significantly higher on average even among those on ART.<sup>97</sup>

These studies demonstrate that inflammation predicts poor health in people with HIV, consistent with research in HIV-negative populations. But a key difference is that the effect of subtle increases in inflammation is much stronger in those with HIV compared with those without it. Also, the average age of the HIV cohorts in which inflammation has been shown to be associated with morbidity and mortality is lower than the cohorts that have provided the basis for much of the literature outside of the HIV field.

## Clinical Implications

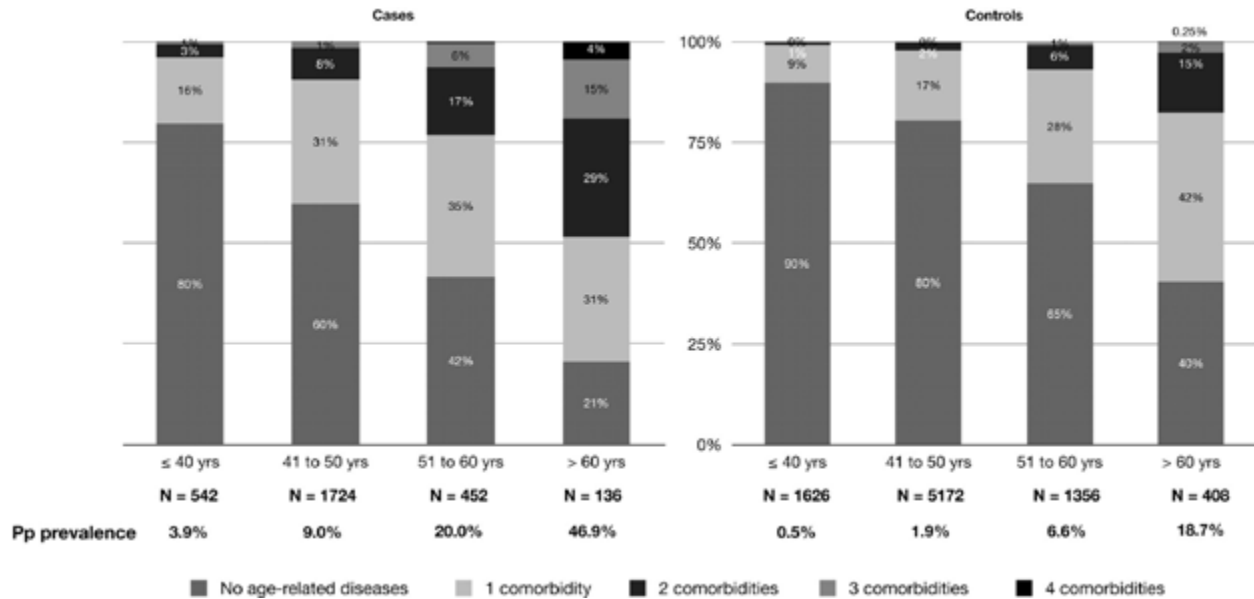
This outline of the immunologic parallels between HIV and aging may appear to paint a grim picture, but it is clear that prolonged virus suppression and robust CD4 T-cell gains greatly reduce the risk of negative health consequences, even if in some cases immune markers suggestive of more advanced age persist. The key research questions raised by the immunologic data include whether people with HIV on ART experience an increased incidence or prevalence of aging-related diseases compared with comparable HIV-negative individuals, and whether the risk is raised at a younger age.

Answering these questions is challenging. Though several analyses from observational cohort studies have been reported, it is not necessarily easy to define what constitutes a comparable HIV-negative control group, nor is it easy to adjust data for confounders and screening biases that are present when comparing patients with chronic diseases with those in the general population (a straightforward example of a potential confounder is that people with HIV may be more likely to smoke and, thus, this needs to be taken into account, but other confounders may be harder to identify). Still, these cohort studies have yielded important data regarding the clinical manifestations of HIV and aging.

