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Non-infective complications for people living with HIV

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Abstract

In 2020, 37.7 million (30.2–45.1 million) people were living with HIV globally, with 27.5 million (26.5–27.7 million) accessing antiretroviral therapy. Women and girls accounted for half of all new HIV infections. HIV is now a treatable chronic health condition, and people diagnosed with HIV can expect to live long and healthy lives with access to antiretroviral therapy. There is evidence, however, that people with HIV are more likely to develop certain age-related diseases, including cardiovascular disease, chronic airway disease, kidney failure, liver failure, cancer, type 2 diabetes and other complications. People with HIV also continue to experience intersecting social stigma, which affects their health outcomes compared with the general population. Amid the coronavirus disease (COVID-19) pandemic, new opportunities and challenges are emerging in HIV medicine and emphasize the need for clinicians to maintain a working knowledge of HIV and its potential complications.

Keywords Ageing; antiretroviral therapy; clinical outcome; co-morbidities; complications; frailty; HIV; inflammation; non-communicable disease; people living with HIV; prognosis

Cardiovascular disease

Cardiovascular disease – defined as myocardial infarction, ischaemic heart disease, cardiovascular/cerebrovascular events and coronary heart disease – is common in human immunodeficiency virus (HIV). People living with HIV (PLWH) are twice as likely to develop cardiovascular disease, and it is estimated that the burden of HIV-associated cardiovascular disease has increased 3-fold over the last 20 years.¹ Although mechanisms for HIV-related cardiovascular disease may be similar among PLWH, there are significant regional variations in risk factors that should be considered. For example, Sub-Saharan Africa has

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Key points

- HIV has the potential to affect all organ systems, and it is important to consider the burden of non-communicable disease in this population
- HIV medicine is increasingly complex and involves caring for an ageing, multimorbid population with complex medical needs and polypharmacy
- Frailty and integrated medical services are relevant for people living with HIV, to reduce the burden of unnecessary hospital visits and prevent inappropriate hospital admission
- Clinicians should incorporate an intersectional approach into their working, and focus local prevention and health promotion efforts to include underserved people with HIV

a younger population with higher rates of elevated blood pressure, despite lower smoking rates and hypercholesterolaemia, compared with Western Europe and North America.

The relationship between HIV and atherosclerotic disease is well characterized. It is thought that underlying chronic inflammation and immune activation in long-term HIV infection contribute to accelerated atherosclerosis, so HIV should be considered an independent vascular risk factor. There is potential for ‘clustering’ of modifiable cardiovascular risk factors among PLWH, including tobacco smoking, recreational drug use, hypertension and dyslipidaemia. Antiretroviral therapy (ART) may also contribute to individual cardiovascular risk, although this remains controversial. In the UK, PLWH >40 years old should undergo baseline and annual cardiovascular risk assessment (QRISK), with annual lipid profile assessment for certain groups.

PLWH are also at risk of other cardiac disease, including pericardial, myocardial, endocardial and aneurysmal disease, arrhythmias, pulmonary hypertension and sudden cardiac death. Pericardial effusion is relatively common, especially in advanced HIV, and important non-infective differential diagnoses include Kaposi sarcoma and lymphoma. Cardiac drug toxicities include heart failure secondary to chemotherapy agents, including doxorubicin.

Respiratory conditions

Beyond opportunistic infections, lung malignancy, chronic airway disease and pulmonary arterial hypertension are more common among PLWH. There is a higher incidence of chronic airway disease, including asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis. HIV can be considered an independent risk factor for COPD and associates with radiographic emphysema and more frequent exacerbations. HIV infection affects several aspects of ‘host defence’ in the lung and respiratory tract, contributing to longer term respiratory complications. There is limited knowledge of the role of ART in lung health in PLWH; however, chronic inflammation and altered immune response probably have a negative impact.

The incidence of lung cancer remains higher among PLWH than the general population, even when accounting for higher

rates of smoking in PLWH. Before ART, lung involvement from Kaposi sarcoma and non-Hodgkin lymphoma was common. However, non-small cell lung cancer (most commonly adenocarcinoma), followed by small cell lung cancer, is now more common. Relevant risk factors for lung cancer in PLWH include ageing, tobacco smoking, co-morbid COPD, severe/chronic lung infection, HIV-related immunosuppression, inflammation, oncoviruses *in vitro* and hypothetical ART toxicity.

Smoking cessation is a critical intervention for PLWH. PLWH are *more* likely to smoke tobacco than the general population and are *less* likely to successfully stop smoking. Health consequences of tobacco smoking are also more severe for PLWH than otherwise ‘healthy’ smokers. PLWH develop lung cancer with fewer ‘pack-years’ of cigarette smoking compared with the general population. PLWH with virological control are more likely to achieve smoking cessation. Further work is needed to implement successful smoking cessation initiatives for PLWH.

