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COMPLICATIONS OF HIV AND ANTIRETROVIRAL THERAPY (GA MCCOMSEY, SECTION EDITOR)

Aging with HIV

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Abstract

Purpose of Review This review points out unmet medical needs and open research questions of older adults living with HIV. Starting from the definition of aging in HIV, it explores the mosaic of this condition at epidemiological, pathophysiological, and clinical level. Antiretroviral management and diverse models of care are critically discussed.

Recent Findings Aging cohorts suggest HIV as a paradigm of chronic inflammation and immune activation with specific aging trajectory patterns in which antiretroviral therapy may play a role. In the absence of randomized clinical trials, observational cohorts show that therapy is driven by duration of HIV infection and burden of non-infectious comorbidities.

Summary This review suggests that geriatric approach should be used to recognize the complexity of aging goes beyond the viro-immunological success and management of progressive accumulation of non-communicable diseases. This requires recognition of frailty and geriatric syndromes to stratify patients' diversity by using comprehensive geriatric assessment tools.

Keywords Aging · HIV · Geriatric medicine · Frailty · Antiretroviral therapy

Introduction

The recent and rapid demographic changes affecting people living with HIV (PLWH) produced a subset of older adults demanding a prompt response both in clinical practice and research setting.

Randomized clinical trials but also large observational studies under-represent this special population, and only recently dedicated cohorts have been developed that comprise older adults living with HIV (OALWH) [1•].

This review aims to describe the graying HIV epidemic underlying the unmet medical needs and open research questions for this population.

This article is part of the Topical Collection on *Complications of HIV and Antiretroviral Therapy*

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What Is Aging?

The changes that constitute and influence aging include the following: at a biological level, a gradual accumulation of a wide variety of molecular and cellular damage [2, 3]; 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 [2].

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 [4].

Frailty might represent an interval parameter reflecting 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 [5].

Epidemiology 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, HIV research has to offer specific cohorts that include PLWH over the age of 50 or 65, aiming to explore the interplay between aging, HIV itself, antiretroviral therapy (ART) and NCDs.

HIV cohorts (50+) comprise the individuals at higher risk of age-related NCDs in comparison with the general population [6]. These cohorts allow a longer follow-up period and may decrease the risk of survival bias that is affecting older age categories [7]. However, the prevalence of frailty and geriatric syndromes in such designed cohorts might be low due to inclusion of younger PLWH.

Geriatric HIV cohorts (65+) include two different phenotypes of PLWH: people aging with HIV and people who acquired HIV at an older age [8, 9]. The first phenotype is characterized by people with longer duration of HIV infection and longer exposure to toxic ART. The second phenotype is represented by older people with a lower awareness of sexual risk [10, 11], who might have had NCDs at time of HIV acquisition. In this scenario, HIV and ART are an additional risk contributing to already present clinical picture of multi-morbidity. These individuals may not experience low nadir CD4 or high levels to "cumulative viral load" (defined as the number of years that patient lives with detectable HIV RNA) [12, 13], due to early initiation of modern ART.

The number of older adults living with HIV (OALWH—aged > 50 years) is predicted to increase by 47% to 6.9 million by 2020 [14]. Despite a growing body of research on HIV and aging in high-income countries, little is known about the intersection of HIV and aging in low- and middle-income countries, especially in sub-Saharan Africa, which accounted for 62% of newly diagnosed infections among OALWH in 2016 [15]. Among PLWH in sub-Saharan Africa, 15% are aged at least 50 years, and modeling predicts that by 2040 this proportion will increase to 27% and the number of OALWH will increase to 9.1 million [16].

Smit et al. generated an individual-based model of PLWH receiving ART in different HIV cohorts. The model predicted that the proportion of OALWH will increase from 28% in 2010 to 73% in 2030 in the ATHENA cohort [17]. In the Italian ICONA cohort, the projection is 76% in 2035 for OALWH, and in a US cohort, 74% for the same projection [18•]. 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.

Figure 1 compares predicted burden of NCDs in HIV-infected patients as simulated by the model in Netherlands between 2010 and 2030 (a), in Italy between 2015 and 2035 (b), and in the USA between 2015 and 2035 (c). Note: the three graphs are not on the same axis nor figure out the same time projection interval [17, 18•].