These findings should be seen as a starting point for designing the longitudinal studies and clinical trials that are needed to further evaluate these biomarkers as surrogate markers of age-related disease progression and treatment efficacy, and to evaluate the usefulness for people with HIV of the best comorbidity management practices that are employed in (and have been validated for) the general aging population.

Among the limited case-control data reported to date are two European studies indicating significantly higher rates of single and multiple age-related diseases among people with HIV receiving ART compared with demographically similar HIV-negative controls.

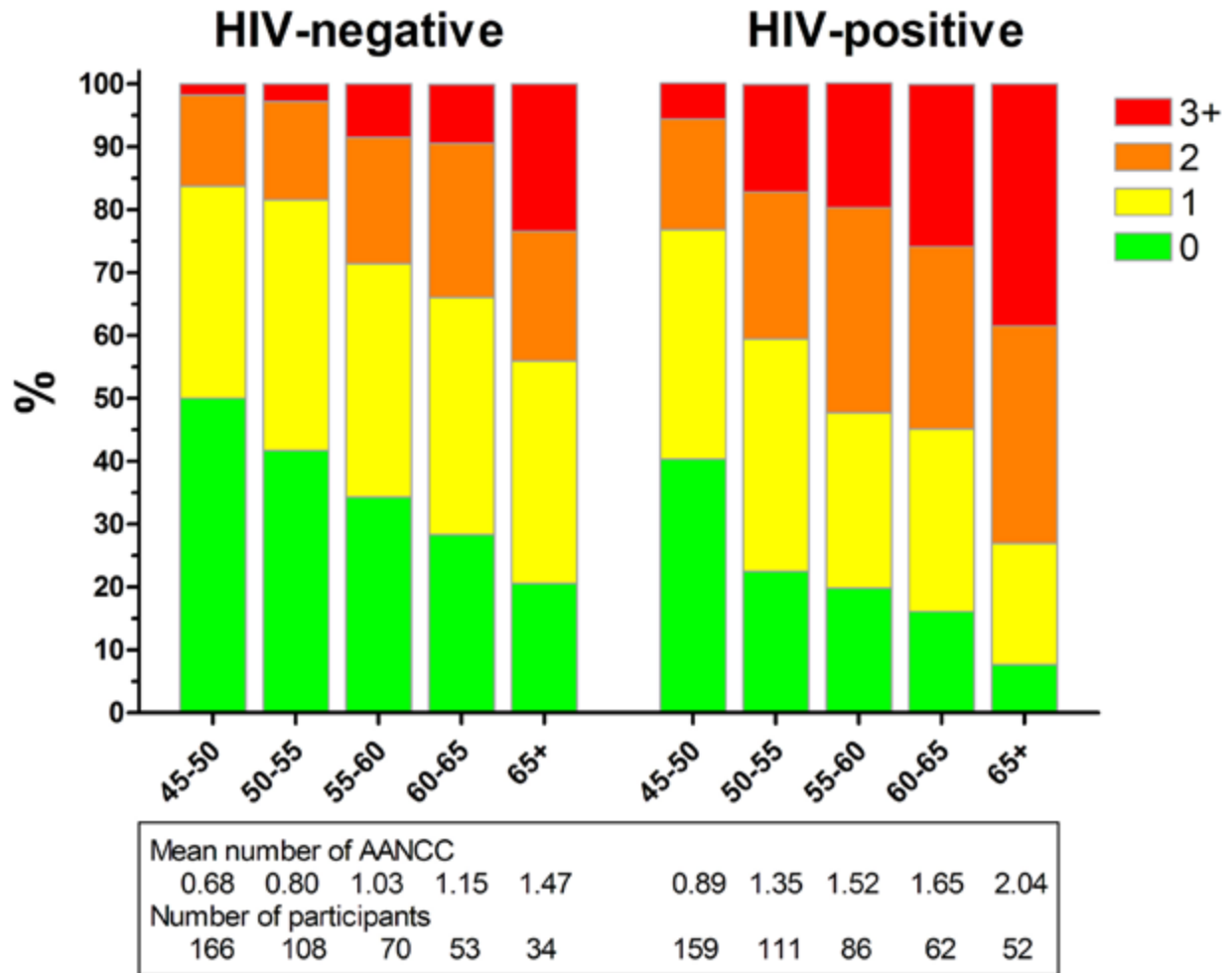
In an Italian cross-sectional retrospective study evaluating health care-related data between 2002 and 2009, rates of cardiovascular disease, hypertension, renal failure, bone fracture, and diabetes were significantly higher among the 2,854 ART-experienced people with HIV, compared with the 8,562 age-, sex-, and race-matched controls from a national registry.<sup>98</sup> The prevalence of multiple age-related diseases was also higher among younger people with HIV—the rate among people with HIV between 41 and 50 years of age (9.0%) was similar to that among controls between 51 and 60 years of age (6.6%). The ART-experienced people with HIV in this study were somewhat unusual in that slightly over two-thirds of them had been referred to the clinic from which the cohort was derived due to metabolic issues (such as lipodystrophy) while 805 participants attended the same clinic for routine care. However, a comparison between these two groups did not reveal a significant difference in the rates of comorbidities.



