PAPER

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HIV – what the general physician needs to know

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ABSTRACT The global spread of HIV infection over the past 25 years presents new challenges to physicians. HIV produces multi-system disease and can present to primary care physicians or to any hospital specialist department. In the twenty-first century, HIV has joined syphilis in the differential diagnoses for many illnesses. This article is aimed at the general physician and describes the common features of HIV infection. The key points to note are: epidemiology; clinical features of opportunistic infections, tumours, and neurological disease; when to test for HIV; benefits of treatment; and complications of treatment. Throughout this article I have avoided the expression 'AIDS' because it means different things to different people. The North American definition is based on laboratory evidence of immunodeficiency but the European definition is based on historical clinical features which are often independent of immunodeficiency. I prefer to speak of HIV and its spectrum of clinical disease.

KEYWORDS Epidemiology, features, HAART, HIV, testing, treatment

LIST OF ABBREVIATIONS Central nervous system (CNS), cerebrospinal fluid (CSF), computed tomography (CT), highly active anti-retroviral therapy (HAART), human immunodeficiency virus (HIV), idiopathic thrombocytopenic purpura (ITP), magnetic resonance imaging (MRI), opportunistic infection (OI), progressive multifocal leukcoencephalopathy (PML), ribonucleic acid (RNA)

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EPIDEMIOLOGY AND LABORATORY TESTS

Global picture

The start of the HIV epidemic was defined on 10 December 1981, when the *New England Journal of Medicine* published three papers describing the clinical features of a new acquired cellular immunodeficiency. HIV was identified as the cause, and in 1985 an antibody test became commercially available. In December 2005, the UN global summary acknowledges 40·3 million people living with HIV, 4·9 million new infections in 2005, and 3·1 million deaths in the same year. The UK has seen its new cases rise from 3,499 in the year 2000, to 7,258 in 2004. There has been a steep rise in heterosexually acquired cases, most of which were infected overseas in high prevalence countries (see Table 1).

Virology

HIV is an RNA virus that only infects cells with the CD4 surface marker. The CD4 glycoprotein is found on T-lymphocyte helper cells. It is also found on dendritic cells, macrophages, and microglial cells, which form a reservoir of chronically infected cells. The normal range for CD4 lymphocytes in peripheral blood is 500–1,000 cells per microlitre (0·5–1·0 x10^9/L). The decline in CD4 cells is a good predictor of clinical features (see Table 2) and is a useful guide for when to commence HAART.

The rate of viral replication can be estimated from measurement of the number of copies of HIV viral RNA in plasma. Current assays detect as few as 40 copies of RNA per millilitre of plasma. This 'viral load' is used to monitor the success or failure of HAART. Clearly it is desirable to have a high CD4 count and a low viral load.

HIV antibody testing is the current method of testing for HIV infection.

CLINICAL FEATURES OF HIV INFECTION

Seroconversion

Within a couple of weeks of infection with HIV the patient may experience a seroconversion illness similar to glandular fever but commonly accompanied by a rash. This subsides over a period of about a week whereupon the HIV antibody test will be positive. Thereafter the patient will be asymptomatic but might have persistent lymphadenopathy as the sole physical feature. Subsequently there is a gradual decline in immune function over several years as the depletion of CD4 cells by HIV exceeds the capacity of the bone marrow to

TABLE 1 Prevalance of HIV.

Country	Prevalence in adults in 2003 (%)
South Africa	21·5
Zimbabwe	24·5
Swaziland	38·8
UK	0·15

replenish them. The rate of decline is immensely variable. Some patients may progress from seroconversion to life-threatening disease in as little as four years. More commonly, a gradual decline takes place over 10–20 years, but some individuals tolerate HIV infection remarkably well and show no sign of progression at all. Host factors determine the response.

Clinical features of established HIV infection

These can be broadly grouped as follows:

- Opportunistic infection.
- Tumours.
- Neurological disease.
- Complications of therapy.

The undiagnosed or untreated patient may present to any hospital department. The following account describes some of the common presentations.

Respiratory

Pneumocystis pneumonia presents with a dry cough and progressive dyspnoea over several weeks. It does not respond to standard antibiotics. Breathlessness and cyanosis may be the only respiratory signs but most patients have a fever and other manifestations of HIV, e.g. oral candidiasis and skin disease. Arterial blood gases show low PaO_2 and low $PaCO_2$. The chest X-ray is often unimpressive with mild bilateral uniform infiltrates. Bronchoscopy or sputum induction confirm the diagnosis. Treatment includes high dose cotrimoxazole and, in patients with hypoxaemia, prednisolone, at least 50 mg daily. The latter prevents acute respiratory failure when the cotrimoxazole starts to work. In the acute illness, complications include respiratory failure, which can be managed by ventilation, and pneumothorax, which is an ominous development.