The Smit's model predicts that in 2030, 28% of PLWH will have three or more NCDs in the Netherlands [17] and by 2035, 29% will have three or more NICM in Italy and 44% in the USA [18•]. This underlines relevant geographical diversity in the NCDs distribution according to different socio-economical environments.

As previously stated, aging does not equate to chronological age and age complexity cannot be depicted by NCD accumulation. In the attempt to use frailty as a public health tool, our group was able to forecast the risk for frailty among 2982 patients over 15 years, using a validated frailty index measurement. Our model suggested that the proportion of the most frail patients will increase from 23.8 to 48.2% over 15 years [19].

Pathogenesis

Clinical and epidemiological data appear to describe an HIV-specific pattern in aging trajectory; however, whether this represents accentuated or accelerated aging phenomena, it is a still matter of debate. From a clinical point of view, the growing prevalence of NCDs and typical geriatric syndromes may suggest that HIV infection leads to an accentuated aging process. Studies with carefully matched controls, which explored age of onset of NCD, failed to demonstrate an accelerated aging process [20].

Few studies support the hypothesis of an HIV-induced accentuated aging process.

The COBRA cohort was set to identify a tool to measure biological age using multiple aging biomarkers in 134 OALWH, 79 HIV-negative age-matched controls, and 35 age-matched random blood donors. Outcome measure was defined as "age advancement" that was calculated as biological age (validated algorithm based on 10 biomarkers) minus chronological age. OALWH had higher age advancement (13.2 (IQR 11.6–14.9) years versus 5.5 (IQR 3.8–7.2) years in HIV-negative controls and − 7.0 (IQR − 4.1 to − 9.9) years in blood donors ($p < 0.001$), respectively. Independent predictors of age advancement were CMV infection, higher burden of HBV co-infection, CD8+ T cell activation, and prior immunodeficiency (defined by nadir CD4 T cell count < 200 cells/μ) [21].

At the molecular level, accentuated aging has been measured with DNA methylation and telomere length in aging PLWH when compared with the general population. In the VACS cohort, PLWH had significantly older DNA methylation age compared with negative age-matched controls [22].

Getting inside the immune-pathogenesis of aging, HIV has been considered and investigated in the context of chronic inflammation and immune activation. This so called

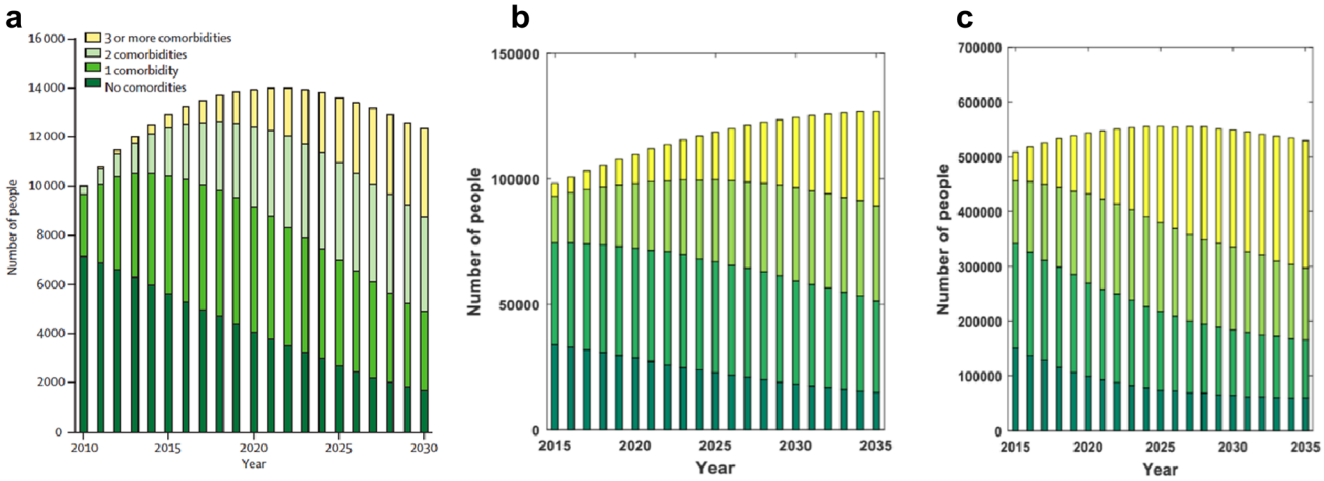

Fig. 1 Predicted burden of NCDs in HIV-infected patients as simulated by the model in Netherlands between 2010 and 2030 (**a**), in Italy between 2015 and 2035 (**b**), and in the USA between 2015 and 2035 (**c**). Note: the three graphs are not on the same axis nor figure out the same time projection interval [17, 18]

"inflammaging" milieu has been evaluated with soluble CD163 (sCD163), soluble CD14 (sCD14), and cytokine storm altered in PLWH [23, 24]. 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 [25].

