EDITORIAL

Surviving HIV beyond prolonged viral suppression

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Unless patients present very late during the course of HIV infection, mortality as the consequence of AIDS has become exceptional. With the current antiretroviral armamentarium, viral replication can be halted and immune reconstitution achieved in almost all patients living with HIV. Unfortunately, prolonged control of viraemia, in many patients for more than a decade now, does not mean that the (very) long-term health outcome of HIV-infected patients will be comparable with individuals not infected by HIV. The virus already irreversibly damages the immune system shortly after transmission and only through very early diagnosis and treatment can this damage be partially avoided. Especially the gut mucosal barrier, corroded by HIV, is a pivotal contributing factor in the continuous low-grade systemic inflammation, which is thought to precipitate the development of non-AIDS-related diseases early in life. On top of this, if the average age at HIV diagnosis is 35 years, antiretroviral therapy will have to be taken for perhaps half a century. This prolonged exposure puts patients at risk for significant therapy-related organ specific toxicities. Several antiretroviral drugs have been withdrawn from the market for reasons of toxicity. Some of these side effects only became apparent years or even 10 years after EMA approval. Although current antiretroviral drug development is now much more focused on short- and mid-term toxicity, it remains to be seen whether current regimens will withstand the test of time. These factors form a strong rationale for extended follow-up of patients in specialised HIV-treatment centres. The management of ageing during follow-up is developing as a complex new research field in HIV care. Its complexity is reflected by the various organ systems that can be prematurely affected. However, the optimal screening approach to diagnose premature ageing in the setting of HIV is unclear. And if ageing is prematurely present, how can these individuals be optimally treated? Do HIV-infected patients just need more pills earlier in life?

One affected organ system in HIV is the bone, where osteopenia seems to develop at a younger age. In this issue of the Netherlands Journal of Medicine, Krikke et al. focused on T-cell activation markers and this condition. Despite the obvious limitations of this small cross-sectional pilot study on a selected group of 16 elderly males on long-term HIV therapy, they did not find an association between T-cell activation and this aspect of ageing. Another Dutch research group could not find an association either between other pro-inflammatory markers and lower bone mineral density in their cross-sectional analysis. Other factors, including advanced HIV at diagnosis and exposure to tenofovir treatment, seem to be predominantly involved. Nonetheless, the results are surprising for three reasons. First, in non-human primate models, disease progression is primarily related to ongoing massive immune activation and not uncontrolled viraemia. Also, strong T-cell activity is pivotal for a subgroup of HIV patients, the elite controllers, who can control the virus without therapy but observational studies show that their massive immune activation comes at the cost of more non-AIDS-related morbidity and mortality. Third, a link between immune activation markers with ageing-related conditions and survival in HIV has been described including ambiguous reports on the role of T cells in this field. With this in mind, an interesting follow-up study would be to see whether changes in innate and adaptive immune activation are associated with bone mineral density over time, especially if younger patients were to be followed from the initiation of HIV therapy. These studies nonetheless underline the complexity of ageing in HIV and the lack of one single biomarker that can reliably predict all comorbidities.

There is a clear need for reliable screening methods to identify conditions associated with premature ageing, including osteoporosis, in the setting of treated HIV.
An interesting Dutch study in this field, the AGEhIV cohort, has untangled important issues regarding ageing with HIV. In lifestyle-matched HIV infected and uninfected individuals aged over 45 years, it confirmed that ageing-related conditions are more prominent in HIV-suppressed patients. This is one example of ongoing studies that explore potential factors associated with premature cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, renal insufficiency, malignancies, and osteoporosis in HIV.

How to prevent premature ageing and frailty in a continuously growing HIV population is a critical question. The relevance of it is strikingly illustrated by the average age of the Dutch HIV population. Indeed, in 1996, only 9% of HIV patients in the Netherlands were over 50 years of age. In 2016, this percentage had increased to 45% and is likely to approach 50% within just a few years. Classical risk equations, such as the Framingham risk score, seem to incorrectly assess the risk in HIV-infected individuals. Despite some additional modest biological effects at best of anti-inflammatory drugs, extra antivirals, statins, or drugs that restrict microbial translocation in HIV-infected patients, clinical outcome studies are still lacking. Importantly, these measures to decrease inflammation are obsolete without viral suppression by antiretroviral therapy or changes in unhealthy lifestyles.

Correctly identifying those at risk and finding additional means to prevent inflammation is one of the major challenges in HIV clinical science. Already over 90% of HIV-infected patients in resource-rich countries die of non-AIDS defining illnesses. Due to premature ageing, these people are affected at a younger age. Preventing morbidity is a significant challenge in this vulnerable population. It is not unthinkable that even if HIV could be cured, this would not affect premature ageing due to irreversible damage to the immune system. Globally, the successful rollout of antiretroviral therapy to those most in need is a major achievement by the international community. Preventing complications of premature ageing should start to accompany these global HIV treatment strategies to prevent massive loss of quality of life. Ensuring survival does not end with achieving viraemic control: it starts there.

REFERENCES