REVIEWS

Human immunodeficiency virus (HIV) in older people

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Abstract

The number of older people living with human immunodeficiency virus (HIV) in the UK is rising. Older people are at risk of acquiring HIV infection for a multitude of reasons. This, combined with effective HIV treatment which has significantly prolonged life expectancy, means that health care professionals working in the UK can expect to see increasing numbers of older people with HIV infection.

In this review article, we summarise the epidemiology of HIV amongst older people, including data from our local cohort in the city of Sheffield, UK. We discuss specific and practical issues in older patients including why older people are at risk, how to make a diagnosis and the importance of doing so early, guidelines for HIV testing and an update on anti-retroviral therapy including drug interactions and side effects.

Keywords: elderly, highly active anti-retroviral therapy, human immunodeficiency virus, older people

Introduction

Human immunodeficiency virus (HIV) was isolated as the causative agent for acquired immune deficiency syndrome (AIDS) in the early 1980s in the USA. It has since become a worldwide health problem with over 25 million deaths being attributable to AIDS. The number of people living with HIV in the UK has continued to rise each year since the mid-1980s [1].

The introduction of highly active anti-retroviral therapy (HAART) in 1996 has revolutionised HIV treatment leading to a steep decline in the number of AIDS cases presenting each year and a significant improvement in patient survival [2]. This, in combination with other factors such as increased HIV risk behaviours in older adults and a lack of targeted prevention campaigns, means that health care professionals working in the UK will encounter greater numbers of older people living with HIV in their day-to-day clinical practice.

Epidemiology

In the UK an estimated 77,400 people were living with HIV at the end of 2007 with nearly a third of these individuals unaware of their diagnosis. During 2008 there were 7,370 new diagnoses of HIV, of which just over half were acquired through heterosexual contact — mostly black Africans who were infected outside of the UK. Approximately 38% of new diagnoses were made in men who have sex with men. Almost a third of new HIV diagnoses were made late (that is, with a CD4 count <200 per mm$^3$) — a group in whom morbidity and mortality is significantly increased [1].

According to the Center for Disease Control and Prevention, in 2005 in the USA, 15% of new HIV diagnoses and 24% of the entire HIV population across 33 states were made up of people aged 50 and over. This prevalence data represents an 8% increase from 2001 [3]. However, true rates of HIV infection in this age group are difficult to determine due to low rates of testing [4].

In Sheffield we have a cohort of 660 individuals with a diagnosis of HIV, of whom 18 (3%) are aged 60 years or over. Of these 18 patients, 14 are male (78%) and 4 (22%) female, the oldest being 76 years old. Eight of the 18 patients (44%) were diagnosed after the age of 60. Since 1993 we have also seen 10 patients aged over 60 die as a result of HIV infection.
Pathophysiology

HIV infects CD4+ T Lymphocytes, and disease manifestations are largely a consequence of the decline in CD4+ T cells causing immunosuppression. Initially, there is a period of rapid cell turnover with CD4+ cells being infected at a high rate but rapidly cleared by cytotoxic (CD8+) T lymphocytes and then replaced from a precursor pool. Eventually, the patient enters the terminal stages of HIV disease as a result of exhaustion of the stem cell reservoir and/or the rapid replication and mutation of the virus to generate wide antigenic diversity which ‘outruns’ the CD8+ cell response. This process takes on average 10–15 years [5].

At a cellular level, HIV surface protein gp120 binds to CD4 and a chemokine co-receptor on the surface of the host cell. The virus then fuses with the cell surface membrane and releases its contents (RNA + viral enzymes) into the cytoplasm. Within the nucleus, viral reverse transcriptase transcribes HIV RNA to create double-stranded DNA. Viral integrase then splices HIV DNA into host chromosomal DNA to create a ‘provirus’. When a CD4+ cell harbouring provirus is activated (either against HIV or another pathogen), it replicates and produces new copies of the viral genome and viral proteins. HIV protease then modifies the proteins produced such that they can be packaged together with copies of viral RNA to create new viral particles which bud from the cell and can infect other cells [5].

