Management of human immunodeficiency virus in older people

CPD

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Background
The proportion of older (aged ≥50 years) people living with human immunodeficiency virus (PLHIV) within the HIV-positive population is increasing. Many comorbidities associated with ageing are observed more frequently and/or occur at an earlier age among PLHIV, compared with people who are uninfected.

Objective
The aim of this article is to improve the confidence of treating physicians who have limited HIV experience in providing care for the increasingly elderly HIV population by presenting a contemporary clinical picture of older PLHIV and discussing the key evidence-based principles of management, with reference to data in the Australian setting where applicable.

Discussion
Older PLHIV, in particular those with complex comorbidities, are likely to benefit from comprehensive multidisciplinary medical and psychosocial support as they age. Physicians are well placed to diagnose and treat HIV as early as possible in older people and ensure counselling to prevent secondary transmission of HIV.

PROJECTIONS INDICATE that the proportion of people living with human immunodeficiency virus (PLHIV) aged ≥50 years is increasing and will continue to increase for at least the next decade in Western countries.[1,2] Many comorbidities associated with ageing, such as cardiovascular disease, osteoporosis, malignancy, metabolic disorders and renal disease, occur more frequently and/or at an earlier age in PLHIV than in people who are uninfected.[3–5] Treating physicians with limited HIV experience are generally expert in early identification, prevention and management of age-associated comorbidities in the general population, and are therefore well placed to manage and care for older PLHIV.

HIV prevalence in older people

In 2017 there were an estimated 27,545 PLHIV, including a total of 963 cases of newly diagnosed HIV, in Australia.[6] The majority were in the exposure category of men who have sex with men (MSM) at the time of diagnosis.[6] At present, approximately 46% of PLHIV in Australia are aged ≥50 years.[6] An increase in diagnoses in older people, as well as an increase in the life expectancy of PLHIV taking antiretroviral therapy (ART), are contributing to an increasingly aged population of PLHIV and consequently a unique presentation of age-related comorbidities that require clinical management.[7,8]

Age-related comorbidities in older people living with HIV

PLHIV have an increased risk of age-associated comorbidities, compared with individuals of the same age in the general population.[2–4] Factors associated with these comorbidities in PLHIV include a lower nadir CD4 cell count, prolonged ART exposure, persistent inflammation secondary to chronic viral activation and various lifestyle risk factors.[3,9] A decreased immunological response due to increasing age in PLHIV can also occur; this typically manifests as a poor response to vaccination, an increased susceptibility to infection and/or an increased risk of other comorbidities.[10,11] In addition, older people with a long history of ART may have medication-associated morbidities from older or experimental agents used in the past.[12] Neurocognitive conditions associated with HIV, including HIV-associated dementia and HIV-associated neurocognitive impairment, are of particular ongoing concern as little is known regarding their progression and management, and they

may result in sub-optimal adherence to treatment and treatment failure. Some cancers have a risk of earlier onset in PLHIV and, while the incidence of Kaposi sarcoma and non-Hodgkin lymphoma is decreasing for PLHIV, the risk of anal, liver and colorectal cancer is increasing.[13] The key characteristics of comorbidities commonly associated with ageing in PLHIV compared with people who are uninfected are summarised in Table 1.

Multimorbidity, which commonly refers to the coexistence of two or more clinically manifest chronic diseases,[14] is also more prevalent in PLHIV than in people who are uninfected.[15,16] Some older PLHIV are newly diagnosed, whereas others have lived with HIV for a long time and may have been treated long term with ART and/or previously diagnosed with one or more acquired immune deficiency syndrome (AIDS)-defining conditions. This is important to note, as older people with a longer duration of HIV infection have a higher probability of multimorbidity than PLHIV who seroconvert at older ages.[15] Therefore, similar to people who are uninfected, the development of age-related comorbidities and multimorbidity for PLHIV likely involve heterogeneous processes. Multimorbidity is of particular concern as it can contribute to frailty and therefore add to vulnerability and complexity in clinical management.[4,16] In fact, emerging evidence indicates that assessment of PLHIV using a frailty index can predict survival and multimorbidity,[17] highlighting the potential negative consequences of frailty in older PLHIV.

