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Aging in people living with HIV

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The greying HIV epidemic affecting people living with HIV (PLWH) produced a subset of older adults demanding a prompt response in clinical practice. The changes that constitute and influence ageing include: at a biological level, a gradual accumulation of a wide variety of molecular and cellular damage; [1,2] at an epidemiological level, an increase in health life expectancy and at a clinical level, a gradual decrease in physiological reserves. This may generate an increased risk of non-communicable diseases (NCDs), and a general decline in the functional capacity of the individual. These changes are neither linear nor consistent, and they are only loosely associated with chronological age. [1]

To put together all these tiles in a construct able to conceptualize the age-related increase in vulnerability, the term "frailty" has been commonly used over the past two decades to define this mosaic as a condition caused by the reduction of homeostatic reserves exposing the individual to higher risk of negative outcomes. [3]

Frailty reflects the biological age of the individual, which could replace the obsolete criterion of chronological age to better stratify patients' overall functional status and intensity of care use. [4]

Epidemiological approach to aging in HIV

The unmet medical needs of this emerging population could be addressed with existing large observational HIV cohort studies, however unfortunately, older adults are rarely represented in these cohorts. Therefore, the scientific community had to properly design studies that include older adults living with HIV (OPLWH), aged more than 50 years, or geriatric PLWH, aged 65 years or more, in order to explore the interaction between aging and HIV itself, antiretroviral therapy (ART) and NCDs. Smit et al generated an individual-based model of PLWH receiving ART in different HIV cohorts. The model predicted that the proportion of older people living with HIV will increase from 28 % in 2010 to 73 % in 2030 in the ATHENA cohort. [5] In the Italian ICONA cohort the projection is 76 % in 2035 for OALWH, and in a US cohort 74 % for the same projection. [6] The most important implication of these models is to forecast HIV related chronic NCDs which will continue to be higher than predicted in the general population.

Older people living with HIV (OPLWH) represent a heterogeneous population almost equally distributed between people aging with HIV and people who acquired HIV at an older age. [7,8] The former are individuals reaching geriatric age after having been exposed for a long time to uncontrolled HIV infection and to more toxic ART. The latter acquired HIV at an older age when NCDs were already present before HIV acquisition. Due to early initiation of modern ART, people who acquired HIV at an older age appear to be more similar to age matched general population.

Pathogenesis

Few studies support the hypothesis of an HIV induced accentuated aging process. Getting inside the immune-pathogenesis of aging, HIV has been investigated in the context of chronic inflammation and immune activation. This so called "inflammaging" milieu has been evaluated with soluble CD163 (sCD163), soluble CD14 (sCD14) and cytokine storm altered in PLWH. [9,10] In the AGEhIV study that included 94 OALWH with undetectable viral load and 95 controls, increased sCD14 and CD4+ T-cell activation (%CD4+ cells expressing CD38 and HLA-

DR) were associated with shorter telomeres and increased regulatory T-cells, suggesting that HIV affects immune function despite of effective ART. [11] Immune activation can be caused by several features such as persistent low level HIV viral replication (even in the presence of effective ART), coinfection with other viruses such as HBV, HCV or CMV, oxidized lipids, or microbial translocation.

Clinical features of OALWH

The paradigm of aging is diversity: thus, while many OPLWH may enjoy good physical and mental functioning, others may be frail and require significant support to meet their basic needs. In part, this is because many of the mechanisms of ageing are random, but also it is due to the fact that these changes are strongly influenced by the environment and behaviors of the individual. For example, heavy smokers, people with sedentary life and low socio-economic status may be at higher risk for frailty.