**Figure 2. Polypathology (Pp) prevalence among patients and control subjects, by age categories.** The following comorbidities were included: hypertension, diabetes mellitus, hypothyroidism, cardiovascular disease, and bone fractures.

Source: Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis.* 2011;53:1120–26.

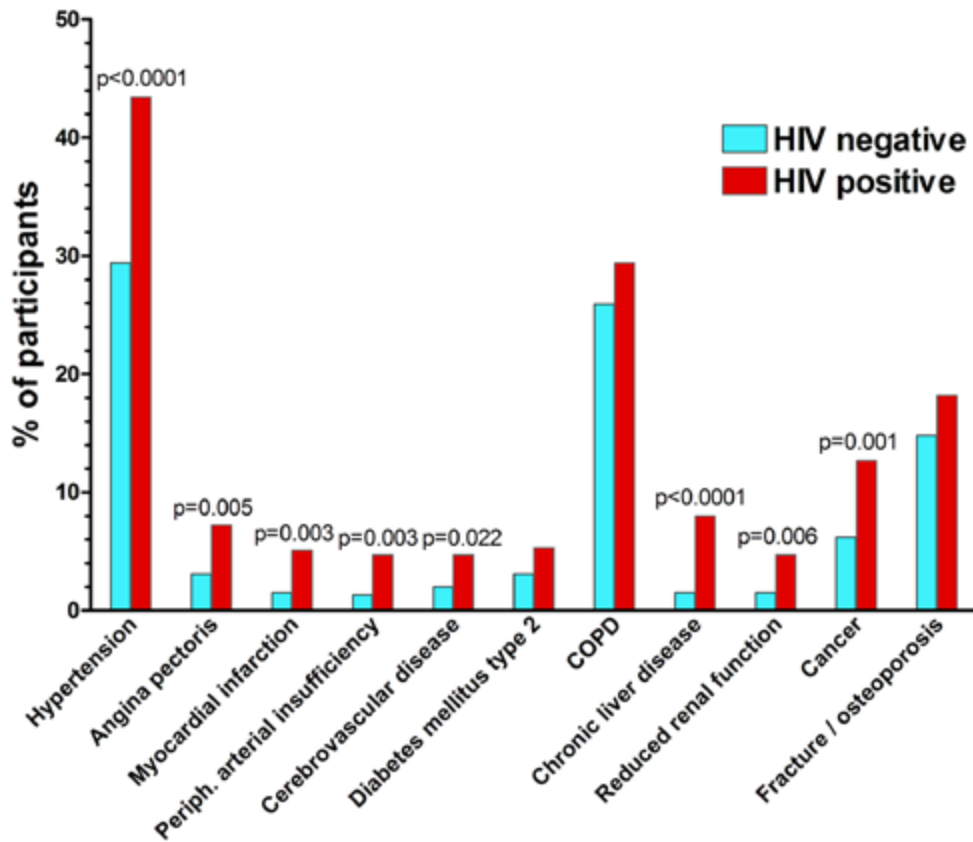
In a Dutch prospective cohort study, the prevalence of at least one age-related disease was 74.4% among 489 people with HIV, compared with 60.4% of 452 age-matched controls.<sup>99</sup> The prevalence of multiple comorbidities among HIV-positive individuals ages 45–50 was similar to that in the HIV-negative controls ages 50–55 (see figure 3). Figure 4 shows the prevalence of specific comorbidities in the HIV-positive versus HIV-negative study participants, with p values indicating statistically significant differences between the two groups. A novel component of the study involved using autofluorescence scans to measure advanced glycation end products, or AGEs, in the skin of cohort participants. Levels of AGEs—nonfunctioning protein and lipid structures that have been implicated in age-related illnesses such as Alzheimer’s disease, cardiovascular disease, and stroke—were higher in people with HIV and were independently associated with a higher prevalence of age-related diseases. However, given the cross-sectional nature of these data, it was not possible to confirm that increased levels of AGEs were a potential cause or effect of age-related diseases in the HIV-positive study volunteers.



