Complications of HIV infection in an ageing population: challenges in managing older patients on long-term combination antiretroviral therapy

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With the use of combination antiretroviral therapy, the proportion of HIV-infected patients over age 50 has greatly increased. The rate of progression of untreated HIV disease, response to therapy and complicating effects of co-morbidities differ in older versus younger patients. Compared with younger individuals, older untreated HIV patients demonstrate faster rates of CD4+ cell loss and more rapid progression to AIDS and death. With treatment, older patients have a better virological response, but a less robust immunological response. The treatment of older HIV-infected patients is further complicated by pre-existing co-morbid conditions including cardiovascular, hepatic and metabolic complications that may be exacerbated by the effects of HIV infection per se, modest immunodeficiency (i.e. at CD4+ counts >350 cells/mm³), and the metabolic and other adverse effects of combination antiretroviral therapy. Based on these considerations guidelines for the treatment of HIV-infected patients state that increased age is a consideration in initiating antiretroviral therapy in persons with 350–500 CD4+ cells/mm³.

Keywords: immunocompromised host, epidemiology, age

Introduction

In both the USA and Europe, the proportion of HIV-infected patients who are ≥50 years of age has increased due to improved survival of younger individuals and increasing rates of infection among older persons.1,2 Thus, in the USA, people ≥50 years of age accounted for 28% of persons living with HIV infection in 2007 and are expected to account for 50% of living HIV-infected individuals by 2015.3,4 These older individuals are at increased risk for complications due to co-morbid medical conditions that are exacerbated by the toxicities of long-term antiretroviral therapy, normal consequences of ageing, and previously unforeseen complications of chronic HIV infection.3,4

Natural history and response to therapy

After seroconversion, older patients have higher HIV-1 RNA plasma titres, lower CD4+ cell counts, greater rates of CD4+ decline, more frequent AIDS-defining events and other co-morbid conditions, and higher rates of mortality than younger patients.5–7 Although older persons have better virological results after initiating combination antiretroviral therapy (cART), their risks of AIDS and death remain greater.9 These inferior clinical outcomes are at least partially due to an attenuated immunological response that is independent of suppression of HIV replication.3,8,9 Critically, lower CD4+ counts are not only associated with higher rates of AIDS events, but also with increased rates of serious non-AIDS events.10 Unfortunately, the inadequate immunological recovery of older HIV-infected patients is exacerbated by delayed diagnosis and presentation for care.3

Clinical manifestations, complications and co-morbidities

The key distinguishing clinical feature of HIV infection in older persons is the impact of co-morbidities.11,12 In one analysis, 61% of HIV-infected individuals between 50 and 59 years of age had at least one medical co-morbid diagnosis.11 As demonstrated by the Strategies for Management of Anti-Retroviral Therapy (SMART) and Evaluation of Subcutaneous Proleukin® in a Randomized International Trial (ESPRIT) trials, in persons with >300–350 CD4+ cells/mm³, the frequency of serious non-AIDS events is approximately 50% greater than that of AIDS events; additionally, the mortality rate following these serious non-AIDS events is more than double that following AIDS events.12 Furthermore, pre-existing co-morbidities, age-related decreases in hepatic and renal function and drug–drug interactions related to

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polypharmacy affect the tolerability of antiretroviral therapy. In particular, it is not surprising that older patients are more likely to develop hypercholesterolaemia, anaemia, hyperglycaemia and renal dysfunction after the initiation of therapy, and that increasing age is associated with increased rates of changes in antiretroviral therapy due to adverse drug events.

While personal habits (e.g. tobacco, substance or alcohol use), ageing per se and various antiretroviral agents promote the occurrence of co-morbidities, HIV replication itself contributes to the development of these conditions via increased immune function as well as through disturbances in endothelial cell function and inflammatory cytokine levels. Thus, lower CD4+ cell counts are associated with higher rates of non-AIDS-defining malignancies, liver-related diseases, cardiovascular diseases and pulmonary or renal diseases. Compared with persons with 350–499 CD4+ cells/mm3, a range in which few AIDS-defining diagnoses occur, mortality is lower in patients with 500–699 CD4+ cells/mm3 or >700 CD4+ cells/mm3. Finally, ongoing HIV replication at any given CD4+ cell count increases the risk of AIDS-related complications and death. These effects are magnified in older patients.

