Integrative biomarkers of biologic aging in HIV

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Aging is a highly complex process impacted by several genetic and environmental factors. Thus, an individual may experience comorbidities and age-associated dysfunction well before they reach the traditional age cut-offs of 'old.' Epidemiological evidence has suggested that certain diseases and/or its treatment may increase the susceptibility of individuals to age-associated dysfunction later in life, as observed with patients surviving cancer and people living with HIV (PLHIV) [1]. This suggests that fundamental cellular and molecular pathways common to the aging process may be altered as a function of the disease or its treatment and understanding this interaction may help alter the trajectory of aging in these individuals.

There has been significant interest in defining biomarkers of aging, which can offer a means of identifying individuals vulnerable to age-associated functional decline [2,3]. As aging is multicausal, a multidisciplinary approach is needed to comprehensively examine the interaction between diseases and aging, and to identify a set of reliable biomarkers. In studies among PLHIV, exploration of biomarkers has largely focused on candidate pathways including markers of immune activation [4], inflammation [5], cell cycle/proliferation [6] or DNA methylation [7], while studies considering the interaction of multiple pathways are lacking. To this end, the study by De Francesco *et al.* [8] leverages on a panel of 10 biomarkers developed by the MARK AGE collaboration to explore if HIV infection and lifestyle factors contribute to 'age advancement.' The biological age of participants was derived from the combination of these biomarkers using a weighted algorithm previously validated in over 3000 individuals (35–74 years) from eight European countries [3]. Participants from the Comorbidity in related to AIDS (COBRA) cohort were studied and included HIV-infected individuals on suppressive ART, lifestyle-matched HIV-negative controls, and healthy blood donors who were stringently screened for sexual risk behaviours and chronic infections. Individuals with neurological or psychiatric conditions were, however, excluded; a bias, which significantly impacts the generalizability of the study findings, given the importance of psychosocial factors in driving age-associated dysfunction [9]. Nevertheless, this is an important study, which assessed not only the influence of HIV-related parameters, but also the influence of lifestyle factors and chronic co-infections on biological age. Importantly, the study found that HIV-infected individuals had an age advancement of 13 years, which was significantly greater than both control groups. Lifestyle-matched uninfected controls reported age advancements of 5.5 years whereas healthy blood donors reported a younger biological age of 7 years, highlighting the contribution of lifestyle factors on the rate of aging.

When all HIV-related factors including exposure to antiretroviral therapy (ART) were assessed in a multivariate analysis, age advancement was independently associated with chronic HBV co-infection (average

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increase = 7.4 years), total cytomegalovirus (CMV) IgG levels (1.9 years for every 1 log AU increase), nadir $CD4^+$ less than 200 cells/μl (3 years), and cumulative saquinavir exposure (1.2 years for every year of exposure). Prior studies both in the general and HIV-infected population have also suggested that increased biologic aging may be associated with chronic viral infections particularly CMV and the extent of immune deficiency previously experienced by PLHIV [10–12]. In the low and middle-income country (LMIC) setting, HIV treatment is generally started late and endemic infections are highly prevalent. These realities raise the question if age advancements differ in ART-suppressed HIV-infected individuals residing in high vs. low-middle income settings. The role of exposure to specific ART regimens and the increased risk of age-associated dysfunction is controversial with some studies reporting increased risks with protease inhibitors [13], Efavirenz [14] and D-drug exposure [15] whereas others not [16]. However, many of these studies have not been sufficiently powered to address this issue comprehensively, a limitation, which also applies to the study by De Francesco *et al.* [8].

Despite the 'older' biological age of lifestyle-matched controls, it was surprising that none of the lifestyle factors of smoking, alcohol consumption, recreational drug use or sexual risk behaviour were independently associated with age advancement in adjusted analysis, a finding, which the authors ascribed to the low frequency of smokers and potential collinearity in their analysis. It is still unknown whether the multiple processes, which converge to drive aging in PLHIV are mechanistically different from those involved in the normal aging process in uninfected individuals. The adaptation of the MARK AGE algorithm, which was developed for the general population in PLHIV assumes it does, though this needs further validation. Ultimately any set of aging biomarkers established to be used in PLHIV will need to be validated against other established markers of morbidity and mortality in HIV including markers of immune activation, inflammation and hypercoagulation; as well as the presentation of not just chronic comorbidities but also geriatric syndromes, which more accurately capture the phenotype of aging.

The work by De Francesco *et al.* [8] illustrates the need to uncover novel biomarkers that take into account the fundamental cellular and molecular mechanisms of the aging process in HIV. Work from our group and others have suggested the involvement of other systems including the oral and gut microbiome [17,18], metabolic pathways of glucose and lipids [19,20], as well as glycomics [21,22] as potential regulators of aging in HIV that warrant further assessment. Plasma lipid classes including phosphatidylethanolamine, triacylglycerol ganglioside and monohexosylceramide are strongly associated with inflammation and frailty in ART-treated individuals [19], suggesting the role of altered lipid metabolism in the development of aging phenotypes. Additionally, glycomic studies in the general population have revealed that IgG glycosylation is closely linked to both chronological and biological age whereas certain glycomic traits predict chronological and biological age better than other markers such as telomere length [21,22]. We have recently shown that HIV infection is associated with certain glycomic alterations that are persistent despite several years of viral suppression [23]. Understanding the link between the host glycome and aging with HIV may provide new insights into the mechanistic underpinnings of age-associated and inflammation-associated diseases in PLHIV.

More studies assessing novel, integrative biomarkers, which reflect the multisystem nature of aging and its biology are needed to meaningfully predict an individuals' biologic age.

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Conflicts of interest

There are no conflicts of interest.

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