Renal disease

PLWH are more likely to experience acute kidney injury and chronic kidney disease. HIV-associated nephropathy (HIVAN) is a well-described complication of HIV, although less common in the current ART era. Chronic kidney disease has become more prevalent for PLWH, with factors including ageing, co-morbid hypertension or diabetes mellitus, and ART nephrotoxicity. Primary renal disease in HIV includes HIVAN, immunoglobulin A nephropathy, immune complex glomerulonephritis, minimal change disease, membranous nephropathy, amyloidosis, thrombotic thrombocytopenic purpura and haemolytic–uraemic syndrome. These conditions cannot be fully expanded on here. However, it is important to emphasize the role of combined HIV–renal outpatient clinics to enhance patient care and reduce the volume of unnecessary outpatient visits. Clinicians working in HIV should always consider nephrotoxicity when prescribing, as well as the need for dose adjustment based on renal function and creatinine clearance.

Gastrointestinal and hepatobiliary effects

HIV can affect any site in the gastrointestinal tract, from oropharynx to rectum. Diarrhoea is the most common gastrointestinal complaint among PLWH. There is evidence that there is rapid and likely irreversible loss of gut-associated lymphatic tissue in early HIV infection, which can lead to altered bowel habit or even the pathogenesis of inflammatory bowel disease. HIV enteropathy remains a diagnosis of exclusion. ART itself, particularly with protease inhibitors, can contribute to gastrointestinal disturbance, although this is often self-limiting.

Hepatitis B and C continue to be globally significant for PLWH, although other causes of acute and chronic liver disease are relevant. These include alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD) and drug-related hepatotoxicity. Risk factors for NAFLD include obesity, hyperglycaemia, diabetes mellitus and dyslipidaemia. Growing evidence suggests that hepatic steatosis is common among PLWH, particularly with hepatitis C co-infection. Excess alcohol intake is also prevalent among PLWH and can contribute to liver disease progression.

Nevirapine, a non-nucleoside reverse transcriptase inhibitor, is most commonly associated with hepatotoxicity. The main mechanisms of liver injury secondary to ART include:

- direct drug toxicity/metabolism
- hypersensitivity reactions
- mitochondrial toxicity
- immune reconstitution inflammatory syndrome.

Other drugs prescribed in HIV can also cause hepatotoxicity, including antifungal, antiviral and anti-tuberculosis agents.

Dermatological conditions

Dermatological manifestations of HIV can provide the prompt for HIV testing and initial diagnosis. Common examples include seborrhoeic dermatitis, xerosis, skin hyperpigmentation, onychomycosis, oral candidiasis, photodermatitis and scabies.

Dermatological side-effects can also be a consequence of ART and other commonly prescribed drugs in HIV. PLWH have a higher risk of developing cutaneous drug reactions compared with the general population. Important examples include:

- abacavir and drug rash with eosinophilia and systemic symptoms (DRESS), especially for those who are HLA-B*5701 positive, in whom abacavir should be avoided
- nevirapine and its association with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)
- co-trimoxazole (trimethoprim/sulfamethoxazole) and its association with SJS/TEN.

Skin problems have a significant impact on self-esteem and stigmatization. Individuals should be provided with appropriate psychosocial support, and counselled when commencing drugs with potential skin side-effects.

Haematological and oncological disease

PLWH are significantly more likely than the general population to be diagnosed with cancer over their life course. Studies have identified that PLWH are more likely to present with advanced cancer, and even those with non-advanced cancer have a higher likelihood of death. These disparities are not fully understood but are thought to include barriers to care, bias among healthcare professionals and perceived stigma by PLWH.

Before ART, approximately a third of PLWH experienced ‘AIDS-defining cancers’, including Kaposi sarcoma, non-Hodgkin lymphoma and invasive cervical cancer. The burden of ‘non-AIDS-defining cancers’, especially lung, liver, oral and anal cancers and Hodgkin lymphoma, has continued to increase with the introduction of ART and with ageing, such that cancer is now the leading cause of death for PLWH in high-income countries. Factors contributing to increased cancer incidence for PLWH include oncoviruses, chronic inflammation, tobacco smoking, injection of drugs, alcohol consumption and ageing.²

Screening programmes exist to detect cancer early, but few are specific to PLWH. Examples include cervical, breast, colorectal, anal and hepatocellular cancer screening. Comprehensive cancer prevention for PLWH has been described as including ART adherence, vaccination against oncogenic viruses, treatment of hepatitis viruses and successful smoking cessation.

There remain significant racial inequalities in cancer diagnosis, treatment and outcome for PLWH, which warrant attention at local and global levels. Black and Hispanic PLWH were

less likely to be given lung cancer treatment in a US cohort, hospitalized black female PLWH were more likely to experience HIV/cervical cancer co-morbidity, and male PLWH identifying as Asian, African, Caribbean or Black were less likely to have had complete screening for anal cancer.

Neurological effects

Approximately 10% of PLWH with seroconversion illness experience neurological symptoms and signs, including encephalitis, transverse myelitis, polymyositis, brachial neuritis, cauda equina, Guillain–Barré syndrome or aseptic meningitis.