**Cardiovascular disease**

Overall, HIV-infected individuals have been reported to have a nearly 2-fold higher adjusted rate of myocardial infarction than uninfected patients. In addition to the effects of ageing, increased rates of cardiovascular disease among HIV-infected patients are attributable to an inflammatory cascade and endothelial activation precipitated by HIV replication, adverse effects of various antiretroviral agents, greater rates of infection by hepatitis C virus (HCV), and increased use of tobacco and recreational drugs.

For each year of exposure to protease inhibitors there is a 15%–16% increase in the adjusted relative rate of myocardial infarction; this risk is more clearly associated with the use of indinavir, fosamprenavir and lopinavir/ritonavir. Although some analyses have found increased myocardial infarction rates in abacavir recipients, this effect actually may be due to disproportionate rates of chronic kidney disease or to cocaine or intravenous drug use among abacavir recipients. While randomized clinical trials have generally not shown increased rates of clinical cardiovascular disease among abacavir recipients, the average age of patients participating in these trials is considerably younger than in the cohort studies that demonstrated such a relationship. Finally, a weak association between the use of didanosine and zidovudine and increased cardiovascular disease has been reported.

**Diabetes, the metabolic syndrome and lipodystrophy**

With the ageing of the patient population, diabetes has become more prevalent in HIV-infected patients. This increase is exacerbated by higher rates of diabetes among persons receiving cART. One study reported a 4.6-fold higher prevalence of diabetes among HIV-infected men on cART than among HIV seronegative persons; smaller increases were found among HIV-infected women with longer cumulative exposure to nucleoside reverse transcriptase inhibitors (NRTIs).

Depletion of skeletal muscle mitochondrial content may explain the association between diabetes and the use of stavudine, zidovudine and didanosine. In contrast, insulin resistance associated with the use of protease inhibitors, particularly indinavir and ritonavir, appears to be largely due to interference with insulin-stimulated glucose uptake. Although one group found a 2-fold higher prevalence of diabetes among HIV-infected men not receiving cART, this was not demonstrated by others.

The metabolic syndrome, i.e. dyslipidaemia, abdominal adiposity, elevated blood pressure and insulin resistance, occurs in 17%–24% of HIV-infected patients. The risk of developing this syndrome has been associated with increased age and the use of stavudine, didanosine and protease inhibitors (particularly lopinavir/ritonavir). Use of stavudine or zidovudine rather than tenofovir or abacavir results in higher cholesterol and triglyceride levels, while nevirapine is associated with smaller disruptions of serum triglyceride and high-density lipoprotein cholesterol values compared with efavirenz.

Most studies have shown that the risk of lipoatrophy and/or lipohypertrophy in HIV-infected patients increases with ageing. Lipodystrophy is associated with the use of antiretroviral therapy agents that cause greater amounts of mitochondrial toxicity and higher rates of diabetes, dyslipidaemia and cardiovascular disease. Hypertension, which is present in 15%–45% of HIV-infected men >50 years of age versus 3%–5% of HIV-infected men <30 years of age, is also associated with lipoatrophy.

**Malignancy**

In recent years, rates of AIDS-defining malignancies (ADMs) have decreased while rates of non-AIDS-defining malignancies (nADMs) have increased; in some cohorts, nADMs now outnumber ADMs. Several nADMs, including cancers of the oral cavity, anus and lung, and Hodgkin’s lymphoma, occur more often in HIV-infected patients than in the general population. Disproportionate rates of cigarette smoking and infection by hepatitis B virus (HBV) or HCV undoubtedly contribute to the increased rates of nADMs in HIV-infected individuals. However, the similarity in the types of cancers observed in HIV-infected patients and transplant patients and the increased rates of Hodgkin’s lymphoma as well as of anal, liver, lung and oropharyngeal cancers in HIV-infected persons as CD4+ cell counts decline suggest that decreased immune surveillance increases the risk of nADMs, particularly those with viral aetiologies. The risk of some cancers may also be increased by ongoing HIV replication.

