Premature Aging and Premature Age-Related Comorbidities in HIV-Infected Patients: Facts and Hypotheses

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(See the article by Guaraldi et al, on pages 1120–6.)

PATIENTS WITH WELL-CONTROLLED HIV INFECTION AGE RAPIDLY AND DIE EARLY

Although even recently human immunodeficiency virus (HIV)-infected patients have mainly encountered AIDS-defining morbid events and early AIDS-related mortality, at present, in Western countries, most of these patients are efficiently treated and their infection can be considered to be in remission. However, many patients encounter the early occurrence of several common age-related comorbidities [1–3], leading to early mortality [4]. In the Swiss HIV Cohort Study [3], the incidence of diabetes, coronary angioplasty, myocardial infarction, osteoporosis, and non–AIDS-related cancers was increased among patients aged >50 years, compared with those aged <50 years, and was not further increased among patients >65 years, suggesting that HIV-infected patients >50 years of age can be considered to be old.

In the present issue of Clinical Infectious Diseases, Guaraldi et al [5] analyze the important cohort of patients followed up at the Metabolic Clinic of Modena (Italy) who underwent a complete set of clinical, biological, and imaging investigations, allowing investigation of comorbidities. The authors analyzed diseases with clear clinical or biological diagnoses, both in HIV-infected patients and in the general population; these diseases included cardiovascular events, fractures, diabetes, renal failure, and hypertension. First, they found the early occurrence of these age-related comorbidities in HIV-infected patients. Second, they were able to compare these patients with persons from the general population who were part of a large Italian observational database, CINECA ARNO, that records health information. At a given age, HIV-infected patients had a greater likelihood of comorbidities than did control subjects paired for age, sex, and ethnicity.

A possible bias acknowledged by the authors is the more careful examination of HIV-infected patients because of their routine care, compared with control subjects who generally do not undergo any investigation if they do not feel sick. There is also a possible selection bias among the patients specifically referred to the metabolic clinic of Modena, compared with the unselected HIV-infected population, even if the authors report a similar occurrence of comorbidities in these 2 groups. Nevertheless, these data are of clinical relevance.

Other age-related comorbidities were also found to be more prevalent in adult HIV-infected patients than in the general population: neurocognitive disorders, non–AIDS-defining cancers, sarcopenia, and frailty [1, 2]. It is now frequently considered that HIV-infected patients are aging prematurely, considered to be old when >50 years of age, compared with 65 years of age in the general population.

HIV-INFECTED PATIENTS ACCUMULATE AGE-RELATED DISEASES

A second important point revealed by Guaraldi et al [5] is the simultaneous presence of ≥2 comorbidities (among cardiovascular diseases, hypertension, diabetes, bone fractures, and renal failure) in a given patient, called poly-pathology. Poly-pathology occurrence was similar in HIV-infected patients aged 40 years and in control subjects aged 55 years, revealing the 15-year-earlier aging. Why? Is the entire aging process accelerated in these patients? Are all HIV-infected patients aging too rapidly? What can be done?

WHAT IS AGING?

Aging is defined by the decreased ability to face stresses, leading to an increased
susceptibility to diseases. Normal aging is associated with chronic sterile low-grade inflammation, as shown by the concept of inflammaging [6]. Moreover, chronic inflammation plays an important role in the initiation and/or progression of cardiovascular diseases, osteoporosis and sarcopenia, metabolic and neurodegenerative disorders, and even cancers, by depleting cell proliferation and resulting in loss of tissue function. Of importance, this chronic inflammation is probably related to long-term immune activation in response to the antigenic burden that we encounter throughout life, with increased production of proinflammatory cytokines, at first by activated macrophages and other immune-cell types, leading to immunosenescence [6]. Inflammation is also closely linked to cell senescence. At the molecular and cellular levels, senescence is induced by accumulation of damages, including genetic and epigenetic alterations but mainly mitochondrial dysfunction resulting in increased oxidative stress. Cells stop dividing, change their phenotype, and secrete a number of factors, including proinflammatory cytokines that participate to systemic low-grade inflammation [6].

Moreover, the farnesylated precursor of lamin A, prelamin A, is involved in the induction of cell senescence and premature aging, as outlined in patients with Hutchinson-Gilford progeria [7]. Of importance, farnesylated prelamin A and senescence are present in the vascular wall of older but not young persons, because of inhibition of the metalloprotease ZMPSTE-24 that maturates farnesylated prelamin A into nonfarnesylated mature lamin A [8].

Finally, increased upper body fat, in particular visceral fat, results in the release of a whole set of factors, including proinflammatory cytokines, associated with metabolic and cardiovascular complications and participating in systemic inflammation [9]. More recently, an important role was proposed for the intestinal microbiota in the control of systemic inflammation and metabolism. Altered bacterial species repartition or dysbiosis, as observed during obesity and aging [10], could activate the innate immune system and result in the release of proinflammatory bacterial products, such as lipopolysaccharide.

