REVIEW CPD

Managing HIV infection in patients older than 50 years

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Antiretroviral therapy has extended the life expectancy of people living with HIV,[1–4] although disparities remain. Patients who are not white, who begin antiretroviral therapy with CD4 cell counts below 350 cells/μL or who use illicit intravenous drugs do not live as long;[5] however, the Centers for Disease Control and Prevention (CDC) estimated that, by 2020, more than half of all people living with HIV in the United States will be older than 50 years of age.[6] The age threshold used to define older people living with HIV is 50 years.

Numbers of older people living with HIV have also increased in Canada. In 1997, 10% of patients receiving HIV care at the Southern Alberta Clinic in Calgary were older than 50 years of age; in 2017, such patients accounted for 48% of care recipients. The primary reason for this change is the aging of people who acquired infection earlier in life. However, adults older than 50 years of age now account for almost one in six new HIV infections in Canada and the US.[5–7]

There are distinct differences between people who are aging with HIV and patients who seroconvert in older age.[8] People who have aged with HIV infection have high rates of comorbid illness at younger ages than people without HIV infection, which leads to increased complexity in the provision of clinical care. Here, we focus on aging with HIV, exploring the effects of many years of infection and treatment on the development and progression of comorbidities. We provide guidance for nonspecialist physicians who are increasingly likely to be involved in the prevention and management of non–HIV related comorbidities in patients older than 50 years. We particularly draw on recent evidence from randomized controlled trials and large cohort and case–control studies (Box 1).

KEY POINTS

- The population of patients living with HIV and AIDS is aging as a result of both longer life expectancies with infection and an increase in newly acquired infections at older ages.
- Sexually active older adults should be considered to undergo HIV screening.
- Age-related conditions and comorbidities (e.g., frailty, neurocognitive impairment, cardiovascular disease, hypertension, dyslipidemia, renal disease, osteoporosis and fractures) develop at younger ages and more often among patients living with HIV and AIDS than among patients without HIV infection.
- Clinical care for patients living with HIV and AIDS is evolving, with an increasing focus on dealing with age-related non-HIV comorbidities and drug-related issues in addition to continued viral suppression.

What contributes to the burden of comorbidity in older patients with HIV and AIDS?

Older people living with HIV are more likely to have complicating comorbidities and polypharmacy, leading to possible drug–disease and drug–drug interactions that can be complicated by age-related pharmacokinetic and pharmacodynamic changes. The risk of resistance to antiretroviral therapy and toxicity is increased because of the long duration of infection.[7]

Observational studies have estimated that the prevalence of select age-related comorbidities among these patients approaches that seen among people without HIV infection who are 5 years older,[9] and the risk of multimorbidity for these patients is similar to that of people without HIV infection who are 10–15 years older.[10] One study found that patients older than 45 years of age living with HIV had higher multimorbidity than was seen in those with a new infection who were of a similar age.[11] However, it is not clear whether the relatively earlier occurrence of comorbidities among people living with HIV is the result of accelerated or accentuated aging.[12] In the former, the aging process itself

Box 1: Evidence used in this review

We performed a narrative literature review of the broad topic "aging with HIV," with the goal of exploring various aspects of this topic. We searched MEDLINE databases using combinations of the terms "aged," "middle-aged," "older," and "HIV," "human immunodeficiency virus," "AIDS," "Acquired Immune Deficiency Syndrome," with no date or language restrictions. Our initial search produced 1117 articles. We screened titles and abstracts for relevance, and removed duplicates, after which we selected 623 unique citations for review that we categorized by topic (e.g., HIV and aging/cardiovascular disease [37 unique citations]). We searched the reference lists of included articles for additional relevant studies. We focused on the most recent studies, in particular randomized controlled trials, large cohort studies and case–control studies. A descriptive synthesis of the results of this search is provided.

speeds up, leading to the earlier onset of age-related conditions; with the latter, these conditions are more likely to develop, but at expected ages. Whatever the contributing factors, care for these patients should incorporate helping them cope with multiple non–HIV related chronic diseases at relatively younger ages, in addition to continuing to treat and manage HIV/AIDS.[13]

Which specific comorbidities present a challenge?