**Figure 3. Comorbidity in relation to age.** Comorbidities analyzed were hypertension, angina pectoris, myocardial infarction, peripheral arterial insufficiency, cerebrovascular disease, diabetes mellitus type 2, chronic obstructive pulmonary disease, chronic liver disease, reduced renal function, cancer, and atraumatic fracture/osteoporosis.

Source: Schouten J, Wit FW, Stolte IG, et al. Comorbidity and ageing in HIV-1 infection: the ageHIV Cohort Study (Abstract THAB0205). Paper presented at: 19th International AIDS Conference; 2012 July 22–27; Washington, D.C.





**Figure 4. Comorbidity distribution.**

Source: Schouten J, Wit FW, Stolte IG, et al. Comorbidity and ageing in HIV-1 infection: the ageHIV Cohort Study (Abstract THAB0205). Paper presented at: 19th International AIDS Conference; 2012 July 22–27; Washington, D.C.

Extensive case-control data have been produced by the U.S.-based Veterans Aging Cohort Study, which comprises a “virtual cohort” of over 40,000 HIV-positive and 80,000 HIV-negative comparators (matched for age, race, gender, and site) complemented by a prospective cohort, VACS 9, which has enrolled more than 7,000 people with HIV and matching HIV-negative controls at nine VA medical centers around the country since 2002. Among more than 150 analyses and substudies from the cohort published in the medical literature, VACS has documented increased risks of heart attack,<sup>100</sup> cardiovascular disease,<sup>101,102</sup> pulmonary disease,<sup>103</sup> decreased physical functioning,<sup>104</sup> fragility fractures,<sup>105,106</sup> renal disease,<sup>107</sup> and cancers<sup>108</sup> among HIV-positive veterans compared with matched HIV-negative controls. However, an analysis of whether heart attacks and end-stage renal disease are occurring at younger ages in the HIV-positive veterans did not uncover any evidence that this is the case. The analysis also looked at non-AIDS-defining cancers, and found that these may occur at just slightly younger ages, on average—the difference was around seven months compared with HIV-negative veterans.<sup>109</sup>

Though the VACS overcomes several limitations of other cohort-based age-related disease analyses—including small sample size, lack of demographically similar comparison samples and limited representation of people of color and older adults—it has some of its own limitations. First, it does not prospectively screen patients for age-related diseases or conduct extensive chart reviews, but instead relies on specific, but insensitive, ICD-9 diagnostic coding. Second, the generalizability of VACS data is questionable: the cohort underrepresents younger patients and women with HIV,<sup>110</sup> and the mortality rate is higher than in other cohorts.<sup>111</sup>