Recurrent episodes of bacterial pneumonia may point to HIV.

Tuberculosis is becoming much more common, particularly in those patients who have lived overseas in high prevalence countries. Both pulmonary and extra-pulmonary tuberculosis are seen. The chest X-ray appearances often lack the tell-tale signs of cavitation.

TABLE 2 Relationship between CD4 count and clinical features.

CD4 count (cells/microlitre)	Implication
>500	Normal
200–500	Minor opportunistic infections
<350	Consider HAART
<200	Risk of major opportunistic infections (North American AIDS definition)
<50	Potentially fatal complications

Gastroenterology

Oral candidiasis, oral hairy leukoplakia on the sides of the tongue, mouth ulcers, gingivitis, and angular stomatitis are common events. Dysphagia, particularly for hot liquids, points to oesophageal candidiasis. Oral hairy leukoplakia is largely confined to HIV patients, but the other features can have other causes.

Opportunistic infection in the small or large bowel produces diarrhoea and malabsorption. Some patients may present with atypical inflammatory bowel disease.

Both hepatitis B and C infection share the same routes of transmission as HIV. Co-infection with two or three of these viruses is common. Chronic liver disease often accompanies HIV.

Dermatology

Seborrhoeic dermatitis, eczema, and psoriasis are frequently observed. The first two benefit from treatment with combined antifungal and steroid creams. Shingles, warts, and molluscum contagiosum are common viral infections. Kaposi's sarcoma presents initially as multifocal, slightly raised brown-purplish spots. At first they are no more than a cosmetic blemish but later spread to lymph nodes and internal organs.

Neurology

HIV also targets microglial cells in the CNS. It can produce subacute encephalitis and dementia. Peripheral neuropathy is not uncommon.

Opportunistic infections in the CNS include cryptococcal meningitis, which is diagnosed by India ink preparation of CSF and culture. Cerebral toxoplasmosis presents with headaches, fever, and localising neurological signs; diagnosis is made by contrast-enhanced CT scanning of the brain, which shows multiple ring-enhancing abscesses. Progressive multifocal leukcoencephalopathy presents in a subacute manner with features similar to multiple sclerosis but lacking any period of remission. Magnetic resonance imaging scans confirm the diagnosis.

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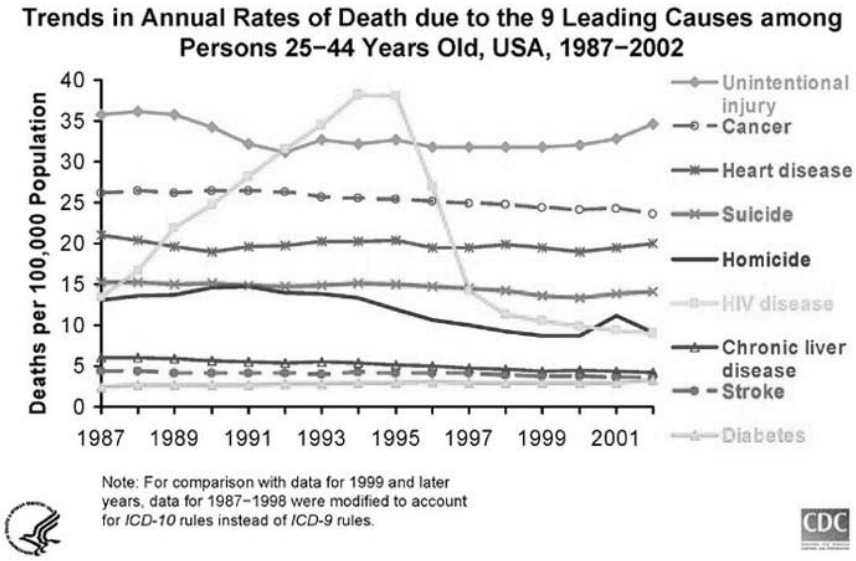

FIGURE 1 Leading causes of death in 25–44-year-olds in US. (From Centers for Disease Control and Prevention, Atlanta, USA: www.cdc.gov).

Haematology

Lymphopenia often accompanies minor opportunistic infections in established HIV infection. Initially it is mild, but a lymphocyte count of $0{\cdot}5 \times 10^9$/L should not be ignored.