Clinical management of older people living with HIV

ART is recommended for all PLHIV, including older people, and early treatment initiation is particularly important for older people because of their potentially blunted response to ART and increased risk of serious non-AIDS events.[18] ART suppresses plasma viraemia, which decreases the risk of drug-resistant mutations, preserves or improves CD4 cell numbers and confers considerable morbidity and mortality benefits. As a result, life-expectancy in people with HIV is now approaching that of the general population.[19]

However, some ART medications can also exacerbate age-related comorbidities (Table 2). As a consequence of these potential toxicities, it is important to employ a proactive approach to ART management in older PLHIV. ART choice should ideally be based on management of comorbidities, multimorbidity,

Table 1. Age-related comorbidities in people living with HIV

Comorbidities	
Acute myocardial infarction	• Up to 50% increased risk of acute myocardial infarction[33] • Leading cause of death in PLHIV on effective ART[33]
Bone disease	• Six-fold increase in low BMD[34] • Four-fold increase in osteoporosis risk[35]
End-stage liver disease	• Progression to end-stage liver disease more rapid with HBV/HIV coinfection than with HBV monoinfection[18] • Three-fold greater risk of decompensated liver disease with HCV/HIV coinfection than with HCV monoinfection[18]
End-stage renal disease	• Earlier diagnosis of end-stage renal disease[5] • TDF and other comorbidities can increase risk[11]
HAND	• More than 50% of PLHIV have some neurocognitive impairment[36] • 2–8% of PLHIV have HIV-associated dementia[37] • HAND and HIV-associated dementia may contribute to treatment failures
Mental health conditions	• 20–40% of PLHIV compared with 7% of the general population report depression[28]
Non–AIDS defining cancer	• Increased risk of lung, anal and liver cancer and Hodgkin lymphoma[13] • Melanoma is common in Australian PLHIV[38]
Type 2 diabetes mellitus	• 4% higher prevalence[39] • More likely to develop at younger ages and in the absence of obesity[39] • Increasing age, HCV coinfection and increasing BMI have a more pronounced effect on the risk of type 2 diabetes mellitus[40]
Geriatric syndromes	
Delirium	• Delirium can occur in young adults and children with HIV[41,42]
Falls	• Fall rate increased in PLHIV[43]
Frailty	• Increased risk of pre-frailty and frailty[32,44] • Occurs in 11–23% of Australian PLHIV[32]
Functional impairment and disability	• Increased risk of functional impairment and disability, including difficulty with mobility, self-care and activities of daily living[45]
Hearing and visual loss	• Poorer lower-frequency and higher-frequency hearing[46] • Vision function abnormalities are common in people with AIDS[47]
Urinary incontinence	• Increased incidence of urinary continence in PLHIV[48]

AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; BMD, bone mineral density; BMI, body mass index; HIV, human immunodeficiency virus; HAND, HIV-associated neurocognitive impairment; HBV, hepatitis B virus; HCV, hepatitis C virus; NADC, non–AIDS defining cancer; PLHIV, people living with HIV; TDF, tenofovir disoproxil fumarate

polypharmacy and frailty, in addition to virological suppression. A complete treatment history is important, and HIV section 100 prescribers should be consulted to review ART regimens and, if clinically appropriate, modify regimens to include safer agents as part of the management of comorbidities. For example, changing from a regimen containing tenofovir disoproxil fumarate to a regimen containing tenofovir alafenamide can result in significant improvements in glomerular function and spine and hip bone mineral densities.[20] Changing to a two-medication regimen, such as dolutegravir/rilpivirine,[21–23] is another possible treatment strategy that may be used to avoid toxicities, although any decision to simplify a treatment regimen should be considered in consultation with an HIV section 100 prescriber.

ART regimens with a high genetic barrier to resistance, such as those containing an agent from the integrase inhibitor class, for example dolutegravir or bictegravir,[24–26] or protease inhibitor class, are particularly important for older PLHIV.