### The VACS Index: Quantifying the Risk of Disease Progression in the ART Era

Much as the Framingham Index has proved useful in research and clinical management in terms of estimating the 10-year risk of myocardial infarction or death in the HIV-negative population, the development and validation of a multivariable risk index for people with HIV has been a priority. The VACS, under the direction of Amy Justice, MD, of the Yale School of Medicine, has risen to the challenge with the rollout of the points-based<sup>112</sup> VACS Index, which places less weight on factors that are easily modified with the use of ART, such as CD4 T-cell counts and viral load, and either equal or greater weight on the factors more clearly associated with morbidity and mortality in the modern-day HIV management era: abnormalities in age and organ system biomarkers, notably hemoglobin, hepatitis C virus infection status, and composite markers of liver and renal function (e.g., FIB-4, ALT/AST levels, and estimated glomerular filtration rate).

In one recent analysis that aimed to assess whether the VACS Index was relevant outside of just the VACS participants, data from a very large North American “cohort of cohorts” named NA-ACCORD was used by Justice and colleagues to compare five-year mortality estimates using both the VACS Index and a restricted index employing only age, CD4 T-cell counts and viral-load measurements.<sup>113</sup> Overall, the VACS Index provided a more discriminating prediction of all-cause mortality among HIV-positive subjects on ART than the restricted index, with 53 percent of the patients being reclassified to substantially different levels of risk using the VACS Index (22% to a higher-risk group and 31% to a lower-risk group). The VACS Index’s higher degree of discrimination remained true with increasing exposure to ART and among key subpopulations, notably those with low HIV RNA levels and those over 50 years of age.

Compared with the restricted index, the VACS Index is also better correlated with biomarkers of inflammation, including interleukin-6, soluble CD14, and D-dimer. Age, CD4 T-cell counts and viral load, compared with hemoglobin, were less correlated with these inflammatory biomarkers.

The VACS Index remains a work in progress. The investigators' choice of risk factors in the index is based on previous research that has validated each biomarker's association with morbidity and mortality in people with HIV. Emerging biomarkers, including lipid profiles, hypertension, and smoking status—as well as the inflammatory markers described above that aren't widely available or readily reimbursed by payers—continue to be explored as a way to further improve the discrimination of the index.

More information on the VACS Index is available at:  
<http://www.vacohort.org/index.aspx>.

The MACS has been particularly focused on the prevalence of frailty phenotype—a syndrome first described in 2001 involving older adults in the general population.<sup>114</sup> In people with HIV, it is arguably the modern-day equivalent of AIDS-related wasting syndrome; its five physical features are unintentional weight loss, weakness, poor endurance and energy, low physical-activity level, and slow walking speed. Adults who meet three of these criteria are believed to be at an increased risk of falls, disability, delayed and incomplete recovery, adverse outcomes of hospitalizations, and mortality.

Building upon the original frailty phenotype description, a series of papers have concluded that men with HIV in the MACS were significantly more likely to have “frailty-like phenotype” compared with age-, race-, and education-matched HIV-negative men;<sup>115</sup> that the prevalence increases exponentially in association with CD4 T-cell counts below 400;<sup>116</sup> and that persistent symptoms of frailty-like phenotype prior to the use of ART are associated with worsened prognosis after HIV treatment is commenced.<sup>117</sup> More encouragingly, at least one study has suggested that successful ART can reverse frailty related to HIV, at least in some cases.<sup>118</sup>