Geriatric medicine introduced frailty to stratify patients' diversity in risk state and to provide a reliable prognostic guide across the life course. [12-15] Nevertheless, this condition can also be defined as a specific geriatric syndrome. [16] The most commonly used measure applying this syndromic approach is the frailty phenotype. The tool leads to frailty diagnosis when at least 3 of the 5 items are present, including unintentional weight loss (self-reported), exhaustion (self-reported), low energy expenditure, walking speed, weak grip strength. The score ranges from 0 to 5, in which 0 corresponds to "robust", 1-2 to "prefrail" and ≥3 to "frail". [17] Frailty can also be operationally associated with the accumulation of multiple multi-system health deficits, including co-morbidities and disabilities. The most commonly used measure applying this cumulative deficit approach is the frailty index. A frailty index is calculated as the proportion of health deficits an individual has out of at least 30 assessed health variables, which can include signs or symptoms (such as unintentional weight loss), diagnoses (e.g. diabetes, cardiovascular disease, chronic kidney disease), impairments (e.g. low hand grip), or laboratory abnormalities (e.g. blood glucose, WBC, hemoglobine) Each variable included in the FI is coded with a value of 1 when a deficit was present, and o when it was absent. Missing values were removed from both the numerator and the denominator of the FI. [20] The FI for each patient visit was calculated as the ratio between the number of deficits present and the total number of deficits assessed. Missing values are removed from both the numerator and denominator of the FI (FI = (∑Deficit)/((36-∑Missingvalues))). Each FI was computed when a minimum of 80 % of valid data for the health variables was available. PLWH are categorized according to FI score as fit (<0.25), frail (0.25-0.4), most frail (>0.4). [18] Other geriatric syndromes are delirium, falls, incontinence and frailty, all of them highly prevalent in HIV and affecting up to 30-50% of patients over the age of 50 in some cohorts. These conditions are multifactorial and associated with substantial morbidity and poor outcomes. [19]

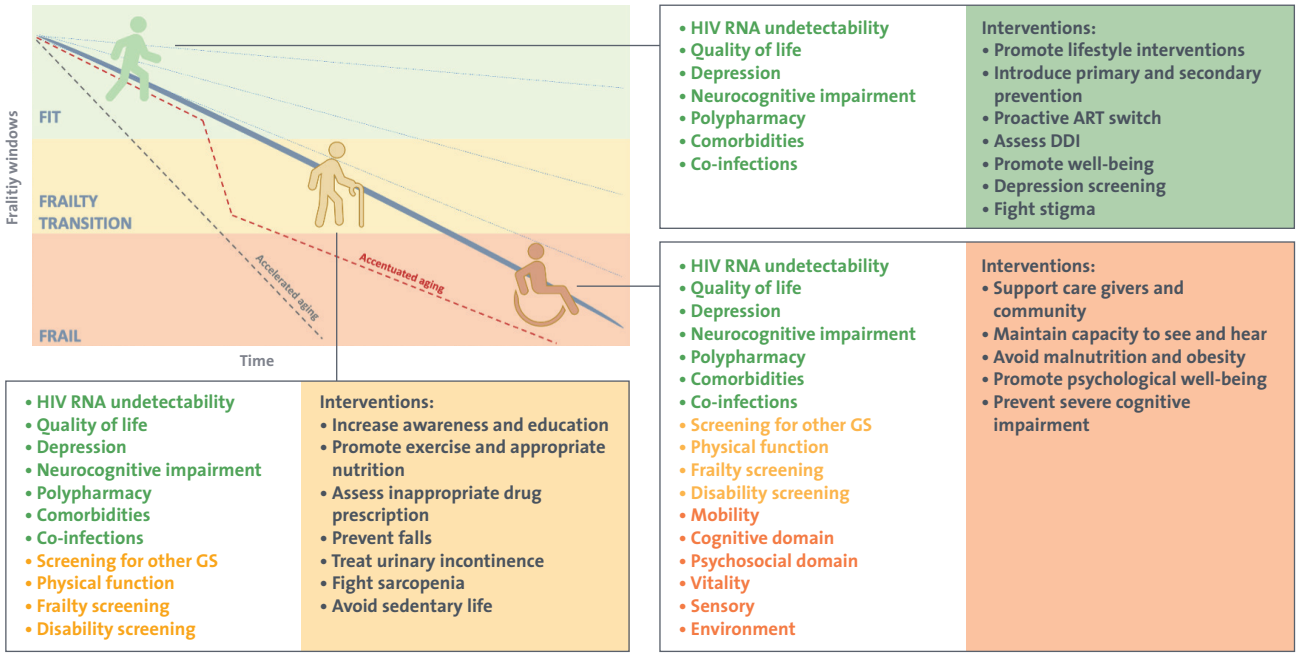
In the geriatric perspective, the management of these conditions extends beyond the traditional medical management of illness and requires a Comprehensive Geriatric Assessment (CGA), defined as a multidisciplinary diagnostic and treatment process that identifies medical, psychosocial, and functional limitations of a frail older person in order to develop a coordinated plan to maximize overall health with aging. [20,21] Figure 2 schematizes the multidimensional components of CGA.

