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Editorial

HIV and aging: an overview of an emerging issue

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While aging may be one of the unavoidable facts of life, in recent years, HIV clinicians, researchers and people living with the virus have noticed an apparent increase in age-related conditions among people living with HIV (PLHIV). This is, of course, partly due to the success of antiretroviral therapy (ART), which means someone infected with HIV in 2011, with lifelong access to modern affordable treatment and healthcare, may expect to live almost as long as their uninfected peers.[1] In their article on the life expectancy of PLHIV in this issue, May and Ingle provide an overview of studies that have estimated life expectancy and explain the factors that determine the calculation of life expectancy.[2] They reach the encouraging conclusion that, in developed countries at least, earlier treatment using better drugs that lead to higher average CD4 counts is likely to see the life expectancy of PLHIV continue to improve.

A decline in mortality notwithstanding, what is of considerable concern to PLHIV is increasing morbidity as they age. Aging, defined as the gradual decline in functional reserve and function in all living things, is not a disease but a natural process.[3] However, aging varies greatly in its effects on individuals and the conditions of aging vary considerably among organ systems. Thus, while aging may be natural and inevitable, age-related morbidities such as heart disease or dementia may be classified as diseases with particular causes (and treatments). What has concerned the editors of this special edition of *Sexual Health* devoted to the topic of HIV and aging is that when these morbidities are disentangled and examined in this population, there seems to be a greater burden of disease affecting PLHIV at younger ages than their non-infected counterparts.

Coming to grips with both the immediate and underlying causes of the premature onset of age-related conditions is one of the aims of this edition. In providing an overview of the changes to the immune system that occur during aging and in HIV-infected individuals, Hearps *et al*. consider the innate immune system and describe what happens normally and in the context of HIV infection.[4] Underlying both processes is immunosenescence, which, in the elderly, is associated with increased inflammation and age-related diseases. It is known that HIV induces premature immunosenescence in T-cells but the effect on the innate immune system is not understood as well. Nonetheless, limited evidence suggests that HIV infection may mimic the effects of age on the innate immune system and the authors consider various drivers of this.

One of the most prevalent age-related conditions is cardiovascular disease (CVD). Petoumenos and Worm discuss the complex aetiology of CVD among PLHIV.[5] This includes traditional risk factors such as family history, age and gender as well as modifiable lifestyle risks such as smoking. They note the prevalence of these factors among PLHIV but also discuss the potential role of ART in increasing plasma lipid concentrations. In addition, HIV infection is independently associated with increased CVD risk and although the mechanism remains unclear, HIV-induced inflammation is a likely candidate. Chan and Dart note the link between inflammation and atherosclerosis, and provide evidence that this is accelerated among PLHIV as measured by large artery stiffness.[6] Both these papers agree on the importance of treating HIV infection, and reducing modifiable risk factors such as smoking and alcohol consumption, as well as treating dyslipidaemia and hypertension.

One of the other major diseases associated with aging, cancer, occurs in PLHIV in association with chronic infections with viruses that may be oncogenic or with impaired immune surveillance, rather than with aging itself. Grulich *et al*. report that cancers that are associated with age in the general population do not occur at higher rates among PLHIV and this fact calls into question the notion of a syndrome of accelerated aging.[7] Notwithstanding this, they do relate the incidence of cancer among this group with immune deficiency and lifestyle risks, emphasising the importance of effective HIV treatment and lifestyle change, and discuss the active research area of anal cancer screening.

The importance of tailoring ART to an aging population of PLHIV is addressed by Cordery and Cooper, who note

the welcome fact that older people tend to have better virological responses to treatment, perhaps attributable to better adherence.[8] However, in older patients, immune reconstitution is not as robust as in younger patients. They advise caution in the administration of some antiretroviral drugs, as some side effects may exacerbate or be mistaken for conditions associated with older age; doses may need to be adjusted to take different body compositions into account, and the effects on lipids, liver and renal function must be considered.

Naftalin *et al*. provide a comprehensive overview of issues that may affect the kidneys in aging PLHIV.[9] Age itself is associated with declining kidney function but chronic kidney disease is more common among PLHIV over the age of 50, especially in people of Black ethnicity. In addition, acute renal failure occurs more commonly in PLHIV. Some antiretroviral drugs are associated with chronic kidney disease to varying degrees (tenofovir, indinavir, atazanavir and lopinavir) and tenofovir is associated with renal tubular dysfunction. Proteinuria is present in up to one-third of PLHIV and is a risk for CVD. The authors recommend screening all PLHIV for signs of kidney disease and point out that, as a highly vascular organ, kidney disease shares many of the risk factors for CVD: smoking, hypertension and dyslipidaemia, all of which are modifiable.