Evidence-based approaches to management of common individual comorbidities in PLHIV are summarised in Table 3. PLHIV benefit from the same age-appropriate health assessments as those for the general population. The Royal Australian College of General Practitioners' *Guidelines for preventive activities in general practice,* 9th edition (www.racgp.org.au/your-practice/guidelines/redbook) is therefore an appropriate guide when manageing older PLHIV, in particular when screening for bowel, skin and anal cancer. Anal cancer in MSM is a particularly important issue, and an Australian study has shown that regular digital anorectal examinations for MSM aged ≥50 years is cost effective and may detect anal cancer earlier.[27] The Australian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) also offers helpful resources for HIV management, including specific recommendations for older PLHIV (www.ashm.org.au/HIV/hiv-management).

Screening for comorbidities should ideally include the collection of modifiable and non-modifiable risk factors, estimation of risk probability using appropriate algorithms and evaluation using markers of subclinical disease. Furthermore, duration of ART should be taken into account when considering surveillance of disease risk, frequency of follow-up, intensity of care and choice of therapy.[15]

When manageing comorbidities in older PLHIV, it is important that patients adhere to ART so that HIV viral load remains undetectable. Physicians are well placed to treat risk factors for existing comorbidities and empower PLHIV to make lifestyle changes.[28] The benefits of ceasing use of tobacco, alcohol and other drugs should either be delivered repeatedly where appropriate, or continued abstinence encouraged.[28] Adherence to ART should also be assessed, ideally every three to six months, and factors that may decrease adherence, such as complicated regimens, unnecessary concomitant medications and neurocognitive deficits, should be identified and managed.[28]

Polypharmacy is particularly common in older PLHIV,[18] leading to a greater risk of drug–drug interactions (DDIs) between ART agents and concomitant medications; consequently, there is an increased risk of non-adherence, cognitive impairment, impaired balance, falls and hospitalisation.[28] It is important that physicians periodically review the potential for DDIs with ART, particularly when starting or changing concomitant non-HIV medications.[18] Furthermore, physicians should routinely check for potentially inappropriate medication prescriptions, particularly in older PLHIV. The University of Liverpool HIV drug interaction checker (www.hiv-druginteractions.org) is a particularly useful tool to assess the potential for DDIs.[29] A recent Australian study showed that medication reviews by HIV specialist pharmacists within the general practice setting may help identify, prevent and/or resolve DDIs and other medication-related problems in PLHIV.[30]

Table 2. Selected age-related comorbidities that may be exacerbated by, or associated with, antiretroviral agents

Comorbidity	Antiretroviral agent effects
Bone disease	• Tenofovir disoproxil fumarate: low BMD and osteoporotic fracture[49]
Cardiovascular disease	• Abacavir: MI[50] • Darunavir:* CVD[51]
Diabetes mellitus	• Zidovudine, stavudine, didanosine, lopinavir, nelfinavir and indinavir[52]
Neurocognitive impairment	• Efavirenz: nervous system side effects and impaired neurocognitive functioning[53] • Dolutegravir: neuropsychiatric side effects including insomnia and sleep disturbance[54]
Renal disease	• Adefovir:† proximal renal tubular dysfunction[55] • Atazanavir: kidney stones[56] • Indinavir: CKD and renal stones[57,58] • Tenofovir disoproxil fumarate: CKD[59]

**While darunavir has been shown to be associated with increased CVD risk, atazanavir has not, suggesting that protease inhibitors as a class may not be associated with an increased CVD risk.*
†Adefovir was used during HIV clinical trials in Australia but rarely outside of the clinical trial setting.
BMD, bone mineral density; CKD, chronic kidney disease; CVD, cardiovascular disease; HIV, human immunodeficiency virus; MI, myocardial infarction

The future of HIV care: A multidimensional approach

Frailty can predispose individuals to increased risks of multimorbidity and mortality.[11] HIV infection increases

frailty risk,[31] and a recent study estimated frailty to occur in 11–23% of PLHIV in one Australian cohort.[32] It is particularly important to identify and manage frailty because frailty can lead to or exacerbate disability. While frailty can be reversed, disability cannot. However, a lack of consensus remains on the defining criteria for diagnosis of frailty, and treatment of frailty can be complex, with no evidence-based strategies yet developed.[31]