Cardiovascular disease

The relative risk of cardiovascular disease among people living with HIV who have received antiretroviral therapy is about twofold greater than for those of a similar age with no HIV infection.[14] There is a 40%–50% higher incidence of myocardial infarction among people with HIV after controlling for traditional cardiovascular disease risk factors.[15] Both higher viral loads and lower CD4 counts are independently associated with this increased risk for ischemia.[16] The incidence of myocardial infarctions in people living with HIV declined in the late 1990s, possibly as a result of better management of HIV and vascular risk factors.[17] However, with increases in life expectancy for people living with HIV, it will be important to proactively manage risk factors for cardiovascular disease to effectively prevent disease.

Chronic kidney disease

Risk factors for chronic kidney disease among people living with HIV include older age, being a woman, diabetes mellitus, hypertension, dyslipidemia, CD4 cell count below 200 cells/μL, AIDS, low baseline creatinine, exposure to tenofovir,[18] heart failure, being black, Hepatitis C (HCV) infection and alcohol misuse.[19] The prevalence of chronic kidney disease appears to be decreasing, possibly owing to improved antiretroviral therapy regimens and increased use of renoprotective agents (i.e., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers).[20] A recent Australian database study estimated that chronic kidney disease (estimated glomerular filtration rate < 60 mL/min per 1.73 m^3) affects about 1 in 20 in this population.[21] Consideration of early chronic kidney disease is important, because its presence should prompt the avoidance or dosage adjustment of certain medications.

Metabolic syndrome and diabetes

People living with HIV are more likely to have certain components of the metabolic syndrome (i.e., diabetes, hypertension, and higher triglyceride levels and high-density lipoprotein levels) than those without HIV infection.[22] Cumulative exposure to older, more metabolically toxic antiretroviral therapies was associated with a higher likelihood of incident diabetes.[8,23,24] Both diabetes prevalence and incidence were as much as fourfold higher for men with HIV who were receiving antiretroviral therapy than for men without HIV.[25] Whether the newer, less metabolically toxic therapies are associated with a lower likelihood of diabetes, hypertension and dyslipidemia is unknown.

Cancer

Mortality attributable to non–AIDS related, non–hepatitis related cancers (particularly of the lung) increased from 11% to 22% among people living with HIV in France between 2000 and 2010.[26] The increased incidence of lung and anal cancers among patients with HIV and AIDS may be suggestive of rates of smoking and infection with human papillomavirus (HPV).[27] With greater use of antiretroviral therapy and the advancing age of this patient population, non–HIV related malignant diseases that are age-related or associated with lifestyle factors such as smoking are likely to increase, and should be screened for (Box 2).[28–30]

Screening recommendations for other cancers are less clear. Clinicians should likely defer to national screening guidelines, such as the Canadian Task Force guidelines for breast, colon, lung, prostate and hepatocellular cancers (https://canadiantaskforce.ca/guidelines/published-guidelines/). Specific recommendations for people living with HIV have yet to be developed.

Liver disease

Results from a collaboration of 11 cohort studies involving more than 200 clinics in Europe, the US and Australia showed that liver disease is responsible for as many as one in five deaths among people living with HIV.[31] Furthermore, HIV and HCV coinfection leads to faster progression to fibrosis and cirrhosis in addition to an increased risk of hepatocellular carcinoma compared with HCV monoinfection.[32] However, a recent meta-analysis concluded that effective antiretroviral therapy may reduce liver-related mortality among patients with dual infection.[33] Most cases of HIV–HCV coinfection occur in patients who use illicit intravenous drugs.[34] Odds of HCV infection are six times higher

Box 2: Advice on cancer screening for people aging with HIV and AIDS[29,30]

- Cervical cancer
  - Annual Papanicolaou (Pap) testing, unless two consecutive tests in a row are negative, after which screening can be done every three years*
  - Human papillomavirus (HPV) cotesting for patients aged ≥ 30 years
  - Annual digital rectal and vaginal examinations, and visual inspection of external genitalia
- Anal cancer
  - Annual history and physical examination for regional symptoms and previous abnormal examination findings (e.g., condyloma or changes in pigmentation), and digital rectal examination
  - Referral to anoscopy and potential biopsy for women with abnormal cervical histology and anyone with abnormal findings on physical examination
  - Pap testing at baseline and annually for men who have sex with men, women with a history of abnormal cervical histology and anyone with a history of anogenital condyloma

Note: Adapted with permission from the New York State Department of Health AIDS Institute (https://www.hivguidelines.org/).