Various theories have been proposed which suggest that elderly patients may be at greater risk of HIV disease progression and poorer response to treatment. These include:

- thymic involution and corresponding low ‘T cell reserve’ which may impair recovery of CD4+ cell numbers with treatment [6]
- the association of ageing with increased expression of key T cell chemokine co-receptors which may facilitate viral entry into certain immune cells [7].
- the fact that older adults have reduced production of IL-2 and IL-2 receptors which affects T cell function and promotes a shift from naïve to more terminally differentiated T cells, and thus leads to immunosenescence [8].

Why are older people at risk?

There are several reasons why the elderly population is at risk of HIV infection:

1. The few HIV prevention campaigns that do exist do not target the elderly.
2. Older people may not consider themselves at risk of HIV infection.
3. Health care providers may not consider the diagnosis in older patients and therefore may not undertake HIV testing or may attribute symptoms of HIV to ‘normal ageing’.
4. Despite the stereotypes, many older people lead sexually active lives. Studies of sexual activity in people aged over 50 showed that 81.5% were involved in one or more sexual relationships including sex with prostitutes [9], and a national US survey suggested that only a small minority of people over 70 consistently used condoms [10]. Older women may be especially at risk because age-related vaginal thinning and dryness can cause tears in the vaginal wall [11].
5. The increase in foreign travel makes access to countries with thriving sex industries easier.
6. The introduction and usage of potency drugs has extended the sex lives of many elderly males.
7. Injection drug usage, despite our misconceptions, is a contributor to HIV transmission in older people. In the USA, injection drug use accounts for more than 16% of AIDS cases in those aged 50 or over [12].
8. The stigma of HIV may be perceived to be greater in the elderly population leading them to hide their diagnosis or avoid testing.

Making a diagnosis

HIV is now a treatable medical condition with the potential for long-term survival. Despite this, there are still a significant number of people living in the UK unaware of their diagnosis. A national audit in 2006 conducted by the British HIV Association (BHIVA) showed that 24% of all deaths amongst HIV positive individuals was attributed to the diagnosis of HIV being made too late for effective treatment [13]. Furthermore, there is evidence that many of these late presenters had been recently seen by a health care professional without the diagnosis of HIV being considered [14].

In our Sheffield cohort, five of the 18 patients (28%) in the over-60 age group presented late (CD4 count <200/mm³). Seven (39%) had recently been seen by a health care professional without the diagnosis being made. Perhaps even more significantly, of the 10 patients that died as a result of their HIV infection since 1993, seven (70%) presented late.

There is still a widely held but erroneous belief that HIV testing requires lengthy pretest counselling by an expert in this field. The outlook for many people testing positive for HIV is significantly better than for many other conditions for which we test routinely. People currently being diagnosed with HIV are considered to have a standardised mortality ratio of 1.4, similar to that for a diagnosis of type 2 diabetes [15]. Whilst patient consent for testing is required, national guidelines on HIV testing state that ‘it should be within the competence of any doctor or healthcare professional to obtain informed consent for testing’ [16].

BHIVA recommends that a fourth generation laboratory assay which tests for both HIV antibody and p24 antigen be used for HIV testing. This has the advantage of minimising the ‘window period’ between infection and positive testing to 4 weeks.

Point of care testing has been introduced in some centres with the advantage of a result from a finger prick or mouth swab being available within minutes. It is hoped that this may increase the uptake of voluntary testing. However, all
positive tests obtained using this method should be confirmed by laboratory serological testing [16].

**Clinical features**

The clinical manifestations of HIV are manifold. Primary HIV infection or acute seroconversion illness can affect up to 80% of individuals and typically occurs 2–4 weeks after infection. The syndrome classically presents as a non-specific flu-like illness with varying degrees of clinical severity. A generalised maculopapular rash may be a striking feature. Symptoms usually resolve after a couple of weeks as the patient mounts an immune response. An asymptomatic period (with or without persistent generalised lymphadenopathy) then ensues which can last for a number of years. During this 'latent period' active viral replication is ongoing and the patient is infectious to others. As the disease progresses, the patient enters a symptomatic phase where the spectrum of the illness changes as the CD4+ T cell count declines [17].

