HIV infection in older patients in the HAART era

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An increasing number of patients over 50 years of age are now living with HIV, owing to highly active antiretroviral therapy (HAART) that prolongs survival on the one hand and to late diagnosis of patients living with occult HIV infection on the other hand. Most studies have shown that compared with younger patients, patients over 50 generally have a slower immunological response to HAART and experience more rapid clinical progression, despite a better virological response. Low thymic output probably plays a role in the poorer CD4 cell response in patients initiating HAART over 50 years. Management of HIV infection in older patients is particularly complex, mainly because they are more likely to have co-morbidities necessitating specific medications that may interact with antiretroviral drugs. More controlled studies of HAART efficacy and tolerability in such patients are needed to establish specific management guidelines. Information campaigns targeting older patients and their doctors are also needed to ensure timely diagnosis of HIV infection and antiretroviral treatment initiation.

Keywords: antiretroviral treatment, elderly, HIV/AIDS

Introduction

HIV-infected elderly subjects are an emerging patient category in industrialized countries. Based on recent studies, including a paper we have published in AIDS, the following article addresses specific management issues relating to HIV infection in patients over 50 years of age, focusing on epidemiological data and the response to HAART.

Epidemiology

Clinicians will encounter increasing numbers of older HIV-infected patients in coming years. Epidemiological data from rich countries show that the HIV-infected population is ageing in parallel with the use of potent treatments, and that the number of older patients who are newly infected or newly diagnosed is increasing. The age cut-off of 50 years often adopted to define ‘elderly’ patients with HIV/AIDS is younger than that usually used in most other settings. Recent data from the CDC show that the cumulative number of AIDS cases among American adults over 50 years of age quintupled during the last decade; in 2000, patients over 50 accounted for ~15% of all AIDS cases recorded in the United States. The figures are similar in France: in 2003, ~15% of patients enrolled in the French Hospital Database on HIV (FHDH), a nationwide hospital-based cohort of >100,000 HIV-infected patients, were over 50 (21% of men, 13% of women).

In contrast to younger patients, the main documented risk factor for HIV infection among patients over 50 is heterosexual intercourse. Injection drug use is rare, and the route of HIV infection is often unknown. Early in the HIV/AIDS pandemic, older subjects represented a large proportion of patients who were infected by blood products or whose exposure group was unknown, but these rates have fallen markedly in recent years: ~15% of American patients aged over 50 years contracted HIV through blood transfusion in the 1980s, compared with only 1.1% in 1999. This decline is of course related to transfusion risk-reduction policies.

In addition to the ‘ageing cohort effect’, most studies have shown that HIV infection tends to be diagnosed at a later stage in elderly patients than in younger patients. This implies that antiretroviral treatments tend to be started later, possibly compromising their efficacy. Our team (FHDH) has examined factors associated with late assess to care, as defined by recruitment to our hospital cohort when the CD4 cell count is <200 cells/mm³ or when AIDS has already occurred. Age at recruitment was independently associated with late access to care. After age 30 years, the risk increased gradually with age at recruitment: relative to patients under 30, the risk of late access to care was increased 1.8-fold (95% CI; 1.6–1.9) between 30 and 40 years, 2.5-fold (95% CI = 2.3–2.8) between 40 and 50 years, 2.9-fold (95% CI = 2.6–3.3)
Factors potentially explaining the late diagnosis of HIV infection in older patients include less common routine screening; poor awareness of the risk of HIV infection or of safer sex practices in this age group; failure of physicians to consider the possibility of HIV infection in these patients; and confusion between symptoms of opportunistic infections and those of frequent co-morbid conditions associated with ageing. In particular, HIV infection itself may mimic neurological disorders such as Alzheimer’s disease, Parkinson’s disease and cerebrovascular dementia. Internists, general practitioners, geriatricians and neurologists should thus be more aware of the possibility of occult HIV infection among their patients.

Treatment and prognosis

As in many other diseases, age is an important prognostic factor in HIV infection.8 Age at seroconversion5,9 and age at a given CD4 cell count10 were shown to be important determinants of progression and survival before the widespread introduction of HAART, starting in 1996. Since this date, many studies, including the ART Cohort Collaboration (ART-CC), which includes 13 cohort studies conducted in Europe and North America,11 have shown that age remains an independent predictor of clinical progression on HAART. The impact of age in the ART-CC study seemed to be less marked than in the pre-HAART era, but a threshold effect was noted at 50 years.

Because older patients are usually excluded from clinical trials, controlled data are lacking on this age group. Studies of the response to HAART in elderly patients have mostly involved small populations and relatively short follow-up.12-18

In a recently published study,1 we examined immunological and clinical responses to first-line HAART according to age at treatment outset in a cohort of 3015 HIV-infected patients, 401 of whom were over 50. This analysis, based on the FHDH, showed that patients over 50 had significantly slower CD4 cell reconstitution than younger patients, despite a better virological response. Among patients with baseline HIV RNA levels >5 log copies/mL (see Figure 1), the mean CD4 cell increase during the first 6 months of HAART was 42.9 cells/mm³/month in patients under 50, compared with 36.9 cells/mm³/month in older subjects. CD4 cell response slowed after 6 months of treatment, counts rising by 17.9 cells/mm³/month in patients under 50, and by 15.6 cells/mm³/month in older patients. This impaired immunological response was associated with a more rapid clinical progression in patients over 50. During the first year of HAART, 10.2% of patients over 50 died or had a new AIDS-defining event, compared with 5% of younger patients. After 5 years the respective figures were 21.9% and 12.4%. In contrast, viral suppression, defined by an HIV RNA level <500 copies/mL, was more frequent in patients over 50 than in younger patients [HR (hazard ratio) = 1.23, 95% CI = 1.11–1.38]. In most studies,19,20 viral suppression was less frequently achieved in younger subjects, a phenomenon usually attributed to poorer adherence to treatment.21