The CGA approach has rarely been used in a structured fashion in OALWH. It can be noticed that the CGA is not dissimilar to the holistic care management approach suggested in HIV care by international guidelines including assessment of co-morbidities, cognition, nutrition, polypharmacy and last but not least the functional status assessment of the OALWH.

Antiretroviral treatment strategies in OALWH

In recent years, some guidelines, such as EACS, [22] have introduced principles for ART management in OALWH. Although all

Figure 2 schematizes the multidimensional components of CGA (Comprehensive Geriatric Assessment).



agree on the need for an intensive screening of comorbidities, only few attempted to recommend preferred options for ART regimens, as many areas of uncertainty still exist in the use of ART in OALWH. Figure 1 lists EACS guideline recommendations for comorbidity screening in PLWH. [23]

Not much high-quality evidence exists to guide ART prescription for OALWH, particularly those with multi-morbidity defined as the contemporary presence of at least 2 NCDs in the same individual. [24] In fact, the proportion of frail OALWH are under-represented in registrational trial, as often requested by inclusion and exclusion criteria. [25-27] In clinical practice, HIV providers need to consider the burden of multi-morbidity, polypharmacy and age when prescribing the antiretrovirals in OALWH. In this context, an increasing number of less drug regimens, dual therapy, has been used. These regimens are used to spare TDF/TAF, ABC, or boosted protease inhibitors combinations, potentially associated with kidney, bone and heart disease. As such, HIV providers appear to choose ART regimens according to the toxicities they want to avoid rather than according to a specific ART geriatric strategy.

Apparently, these dual regimens go in the same direction of the "deprescribing" approach specifically suggested by geriatricians in the management of polypharmacy in geriatric patients. However, these strategies need to be further tested in the HIV geriatric setting.

General care management of OALWH

The frail and geriatric patients living with HIV becomes the candidate for an adapted care approach aimed at designing personalized interventions respectful of his/her reserves and priorities. Not surprisingly, over the past few years, the birth of a geriatric HIV-medicine has been evoked. [28]

More broadly DHHS guidelines underlines that HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older patients with HIV with complex comorbidities. It is emphasized that polypharmacy is common in OALWH; therefore, there is a greater risk of drug-drug interactions between antiretroviral drugs and within concomitant medications used for NCDs treatment. Potential for drug-drug interactions should be assessed regularly. EACS guidelines also point out that in older adults living with HIV potential inappropriate medication (PIM) should be searched (Figure 3). PIM derives [29] from age related changes that may impact pharmacokinetics and pharmacodynamics and may lead to inappropriate drug and dosage use. The geriatric STOPP/START and Beers criteria can be used to evaluate PIM trough lists of drugs, drug classes and drug-disease interactions that should be avoided in adults over 65 years. [30,31]

A well know example of deprescription is to avoid alfa-blockers in hypertension treatment to the reduce the risk of falls secondary to postural hypotension.

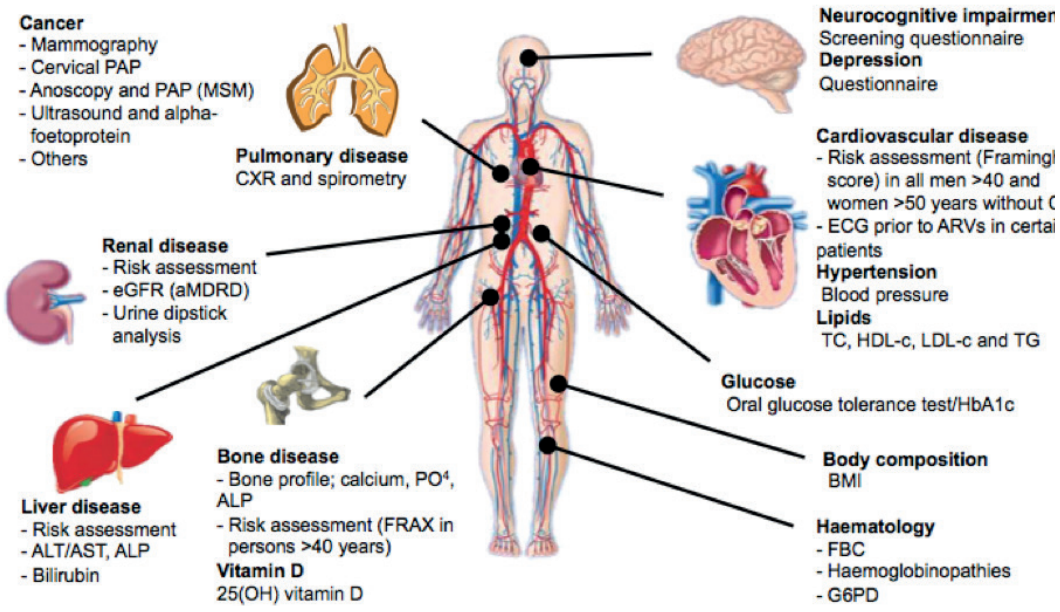
This framework requires an individualized approach, which necessarily integrates HIV care in the setting of primary care, but it also involves a strong participation of the patient itself and its community. All this could be made possible through regular education of health care workers and providers and at the same time increasing patients' awareness. Education activities are specifically related in acquiring healthy lifestyles with the support of occupational therapist, dieticians, and psychologist in the HIV clinic.

