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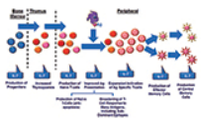

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EDITORIAL

Geriatric-HIV medicine: A science in its infancy

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In the last decades a dramatic increase in human lifespan has taken place. This is due to relevant ameliorations not only of living and behavioral conditions, including the prevention of diseases and vaccinations, but also of different therapeutic approaches to several disease, including infections. As a result, HIV-infected elderly persons are no longer exceptional, but rather a growing population experiencing a progressive risk for illnesses and syndromes traditionally associated with aging. The implications for HIV+ patients and their medical providers are becoming clear: HIV care will intersect routinely with geriatric medicine.[1] This overlap of traditionally distinct clinical disciplines already occurred within other medical specialties, including "ortho-geriatrics,"[2] "cardio-geriatrics,"[3] or "onco-geriatrics."[4]

In this issue, *Virulence* invited a series of key experts in the field of aging in HIV to contribute 8 papers to the birth of geriatric HIV medicine.

This science is definitely in its infancy. Still, it reflects the acknowledgment that the emergence and prominence of traditionally age-related illnesses among antiretroviral therapy (ART)-treated HIV-infected persons at younger-than-expected ages involves diverse pathophysiological processes characteristic of both HIV infection and aging.

The debate regarding accentuated or accelerated aging processes affecting HIV has not yet been resolved.[5] From a clinical perspective, however, the increased prevalence of frailty and geriatric syndromes[6,7] supports the likelihood of HIV specificity in geriatric syndromes. Many HIV-specific potential contributing factors have been proposed, including chronic inflammation, long-term antiretroviral drug toxicity, neurocognitive impairment and higher rates of social and behavioral risk factors. Last but not least is the change of body composition observed in HIV patients, in whom peripheral lipoatrophy characterizing thymidine-analog treated patients, apparently evolves into a sarcopenic/obesity phenotype portraying advanced age.[8] All this suggests that, to establish what is "HIV-driven" in the patho-physiology of aging, the selection of HIV negative control groups is of paramount importance to discriminate, in each different geographical setting and for each clinical condition, what clinical condition is more prevalent (accentuated risk) or rather occurs at an earlier age (accelerated risk) due to HIV. Moreover, in the contemporary antiretroviral era, where HIV viral load un-detectability is a paradigm to all, the point is not so much to demonstrate that frailty can be reverted by early start and successful ART. What matters most, once a patient has reached virological success, is how to reduce the still perpetuating inflammatory burden to decrease frailty progression.[9]

The immune system is clearly of paramount importance in the aging process, and its changes can ultimately drive this phenomenon. Indeed, immunosenescence can be defined as the sum of decreased/altered immune functions in elderly individuals, resulting in age-associated immune changes that lead to gradual immune dysfunction. The impaired immune functionality increases susceptibility to several diseases including infections, cardiovascular diseases and cancer. Although the main driving force of immunosenescence is still unclear, evidence suggests that one or several chronic infections such as that by the cytomegalovirus (CMV) can cause the exhaustion of the system.[10] CMV and other chronic infections, along with the response required for their control,[11] can be at least in part responsible for the so-called inflammaging. This is a situation in which the neutralization of agents that are dangerous or harmful becomes detrimental during aging.[12] Such a situation causes a chronic, low grade pro-inflammatory status that is associated with or causes the onset of age-associated diseases.

Most immunological studies agree that an HIV aging specific phenotype does exist, and accelerated aging is well evident in patients with HIV infection.[13,14] In the papers published in *Virulence*, the groups of Appay[15] and Tambussi[16] discuss the parallels between the progression of

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HIV infection and the aging process. Decades before uninfected subjects, HIV+ patients can experience changes in innate and adaptive immune responses. In peripheral blood mononuclear cells from HIV+ patients, telomere length shortens at a very accelerated rate in comparison with healthy donors. Lymphocyte populations change, and cells with a senescent phenotype, particularly cytotoxic T cells that do not express CD28 but are CD57+, can accumulate regardless of the presence of markers related to cell exhaustion, e.g. PD-1. Furthermore, cells tend to enter a state in which they undergo irreversible cell cycle arrest in response to intracellular stress or external stimuli of various kinds, and acquire the so-called senescence-associated secretory phenotype (SASP). SASP is characterized by the increased secretion of various secretory proteins into the surrounding extracellular fluid, among which pro-inflammatory cytokines, chemokines, growth factors, and matrix metalloproteinases. Other aspects of immunological senescence are crucial, and regard quantitative and qualitative changes in naïve T lymphocytes, memory B cells, expanded NK cells of inflammatory monocytes and plasmocytoid dendritic cells.