The incidence of opportunistic infections and other AIDS-related illnesses increases in inverse proportion to the fall in the CD4 cell population, particularly with a CD4 cell count below 200 cells/ml. However, many individuals remain asymptomatic until a very late stage of the infection.

The most common opportunistic infections across all age groups are:

- (1) Pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia (PCP)) — 75% of cases
- (2) Oesophageal candidiasis — 15% of cases [18].

PCP often presents with an insidious onset of breathlessness and malaise, not always accompanied by fever. In the older patient in particular, the symptoms may mimic cardiac disease in the early stages. Oropharyngeal candidiasis which relapses after adequate treatment, whether or not there are associated gastrointestinal (GI) symptoms, should raise suspicion of an underlying immune paresis.

Other opportunistic infectious organisms include atypical mycobacteria, cryptococcus, cryptosporidium and cytomegalovirus, which would not normally occur in patients with intact cell-mediated immunity. However, more common infections also have increased prevalence in HIV-infected individuals: tuberculosis, bacterial pneumonia, salmonellosis, shingles and recurrent herpes simplex infections.

Symptoms of blood dyscrasias, such as thrombocytopenia, neutropaenia and lymphopaenia, may be the first presenting feature of HIV infection, as can unexplained weight loss, chronic diarrhoea and dementia. Diagnosis of HIV-associated dementia requires deficits in two or more cognitive domains causing impairment in the patient's ability to perform activities of daily living and an abnormality in either neurobehavioural or motor function in the absence of an alternative aetiology.

HIV-related malignancies include Kaposi's sarcoma, primary cerebral lymphoma, non-Hodgkin's lymphoma and cervical carcinoma. Screening for HIV is recommended in all patients presenting with these tumours, and also in cancers of the head and neck, lung and anus and Hodgkin's disease [16].

Increased awareness of the broad spectrum of HIV-related pathology should encourage more screening for the underlying cause. Interestingly, prognosis in individuals affected by these illnesses can be better than in HIV-negative patients once HIV treatment is instituted alongside standard therapy. An appropriate enquiry about a full sexual and travel history may reveal unexpected risk factors which point towards HIV as a possible diagnosis. An individual's age, sex, race or marital status should not be assumed to make them more, or less, at risk.

**Treatment**

**HAART**

HAART has dramatically improved the prognosis of HIV-infected individuals. It is the combination of at least three different anti-retroviral drugs (ARVs) to suppress viral replication.

Existing ARVs act at specific points in the HIV replication cycle:

- (1) block formation of dsDNA from viral RNA by reverse transcriptase — nucleoside, nucleotide and non-nucleoside reverse transcriptase inhibitors (NRTIs, NtRTIs and NNRTIs)
- (2) inhibit the final protein cleavage step so that new viral particles cannot be assembled — protease inhibitors (PIs)
- (3) prevent fusion and entry of virus into host cell — fusion inhibitors
- (4) block CCR5 co-receptor preventing viral entry — CCR5 antagonists
- (5) block integration into host chromosomal DNA — integrase inhibitors.

Infected individuals harbour cells in which the HIV provirus is quiescent. These are termed sanctuary sites and are thought to include central nervous system tissue, the ovaries and testicles. These cells are not targeted by the existing ARVs, therefore current drugs can never eradicate the virus completely [19].

The viral load and CD4 cell count are effective surrogate markers for HIV disease progression and are used to guide management decisions such as when to start treatment and how effectively control is being maintained.