This multidisciplinary patient centered approach recognize health related quality (HRQoL) of life as the ultimate goal of treatment. HRQoL often is assessed by using patient-reported outcome measures (PROMs), which provide a means to look beyond biomedical outcomes at people's subjective perceptions of their health-related experiences. [32]

Ageism in OPLWH

Stigmas accompany the whole life of people living with HIV, in later life this is Ageism. This encompasses a multidimensional concept that encompasses multiple components related to the individual, the social group and the institution in different

Figure 1: EACS guideline recommendations for comorbidity screening in PLWH



cultural and environmental settings. [33] World Health organization defines "ageism" as the stereotypes (how we think), the prejudice (how we feel) and the discrimination (how we act) directed towards people on the basis of their age". [34] The intersecionality of ageism implies a multiplication effect of the many stigmas that people living with HIV often experience, making ageism take on several HIV specificities including self-inflicted ageism and loneliness, particularly affecting vulnerable communities.

Ageism can be considered the last pillar of this "stigma cascade" and the most important barrier to reach healthy aging in people living with HIV. This is the goal of a novel model of care, based on person-centred intervention. It must be recognised that the issue is not simply to introduce geriatric tools in the care of older people living with HIV but also to have a "geriatric mindset" attentive to recognize and fight ageism. All stakeholders and the community must find alliance to draw institutional strategies, educational programs and intergenerational dialogue without ageist prejudices to create an HIV stigma free future.

Conclusion

The aging epidemic affecting PLWH is still not followed by adequate changes in clinical management including ART prescription and age-related conditions. However, the development of observational cohorts including older adults living with HIV (OALWH) can pave the way to a better understanding of the unmet needs of this population and ultimately to the introduction of new care models. The road map is clearly shown by geriatric medicine which support a multidimensional approach of the individual and a coordinated care in clinical assessment, including functional assessments, geriatric syndromes, frailty, and evaluation of neurocognitive and social domains.

Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

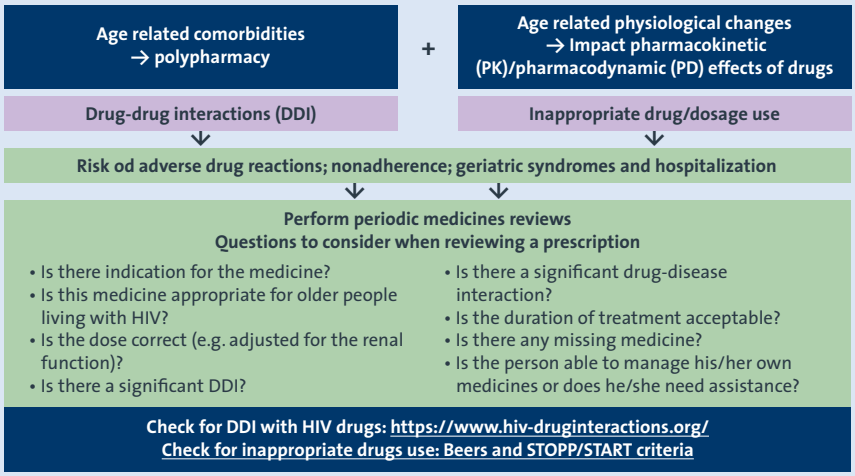


Figure 3: Assessment of polypharmacy, drug-drug interactions and inappropriate drug use in older adults living with HIV (adapted from 11th EACS Guidelines, 2022).

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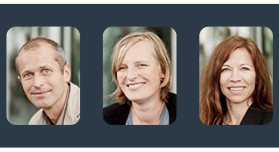

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