One of the most feared consequences of aging is impaired cognition. Studies have compared incidence and prevalence rates of neurocognitive deficits among people with HIV and matched controls, yielding conflicting results. In a MACS analysis involving 2,083 men with HIV and 2,083 HIV-negative male participants followed from July 1, 1996, to July 1, 2011, the incidence of diagnosed neurological disease was significantly higher among people with HIV using ART compared with cohort volunteers not infected with the virus in all age strata (<40, 40–49, 50–60, and >60).<sup>119</sup> Among the excess of neurological diseases was dementia, a common comorbidity of aging. Conversely, cross-sectional data from a San Francisco cohort found limited evidence of an association between HIV and age on neuropsychological performance, with only marginal differences between people with HIV compared with a population of controls consisting of individuals from similar socioeconomic backgrounds.<sup>120</sup> To some extent these differences may reflect different treatment histories and durations of infection; to date no study has looked at these issues in individuals who started on optimal modern ART regimens.

Fewer studies have investigated aging issues specifically in cohorts of injecting drug users (IDUs). But a particularly important concern in this population is hepatitis C virus (HCV), and it has been reported that IDUs coinfecting with HIV and HCV show a severity of liver fibrosis similar to that of comparable individuals infected with HCV alone who are 9.2 years older. This finding is consistent with the idea that HIV infection may reduce immune surveillance against HCV in a manner akin to the effects of more advanced age in HCV-positive, HIV-negative people.<sup>121</sup>

Although there is vastly more literature on individual aging-associated diseases in HIV-positive people than can be covered in this report, one possible explanation for the lack of clarity regarding the extent to which risk may be increased at younger ages is that population-based studies have yet to include detailed measures of immunologic aging. Such analyses might help reveal if there are segments of the HIV-positive population in whom risk is more elevated due to greater immune senescence (as may be suggested by the research showing associations between inflammatory biomarkers and morbidity and mortality). This will be an important issue for future research to address.

## Antiretroviral Drugs and Aging

The potential effects of antiretroviral toxicity on the aging process cannot be discounted.<sup>122</sup> Though studies have indicated that persistent immune activation and inflammation, along with lifestyle risk factors, are independently associated with the diseases of aging in people with HIV, data also suggest that drug- and drug class-specific toxicities may contribute, at least in some cases.

Unfortunately, many papers published to date—particularly those focusing on ART-induced mitochondrial dysfunction and oxidative stress—fail to consider immunologic perturbations (e.g., low naive CD4 T cells, inverted CD4:CD8 ratios, elevated CD28-negative senescent CD8 T cells) that can persist in those achieving HIV RNA suppression and CD4 T-cell count gains while receiving ART. Hence, the question isn't whether it is HIV or ART that is associated with aging, but rather how the two contribute to what is likely a multifactorial process.

Though the association between nucleoside reverse transcriptase inhibitor (NRTI) use and mitochondrial DNA (mtDNA) toxicity is well established, at least two studies have explored mtDNA dysfunction as a contributor to premature aging in people with HIV.

A Newcastle University study noted that NRTIs can lead to progressive accumulation of somatic mtDNA mutations, as evident in muscle fibers deficient in the essential enzyme cytochrome-c oxidase (COX), which is necessary for energy production, mirroring those typically associated with aging.<sup>123</sup> Whereas 10 HIV-negative and 12 ART-naive people with HIV had normal muscle fibers, the 21 NRTI-treated people with HIV had an increased frequency of COX-deficient muscle fibers (up to 9.8%)—reaching or exceeding levels expected in healthy elderly individuals—with the severity strongly predicted by cumulative lifetime NRTI exposure.

Previously, Institut National de la Santé et de la Recherche Médicale (INSERM) investigators in France reported that the thymidine NRTIs stavudine and zidovudine induced mtDNA dysfunction and increased reactive oxygen species production in fibroblasts (cells of the connective tissue), with an eventual slowing of cell division.<sup>124</sup> Markers of senescence were also found, *in vitro*, in adipocytes exposed to the thymidine analogs for seven days, and in adipose tissue samples from HIV-positive people with lipodystrophy receiving regimens containing either stavudine or lamivudine.