*There is insufficient evidence to suggest stopping screening at 65 years of age.

for people living with HIV, presumably because of shared risk factors (e.g., intravenous drug use), enhanced transmission of HCV among these patients and decreased clearance of HCV in patients with HIV who are not receiving antiretroviral therapy.[34]

Metabolic liver diseases, such as non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, have become increasingly common among people living with HIV.[35] A 2015 prospective cohort study of patients with HIV who showed persistent (≥ 6 mo) elevations in aminotransferase levels without evidence of viral hepatitis reported that 73% and 54% of patients had evidence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, respectively; these rates are higher than those seen among patients without HIV and viral hepatitis who underwent biopsy for similar indications.[36] Associations are reported between non-alcoholic steatohepatitis and fibrosis and insulin resistance and obesity, but not HIV or antiretroviral therapy duration or specific antiretroviral agents.[36] Both infection with HIV and antiretroviral therapy may contribute to insulin resistance, dyslipidemia and atherosclerosis, which in turn may contribute to the risk for non-alcoholic steatohepatitis and non-alcoholic fatty liver disease.[35]

Specialist expertise in the selection of HIV antiretroviral therapy is needed for patients with a higher baseline risk of fatty liver disease because of pre-existing obesity, insulin resistance or dyslipidemia.[35] The European AIDS Clinical Society (EACS) guidelines recommend baseline determinations and subsequent testing every 3–12 months for aspartate and alanine aminotransferase, alkaline phosphatase and bilirubin levels.[37] In patients with HIV and non-alcoholic fatty liver disease who are overweight, weight loss of 7%–10%, avoidance of processed foods and added fructose, and adherence to a Mediterranean diet are recommended.[35] Nonalcoholic steatohepatitis and nonalcoholic fatty liver disease should be considered in adults with HIV who have liver disease, particularly in the absence of coinfection with hepatitis B virus or HCV.

Which syndromes associated with aging may occur earlier?

Neurocognitive impairment

Profound immunosuppression, high viral loads and opportunistic infections are associated with HIV-related dementia, which is now recognized as the most severe end of a spectrum of cognitive impairment known as HIV Associated Neurocognitive Disorder.[38] Although moderate to severe impairment has become less common with the widespread use of antiretroviral therapy,[39] about one-third of patients with HIV or AIDS have at least subtle neurocognitive impairment, which is associated with deficits in attention, working memory, executive function, motor control, motor processing and information processing speed more often than impairments in short- and long-term memory and language abilities.[40] Differentiating HIV Associated Neurocognitive Disorder from other causes of cognitive impairment, such as Alzheimer and cerebrovascular disease, is challenging yet important for determining prognosis and management. Cognitive impairment may compromise adherence to antiretroviral therapy and other aspects of care.[41]

Frailty

Frailty is common and occurs at an earlier age among people living with HIV; it is associated with higher risks of multimorbidity, admission to hospital or long-term care and death.[42–44] How best to detect and manage frailty for these patients requires additional research.

Osteoporosis and fractures

Recent observational evidence has found that HIV infection is associated with about a twofold increased risk of fractures among men aged 50–59 years compared with men without HIV.[45] Randomized controlled trials of older antiretroviral drugs showed more rapid decline of bone mineral density with continuous therapy.[46] Proven risk factors for osteoporotic fractures among people living with HIV include older age and being white, as well as exposure to tenofovir and protease inhibitors.[47,48] Evidence from randomized controlled trials suggests that alendronate is a safe and effective option for treating osteoporosis in patients with HIV and AIDS who are taking older continuous antiretroviral therapies.[49] Guidelines recommend baseline bone mineral density screening for osteoporosis among postmenopausal women and men with HIV who are older than 50 years.[50,51] These recommendations are based on studies conducted between 1988 and 2010 with older, potentially more toxic antiretroviral therapies and no adjustment for other osteoporosis risk factors (e.g., low body mass index, smoking, alcohol use, poor nutrition), which may be more common in people living with HIV. More current research and updated guidance are needed.