**Liver disease**

Liver-related diseases are the most common non-AIDS-related cause of death among persons with HIV infection. Independent predictors of liver-related death include older age, intravenous drug use, HCV and HBV infection, decreased CD4+ counts and increased HIV replication. CART contributes to liver injury via mitochondrial toxicity due to NRTIs (i.e. zalcitabine,
didanosine and stavudine), complications of the immune reconstitution inflammatory syndrome and hypersensitivity reactions. Nevertheless, cART-mediated reversal of immunosuppression decreases progression of HCV-related fibrosis and cirrhosis-related clinical consequences, including hepatocellular carcinoma and death.

Renal disease

Risk factors for renal failure unique to HIV-infected patients include CD4+ depletion, incomplete viral suppression and deleterious effects of cART. Analysis of a large prospectively monitored cohort demonstrated that longer cumulative exposure to tenofovir, indinavir, atazanavir or lopinavir/ritonavir increased the risk of chronic kidney disease, defined in this study as either a decrease in the estimated glomerular filtration rate (eGFR) from >60 mL/min to a lower value, or a confirmed decline in eGFR for persons with baseline eGFR of ≤60 mL/min. Other risk factors for the development of renal impairment include increased age, decreased baseline renal function, receipt of concomitant nephrotoxic medications, diabetes, hypertension and HCV infection. A randomized clinical trial demonstrated greater renal damage among persons receiving tenofovir in combination with a boosted protease inhibitor (i.e. lopinavir/ritonavir) rather than efavirenz. Although follow-up data are limited, the nephrotoxicity of tenofovir, atazanavir and lopinavir/ritonavir appears to be reversible.

Bone disease and vitamin D

The prevalence of osteopenia has been estimated to be 6-fold higher and that of osteoporosis nearly 4-fold higher in HIV-infected than in non-HIV-infected individuals. Evidence that cART exacerbates bone disease includes bone mineral density (BMD) reduction after initiation of therapy. A meta-analysis found the odds of osteoporosis to be 2.4-fold higher in patients receiving cART than in treatment-naive individuals.

Proposed mechanisms for bone disease include mitochondrial toxicity caused by NRTIs, urinary phosphate wasting induced by tenofovir, and dysregulation of osteoblasts and osteoclasts by protease inhibitors. In addition, vitamin D deficiency affects up to 42%–72% of HIV-infected persons. Risk factors for vitamin D insufficiency include increased age, longer duration of antiretroviral therapy and receipt of tenofovir or non-nucleoside reverse transcriptase inhibitors (NNRTIs), particularly efavirenz. Furthermore, HIV infection per se may augment bone resorption by promoting osteoclast differentiation through direct effects of viral proteins or indirectly through increased levels of tumour necrosis factor-a (TNF-a) and interleukin-6 (IL-6). Finally, risk factors for osteoporosis and osteoarthropathy, such as low body weight, cigarette smoking, alcohol abuse, glucocorticoid use and hypogonadism, are more prevalent among HIV-infected individuals.

Clinical studies demonstrate that among the NRTIs, tenofovir is synergistic with natural ageing. In this study, frailty was identified as the self-reported presence of three of the following symptoms: (i) unintentional weight loss of at least 10 pounds; (ii) exhaustion (decreased ability to work or persistent fatigue); (iii) decreased ability to walk; and (iv) low physical activity levels. In other work, increased frailty has been shown to predict poor health outcomes.

Conclusions

As a consequence of the increasing importance of medical co-morbidities, optimal care of older HIV-infected patients requires systems of care that provide coordination of primary care and specialty services. This is necessary to minimize the interactions of antiretroviral therapy with concomitant pre-existent and emergent medical co-morbidities. Additionally, it is imperative to ensure proper management of non-HIV medical needs, as many providers of HIV specialty care are less comfortable with providing primary care. These complicated older patients will benefit from the development of programmes to comprehensively assess the risks of morbidity and mortality, identify modifiable mediators of risk and prioritize the delivery of high-quality medical care. The decreased immunological responses among older persons and their increased susceptibility to medical co-morbidities have led the European AIDS Clinical Society, United States Department of Health and Human Services, and International AIDS Society–USA to recommend that age be a consideration in initiating antiretroviral therapy in persons >50–60 years of age who have >350–500 CD4+ cells/mm3.

Transparency declarations

None to declare.
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