As for nonthymidine NRTIs, tenofovir has been shown, *in vitro*, to inhibit telomerase activity in activated (but not nonactivated) peripheral blood mononuclear cells (PBMCs) at therapeutic concentrations.<sup>125</sup> Whether this impairment of telomerase activity results in more rapid shortening of telomere length in activated cells *in vivo*, or has any consequences for aging, remains to be studied.

Protease inhibitors (PIs) have also been implicated.<sup>126</sup> Evaluating the effects of ritonavir or ritonavir/lopinavir on human coronary artery endothelial cells, an INSERM study found that the PIs induced senescence markers, oxidative stress, and inflammation in the samples.

Senescence markers were also increased in PBMCs from people with HIV receiving a PI-inclusive regimen. The authors suggested that senescence was associated with PBMC- and endothelial-cell accumulation of prelamin A, which is known to disrupt mitosis and induce DNA damage in smooth muscle cells, potentially leading to genomic instability and premature senescence. However, a more recent study from the French AIDS research agency ANRS has challenged these findings: in an analysis of 35 HIV-positive individuals on PI-containing ART, no evidence of prelamin A accumulation was observed.<sup>127</sup>

Several studies have specifically investigated whether there is any evidence that ART can contribute to mortality in cohorts of HIV-positive individuals, as might be expected if their use was significantly accelerating the aging process. The data reported to date show no evidence of a negative effect on mortality.<sup>128,129</sup>

Beyond the roles specific antiretroviral drugs may play in the pathogenesis and etiology of aging are important clinical issues that are likely to arise in older patients or those with age-related diseases and other comorbidities. In addition to the potential for less robust CD4 T-cell recovery despite ART-induced viral-load suppression,<sup>66,67,68</sup> there is the potential for important pharmacokinetic differences, compared with those in younger people with HIV, due to altered hepatic metabolism and renal elimination,<sup>130</sup> and an increased risk of drug-drug interactions and adverse events, particularly when polypharmacy is employed to manage HIV, coinfections, and aging-related health complications.<sup>131</sup>

### **CHARPA and the Demand for an HIV and Aging Agenda**

In April 2010, a coalition of community-based organizations, including TAG, sponsored the HIV Research Catalyst Forum (HRCF), bringing together over 200 activists and advocates to discuss issues in HIV treatment and prevention research. One of the sessions at HRCF focused on HIV and aging, and attendees decided to form an informal, ongoing coalition named the Coalition for HIV and Aging Research and Policy Advocacy (CHARPA).

In the fall of 2010, CHARPA organized a sign-on letter to the National Institute of Allergy and Infectious Diseases highlighting the importance of research into HIV and aging, which led to a meeting with the Office of AIDS Research (OAR) at the National Institutes of Health to discuss the topic further. The OAR meeting took place on December 8, 2010. The result was the formation of an OAR committee named the HIV and Aging Working Group that assessed the current state of knowledge and, in July 2012, issued a report including detailed recommendations for future research. The report was published in the *Journal of Acquired Immune Deficiency Syndromes* and is available free online.<sup>132</sup>

## Implications for Therapies

The life expectancy studies indicating the importance of reaching CD4 T-cell counts of 500/mm<sup>3</sup> or greater, as well as the data on inflammatory markers, strongly suggest that research into interventions that may address poor CD4 T-cell recovery and elevated inflammation needs to be prioritized. There are a range of potential candidates under consideration: the cytokine IL-7 has been shown to significantly increase both naive and memory CD4 and CD8 T-cell levels,<sup>133</sup> and a recent analysis suggests it might also lead to some reduction in inflammatory markers.<sup>134</sup> Early studies of a gene-therapy approach developed by Sangamo Biosciences, involving infusions of CD4 T cells modified to lack the HIV coreceptor CCR5, have reported greater improvements in CD4:CD8 ratios than have been observed with ART alone.<sup>135</sup>