Thus, alterations that define the immunological age participate in the decline of immune competence with HIV disease progression. It is therefore important to characterize these changes, which point toward the accumulation of highly differentiated immunocompetent cells, associated with overall telomere length shortening, as well as understanding their etiology, most of all with a view to the impact of chronic immune activation. Particular attention should be paid to the exhaustion of primary immune resources, including haematopoietic progenitors and naïve cells, which holds the key for effective hematopoiesis and immune response induction, respectively. The alteration of these compartments during HIV infection certainly lays the foundations of the immune parallel with aging.

Effectively treated HIV infection is associated with excess risk for multiple non-communicable diseases (NCDs). These conditions including diabetes, cardiovascular disease, osteoporosis, kidney disease, and chronic obstructive pulmonary disease, may recognize the unhealthy life-style prevalent in PLWH or HIV per se as a risk factor which justifies a disease burden higher than expected in the general population. NCDs span different physiologic systems and frequently aggregate in complex multi-morbidity (MM) pictures.[17] These conditions are all strongly age-related. Therefore, guidelines[18] have developed labor-intensive screening algorithms for the assessment of clinical and subclinical organ diseases appropriate to different age strata.

Virulence selected 3 comorbidities to explore clinical data that support the role of aging as a contributing factor to metabolic dysregulation, cardiovascular disease and neurocognitive impairment (NCI).

Aging exhibits an impaired lipid metabolism owing to hepatic hypo-perfusion, hepatic volume shrinkage and a decline in overall liver function.[19]

We therefore argue that, in HIV-infected persons, the assessment of NAFLD provides a window through which overall metabolic health can be accurately evaluated. Furthermore, we assert that liver fat content is the modern "barometer of metabolic health."[20] Martinez suggests that well-designed studies on dietary interventions and pharmacological interventions mimicking calorie restriction characterizing the epidemiology, pathogenesis, clinical outcomes and potential therapeutic interventions for liver disease and associated metabolic dysregulation in older HIV-infected patients, are urgently needed.[21]

Cardiovascular disease has become a leading cause of morbidity and mortality in HIV infected patients. Therefore, refining risk assessment in a timely fashion is of paramount importance in this population. Raggi discusses the contribution of vascular imaging in assessing coronary age and uncovers valuable prognostic information through these tools in this patient category. Vascular age assessment goes beyond any statistical probability of risk and allows to identify patient vulnerability in patients with preclinical cardiovascular disease.[22] Finally, it may be inappropriate to utilize in HIV patients cardiovascular risk prediction algorithms (namely Framingham Risk score and ASCVD) calibrated to predict an "atherosclerotic event" in the general population, to estimate the risk of events which, in more than 50% of the cases, are non-atherosclerotic in HIV+ patients, including sepsis, vasospasm due to cocaine use, anemia, acute volume fluctuations etc.[23] Future studies may need to address the calibration of various algorithms to separate the risk of type-1 from type-2 MI.[24]

Cognitive impairment and dementia can be included in geriatric syndromes.[25] HIV-infected patients are considered at increased risk for developing these neurologic disorders, probably due to a complex chronic inflammatory response to the virus in the CNS.[26] Whether premature brain aging is a real feature of HIV has been addressed by Krut, using CSF p-tau as a potential marker for brain aging in HIV. In this large study published in *Virulence*, authors found no support for premature CNS aging in HIV-infected patients as measured by CSF p-tau concentrations.[27]

The pathophysiology of age-associated comorbidities is very complex and includes diagnoses of hypogonadism. In this issue of *Virulence*, Rochira discusses trajectories of sex steroid changes overtime in men and their clinical significance. He suggests that coupling hypogonadal symptoms with documented low serum T

represents the best strategy to refine the diagnosis of hypogonadism in older men, and to avoid unnecessary treatments.[28]

The transition from co-morbidities to geriatric syndrome assessment in HIV implies both a structural and a cultural change in patient assessment. Greene and co-authors discuss the assessment of geriatric syndromes and physical function as useful tools for HIV clinicians and researchers to help identify the most vulnerable older adults, and to better understand the aging process in people living with HIV.[29] The geriatric approach goes beyond a multidisciplinary assessment and involves a multidimensional process, designed to evaluate an older person's functional ability, physical health, cognition and mental health, and socio-environmental circumstances. It differs from a standard medical evaluation by including nonmedical domains and by emphasizing functional capacity and quality of life. This so called Comprehensive Geriatric assessments, as explained by Cesari, includes treatment issues (first of all polypharmacy) that in "biologically aged" HIV-positive persons might benefit from models of adapted and integrated care developed by geriatricians over the years for the management of their frail and complex patients.[30]

The next step is to identify clinical and research end points to be used in HIV-geriatric medicine. The successful accomplishment of such cross-disciplinary collaboration will not only markedly enhance the care of aging HIV-infected persons. In fact, it can also constitute a model of successful healthcare management to be applied to all aging persons with care needs that increasingly involve geriatric considerations.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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