Immune reconstitution during HAART: impact of age

HIV infection is associated with a gradual decline in circulating naive and memory CD4 T cell counts. Immune restoration following HAART can be divided into two phases: an initial rapid increase in the CD4 T-cell count during the first 8 weeks of therapy, resulting mainly from a redistribution of memory T lymphocytes sequestered in lymph nodes; and a slower phase mainly involving accrual of naive T cells. This increase in naive CD4 T-cell numbers could be due to peripheral expansion of existing naive T cells and/or to thymic production of new naive T cells. Douek et al.22 quantified peripheral TCR-excision circle (TREC)-bearing recent thymic emigrants and obtained evidence that the adult thymus could contribute to CD4 T-cell reconstitution during HAART. This was subsequently confirmed by other groups.23 Thymic involution during ageing would thus have a negative impact on HAART-induced CD4 T-cell reconstitution. Indeed, CD4 TREC levels correlate negatively with age, both in healthy individuals22 and during immune reconstitution in cancer patients undergoing autologous
bone marrow transplantation. Thymic output has been found to reach a minimum after the age of 55 years. Accordingly, low thymic output probably plays a role in the lesser CD4 cell response observed in patients initiating HAART over 50 years of age. In our study the risk of clinical progression during HAART was 1.5 times higher (95% CI = 1.2–2.0) among patients over 50 than among younger patients. Overall, three-quarters of clinical events occurred in patients with <200 CD4 cells/mm³. Interestingly, the nature of AIDS-defining events differed between the two age groups. Older patients had a significantly higher risk of CMV disease (HR = 5.0), HIV encephalopathy (HR = 2.8) and Kaposi’s sarcoma (HR = 2.3), while the risk of PCP (HR = 1.9), recurrent bacterial pneumonia (HR = 2.0) and progressive multifocal leucoencephalopathy (HR = 3) also tended to be higher, although not significantly, probably owing to a lack of statistical power in our analyses. The mean CD4 cell count at which each disease occurred did not differ between the two age groups, indicating that it is the CD4 cell count reached while on HAART rather than age itself that determines the risk of onset of a particular disease.

Since low CD4 cell counts are associated with a higher risk of disease progression, interleukin-2 (IL-2) administration has been investigated and found to lead to a substantial and sustained increase in circulating CD4 T-cell counts in HIV-infected patients, including patients over 50 who are virological responders/immunological low-responders. However, younger age was an independent predictor of a better CD4 cell response to intermittent IL-2 therapy in the ESPRIT trial. Anyway, whether the increase in CD4 cell count following IL-2 administration will be associated with a clinical benefit is currently being assessed in two large Phase III international trials (ESPRIT and SILCAAT).

Whether or not the slower CD4 cell response in older patients has implications for the optimal timing of HAART initiation remains to be determined. Such studies must take into account the relative contributions of the age-related impairment of CD4 cell responses on the one hand, and of late diagnosis and treatment on the other hand. However, HIV infection must be diagnosed and treated with antiretroviral drugs are at higher risk of cardiovascular disease progression, interleukin-2 (IL-2) administration has been determined as an independent predictor of a better CD4 cell response to intermittent IL-2 therapy in the ESPRIT trial. Also, whether the increase in CD4 cell count following IL-2 administration will be associated with a clinical benefit is currently being assessed in two large Phase III international trials (ESPRIT and SILCAAT).

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Comorbidity and toxicity

Older patients are more likely to have comorbid conditions such as metabolic disorders (diabetes mellitus), malignancies and renal, hepatic or cardiac dysfunctions. In addition, the overall risk of cancer is ~2-fold higher among HIV-infected patients than in the general population. Moreover, HIV-infected patients treated with antiretroviral drugs are at higher risk of cardiovascular disease and of metabolic complications. The risk of myocardial infarction has been shown to increase significantly both with age and with the duration of exposure to HAART. Whether or not older patients are at higher risk of severe toxicities as a result of hepatic or renal dysfunctions remains to be explored but is likely. Such conditions can interfere with the drug metabolism and/or can require treatments that may interact with antiretroviral drugs and be responsible for higher blood concentrations of the drugs. As a consequence, management of antiretroviral therapy in elderly patients is particularly complex, and must take into account together with HIV infection multiple factors, including co-morbidity, concomitant treatments, and age-specific pharmacokinetics. There are currently no specific management guidelines for this age group. In addition, controlled data on efficacy and tolerability are sparse or nonexistent, as older patients and patients with co-morbidities are usually excluded from clinical trials. These data are needed to establish specific recommendations.

Conclusions

The HIV-infected population is ageing in industrialized countries, as a result of both prolonged survival due to effective antiretroviral treatment and the increasing proportion of diagnoses made among patients over 50 years of age. Older patients are at a higher risk of HIV disease progression, for at least three reasons: first, they tend to be diagnosed at a more advanced stage; second, they have a slower immunological response to HAART; and third, they are at a higher risk of complications, such as cancer and cardiovascular disease because of the combined effect of ageing, HIV infection and antiretroviral treatment. More studies of this age group are needed to establish specific management guidelines. Information campaigns targeting older patients and their doctors are required, both to prevent HIV transmission and to diagnose and treat HIV infection in a timely manner.

Transparency declarations

No declarations were made by the authors of this paper.

References

Leading article