Neurological complications can emerge as a direct result of HIV (distal sensory peripheral neuropathy, HIV dementia, vacuolar myelopathy, HIV polymyositis), concurrent malignancy (primary central nervous system lymphoma), drug toxicity (zidovudine, stavudine, zalcitabine, didanosine) and opportunistic infection. HIV-associated neurocognitive disorders are subject to controversy: some studies estimate that half of PLWH have a degree of cognitive impairment despite the advent of ART, but others show a variation dependent on the selected population and assessment methods.³ Uncertainty remains regarding the need to routinely screen cognition in asymptomatic PLWH.

Endocrinological and metabolic conditions

HIV is associated with metabolic syndrome and insulin resistance, which can predispose PLWH to abnormal glucose and fat metabolism.

Type 2 diabetes mellitus is up to four times more common in PLWH. There is lack of consensus over whether HIV represents an independent risk factor for diabetes mellitus, but it is apparent that ageing, obesity, hepatitis C co-infection and certain medications might all contribute. Protease inhibitors have been described as increasing insulin resistance through effects on decreased insulin secretion and GLUT 4 (glucose transporter type 4) transporters. Meanwhile, lipodystrophy secondary to first-line ART may be associated with diabetes mellitus and cause significant psychological distress. There is uncertainty regarding the risk of weight gain and metabolic syndrome with the use of modern ART agents (second-generation integrase strand transfer inhibitors, and tenofovir alafenamide-based regimens in particular). PLWH should therefore undergo baseline and annual screening for diabetes mellitus.

With respect to bone health, PLWH are more likely to experience osteonecrosis, osteomalacia, osteoporosis and bone fracture over their life course. Tenofovir disoproxil fumarate is commonly used and has been associated with bone disease. PLWH aged >50 years should undergo FRAX scoring to estimate risk of fracture (age >40 years if there are significant risk factors), and dual X-ray absorptiometry scanning can provide an indication of bone mineral density. Vitamin D deficiency is common among PLWH, and there may be a role for supplementation to mitigate risks to bone mineral density.

Pituitary growth hormone secretion appears to be altered by HIV infection, and an estimated third of PLWH have biochemical growth hormone deficiency. This can contribute to insulin resistance and eventually lead to primary (testicular failure) and secondary (hypothalamic and pituitary failure) hypogonadism, impairing quality of life.

Women's health

Women living with HIV are eight times more likely to die in pregnancy or the postpartum period, but little is known of the interaction between pregnancy and HIV. Despite antenatal screening providing a unique opportunity to diagnose HIV and reduce mother-to-child transmission, it has been hypothesized that pregnant women with advanced HIV can be at risk of infection, haemorrhage secondary to HIV-induced thrombocytopenia, and discrimination and stigma that limits their access to care.⁴

Amenorrhoea, altered menstrual cycles and erratic bleeding are reported as more common for women living with HIV. Hormonal contraception can be helpful, but interactions with ART should be considered. Women living with HIV are reported to experience earlier onset menopause, and are more likely to experience menopausal symptoms, although the reasons are not well understood. Given that early menopause can also contribute to ageing, reduced bone density and increased risk of cardiovascular disease, further research is needed.

Women with HIV have a 6-fold higher risk of cervical cancer compared with their counterparts. Women with HIV are more likely to acquire and less likely to clear human papillomavirus (HPV), and HIV-related immune suppression can result in accelerated disease progression and disease recurrence. Integrated cervical screening and HPV vaccination uptake are key in eliminating cervical cancer.

Psychiatric conditions

Substance use, depression, anxiety, post-traumatic stress disorder, insomnia and psychosis are more prevalent among PLWH. PLWH are twice as likely to develop a depressive disorder over their life course. Suicide is attributed to 2% of deaths for PLWH – double the rate among the general population. Male PLWH are most likely to commit suicide, especially in the first year after HIV diagnosis. Substance use, including alcohol, γ -hydroxybutyrate/ γ -butyrolactone (GHB/GBL, G), crystal methamphetamine and mephedrone, can change or enhance sexual behaviours ('chemsex'), which can affect risk-taking behaviours (condom use, pre- and post-exposure prophylaxis for HIV uptake, ART adherence, needle sharing and type of intercourse).

People with mental illness are more likely to acquire HIV, and PLWH are also more likely to develop mental illness. Addressing mental illness and substance use is critical to improving HIV treatment adherence and reducing risk of transmission.⁵ Structural factors – such as poverty, racism, lack of education and intersecting social/cultural stigma should be considered in the design of integrated substance misuse and mental health services for PLWH.

Ageing and frailty

Frailty and ageing among PLWH have been described as 'the silent epidemic'. PLWH are more likely to experience frailty, and to present with 'premature' frailty. Frailty in HIV is partly attributed to ageing, but also chronic inflammation, oxidative stress and mitochondrial damage despite ART. There are limited guidelines or validated frailty scores for PLWH, the Veterans Ageing Cohort Study Frailty Index being an example. It is

therefore important to adopt a holistic, multisystem approach and to recognize the unique impact of ageing for PLWH. ◆

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