A panoply of anti-inflammatories are being considered for pathogenesis and treatment studies, including statins, COX-2 inhibitors, angiotensin II receptor antagonists, peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) agonists, and drugs such as the phosphate-binding agent sevelamer that may prevent leaking of gut bacteria into the circulation (a problem known as microbial translocation, which can contribute to inflammation in HIV). For this research to advance with haste, however, there will need to be close collaboration between pharmaceutical companies and biotechnology groups with little or no HIV research expertise (or interest in the HIV market), HIV research networks and independent investigators, and regulators. Some aspects of this research mirror work in the HIV-negative elderly; for example the ongoing *VITamin D and Omega-3 Trial (VITAL)* is investigating whether these potentially anti-inflammatory supplements can reduce the risk of cancer, heart disease, and stroke in men over 50 and women over 55.<sup>136</sup>

Perhaps the least technological intervention that has been suggested to reduce immune senescence is moderate exercise, which has long been known to be beneficial for health and longevity. Although it is still new territory, a number of studies have reported that exercise may lead to declines in levels of senescent T-cells.<sup>137,138</sup> A small, preliminary study in HIV-positive people has found that regular brisk walking, with or without additional resistance training, reduced levels of several inflammatory biomarkers.<sup>139</sup> Also in the realm of lifestyle modification, a large trial has offered evidence that the Mediterranean diet can significantly reduce the incidence of cardiovascular disease, suggesting the diet could have benefits for people with HIV.<sup>140</sup>

The potential contributions of drug toxicities, while at this point largely theoretical, nevertheless reinforce that the development of ART should not be considered at an end; improved drugs are needed, and the design of novel first-line regimens lacking NRTIs and PIs should still be pursued. In parallel, the ultimate means of eliminating ART—a cure for HIV infection—must remain at the forefront of the research agenda.

Clinical research to guide evidence-based practice intended to prevent and manage aging-related illness is also required. Goals for this research include:

- Define safe and effective prevention and treatment modalities for coinfections (particularly HCV), cancers, cardiovascular and pulmonary diseases; liver and kidney impairment; decreasing bone mineral density and increasing fragility fracture risk; neurological disease; and neurocognitive decline;
- Define interventions to reduce behavioral risk factors of aging-related comorbidities (such as tobacco- and illicit drug use);
- Develop strategies to minimize polypharmacy risks; and
- Standardize approaches required to overcome structural, psychosocial, and socio-economic barriers that prevent older people with HIV and those at increased risk for aging-related health complications from linking to, and being retained in, clinical care.

The recommendations from the OAR HIV and Aging Working Group encompass all the issues described here, in greater technical detail, and it will be critical for advocates to ensure that all the routes laid out in the OAR's comprehensive map for future research are followed. If they are, we can realistically hope that the remaining risk for earlier morbidity and mortality among people with HIV can be addressed.



## General Resources on HIV and Aging

**The HIV and Aging Consensus Project:** *Recommended Treatment Strategies for Clinicians Managing Older Patients with HIV*  
<http://hiv-age.org/clinical-recommendations>

**The HIV Training and Resource Initiative:** *Coming of Age — A Guide to Ageing Well With HIV*  
<http://www.natap.org/2011/PDF/ComingAgeBook.pdf>

**National AIDS Treatment Advocacy Project (NATAP)**  
<http://www.natap.org>

**AIDSMap:** *Ageing and HIV*  
<http://aidsmap.com/Ageing-and-HIV/cat/1985>

**HIVInSite: HIV and Aging Related Resources**  
<http://hivinsite.ucsf.edu/InSite?page=kbr-03-01-16>

**Department of Health and Human Services:** *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*  
<http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

**The START Study**  
<http://thestartstudy.org>

**The Veterans Aging Cohort Study**  
<http://www.vacohort.org>

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