What else may affect the health of older people living with HIV?

Falls

About 30% of men living with HIV with a mean age of 52 years report falling during the previous year compared with a fall rate of 16% over two years in a community-based sample of 45- to 65-year-old men.[52,53] Difficulty with tandem gait, prescribed drug use (i.e., antidepressant, sedative, opioid, didanosine), self-reported exhaustion, diabetes, female sex and weight loss are associated with future fall risk.[52] The combination of osteoporosis and falls markedly increases the risk of fragility fractures in the general population.[54] Falls may also lead to fear of future falls, resulting in decreased mobility and deconditioning. Effective interventions for both osteoporosis and falls could decrease the risk of fractures and traumatic brain injury among people living with HIV, but further research is required.

Polypharmacy

Prescription of five or more non-antiretroviral medications is common among patients with HIV and AIDS, and exposes patients to a variety of adverse drug–drug interactions.[55] In one population-based study, 7% of patients with HIV had prescriptions for a contraindicated antiretroviral/non-antiretroviral combination, and 33% had prescriptions for a combination with moderate to high likelihood of an adverse reaction.[56] In another study, 70% of patients were exposed to category D drug–drug interactions (i.e.,

an interaction that should prompt consideration of therapy change) and 11% were exposed to a category X interaction (i.e., a combination that should be avoided).[57] Adverse effects can occur even after a drug is withdrawn, as exemplified in a recent case report describing adrenal insufficiency in a 65-year-old man whose ritonavir was discontinued while he remained on inhaled budesonide.[58] Medication review (including consideration of over-the-counter and complementary agents) and careful communication between all prescribers and dispensers of medications can help minimize the risk of adverse interactions.

Vaccinations

Live vaccines are contraindicated for people living with HIV whose immune systems are suppressed or who have a CD4 count of 200 cells/μL or less. Box 3 provides information on recommended vaccinations for older people living with HIV.[50,59] Patients with other risk factors for liver disease (intravenous drug use, HCV coinfection) are at increased risk of acquiring hepatitis, and particular care should be taken to ensure that vaccinations for hepatitis A and B are received.

Box 3: Recommended vaccinations for older adults living with HIV[59]

- Annual influenza vaccine for all patients (inactivated injectable or live intranasal vaccine if the patient does not have immune suppression, preferably during autumn)
- Zoster live vaccine for patients aged ≥ 50 years who have a CD4 cell count ≥ 200 cells/μL; previous zoster infection is not a contraindication, but vaccination should wait until 1 year after last episode
- Pneumococcal vaccine for patients with CD4 cell count ≥ 200 cells/μL (single dose pneumococcal 13-valent conjugate [Prevnar], followed at least 8 wk later by a single dose of pneumococcal polysaccharide [Pneumovax], with a booster dose of pneumococcal polysaccharide at least 5 yr later)
- Hepatitis A vaccine for men who have sex with men, people who use drugs intravenously, travellers to endemic countries, patients with chronic liver disease, and patients with hepatitis B or C coinfection who are nonimmune to hepatitis A virus (single dose of monovalent vaccine, with a booster at least 6 mo later)
- Hepatitis B vaccine for all patients who have no evidence of past or current infection (40 μg of monovalent vaccine at 0, 1 and 6 mo, with revaccination if postvaccination serology shows ≤ 10 IU/L anti–hepatitis B antibodies)
- Meningococcal vaccine for all patients* (2 doses of Men-C-ACYW 8 wk apart, and 2 doses of 4CMenB at least 4 wk apart)
- Tetanus, diphtheria and pertussis vaccine for all patients (every 10 yr)
- Hemophilus influenza type b vaccine for all patients (single dose recommended regardless of vaccination history)

All live vaccines (Bacillus Calmette-Guérin, herpes zoster, live influenza, measles–mumps–rubella, typhoid, varicella) are contraindicated in cases of advanced HIV and AIDS

Note: Adapted from the Government of Canada, Canadian Immunization Guide Part 3: Vaccination of Specific Populations.[59]

*Neither vaccine is authorized for use in patients older than 50 years, but limited evidence and expert opinion suggest their use is considered appropriate.