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 50-year-old PLWHs 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 aging are random, and also it is due to the fact that these changes are strongly influenced by the environment and behaviors of the individual.

Geriatric medicine introduced frailty to stratify patients' diversity in risk state and to provide a reliable prognostic guide across the life course [26–29]. Nevertheless, this condition can also be defined as a specific geriatric syndrome [30].

The most commonly used measure applying this syndromic approach is the frailty phenotype, which assesses five specific features: self-reported weight loss, self-reported exhaustion, low levels of physical activity as measured by a standardized questionnaire, measured 15-ft walk time, and measured grip strength [31].

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, diagnoses, impairments, or laboratory abnormalities [32].

Other geriatric syndromes are delirium, falls, incontinence, and frailty; all of them are 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 [33].

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 [34, 35]. 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 have introduced principles for ART management in OALWH. Although all agree on the need for an intensive screening of comorbidities, only

Fig. 2 The multidimensional components of comprehensive geriatric assessment (CGA)

few attempted to recommend preferred options for ART regimens [36], as many areas of uncertainty still exist in the use of ART in OALWH.

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 [37]. In fact, these patients are generally excluded from clinical trials [38–40]. In clinical practice, HIV providers are trying to take into account the burden of multimorbidity, polypharmacy, and age when prescribing the antiretrovirals in OALWH.

Data from the GEriatricPatients living with HIV/AIDS (GEPPO) cohort, analyzing ARV prescription in 1222 HIV people aged > 65 years demonstrated that triple therapy was present in 66.4%, dual therapy in 25.3%, monotherapy in 6.5% and "mega-ART", with more than three drugs, in 1.64% of patients. Multi-morbidity and polypharmacy (defined as the presence of at least 5 chemical compounds other than ART) were predictive for mono- or dual therapy, and NRTI-sparing and TDF-sparing combinations [41].

In this context, an increasing number of less drug regimens, dual therapy in particular, has been used, albeit supported by limited data from randomized clinical studies. These regimens are used in an attempt to spare TDF, ABC, and NRTI as a class or boosted combinations, potentially associated with kidney, bone, and heart disease. As such, HIV physicians 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.

The next step is to identify clinical and research end points to be used in antiretroviral clinical trials. The European Medicines Agency (EMA) has developed tools to define inclusion criteria for clinical trials in geriatric population. These tools comprise assessment for multi-morbidity, physical frailty, malnutrition, and neurocognitive impairment [42]. The same criteria can be applied in HIV setting in investigating antiretroviral agents' impact beyond viral suppression outcome in OALWH.

General Care Management of OALWH

The frail and geriatric patients living with HIV thus become the candidates 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 [43•].

As occurring in other disciplines that have formally included geriatric medicine in the management of the frailest individuals (e.g., oncogeriatrics for frail older persons with cancer [44] and orthogeriatrics for frail older persons with hip fractures [45]), HIV geriatric medicine should be built on the assumption that the complexity of the frail individual with HIV cannot be adequately addressed in the absence of a multidisciplinary team able to comprehensively evaluate the individual and design a coordinated and integrated plan of care.

Given these evidences, Italian HIV guidelines have suggested the screen for frailty in PLWH aged more than 50 years old [46]. Of course, this age cut-off is totally arbitrary and simply based on epidemiological data which suggest that a significant number of PLWH may be frail in this age category [5]. The results of such activity will then inform about the strengths and weaknesses of the individual, about his/her priorities and values.

Singh and colleagues examined several geriatric consultation models: referral to a geriatric clinic, assessment within a PLWH practice, and/or assessment in home. We do not know yet which is the most effective strategy to incorporate CGA into HIV care [47]. This will support the generation of a plan of action that may lead to the adaptation of the management in order to guarantee the optimal therapeutic solution, promote the highest adherence to the intervention, and facilitate the follow-up of the case.