Thrombocytopenia may be the initial presentation of HIV infection. Platelet consumption by the reticuloendothelial system is excessive while platelet production from the bone marrow is plentiful. It may be mistaken for ITP but it is very important to consider HIV at an early stage because it responds very well to HAART. Splenectomy is unnecessary.

Anaemia, weight loss, and elevated liver enzymes suggest disseminated *Mycobacterium avium* infection, a late-stage manifestation of HIV.

High grade B-cell lymphoma is a late-stage feature of HIV infection. It arises when the CD4 count is very low and heralds a very poor prognosis.

Rheumatology

HIV can cause arthralgias which mimic rheumatoid or lupus joint disease. Early morning stiffness and joint pain with very little evidence of joint swelling are the usual features. Serological tests for rheumatoid and lupus are negative but anti-cardiolipin tests may be positive.

Gynaecology

Carcinoma of the cervix is associated with HIV infection, so women with HIV are advised to have an annual cervical smear.

WHEN TO TEST FOR HIV INFECTION?

1 If a patient requests a test or declares a worry about HIV it is wise to explore their reasons, but offer them a test even if their story of exposure to HIV is apparently trivial. Remember that the patient may be too embarrassed to tell you the full account of the event in question.

2 If you feel the clinical features of a patient's illness might be explained by HIV, then you should raise the possibility with the patient and advise HIV antibody testing. Stress the advantages of early detection of HIV including the clear benefits of HAART (see below) and the opportunity to prevent spread to their sexual partner. In general your suspicions of HIV should be aroused in patients who attend multiple hospital departments with atypical features in each department and the lack of a unifying diagnosis. Weight loss and failure to explain lymphopenia are worrying features.

The discussions about HIV testing should take place in a room with auditory privacy. You must remember that the subject of HIV has significant psychosocial issues

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THE BENEFITS OF HAART

The treatment comprises a combination of three or more anti-HIV drugs taken concurrently and regularly to avoid the development of drug resistance. The benefits include:

- Elimination of mother to child transmission during pregnancy and delivery.
- Reversal of immunodeficiency.
- Improved quality of life.
- Prolongation of life expectancy by several years or more.

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- Prevention of infection following needle-stick injuries: 'Post-exposure prophylaxis'.

COMPLICATIONS OF HAART

In the first few weeks or months after commencing HAART, rashes, disturbance of liver function tests, and anaemia may prompt a change to a different combination of drugs.

The late complications include hyperlipidaemia, coronary artery disease, mitochondrial toxicity, and lipodystrophy (a redistribution of body fat from the face and limbs to the thorax and abdomen).

Mitochondrial toxicity arises because nucleoside analogue drugs are used in almost all forms of HAART. These nucleoside analogues are harmless to DNA synthesis in cell nuclei but interfere with the DNA polymerase found in mitochondria. This toxicity manifests as one or more of the following:

- Diabetes
- Pancreatitis
- Myopathy
- Cardiomyopathy
- Neuropathy
- Chronic lactic acidosis
- Hepatic steatosis

CONCLUSION

HIV has opened a new chapter in all textbooks of medicine. The public health challenges are immense, particularly in developing countries. The impact in the developed nations is best illustrated in the graph in Figure 1, which plots the top nine causes of death in young adults in the USA. All causes are stable except HIV, which rises from obscurity to become the most frequent cause of death in young adults by 1993. Its inexorable rise was only halted in 1995 by the introduction of HAART. The benefits of this very effective treatment are only available to those who have a diagnosis of HIV. The general physician's duty is to consider the diagnosis when the clinical picture points in that direction.

KEYPOINTS

- The UN global summary acknowledges 40·3 million people living with HIV, 4·9 million new infections in 2005, and 3·1 million deaths in the same year.
- You should consider the possibility of HIV infection in patients who visit multiple hospital departments without a unifying diagnosis, particularly if they have lymphopenia and/or thrombocytopenia.
- Discussions about HIV testing should take place in a room with auditory privacy.
- HAART comprises a combination of three or more anti-HIV drugs taken concurrently and regularly to avoid the development of drug resistance.
- After commencing HAART, rashes, disturbance of liver function tests and anaemia may prompt a change to a different combination of drugs.

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FURTHER READING

- www.unaids.org Useful source for up-to-date epidemiology.
- www.HIVMedicine.com An online textbook of HIV. European.
- www.hopkins-aids.edu An online textbook of HIV. USA.

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