Liver-associated morbidity and mortality is a significant and common concern among the population of aging PLHIV. Falade-Nwulia and Thio provide a review of liver-associated issues, beginning with the observation that in HIV-negative individuals, aging is associated with decreased liver volume, blood flow, drug metabolism and hepatic regenerative capacity.[10] HIV has the effect of accelerating liver damage from hepatitis C virus (HCV), which is a significant problem, given that about one-fifth of PLHIV internationally are also infected with HCV. While previously it was thought that rates of HCV infection among non-injecting HIV-positive western gay men would be low, it has become increasingly apparent that HCV is being transmitted sexually among some in this group. Hepatitis B virus (HBV) is also a serious problem among PLHIV, as the two viruses are both transmitted sexually. HIV decreases the likelihood of clearance of HBV and increases the likelihood of developing chronic HBV infection. The authors raise concern over the level of alcohol use among PLHIV over 50 years old in the USA; 47.3% said they consumed any alcohol in the past 12 months compared with 31.2% of the general population. Although they are not stratified by age, it is interesting to compare these figures with the much 'wetter' culture of alcohol consumption in Australia, where 76% of PLHIV[11] in the Futures sample consumed alcohol in the previous year and 83% of the general Australian population[12] did so. In the next few years, it will become increasingly important to ensure that HIV–HCV co-infected individuals gain access to new HCV treatments and that their effects are carefully studied in this population.

Another of the major effects of advancing age is low bone mineral density (BMD) and the associated conditions osteopaenia and osteoporosis. Cotter and Mallon note that these conditions are more common in HIV-infected patients, requiring physicians to screen, diagnose and manage BMD among this group.[13] Evidence also exists for a role of ART in reducing bone mineral density, especially upon initiation. Certain traditional risk factors – smoking, lack of physical activity, illicit drug use and low body mass index – are also prevalent among PLHIV. While addressing these risk factors, the authors also explore the role of vitamin D and bisphosphonates in the management of low BMD. They also advise caution if considering changing ART regimens, stating that the primary consideration should be maintaining viral suppression.

The authors of the article on neurocognitive impairment note that this condition significantly affects older people (>65) in the general population. Given that PLHIV are at greater risk of cognitive impairment,[14] we should expect to see a greater incidence of dementia in PLHIV as they age. They also note that even as ART has almost eradicated AIDS in the treated population, the prevalence of HIV-associated neurocognitive disorders (HAND), including HIV-associated dementia and mild neurocognitive disorder, has not changed. Their article develops a model for estimating the number of people living with HIV in Australia to the year 2030 and uses data from a Sydney hospital to estimate the numbers of people expected to be living with HAND in 2030. This information is useful for planning health service requirements as the population of PLHIV ages.

Sexuality is an important element of wellbeing in all people, including those with HIV and older people. Recognising this, Russell provides a comprehensive overview of sexual function and dysfunction in older PLHIV.[15] Sexual function changes with age due to a range of factors from the psychological to the hormonal. In PLHIV, both the virus and ART are likely to have an additional impact. Treatment for sexual dysfunction may include hormone replacement therapy and, for various reasons, it is worth measuring testosterone in PLHIV who report sexual dysfunction. For men who report erectile dysfunction, the use of phosphodiesterase-5 inhibitors (PDE5I) is warranted and has not been associated with an increase in risky sexual behaviour among PLHIV. Drug interactions between PDE5I and some antiretroviral drugs do exist, and should be considered.

A further important element of sexual health is the testing and treatment of sexually transmissible infections (STIs). Poynten *et al*. note that there is a tendency for older people to have less sex and therefore the population experiences lower rates of STIs.[16] However, among a significant group of older men who have sex with men in Australia, there is a tendency to engage in riskier sexual practices that place them at high risk of STI. These findings are repeated in various overseas studies. For this group, regular STI testing should be incorporated into clinical visits for HIV.

Mental health is an important issue among PLHIV, with both an HIV diagnosis and the stigma of the virus weighing heavily on many individuals. As people age and face increasingly complex health challenges, this is likely to remain the case. The most common mental health issue among PLHIV in Australia is depression.[11] This is mirrored in data from the USA presented in this issue. In a major study of older people with HIV in New York, Havlik *et al*. used a standardised scale to assess depressive symptomology in a sample of 1000 people. They found that depression was the most frequently reported comorbid condition. The paper explores correlations with other

comorbidities in some detail and seeks to ascertain whether high numbers of other comorbid conditions cause increased levels of depression. Although the answer to this remains equivocal, they ask that treatment of depression be accorded a greater priority in the HIV clinic than it is currently.

Finally, one of the successes of Australia's HIV response has been the strength of community engagement, so with this in mind, we have invited an article from someone who has lived with HIV for many years to provide a personal perspective that gives context and meaning to the science included in this special issue.[17]

Do people with HIV age more rapidly?

The collective wisdom of the papers in this edition present a complex set of answers to this question. The biological argument that HIV causes immunosenescence, which is a characteristic of older individuals, is persuasive. However, we can only be sure that T-cells are affected. Evidence is more limited when it comes to the innate immune system. So at this stage, the evidence is unable to answer the question of whether HIV in its own right accelerates the aging process. What is clear, though, is that certain diseases of aging, most notably CVD and dementia, are occurring at a higher rate and at an earlier age among PLHIV. Whether this is wholly explained by lifestyle factors or contributed to by additional aging processes specific to HIV and its treatment is not known. Future research that explains this aetiology will be important for developing effective interventions. For some long-term survivors of HIV infection who have received ARV treatment since the 1980s and 90s and who have experienced persistent body shape changes, and consequent metabolic syndrome, a question remains about the relative contribution of some treatments to their diminished health and well-being.

Although the causes for these high rates of chronic disease are being elucidated, prevention and management of adverse disease outcomes through lifestyle modification, screening for early disease, and pharmacological intervention are now at the centre of managing older patients with HIV.

Conflicts of interest

None declared.

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