More broadly, DHHS guidelines underline 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 NCD treatment. Potential for drug-drug interactions should be assessed regularly [48].

EACS guidelines also point out that in OALWH, potential inappropriate medication (PIM) should be searched (Fig. 3). PIM derives [47] 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 [49, 50].

This framework requires a personalized approach, which integrates HIV and primary care with 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.

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 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 supports 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.

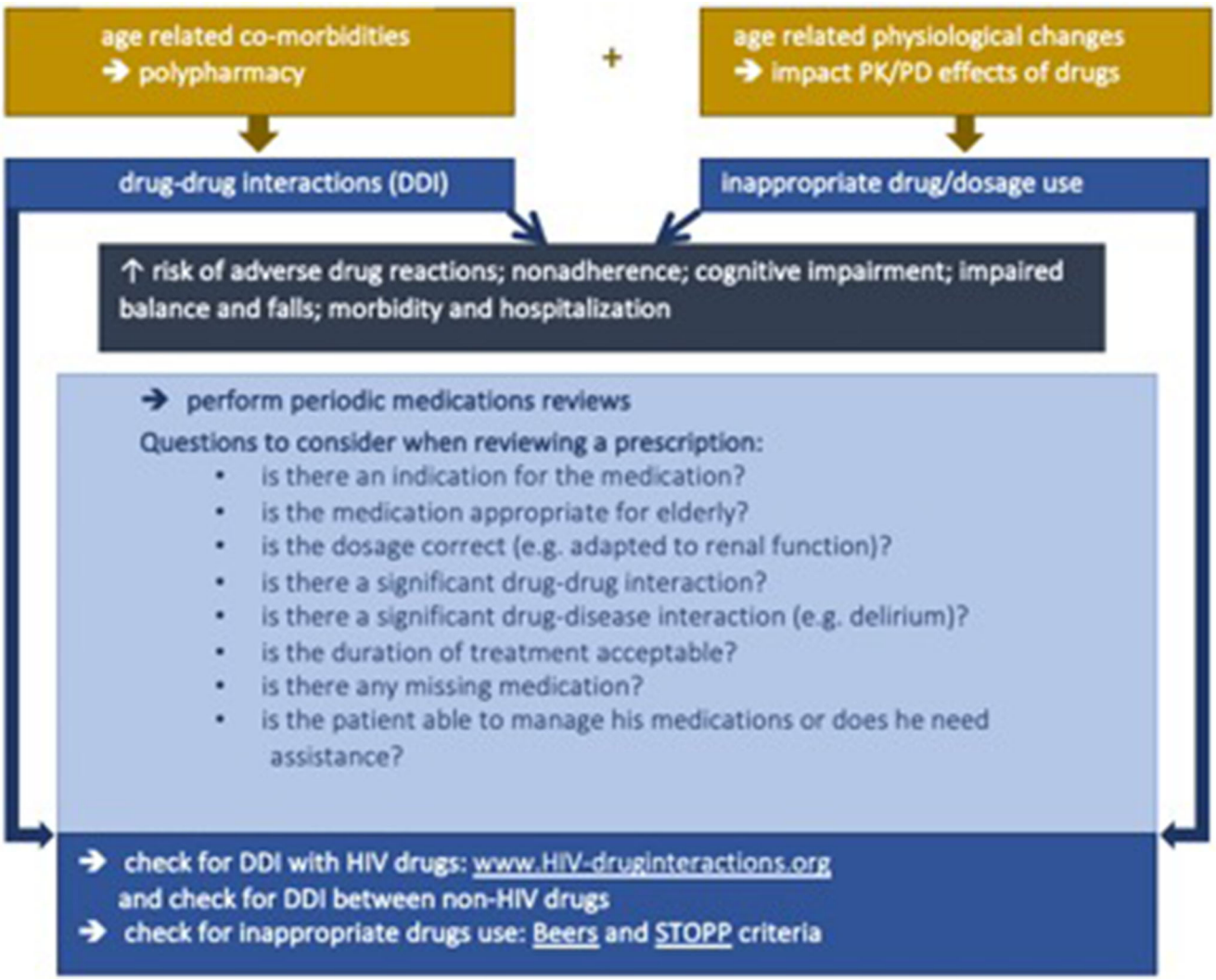

Fig. 3 Management of polypharmacy in OALWH. Freely adapted from EACS guidelines 2017 9.0

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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