Current BFIIVA guidelines recommend starting anti-retroviral therapy in all individuals with symptomatic disease and/or an AIDS diagnosis, regardless of CD4 count or viral load, in all patients with CD4 < 200 regardless of viral load and in the majority of patients with CD4 201–350 (in whom the timing of initiation is based upon
Table 1. Adverse effects of ARVs

<table>
<thead>
<tr>
<th>Class</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>GI upset, hepatic steatosis (class effect)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Hypersensitivity reaction, hyperlipidaemia</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Peripheral neuropathy, pancreatitis, lactic acidosis</td>
</tr>
<tr>
<td>Lamivudine/emtricitabine</td>
<td>Hepatotoxicity, lactic acidosis</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Fanconi’s syndrome, osteoporosis</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Lactic acidosis, hyperlipidaemia, lipodystrophy</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Bone marrow suppression, hyperlipidaemia</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Rash and raised transaminases (class effect)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Vivid dreams, somnolence, depression</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Diabetes, hyperlipidaemia</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Hyperglycaemia, lipodystrophy, hyperlipidaemia, GI upset (class effect)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Increased cardiovascular events</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Nephrolithiasis, increased bilirubin, headache</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Pronounced GI effects</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Transaminitis, headache</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Pancreatitis, raised transaminases, paraesthesiae</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Raised transaminases</td>
</tr>
<tr>
<td>Others</td>
<td>Matravir</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Enfuvirtide</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Hepatotoxicity, hypertriglyceridaemia, depression, neuropathy</td>
</tr>
</tbody>
</table>

Ritonavir is used in low dose in combination with the other PIs to boost activity. At such level, it has no intrinsic anti-viral activity and minimal side effects.

Side effects

Factors including patient preference, rate of CD4 decline, viral load and co-morbidities [16].

Current recommended first-line regimes are dual nucleoside analogue (NRTI) therapy with either a NNRTI or PI [20]. Once therapy is started, viral suppression should occur within 16 weeks and this is normally associated with a rise in CD4 cell count. The aim is to achieve viral loads of <50 copies/ml. This allows restoration of CD4 cell numbers and immune function [19].

All HIV patients should be managed by a specialist who will have access to a multi-disciplinary team to support the individual and their carers.

Prognosis for patients on HAART

Prognosis for patients starting treatment in the modern HAART era is excellent with life expectancy close to that of age-matched controls. Factors associated with poorer outcomes include a low nadir CD4 count, age being 50 years or greater, a prior diagnosis of AIDS and infection through intravenous drug use [21].

There is an increased association of cardiovascular disease with HIV infection per se and also with HAART drugs. An effect on lipid metabolism is partly responsible for this, although chronic inflammation is also postulated as playing a role. In addition, patients have an increased risk of osteoporosis and renal disease. With the availability of HAART, HIV has become a chronic disease process, and patients with good compliance with anti-retroviral treatment are now more likely to die of a non-HIV-related illness [22].

HAART in the elderly

Efficacy

Patients over the age of 50 do have good immunological and virological responses to HAART. A Spanish study in 2006 found that patients aged over 50 showed parallel profiles in terms of increase in CD4+ cell numbers and reduction in viral load from their baseline values compared with the under-50 age group. However, the older patient population had higher viral load and lower CD4+ counts at the time of enrolment and they never achieved the same CD4 counts as younger individuals. Interestingly, the older patients achieved lower viral loads than the under-50 group, possibly due to better adherence to treatment [23].

In terms of clinical progression, shorter survival times and higher rates of progression to AIDS were noted in the over-50 group. This was postulated to be due to delay in diagnosis and thus lower numbers of patients on HAART and lower CD4+ counts at enrolment [23].

Other studies have confirmed these findings. A French study including over 400 patients aged >50 showed that CD4+ cell reconstitution is significantly slower than in younger patients despite a better virologic response and that older patients have a significantly higher rate of clinical progression. Of note, older patients included in this study were more likely to have already had an AIDS-defining illness and had lower CD4 counts and higher plasma viral load at the time of initiation of HAART. The older patients also tended to have been diagnosed more recently than younger patients, implying that older patients received their initial diagnosis at a later stage of HIV infection [24].