Depression, diminished health-related quality of life and social isolation

HIV status has been independently associated with depression and poorer health-related quality of life.[60] Observational evidence has highlighted higher rates of social isolation among people living with HIV, which worsens with age.[61] Over time, more people with HIV may need to move into retirement homes or long-term care facilities. Qualitative research among older people living with HIV and AIDS in Ontario found concerns around their acceptance into retirement facilities, access to subsidized housing and homelessness.[62] Homelessness is associated with reduced adherence to antiretroviral therapy, disease progression and HIV transmission.[62] A recent scoping review on aging with HIV reported a lack of qualitative studies that explore the lived experiences of people aging with HIV and end-of-life care.[63]

New HIV infection in older adults

People more than 50 years of age now account for almost one in six people with a new HIV infection in Canada and the US.[5–7] Clinicians should maintain a high index of suspicion for HIV infection throughout the lifespan, particularly among people with risk factors for infection. Rates of HIV testing decline with age,[64] with only 25% of Americans over 50 years of age reporting ever having been tested.[65] Barriers to testing include lack of awareness of HIV risk in older adults, discomfort among health care providers with speaking to older adults about sex, and beliefs that older adults are not sexually active.[66] Facilitators of testing are patient-initiated requests for treatment of sexual dysfunction or infections.[66] Older patients may not view themselves as being at risk, and they may associate condom use with pregnancy prevention rather than protection from sexually transmitted infections.

The Public Health Agency of Canada recommends one-time HIV testing of people who are or have been sexually active without age restrictions.[67] The CDC recommends testing for adults less than 65 years of age at least once, with annual testing for higher risk populations.[68]

After HIV is diagnosed, antiretroviral therapy should start as soon as possible regardless of patient age. Because suboptimal treatment adherence (i.e., taking < 80% of drugs prescribed) is associated with poorer outcomes, it is important to take steps to optimize adherence.[69] Overall, older adults with HIV are at lower risk of nonadherence, possibly because they are more accustomed to taking medications.[70] A variety of factors, such as neurocognitive impairment,[71] depressive symptoms, lower social support[72] and comorbidity,[55] may compromise medication adherence. Presence of these factors should lead to more intensive monitoring of therapy and use of aids to improve adherence (e.g., prompts or cues, linking medication taking with existing habits).[73] People who inject drugs and people who live in less affluent areas have lagged in achieving the benefits possible with antiretroviral therapy,[74] and should receive particular attention.

Conclusion

People are both aging with HIV infection and acquiring infection at older ages. Not everyone has benefitted from the

improvements to mortality and quality of life that have arisen as a result of antiretroviral therapy. Continuing to provide comprehensive HIV care while addressing an increasing burden of age-related, non–HIV related health conditions is a growing challenge. Future research will hopefully address gaps in existing knowledge (Box 4). The care for people aging with HIV and AIDS will increasingly involve nonspecialist health and social care personnel, who should be aware of the changing demographics of this patient population in Canada.

Box 4: Unanswered questions

- How do we improve sexual education of older adults and the people who care for them?
- How do we best care for an aging population of patients living with HIV and AIDS?
- Where is care best provided? Do we have the resources to provide multidisciplinary care?
- How do we prepare as a society for the future medical, social and housing needs of this vulnerable population?
- Should we be placing a greater focus on education of Canadians and clinicians in considering HIV among older adults to facilitate early identification and treatment?
- Should we be routinely screening for frailty and cognitive impairment among patients with HIV?
- How should we address the stigma associated with a diagnosis of HIV?

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