Ageing with HIV: is the virus or the treatment guilty?

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Due to the availability of antiretroviral drugs (ART) able to efficiency control the virus, people living with HIV (PLWH) are aging and endure, at a higher prevalence than the general population, diverse age-related comorbidities as cardio-metabolic, bone, liver and kidney diseases and some cancers[1,2]. This led to propose that PLWH suffered from premature aging[1] meaning that their body's age, or biological age, was higher than chronological age.
Biological age can be estimated by performing analysis of epigenetic changes affecting specific DNA methylation sites. In The Lancet HIV, A. Esteban-Cantos and colleagues[3] used four epigenetic age estimators (Horvath's and Hannum's clocks, GrimAge, PhenoAge), validated in the general population, in 168 PLWH included when ART-naïve in the NEAT001/ANRS143 study, and followed 2 years after initiation of darunavir/ritonavir plus either raltegravir or tenofovir disoproxil fumarate/emtricitabine. PLWH were compared to 44 HIV-negative controls. The authors observed that i) whatever the epigenetic age evaluator, ART-naïve PLWH were biologically older than age-paired controls, ii) epigenetic age was consistently reduced two years after ART initiation, with no difference between the two ART regimens, but iii) remained globally higher than in controls. Therefore, biological age only partially improved with ART. Previous smaller studies already indicated advanced epigenetic age in ART-naïve and also ART-controlled PLWH[4].

Several important points are pinpointed by this study. The severity of the initial infection increases epigenetic age. The persistent role of HIV, even controlled, could result from a higher size of HIV reservoirs, remaining immune dysfunction, gut dysbiosis, chronic low-

grade inflammation[5]. Nadir CD4 and CD4/CD8 levels reflect this severity and are recorded. Some recent studies indicate that PLWH suffer enhanced, rather than premature or accelerated, aging, the enhancement occurring during the initial untreated period. Thus, brain aging, assessed by neuroimaging and function, is higher but worsens at the same rate in ART-controlled infected versus non-infected individuals in the COBRA study, stressing for the important beneficial role of ART[6].

However, the role of ART is ambivalent. Controlling infection and restoring immunity probably explain the ART beneficial effect on epigenetic aging in the Esteban-Cantos study[3], but the follow-up was short and the patients young (median 37 years). Some ART classes/molecules have been associated with a higher occurrence of some age-related comorbidities[5,7]. Whether long-term given ART molecules are beneficial or deleterious regarding biological age and associated comorbidities is an important medical issue.

Epigenetic markers differ between the leukocyte subsets. The leukocyte composition was markedly different in the Esteban-Cantos study[3] between ART-naïve, ART-treated PLWH and controls, as expected. After adjustment on this composition, the epigenetic differences fainted. This point needs to be further addressed.

The authors compare PLWH with a control group for which only age and sex are recorded. This is a concern. It has been shown that using a control group paired for most environment-related factors markedly reduced the difference between biological ages estimated by a complex set of parameters[8]: PLWH remained biologically older (+12.2 years) than non-infected paired subjects (+5.5 years) but both groups markedly differed from very healthy controls (blood donors, -7 years). The proportion of CMV-coinfected patients, not evaluated in the Esteban-Cantos study[3], is generally markedly higher in PLWH than in the general population. This parameter accounted for the high and similar level of immunosenescent T-cells found in PLWH and paired uninfected subjects in the COBRA study, markedly higher than in healthy blood donors[9].

The difference in the biological age between PLWH and controls reported in the Esteban-Cantos study[3] is +2.5 years before and +1.5 year after ART. This is markedly less than previous studies estimating epigenetic age in the blood (+5.2 years) and brain (+7.4 years) of ART-controlled PLWH compared to controls[4] and also in the COBRA study presented above[8].

The NEAT001/ANRS143 study[3] is a clinical trial, with selected patients, mainly men and Caucasian. Whether the results could apply in the real-life setting, in women and persons from other ethnicities is not known. Thus, recent reports found that some integrase inhibitors induced weight gain in PLWH mainly in women and Black people, while Caucasian men were minimally affected[10]. Moreover, the responsibility of advanced biological age in the worsening of clinical outcomes needs to be addressed in PLWH.

What could be the clinical recommendations regarding evaluation of the epigenetic age in PLWH, especially since the advance is small and has not been associated with clinical outcomes. I don't recommend evaluation at the individual level. However, I recommend its evaluation in clinical studies, especially in aging PLWH. The role of coinfections (CMV, HCV, HBV) and some ART is worth being addressed. Nevertheless, the enhanced epigenetic age in late ART initiators, even if well controlled thereafter, stress for their careful follow-up regarding age-related comorbidities.

Declaration of interests

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