Side effects

Side effects and toxicities of ARVs may be expected to occur more frequently in older patients who have more co-morbidities and a higher chance of pharmacological interactions with concurrent medications. An Italian study evaluated the incidence of adverse metabolic events or new co-morbidities in patients aged over 50 compared with a control group aged between 25 and 35 years. At baseline, older patients and controls were comparable for stage of HIV infection and for other co-morbid conditions. They found that the percentage of patients who developed abnor-
mal biochemical tests during the study period (including glucose >6.1, triglycerides >2.1, total cholesterol >4.9 and serum creatinine >105.6) was significantly higher in the older patient group. Only alanine transferase (ALT) levels were higher in controls compared with the older patients, although more ‘severe toxicity’ episodes (ALT >500) were recorded in older patients. In addition, the rate of new co-morbidities (such as neuropathy, cardiovascular and metabolic disorders) was higher in older patients (24.52 per 100 patient-years vs 3.39 per 100 patient-years in control group). This was hypothesised to be a combination of naturally occurring age-related events and the toxic effects of anti-retrovirals ‘acting synergistically with senescence’. For example, coronary artery disease has been correlated with protease inhibitor-induced metabolic disturbances, and systemic hypertension may be related to atherosclerosis induced by HAART [25] (see Table 1).

Interestingly, despite the increased incidence of biochemical abnormalities and co-morbid conditions in the older patient group, there was no significant difference in reported side effects or tolerability of treatment [25].

Drug interactions

Drug interactions can be classified into two major categories:
- Pharmacodynamic (in which interactions alter the pharmacological effect of drugs — such interactions may enhance or antagonise therapeutic efficacy)
- Pharmacokinetic (in which concentrations of active metabolites are altered, most commonly through interactions involving either induction or inhibition of drug metabolism).

Interactions involving NRTIs tend to be pharmacodynamic, causing enhanced toxicities when used together with certain other drugs [26]. The NRTI backbone of treatment tends to contain lamivudine or emtricitabine in combination with newer nucleoside analogues such as abacavir and tenofovir. These are used in preference over zidovudine, stavudine and didanosine, all of which have significant toxicities and increased pharmacodynamic interactions with other drugs [20, 26].

NNRTIs and protease inhibitors are metabolised by the cytochrome P450 (CYP) enzyme system in the liver and tend to cause drug interactions via their pharmacokinetic effects. Inhibition of CYP enzymes by these drugs may increase the concentration of other drugs metabolised by the CYP enzyme system. (NRTIs are renally excreted and are not involved in CYP-mediated drug interactions) [26].

Modern HAART regimens are considerably less toxic and better tolerated than previously. The main strategy to avoid enhanced drug toxicities is to avoid co-prescribing drugs known to interact with ARVs or to use alternative agents if possible. Where avoidance is not an option, co-prescribed drugs should be used with caution and patients should be monitored closely for adverse effects [26].

Conclusion

HIV is on the increase in older people. The reasons behind this are multiple, health care providers need to be aware that being old does not automatically equate to being at low risk.

HAART has significantly prolonged survival times for individuals with HIV, and early diagnosis is the key to ensuring that patients receive optimal treatment. Older patients do have good immunological and virological responses to HAART, but studies consistently show that older people are being diagnosed late on in HIV disease which impacts negatively upon their prognosis. All patients who may be at risk of HIV infection should be offered testing. Lengthy pretest counselling is not necessary unless the patient specifically requests it.

Finally, clinicians should be aware of the co-morbidities associated with long-term HAART (such as dyslipidaemias, cardiovascular disease and osteoporosis) and these risks should be addressed when assessing patients. Knowledge of the common side effects of treatment and potential drug interactions is also essential to ensure optimal patient management and to avoid toxicity.

Key points

- The incidence and prevalence of HIV in older people is increasing.
- Making an early diagnosis is the key to optimising prognosis.
- HAART has revolutionised the treatment of HIV and significantly prolonged life expectancy.
- CD4 count at presentation is the single best predictor of outcome.
- Patients treated with HAART have a significantly increased risk of other medical co-morbidities such as cardiovascular disease, dyslipidaemia and osteoporosis.
- HAART side effects and drug interactions are more common in the older population.

Conflicts of interest

None.

References

Ageing with cerebral palsy: psychosocial issues

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Abstract

Background: although much has been written about biomedical concerns in adults ageing with cerebral palsy (CP), few studies or reviews have addressed psychosocial aspects.