To effectively manage ageing as a whole, the future of care for PLHIV will likely require a shift from the traditional interdisciplinary approach to a comprehensive 'geriatric-type' multidimensional, multidisciplinary assessment aimed at evaluating a combination of medical, psychosocial and functional capabilities and limitations.[28] Diverse consultation approaches that are built into individualised management plans, and focus on quality of life and prevention of disability, are likely to be of benefit. The increasing proportion of older PLHIV who have comorbidities, multimorbidity and/or frailty also suggests an evolving geriatric-HIV scenario in which evidence-based screening, monitoring and treatment guidelines will almost certainly be of value to ensure high-quality care.

In the meantime, current guidelines recommend that HIV experts, primary care providers and other specialists work together to optimise care for older PLHIV, particularly those with complex comorbidities.[18] Early HIV diagnosis in older people can be facilitated by enquiring in a non-judgemental manner about risk factors for HIV, including sexual history and intravenous drug use, and regularly testing those at risk. Counselling remains important to prevent secondary transmission of HIV. Older people are also likely to benefit from comprehensive multidisciplinary medical and psychosocial support to help them age as successfully as possible with HIV.

Conclusions

As a result of the ageing HIV population, comorbidities, multimorbidity and frailty will increasingly become a major focus of care. Continued research into ageing in older PLHIV is required for the management, and perhaps prevention, of comorbidities, multimorbidity and frailty, and may form the basis of a new model for manageing ageing in the general population.

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Table 3. Overview of key aspects to management of common individual comorbidities in older people living with HIV*

Comorbidity	Key management aspects
Bone disease	• Consider DEXA† for those with risk factors[28] • Address fall risk and ensure sufficient dietary calcium and vitamin D[28] • Refer complicated cases to an osteoporosis specialist[28] • Replace TDF with TAF[18] ‡§
Cardiovascular disease	• Assess risk with D:A:D score[60] or Framingham score every 2 years in all men aged >40 years and women aged >50 years without CVD[28] • Use ABC with caution in cases of high CVD risk (>20%)[18] ‡§ • Reduce all modifiable risk factors, particularly blood pressure, glucose and lipids[28] • Encourage lifestyle modification, particularly smoking cessation[28]
Neurocognitive impairment	• Neuropsychological evaluation[28] • Neurological examination, brain MRI and CSF examination[28] • Address adverse lifestyle habits and encourage adherence to ART if needed[28] • Avoid EFV, particularly in patients with mental illness[28] ‡§
Renal disease	• Annual assessment for risk factors of CKD, or more frequently as indicated[28] ‖ • Adjust ART dose or modify ART regimen[28] ‡§ • Replace TDF with TAF[28] ‡§ • Refer to nephrologist if new CKD or progressive decline in eGFR[28]

**This table summarises the management of individual comorbidities only, and not aging, which includes multimorbidity, frailty and disability. While there is a plethora of evidence-based guidance for the management of individual comorbidities in HIV, little is currently known about achievement of successful ageing with HIV, which consequently remains major clinical challenge.*

†DEXA is not funded for all patients by the Medicare Benefits Schedule in Australia.

‡To avoid drug–drug interactions with HIV medications, always consult the University of Liverpool HIV drug interaction checker before prescribing new medications (www.hiv-druginteractions.org)

§In Australia, refer to an HIV section 100 prescriber to review and reactively or pre-emptively switch ART when appropriate.

‖More frequent monitoring is required if eGFR <90 mL/min, CKD risk factors present and/or prior to starting and treatment with nephrotoxic drugs.

ABC, abacavir; ART, antiretroviral therapy; CKD, chronic kidney disease; CSF, cerebrospinal fluid; CVD, cardiovascular disease; D:A:D, data collection on adverse events of anti-HIV drugs; DEXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EFV, efavirenz; MRI, magnetic resonance imaging; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

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