Therefore, chronic low-grade inflammation constitutes a common soil for age-related comorbidities and could result in the simultaneous occurrence of different comorbidities (ie, polypathology).

WHAT IS WRONG IN HIV-INFECTED PATIENTS?

Immune activation is increased in HIV-infected patients because of residual HIV infection; other viruses, such as cytomegalovirus reactivation; increased bacterial translocation; and altered gut permeability [11]. Markers of bacterial translocation, such as lipopolysaccharide, and of innate immunity activation, such as sCD14, together with indications of elevated immune activation, have been linked to neurocognitive and cardiovascular comorbidities and to mortality [12–14]. Of importance, levels of sCD14 were related to those of interleukin 6 and C-reactive protein. Increased levels of all these markers were observed in patients with well-controlled HIV infection and associated with increased mortality [14–17].

Therefore, if we consider that increased immune activation and long-term chronic inflammation are major players in the aging process in the general population, it is obvious that these processes are more prevalent in HIV-infected patients, even when the infection is well controlled, than in the general population; HIV-infected patients will be more prone to develop, in advance, age-related diseases.

Otherwise, a high level of immune activation has been related to a poor CD4 cell recovery during treatment. Of importance, the occurrence of several non-AIDS-related comorbidities has been clearly linked to the presence of immune depletion, as indicated by a low CD4 cell count [18].

The severity of initial HIV infection, as evaluated by the nadir CD4 cell count, has also been related to the occurrence of different comorbidities. This could be explained, at least in part, by persistent low-grade viral replication in the reservoirs. Macrophages participate in HIV reservoir and are resident in a number of tissues affected by comorbidities, such as adipose tissue, liver, bone, vascular wall, and brain. If infected macrophages are activated and release proinflammatory cytokines inside these tissues, they could participate to local inflammation and related comorbidities.

Some antiretroviral therapy (ART) can also be involved in increased inflammation [19]. Protease inhibitors (PIs) can directly affect the vascular wall but also induce oxidative stress and inflammation through their ability to inhibit ZMPSTE24, leading to prelamin A accumulation and cell senescence [20]. PI treatment has been associated with increased incidence of myocardial infarction and osteoporosis. Finally, ART was clearly involved in the lipodystrophic phenotype: thymidine–nucleoside reverse-transcriptase inhibitors in lipoatrophy and PIs in trunk fat hypertrophy [9]. Obviously, lipodystrophy, in particular increased trunk fat, is associated with systemic inflammation [21] and is a risk factor for cardiovascular diseases [22] and even mortality [23].

HOW CAN WE EXPLAIN THE CONCEPT OF POLYPATHOLOGY IN HIV-INFECTED PATIENTS?

Gualardi et al [5] found that independent predictors of polypathology were age and male sex, as expected, but also a nadir CD4 cell count <200 cells/mm³. Low nadir CD4 cell count could result in the constitution of increased macrophage
reservoirs in several tissues, thereby participating in local inflammation and tissue-related complications.

Finally, the authors found ART to be an independent risk factor for poly-pathology. Thymidine–nucleoside reverse-transcriptase inhibitors are associated with mitochondrial dysfunction and cell senescence, and some ritonavir-boosted PIs induce prelamin A accumulation, oxidative stress, inflammation, and cell senescence in vitro [9, 19, 20]—all alterations associated with aging.

Do all HIV-infected patients age too rapidly or only some of them? In the Modena cohort [5], patients had a median exposure to ART of 10 years, and 74% presented with lipodystrophy. These long-term infected patients were probably older, with a more severe initial infection, and were exposed long-term to the virus at a time when the quality of the viral control was often poor; they may have also been exposed to toxic ART and remain lipodystrophic. These older patients have accumulated deleterious conditions and are now affected by comorbidities.

IMPORTANT ROLE OF ENVIRONMENTAL FACTORS

In addition to all the factors related to the virus and the treatment, a number of environmental factors could also prematurely induce aging, such as smoking, sedentary lifestyle, low-nutrition diet and resulting fat gain, or drug use. Even if difficult to do, these factors need to be aggressively taken in charge.

WHAT CAN WE PROPOSE?

It is important to diagnose and treat the comorbid conditions. To date, use of immunomodulatory or anti-inflammatory agents, such as statins, aspirin, or hydroxychloroquine, to decrease this inflammatory and/or immune activation burden is not validated but should be considered. In addition, the early treatment of HIV-infected patients may help to delay aging.

Some HIV-infected patients may encounter a process of general premature aging, leading to the early occurrence of a number of age-related comorbidities. These patients are the oldest, with long-term infection. In routine care, they require an even closer follow-up than do other patients to ensure early diagnosis and treatment of complications.

Notes

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